The Anabolic Steroid, Stanozolol

Its Evaluation in Debilitated Children

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As testosterone and its derivatives came to be used for their androgenic effect, and later for cancer of the breast, it soon became apparent that many patients had general clinical improvement which seemed attributable to the anabolic activity of these steroids. The increases in weight, appetite, and hemoglobin and serum albumin levels, all highly desirable features that go along with increased vigor, strength and sense of well-being, were side effects which opened up a promising new area of application. Such new uses were hampered, however, by the strong androgenic qualities. It was logical, therefore, that the pharmacologic chemists should extend their efforts to produce related new steroids that were more anabolic and less androgenic. These labors resulted in several new compounds that have met with varying success in their clinical application.[1,2] Androgenicity, salt retention and occasional jaundice due to cholangitis, still limit the clinical usefulness of some of these products.

The new anabolic steroid, stanozolol † (Fig. 1), is a steroidal pyrazole first described by Clinton in 1959.[3] According to mouse and rabbit assays it is about 30 times as anabolic as methyltestosterone and about one-quarter as androgenic.[1] It is active orally at a dosage of 6 mg. per day for adults, is only slightly and variably salt retentive, has some calcium retentive quality, and a wide margin of safety.[8] Many reports have appeared supporting the anabolic rather than androgenic nature of this drug.[2,4,5,7,10,13] In extensive clinical use, cholangitis has not been observed. Because of these qualities it shows promise of filling the clinical need for a potent anabolic steroid.

The present study is an evaluation of its use with a group of severely undernourished, brain damaged, non-ambulatory, pre-adolescent children. Since all of the known anabolic agents stimulate bone growth and increase bone age in children, particular attention was paid to these parameters.

The type of patient utilized justifies to some extent the measurements to determine improvement. The commonly accepted technics do not apply as successfully here as with normal children.

Test Subjects

The patients used for this study were 22 children hospitalized at the Sunland Hospital in Orlando, Florida. These were affected with chronic neurologic disorders resulting from birth injuries, trauma, congenital defects, or infections, all of such a serious nature that hospital care was essential. Most patients were bedridden, and the maintenance of good nutrition, even with adequate nursing care, was a major problem. Though the neurologic disorder was static in some patients, in others, notably the hydrocephalics, the general course was downhill.

A control group was selected, made up of 22 other children, on the same wards to insure equal care. These were chosen carefully to correspond to the test group according to

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17β-hydroxy-17α-methylandrostano [3,2-c] pyrazole

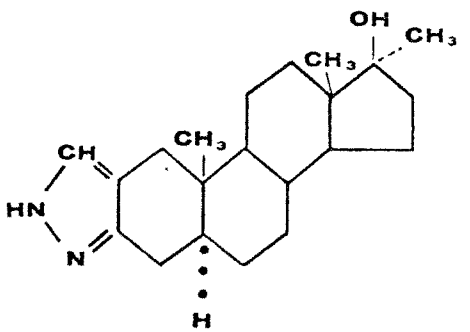


FIG. 1. Chemical structure of stanozolol (Winstrol).

age, sex, diagnosis, weight and nutritional state.

The age of the patients ranged from four to ten years, the average being seven years. The sex distribution was 21 females and 24 males. The diet consisted of Diet-All ‡—balanced, all-purpose, dehydrated blend of nutrients which was reconstituted with milk. As much of this was given as the patients would eat before and during the 18-month study period.

Testing Program

The 22 patients were given stanozolol, 1.5 mg. per day by mouth, for a period of six months. The drug was then stopped for six months, and then given again for a second six-month period in dosage of 1 mg. per day. Thus all the patients were observed for 18 months. The nursing staff was given the impression these patients were receiving a vitamin supplement. The control patients received a multiple vitamin preparation.

Before treatment was started, baseline determinations were made of the following parameters: Weight, calf circumference (measured one-third of length of lower leg down from the knee), mid thigh circumference, hemoglobin level, serum albumin and serum globulin levels, appetite, and general condition. These determinations were repeated at monthly intervals during the six-month treatment periods. Unfortunately, measurement of length was not initiated on all patients until the last six months.

Photographs were taken initially and at the end of the 18-month period of observation to document the general appearance of the patients as were x-rays of the skull, long bones and wrists to determine bone age and growth.

Observations

Weight and Length. The average initial weight in the 22 patients was 35.5 lb. The average weight gain of these patients during the six months previously had been 2.2 lb. After six months of stanozolol, 1.5 mg. orally per day, the weight averaged 39.8 lb., an average gain of 4.3 lb. During the second six-month period of observation without anabolic therapy there was further gain to an average of 43.3 lb., or an average of 3.5 lb. per case. Thus the gain for the first year of observation averaged 7.8 lb. per patient. During the second six-month period of treatment with stanozolol, 1 mg. per day, the average weight increased to 47.6 lb., an average gain of 4.3 lb. for this period. Thus there was an average gain of 12.1 lb. per patient for the entire 18 months of observation (Fig. 2). Nineteen patients gained and three lost weight. The fractional losses that occurred were associated with systemic disease of a serious nature in which the general course was downhill. This represents a gain of 34 per cent of the initial body weight during the 18 months of observation, during 12 months of which the patients were receiving anabolic therapy. This rate of gain has been maintained since therapy was discontinued.

In the control group the average weight gain during this 18 months was 5.25 lb. The 22 patients were not measured for length, but this has been done for a one-year period since the study. During this year the patients who received the drug had an average gain in length of 4.92″, a monthly average of 0.41″ per month. The control group had a gain in length of 4.26″ for the year, an average of 0.36″ per month.

Since the treated patients were all children in whom growth and gain in weight would be

‡ A product of the Mainland Corporation, 3356 East Atlantic Avenue, Pompano Beach, Florida.

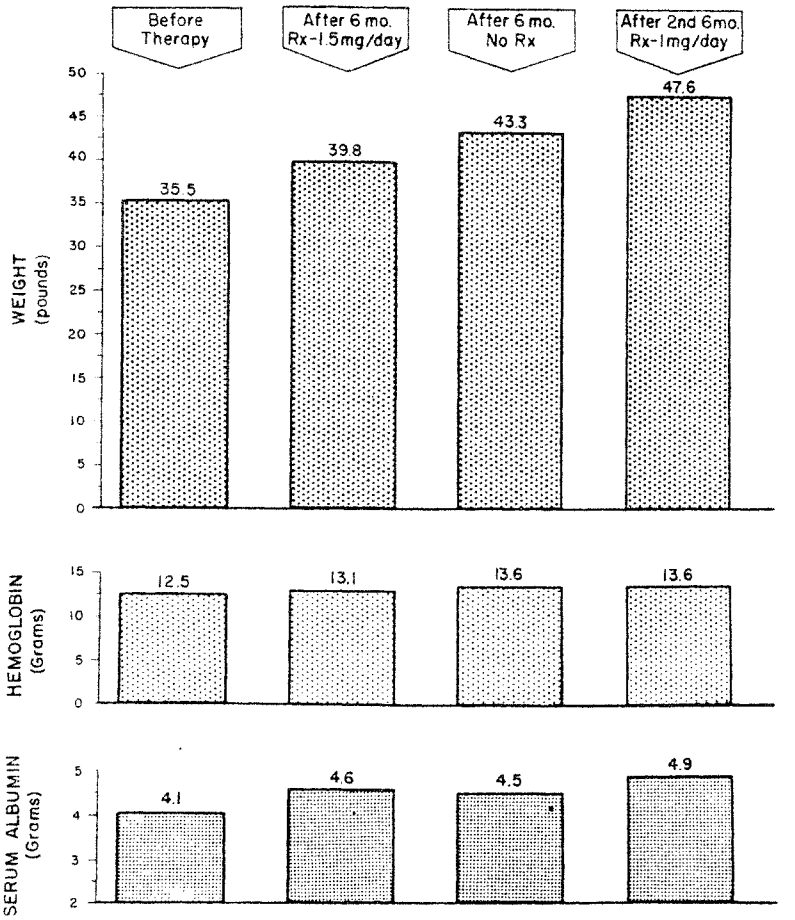


FIG. 2. Average changes in body weight, hemoglobin and serum albumin by six-month periods for 22 undernourished handicapped children treated with stanozolol. The average weight gains were greater during the periods of treatment. A rapid rise in hemoglobin was seen during the first 12 months. A rapid rise in serum albumin level was seen during periods of therapy, but not in intervals.

expected without anabolic therapy, the question arises whether this gain of 34 per cent in 18 months was greater than might be expected.

To shed some light on the significance of this gain in weight, the expected weight gain for an average group of seven years can be compared with that actually found under treatment (Fig. 3). The average normal expected gain for the 18 months between seven and eight and one-half years is 9 lb., from 53 to 62 lb., or 17 per cent of the initial body weight. In the stanozolol treated patients it was 34 per cent, or twice what might have been anticipated.

Another method used to appraise the gain in weight in these children is plotting the weight on a standard weight graph as described by Reed and Stuart [11] (Fig. 4). The average initial weight of 35.5 pounds at the average age of seven years shows the study group markedly underweight; indeed this weight corresponds to four years of age (not shown) at the 50 percentile line. Another way of stating this is that the study group was three years below normal weight. Eighteen months later when the average age was eight and one-half years, the average weight was 46.6 pounds. While this is still below normal, the average gain brought weight up to the six plus year level, a gain of two plus years in weight during the 18-month study period.

The striking weight gain due to stanozolol is thought to be largely in the deposition of body protein rather than fat or fluids, for associated with the weight increases were increased physical strength, vigor and activity. The fact that the weight gain was not due to fluid retention is borne out by the continued gain even when patients were not receiving the drug and by the gain sustained for over

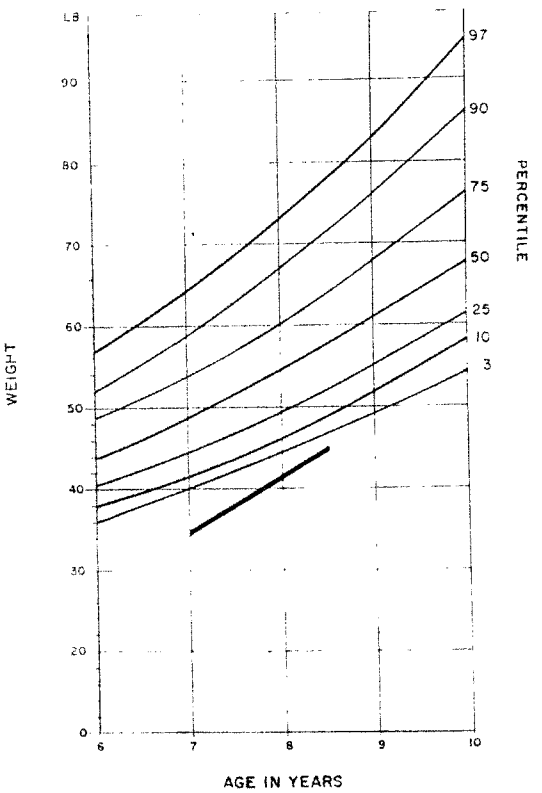


FIG. 3. Comparison of the percentages of weight gain of the treated group and the controls. Weight gain of treated children (heavy line) shows rapid rise as compared to standard weight gain graph.

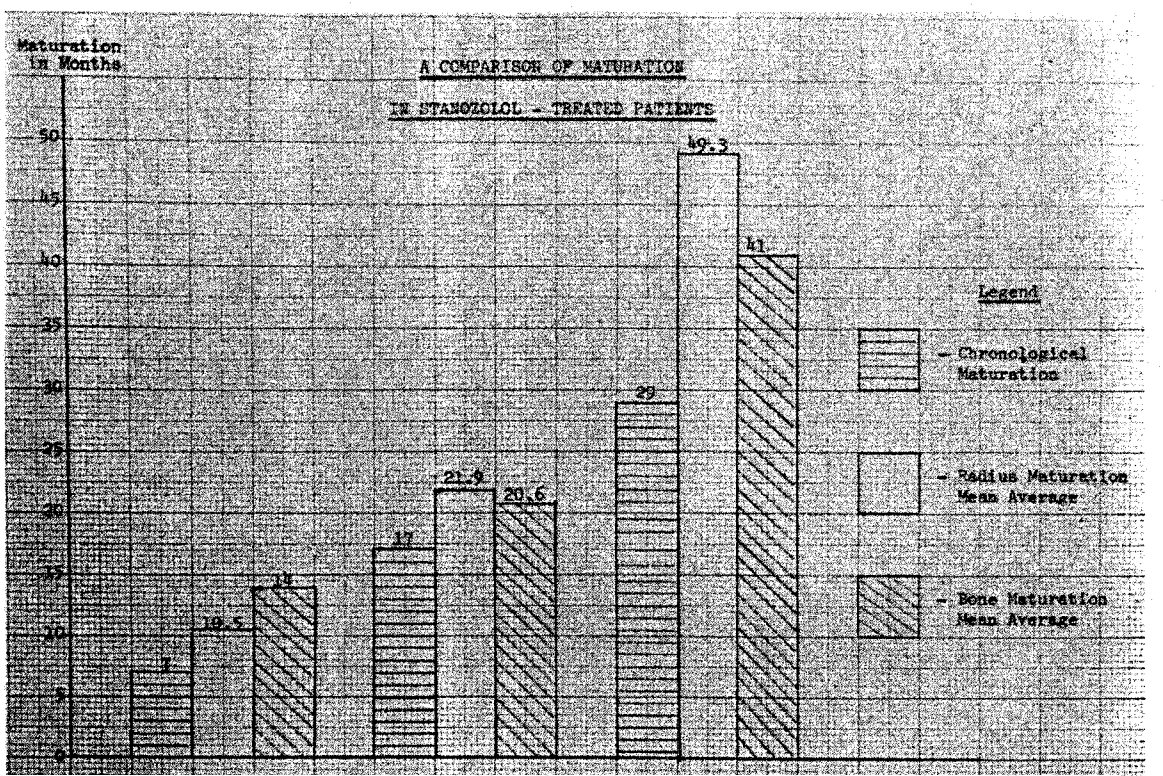
a year after therapy was discontinued. The correlation between gain in weight and retention of androgen as determined by nitrogen balance studies strongly supports this view. It was thought that the weight gains were commensurate with increased appetite. The mechanism by which this occurs is not clear. Absorption studies [6] have not demonstrated any consistent improvement in protein absorption from the digestive tract under anabolic therapy. Still the consistent increases in weight, hemoglobin and serum albumin levels, as described below, suggest that either more protein is absorbed or that the amount absorbed is better utilized.

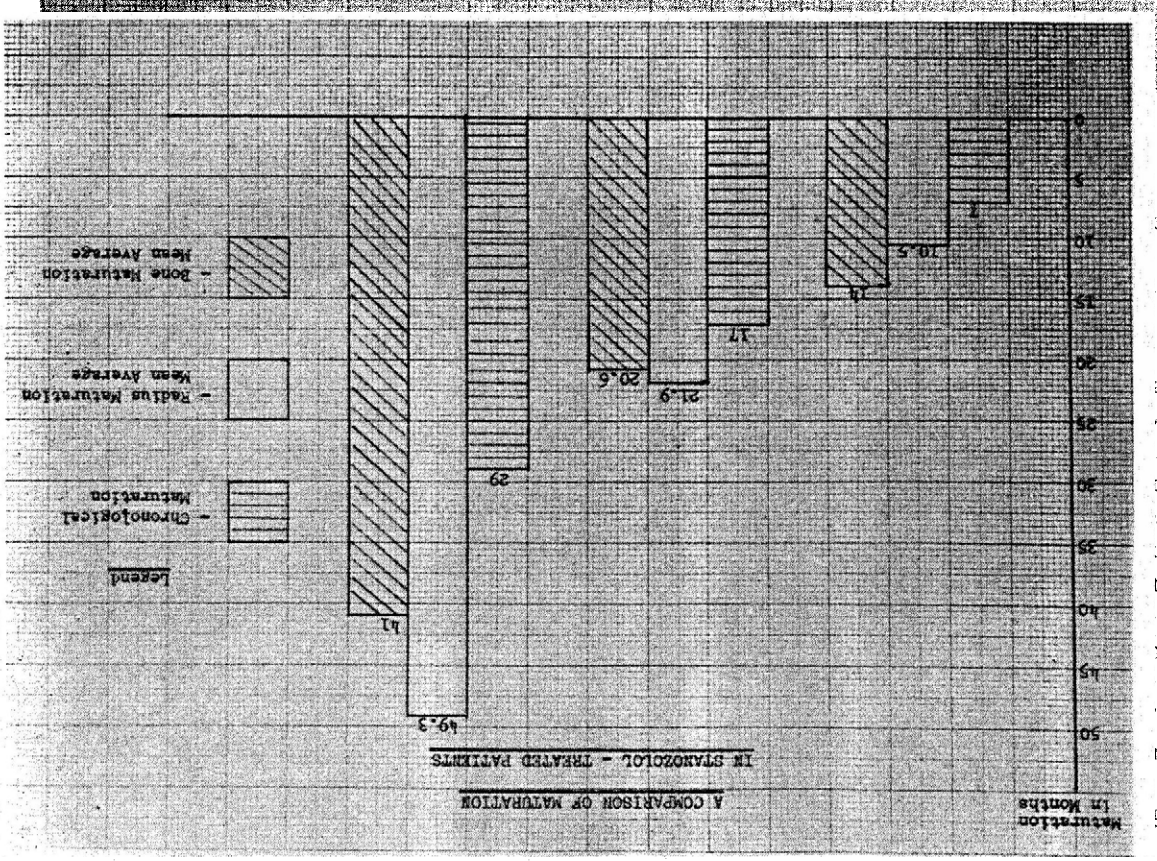
Calf and Thigh Measurements. The general increase in weight of the 22 patients was reflected in increased calf and thigh measurements, which were taken at monthly intervals during the 18 months of observation. The average calf measurement increased ¾″ and the thigh measurement 1½″. All but three patients registered an increase; in these three the fractional losses were consistent with deterioration in their general condition. In the control group the average calf circumference increased ¼″ and the average thigh circumference 1″.

With respect to giving the anabolic drugs to improve the nutritional state and to stimulate the growth of bone, premature closure of the epiphyses, a slow process which takes ten or 11 years under the influence of excessive androgen, is a risk that under some clinical circumstances should be accepted. It seems likely that the mildly androgenic qualities of stanozolol may permit its use for periods of one to two years without excessive effects on epiphyseal closure. Proof of this in humans, however, will be many years in forthcoming, for even with extreme cases of excess androgen therapy the effect is slow to develop.

For these reasons, the growth of the children in this study is of considerable interest. Most of these were bed-ridden cripples with a variety of birth injuries and congenital deformities, and accurate measurements of body length and height could not be made. X-rays were taken of 20 patients, before, during, and after therapy to determine (a) bone growth as shown by changes in the length of the radius between the epiphyseal lines and (b) bone age as shown by the carpal and metacarpal bones. These growth studies were made 27 months after initiation of therapy in ten patients; 17 months after in seven patients; and seven months after in three patients. Using standard tables for normal bone development, the radius age and bone age were determined and compared with the actual age of each patient. These measurements are shown in Fig. 4.

It should be noted in Figures 6 through 9, that of 13 males only three had radius ages and bone ages greater than their actual ages after treatment (male cases 8, 10 and 13). In Figure 10 and 11, of the seven females who were measured, four developed radius ages slightly greater than their actual ages (female cases 2, 3, 5, and 6), although the bone age of





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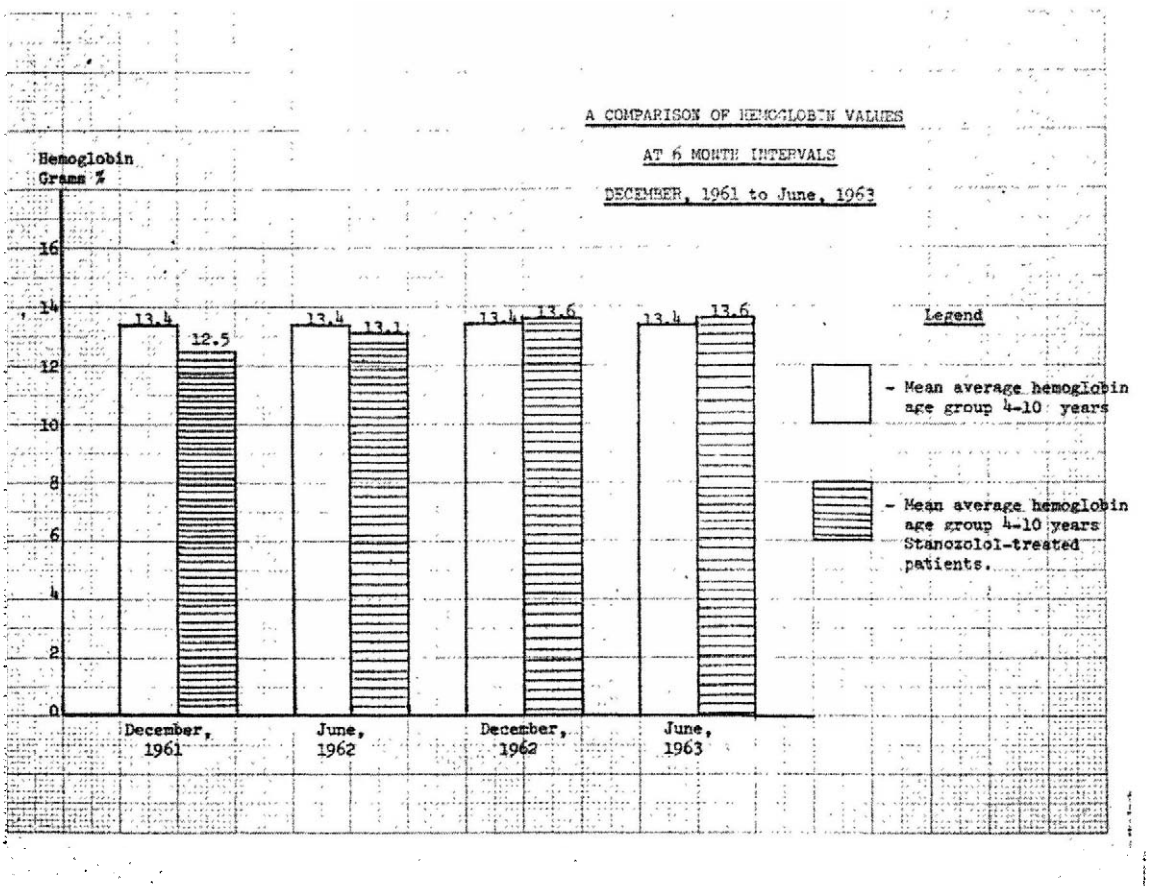

FIG. 5. Hemoglobin values rose until within normal limits, and maintained after therapy was discontinued.

Gm. to 13.2 Gm. None of the patients with low initial values failed to have significant increases. The three cases whose levels fell had high initial values, and the losses were all minor.

The mechanism behind this hematopoietic effect is obscure. The patients were receiving the standard hospital diet which is adequate in iron, and no iron therapy was added. There was an increase in appetite and weight, and more food iron was thereby consumed. It seems likely that the drug affects directly the synthesis of hemoglobin from amino acids, stimulates the bone marrow directly, or both. This concept is consistent with the findings of Mullin and DiPillo [9] in their study on the influence of stanozolol on hemoglobin levels. They had six patients with nutritional anemia which had failed to respond to intensive iron and vitamin B_{12} therapy. Under stanozolol treatment the hemoglobin levels rose sharply.

Serum Albumin. Serum albumin levels were measured before treatment and at monthly intervals during treatment. During the first six months on stanozolol 1.5 mg./day the average initial reading rose from 4.1 Gm. to 4.6 Gm. per 100 ml., an average gain of 0.5 Gm. Eighteen patients gained while four lost. During the following six months without therapy the average went down slightly to 4.5 Gm., a loss of 0.1 Gm. Twelve cases gained, eight lost and two remained unchanged. In the second six-month period of therapy further rise to an average of 4.9 Gm. was noted, or 0.4 Gm. per case. Seventeen gained, four lost and one remained unchanged. During the total 18-month observation period the average gain was 0.8 Gm. (Fig. 2). Thus, serum albumin

levels increased appreciably during anabolic therapy. The gain was gradual during the period of therapy and was maintained fairly well for the following six-month period without therapy. Once therapy was resumed there was further significant increase. In the control group the serum albumin showed an average decrease of 0.1 Gm. during the 18-month period of observation.

Just as with the hemoglobin changes, the gains were greater in those patients who had lower initial values, and the few that lost had higher initial values. The increase noted in hemoglobin values during the six months without therapy was not exhibited by the albumin levels. Conversely, the serum albumin rose again during the second six-month period of therapy whereas the hemoglobin values did not, except in a few individuals. There was no direct correlation between the serum albumin and hemoglobin increases.

Serum Globulin. The serum globulin level averaged 2.6 Gm. per 100 ml. at the start of therapy and 2.5 Gm. at the end of the 18 months. During this period the serum albumin had gone up an average of 0.8 Gm. The serum globulin changes are consistent with the generally poor nutritional state of most of the patients. In the control group no change was noted in the serum globulin over the 18-month period.

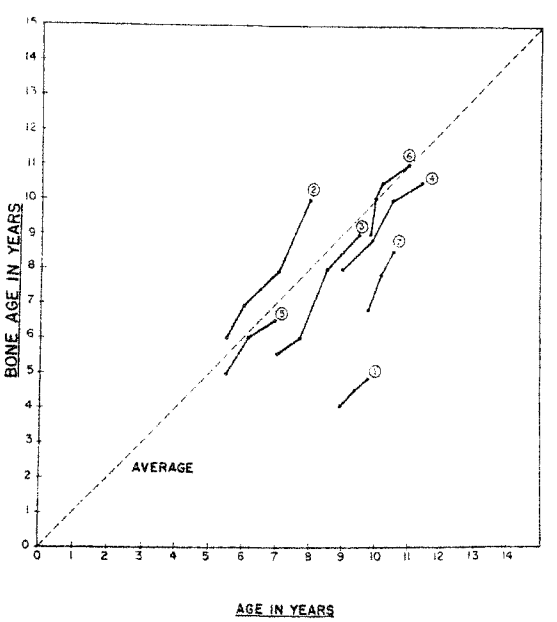

FIG. 6. The bone age growth in seven females as compared to the 50 percentile line for females.

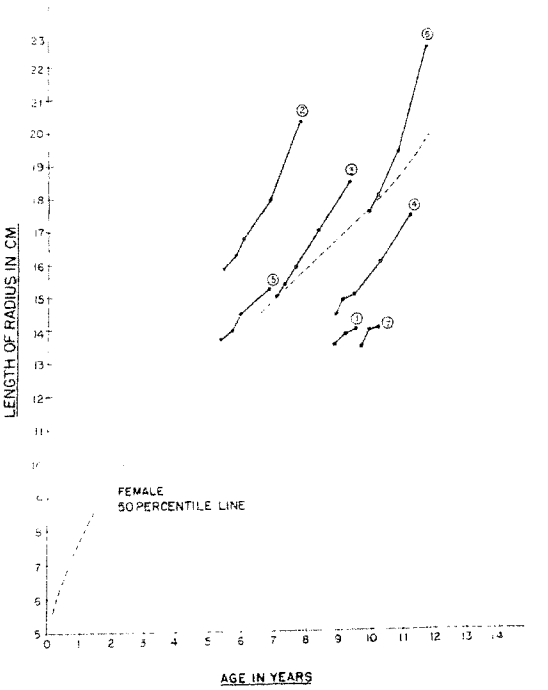

FIG. 7. The growth in length of the radius in seven females as compared to the 50 per cent line for females.

Bone Growth and Bone Age. The physiology of bone growth is complex and not fully understood. Factors known to play a role are the growth hormone from the pituitary, the thyroid hormone, and the nutritional state. Whether stimulation of bone growth and maturation can be ascribed to androgenicity or anabolicity is debatable. Two related and probably interdependent effects of a normal balance of the above factors are: First, increase in length of the bone or "growth" of the individual; and second, maturation of the bone, resulting in the closure of the epiphyses at about 16 to 17 years in humans. It is known that an oversupply of androgenic steroids increases the rate of bone growth, and also causes closure of the epiphyses at an earlier age. A good clinical example of this is the untreated adrenogenital syndrome. These children grow rapidly early in life and stop grow-

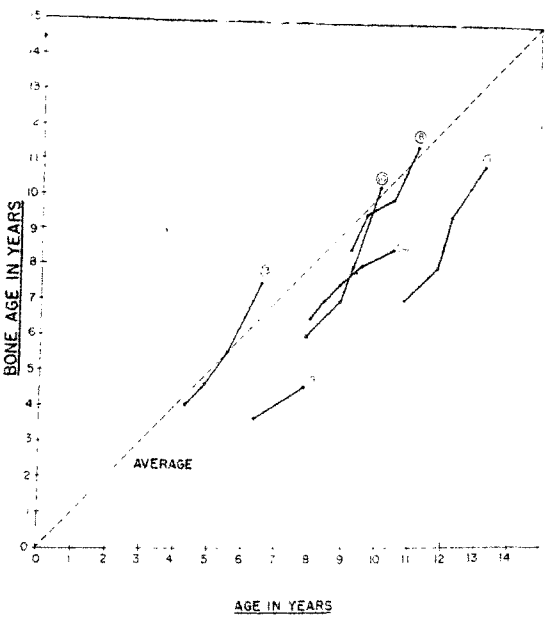

FIG. 8. The bone growth in 6 males as compared to the 50 percentile line for males.

ing at the age of ten or 11 years when their epiphyses close. In spite of the increased rate of growth they are smaller than normal in stature because of this premature closure. Since all of the known anabolic agents have some androgenic activity, pediatricians have quite properly been cautious about their use in children.

Another definite but even less clearly understood factor in bone growth is the retardation that occurs in children with chronic disease. To what extent this is simply a reflection of malnutrition is unclear, but it seems likely that more fundamental hormonal imbalances may be operative in the sick child. Regardless of the mechanisms, the clinician is frequently faced with the spectacle of a child not only greatly underweight, but with bony development far below normal for his age. Thus though bone growth and bone maturation were accelerated during the course of therapy and is still continuing, the drug did not cause excessively rapid epiphyseal closure.

Figures 6 through 11 show the bone growth and bone ages for each of the children as they were measured at intervals throughout the period of treatment. These measurements can be compared with a normal (50 percentile) curve (Vogt and Vicker's standards) which is shown as a dotted line on each of the charts.

The patients and their controls are still being followed for bone development. There has been no significant difference in bone age development of the two groups, and the rate of closure appears to be approximately the same. There has been no evidence of acceleration of closure of the physical lines in the study group after two years.

The control group showed two females with some breast enlargement and clitoral enlargement. Four females and five males showed an increase in pubic hair. Acne was seen in none of the control patients. It is the personal opinion of the author that approximately 50 per cent more virilization would be seen if methyltestosterone or a related drug had been used. Animal studies indicate stanozolol to be one-twenty-fourth to one-thirtieth as androgenic as testosterone.

Side Effects. No gastro-intestinal, skin, or other toxic manifestations were recognized in the 12-month period of stanozolol treatment. Twelve of the 22 test patients had some virilizing effect that came on slowly and progressed

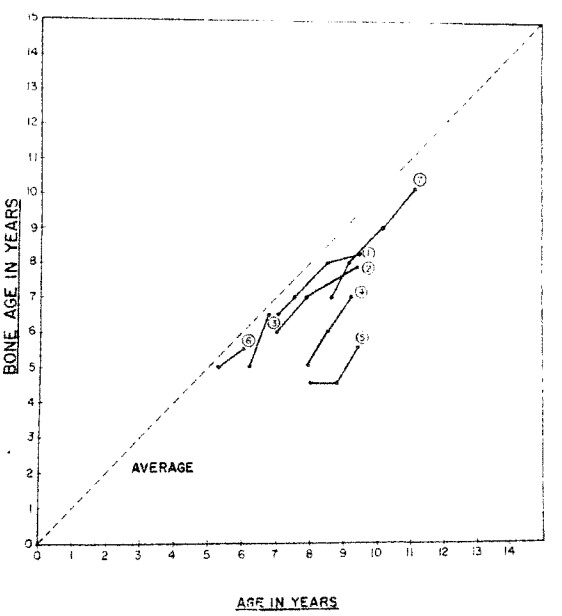

FIG. 9. The bone growth in 7 males as compared to the 50 percentile line for males.

gradually with the 1.5 mg. dosage. The virilization did not progress during the six-month interval when therapy was not given, and it was our impression that it progressed more slowly during the second six-month period of treatment when the daily dose was 1 mg. In these 12 patients the virilizing effects were mild in six and fairly marked in six—there was enlargement of the penis with development of pubic hair in the males, and development of pubic hair only in the females. Clitoral enlargement was not marked. None of the males had breast enlargement. There was slight breast enlargement in one ten-year-old female. Acne was not encountered. No other virilizing signs were noted, or changes in secondary sex characteristics. There was no evident relation between the gain in weight and the extent of virilization.

While the development of pubic hair and of the genitalia seems clear evidence of androgenicity, this side effect is not a clinical problem. The improvement in general condition outweighs in importance the acceleration of sexual development.

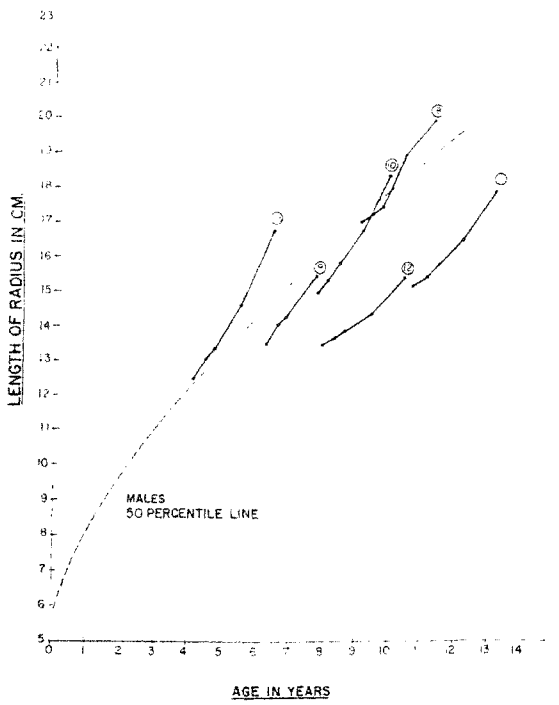

FIG. 10. The growth in length of the radius in 6 males as compared to the 50 per cent line of radius growth.

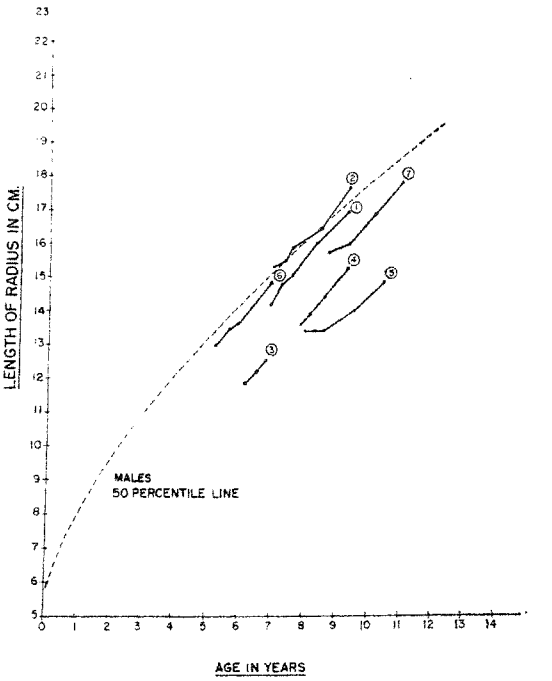

FIG. 11. The growth in length of the radius in 7 males as compared to the 50 per cent line of radius growth.

In the control group, three male patients showed pubic hair and enlargement of the penis and two females showed pubic hair and enlargement of the clitoris. These changes were ascribed to early onset of puberty.

Summary and Conclusions

Twenty-two debilitated children, bedridden and crippled because of a variety of birth injuries and congenital deformities, were treated with a new anabolic steroid, stanozolol (Winstrol), to determine whether this drug would improve their physical conditions without undesirable androgenic reactions. Stanozolol, 1.5 mg. per day by mouth, was given for six months, withdrawn for six months, and then reinstituted for another six months at a dose of 1 mg. per day.

After 18 months which included two six-month courses of stanozolol therapy, the 22 children gained an average of 12.1 pounds

per patient or 31 per cent of the initial body weight. This is twice the 17 per cent weight gain expected in normal with comparable ages. The general increase in weight was reflected in average calf measurements which increased ¾″ and in average thigh measurements which increased 1½″. Hemoglobin levels increased for eight, decreased for eight, and remained unchanged for seven with an over-all gain of 1.1 Gm. Serum albumin rose an average of 0.9 Gm. in 18 months and serum globulin remained essentially unchanged.

In all patients both bone growth and bone age were accelerated; but the increase in bone age did not seem sufficient to cause premature closure of the epiphyseal spaces.

Twelve patients exhibited mild virilization, but this was not looked upon as a clinical problem. The improvement in general condition far outweighed in clinical importance the acceleration of sexual development. No gastro-intestinal, skin, or other toxic manifestations were observed.

As a result of the responses seen in this study, it is concluded that stanozolol in dosages of 1.5 or 1.0 mg. orally per day improve the physical status of debilitated, crippled children. These dosages do not induce marked virilization or excessive bone aging.

Final Comment

This is a preliminary report: the evaluation of these patients is continuing and will continue until each child reaches puberty. The accelerated gains in growth and weight appear to be sustained during the time this paper has been in preparation.

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