

A New Approach to the Natural Treatment of Protein Malnutrition: Result of a Double-Blind Clinical Trial

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Many hospital patients, suffering from a variety of conditions but all in poor general health, with asthenia, anorexia and significant weight loss, show a severe degree of protein malnutrition. Other patients, who present mainly to their general practitioners, show the same symptoms to a less extreme degree; they are in a state of moderate protein malnutrition, or at least, as Apfelbaum puts it, "potential malnutrition".

In both types of case, apart from treatment directed at the underlying cause, the therapeutic options have so far been limited to anabolic hormones (whose virilising effect, related to their steroid structure, is well known) or to appetite-stimulating antihistamines, whose side-effects, particularly on alertness, are also well known. Furthermore, these two types of treatment can only be given to certain age groups, so that they cannot be prescribed in every case.

It was therefore of interest to test a natural product¹ whose pharmacological effects on protein. Syntheses were known to us, as was its absolute safety.

The product in question consists of extracts of pollen^{**}, of constant composition both as regards starting materials and active principles: the extracts are thus standardized, and due to the hydrolysis of the proteins originally present they are free from allergic side effects.

Brief Pharmacological Review

Sthenorex is not an anabolic hormone, yet it does affect protein synthesis, as shown in studies on oral administration to animals after traumatic laparotomies or wounds with loss of tissue. In both cases, accelerated scar formation and improved quality of the scar were observed. Tests of compensatory liver hypertrophy in animals after partial hepatectomy showed an increase in RNA concentration and in the concentration of hepatic triglycerides (reflecting storage of esterified fatty acids, an essential feature of weight gain).

Traditional clinical trial

Clinical screening was carried out in a chronic diseases clinic; this enabled us to assess the efficacy of the product in restoring appetite, correcting the weight gain curve, and increasing physical and psychic energy; these effects were monitored by ergometric and psychometric tests and by improvement in certain biological tests (total blood protein, urinary steroid excretion). Biological and clinical tolerance of the product was excellent.

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** Sthenorex (6 mg lipid-soluble pollen extract and 20 mg aqueous pollen extract per gelule). Supplied by Ozothine Laboratories.

This led to a second and larger-scale study on 64 adult hospital patients, of various ages and both sexes, suffering from a variety of medical or surgical conditions but all in mediocre or frankly poor general health, with loss of appetite, emaciation sometimes of considerable degree, and marked asthenia.

The conditions from which they suffered included chronic digestive, vascular and broncho-pulmonary disease, as well as a variety of cancers at various stages. Such severely ill patients were deliberately chosen to provide an unfavorable testing-ground for an appetite-stimulant and bio-stimulant drug. The dose employed was 3 to 6 gelules daily for a mean duration of one month (range - from 8 days to 2 months).

The activity of the product was assessed on:

- reduction in asthenia. Out of a total of 64 cases, it diminished or disappeared in 44, or 70% of the total;
- restoration of appetite. Out of 54 anorexic patients, clear restoration of appetite was seen in 38, or 70% of such cases;
- weight gain. Out of 44 patients who could be weighed regularly, 27 showed weight gain ranging from +0.500 kg to + 3 kg, and in one extreme + 6 kg; 61% of these cases thus showed weight gain.

Summarizing these results at the clinical level, there were a total of 16 very good results (25%), 27 good results (42.2%), 8 moderate results (12.5%), and 13 mediocre or negative results (20.3 %), or total of 67.2% of very good or good results.

Tolerance was excellent at all levels.

Patients suffering from asthma-like dyspnoea or bronchitis with bronchospasm were able to take the full course of treatment without showing any allergic responses.

Being well aware of the subjectivity of our interpretation of the results obtained - with the exception, of course, of weight gain - we felt it essential to submit the product to more precise tests in a double-blind trial on groups of patients of comparable age with comparable conditions, and to study the results obtained by statistical analysis of symptoms and of physical and biological parameters.

Double-blind clinical trial

This was carried out on 128 patients, who were divided into four separate series, three consisting of adult patients (80 in number) and one of aged patients (48 in number). Half of all patients (groups A) received the active product (64 patients); the other half (groups B) received placebo (64 patients); within each series, allocation to one or other treatment was random. The patients within each series were of comparable mean age and had very similar clinical conditions.

First series

Patients with cancer of the oropharynx receiving deep X-ray or cobalt therapy

This series consisted of 30 adult males, some but not all of whom had had a laryngectomy, all receiving primary or adjuvant treatment with deep X-rays or cobalt. It is known that such treatment, after the first

few sessions causes asthenia and anorexia and carries a risk of malnutrition, often accompanied by distress or depression.

Patients in group A have a mean weight of 52 kg, those in group B a mean of 56 kg; all were asthenia and anorexic. The results obtained after eight weeks' treatment with 4 (gelules daily are shown in Table 1; the statistical interpretation* shows the probability value for the group given active treatment versus the group given placebo.

Table 1.

	Group A	Group B	P value
Appetite stimulation	+ in 75% of cases	+ in 20% of cases	0.61
Mean weight gain	+ 2.7 kg	- 1.37 kg	0.001
Anti-asthenia action	+ in 66% of cases	+ in 6.7% of cases	0.01
Mean serum protein	+ 2.13 g/l	- 0.33 g/l	0.01
Mean rise in urinary	17-OH: + 0.39mg/24h	- 0.02mg/24h	0.02
Steroid excretion	17-oxo: + 1.07mg/24h	- 0.38mg/24h	0.001

In conclusion, the product is shown to have a significant appetite stimulating effect. Weight gain is statistically significant and certainly due to the product. The statistically significant regression of asthenia in group A is certainly due to the treatment, and there is a significant correlation between weight gain and regression of asthenia. The increase in urinary steroid excretion is significant and certainly due to the product; and the same applies to the serum total protein levels.

* These parameters were studied following histological observations on the suprarenal glands of rats given the product for 12 weeks, and rabbits given it for 6 weeks. Fine vacuolation of spongiocytes in the zona fasciculata was observed, suggesting that the product had caused accumulation of available reserves of cortisol in the gland, enabling it to be more rapidly mobilized in case of need; there was, however, no change in gland weight.

Second series

Patients with significant physical asthenia.

This series consists of 50 adult patients (15 males and 15 females), all characterized by significant asthenia. They received 4 gelules daily for a month. The mean weight of group A was 62.4 kg, and of group B 64.9 kg. These patients did not complain of loss of appetite.

The results are shown in table 2.

The difference in urinary steroid excretion between the two groups, though small, is statistically significant.

Table 2.

	Group A	Group B	P value
Mean weight gain	+ 0.9 kg	- 0.8 kg	0.001
Anti-asthenia action	+ in 66% of cases	+ in 13.3% of cases	0.01
Mean serum protein	+ 2.14 g/l	+ 0.86 g/l	0.001
Mean serum calcium	+ 2.75 mg/l	- 0.57 mg/l	0.001
Mean rise in urinary	17-OH: + 0.38mg/24h	- 0.21mg/24h	0.001

Steroid excretion	17-0x0: - 0.96mg/24h	- 0.35mg/24h	0.001
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* Statistical analysis was carried out by the institute of Experimental therapeutics and Clinical Research, Computer (Informatique) Department, 92-Montrouge.

The rise in serum protein should be seen in relation to the rise in serum calcium; but the concomitant rise in both measurements should lead one to conclude that the rise in calcium represents the non-ionisable fraction.

Third series

Patients with a variety of fractures showing failure of union or defective union over the course of a normal healing period.

This series comprised twenty patients (3 female and 17 male).

Union of fractures was assessed radiologically. Measurements carried out in parallel were estimations of serum calcium, phosphate, and the phosphate: calcium ratio, total serum protein and urinary calcium.

The purpose of the study was to investigate any action of the product on the protein matrix at the fracture site, or on the deposition of calcium within the matrix.

Table 3 shows the results after treatment with 4 gelules daily over a period of 2 months.

Table 3

	Group A	Group B	P value
Fracture union	Median: +++ (complete median: + (Beginning of formation of radiologically formation physically confirmed of a bony callus) callus, proceeding towards union)		
Serum calcium (mean)	+ 5 mg/l	+ 1.7mg/l	0.02
Serum phosphate (mean)	- 6.7 mg/l	- 0.8 mg/l	0.001
P:C ratio (mean)	- 0.09 mg/l	- 0.01 mg/l	0.001
Serum protein (mean)	- 3.30 g/l	- 8.40 g/l	0.001
Urinary calcium (mean)	- 30.5 mg/24h	- 1.50 mg/24h	0.01

The fall in serum phosphate and calcium, and the rise in urinary calcium and in serum proteins, (these two variations being statistically significant), justify the supposition that formation of the protein matrix of the callus has been facilitated, has the deposition of calcium within it.

The correlation between calcium retention (variation in serum and urinary calcium) on the one hand, and the formation of bony callus on the other, was studied using a non-parametric test: it shows a p value of 0.001.

Fourth series

Aged patients with senile decay or geriaesthesia

The mean age of the 24 patients in group A was 70 years, and that of the 24 in group B was 72; there

were thus 48 (male) patients altogether. All were chronic in-patients of at least two months' standing, suffering from a variety of disorders but all having in common a significant degree of anorexia and asthenia (both physical and psychio).

The aim of the study was to confirm the findings of the preliminary investigation, while as far as possible eliminating all subjective factors.

All patients received 4 gelules daily for 4 weeks. The results are shown in table 4.

Table 4

	Group A	Group B	P Value
Overall results	13 very good 10 good 1 mediocre	3 moderate 11 mediocre 10 negative	
Appetite stimulation	+ in 75% of cases	+ in 0% of cases	0.001
Weight gain	+ 3.271 kg	+ 0.021 kg	0.001
Anti-asthenic action	+ in 83.3% of cases	+ in 0% of cases	0.001
Energometric test (mean TPE in Kgm) (1)	Appx. 50% rise	Appx. 13% fall	0.001
Psychological sorting test (2) – mean:			
- rapidity	- 114 sec (from pretreatment score)	+ 11 sec (from pretreatment score)	0.01
- increase in attentiveness	58.3% showed fewer errors	20.8% showed fewer errors	0.02
Mean serum protein	+ 6.12 g/l	- 0.37 g/l	0.05
Blood cholesterol	+ 0.29	+ 0.05	n.s.
Mean rise in urinary	17-OH: + 0.721 mg/24h	+ 0.063 mg/24h	0.001
Steroid excretion	17-oxo: + 0.954 mg/24h	- 0.042 mg/24h	0.00016

Mean overall variation in biological parameters

- Serum proteins

Most patients showed a reduced total protein, in accordance with their clinical signs of malnutrition.

The mean rise in the different series ranged from 2.13 to 6.2 g/litre, bringing the mean post-treatment level to 70 g/litre.

- Urinary steroids.

17-oxosteroids: the mean rise was 1 mg/24h, bringing the post-treatment excretion rate to 1.11 mg/24h in the adult series and 6.16 mg/24h in the aged series.

17-hydroxysteroids: the mean rise was from 0.4 to 0.72 mg/24h, bringing the post-treatment excretion rate to 5.8 mg/24h in the adult series and 4.16 mg/24h in the aged series.

- Serum and urinary calcium.

In patients suffering from delayed union of fractures, the rise in.

(1) Bidoux's ergometric method. Flexion/extension of the foot, rotation at the wrist and grasping with the hand are studied; all patients are made to carry out these movements against a uniform resistance of 7 kg. The sum of the number of different movements is multiplied by their mean amplitude to obtain the total distance moved: this figure is divided by a factor corresponding to the mean physiological weight of the muscles studied. This yields:

TPE = total potential energy = distance moved x factor corresponding to real load. Result is quoted as percentage rise or fall from pre-treatment score.

(2) Subjects are asked to sort counters, arranged in a predetermined order, into numbered lots. Time taken to complete the task and number of errors are scored before and after treatment. Rapidity of execution and attentiveness are assessed on these figures.

Serum calcium was 5 mg/litre, bringing the post-treatment value to 100 mg/litre, while urinary calcium fell from 238 to 202 mg/litre.

In subjects with profound asthenia, serum calcium rose by 2.75 mg/litre. Bringing the post-treatment value to 100 mg/litre.

- Serum phosphate.

This was studied in patients with delayed union of fractures. The overall mean level fell from a pre-treatment value of 38.8 mg/litre to 32.1 mg/litre.

The serum phosphate/serum calcium ratio fell from 0.4 to 0.31.

Tolerance

As in the preliminary study and the traditional clinical trial, tolerance was excellent at all levels: digestive, general and biological.

Tolerance studies included, in almost all cases, a blood count and differential, and the following blood levels:

Glucose, urea, calcium, phosphate, cholesterol, total protein, total lipids, transaminases (SGOT & SGPT), 4 flocculation tests, electrolytes.

Urine tests comprised: volume, deposit, steroid excretion, creatinine, calcium,

No pathological values were found in these tests.

No side effects were observed, and no contra-indications were noted.

Conclusion

The four double-blind test series thus confirmed, by objective tests yielding statistically significant results relating to symptoms and to physical and biological parameters, the effects of the product that had been observed in the preceding traditional trial:

- Stimulation of appetite with weight gain regularly observed over the course of a number of weeks (this weight gain was not due to water retention since no metabolic disturbance was observed);
- Restoration of physical and psychic energy in patients with asthenia from a variety of causes, even in the seriously ill; with a concomitant rise in urinary steroid excretion;
- Stimulation of protein synthesis with a rise in serum proteins. In patients with defective union of fractures, this action may be accompanied the formation of a protein matrix and by the restoration of normal calcium metabolism, thus favoring the formation of bony callus and its subsequent consolidation.

These conclusions are based on the analysis of results in 208 patients, of whom 144 received the active product (80 in a traditional trial and 64 in a double-blind trial), and 4 received placebo.

Important Notes

The product is not a “dope”: no side-effects are reported. It has no effect on arterial pressure even in old patients. It has no allergic effect. Its constituent extracts are known to be freed of allergens by hydrolysis of the protein: originally present.

Study of biological parameters has shown that treatment brings about a rise in serum protein, serum calcium and urinary steroid excretion towards normal or near-normal levels, without over overshooting them; there is a similarly appropriate fall in serum phosphate and urinary calcium.

The phase of correction of asthenia and other physical signs is accompanied by a rise in urinary steroid excretion, doubtless reflecting reduced protein. Catabolism, due to the well-known metabolic role of these steroids. Increased excretion could be due to progressive stimulation of the suprarenal cortex; and the histological observations made on the suprarenal glands of animals treated for a number of weeks provide confirmation of this hypothesis. Increased urinary steroid excretion must in any case be seen in relation to the concomitant rise in serum protein levels.

