

**EFFICACY OF AN INTEGRATIVE
PROGRAM INCLUDING INTRAVENOUS
AND INTRAMUSCULAR NUTRIENT
THERAPIES FOR ARRESTED
GROWTH**

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Objective

To report the clinical outcome of an integrated management plan, including the use of intravenous and intramuscular nutrient protocols, for restoring growth in six children and adolescents with arrested growth.

Patients

All six patients who presented at the Institute with arrested growth (no gain in height and weight for a period of nine or more months) were included in this study. Two children had stopped growing after chemotherapy (one for rhabdomyosarcoma and the second for Wilms' tumor). Two girls were severely malnourished due to Crohn's disease treated with long-term immunosuppressant therapies. An 11-year-old boy stopped growing after steroid therapy and multiple hospitalizations for Glanzmann's thrombasthenia. The cause of growth arrest in the sixth patient was obscure.

Methods

The integrated management plan included the following: choices in the kitchen designed to provide for optimal hydration, elimination of foods causing incompatibility reactions and rapid glucose-insulin-adrenaline shifts; supplementation with vitamins, minerals, and some redox-restorative substances (RRS) such as glutathione, taurine, selenium; ample herbal support for the bowel, blood, and liver ecosystems; endocrine support when indicated; intramuscular and intravenous nutrient protocols; gentle stretching and

noncompetitive (limbic) exercise; and training in effective methods for self-regulation and stress reduction.

Clinical Outcome Measures

Clinical evaluation using general health parameters and measurements of growth parameters. Weight and height measurements before and after institution of the integrated program lasting for a minimum of nine months.

Results

All six children and adolescents showed satisfactory improvement in general health parameters and resumed growth in height and weight (as well as secondary sexual development in two girls) within six to fourteen months of beginning the program.

Conclusion

Preliminary data of this clinical outcome study show efficacy of an integrated plan for restoring growth in children and adolescents with arrested growth and failure to develop secondary sexual characteristics. If validated by larger clinical trials, such a management plan should be of considerable value for growth failure caused by: (1) chemotherapy; (2) steroid and other immunosuppressive therapies for autoimmune disorders; (3) digestive/absorptive disorders; (4) inflammatory disorders of the bowel; (5) certain constitutional disorders; and (6) some cases of arrested growth of obscure origin.

INTRODUCTION

There are no generally accepted management plans for children and adolescents with arrested growth caused by a variety of causes. Special nutritional needs of such children and adolescents are generally ignored except for the wholly inadequate prescriptions of vitamins and minerals in RDA doses. Important issues of battered bowel, blood and liver ecosystems go unrecognized and unaddressed. No serious efforts are made, as attested by the six cases described in this report, to: (1) assess the integrity of the major ecosystems of the body; (2) evaluate the functional nutritional status; (3) address issues of rapid hyperglycemic-hypoglycemic shifts (and the glucose-insulin-adrenaline roller coasters triggered by them); (4) diagnose and manage food sensitivities and mold allergy; (5) consider substituting restorative nutrient and herbal protocols for long-term use of drugs that block one or more membrane receptors, channels,

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pumps, or inactivate some mediators of physiologic responses; and (6) teach effective self-regulatory methods for relief of local and systemic effects of illness. Indeed, the eleventh edition of *Nelson Textbook of Pediatrics* does not even mention steroid and chemotherapy-induced severe digestive/absorptive dysfunction as a cause of malnutrition and arrested growth, let alone describe any corrective management plan.¹

The short-term use of recombinant human growth hormone for pediatric patients with severe malnutrition has been recently reviewed². However, such clinical trials have been limited and have failed to show significant benefits. Beyond that, the potential for long-term adverse consequences of such hormonal therapies, including their effects on the future offspring of the recipients of such therapies, remains unknown. For those reasons, such therapy is generally not offered to children with arrested growth as was the case with the six subjects of this report. Recently, a gain in height of 2.4 to 3 inches was reported in seven English girls ranking in the lowest 2 percentile of girls in England after daily somatotropin injections were given between the ages of 8 and 14. The drug cost per inch gained in height was reported to be about \$46,000.³ Quite apart from the enormous cost of such an undertaking, the study did not address the potential adverse long-term effects on girls who received hormone therapy and their future offspring.

Another possibility for restoring growth in children with arrested growth is to consider a broad-based, holistic, "ecologic-integrative" clinical plan. The scientific and philosophic perspectives for such a plan have been presented.⁴⁻⁸ Such a plan must address all issues of the various body organ ecosystems schematically expressed in the Pyramid of Trios of the Body Ecosystems (see page 49 of this issue of the *Journal*). As discussed at length in that article, such a management plan is based on a systematic assessment of *all* oxidative stresses on the homeostatic dynamics of *all* the microecologic cellular and macroecologic tissue-organ ecosystems of the body. We have previously described the following components of such an ecologic-integrative plan: (1) digestive/absorptive dysfunction^{10,11}; (2) prolonged bowel transit time¹²; (3) increased bowel permeability¹³; (4) altered bowel flora with overgrowth within the bowel and blood ecosystems of yeast and yeast-like primordial life forms (PLFs)¹⁴; (5) excessive

production of toxic organic acids, such as tartaric acid and arabinose, that impair tissue perfusion and diminish cellular oxygenation¹⁵; (6) functional aspects of critical nutrients in health and disease¹⁶; (7) broad-based intramuscular and intravenous nutrient protocols to "prime the nutritional and metabolic pumps"¹⁷; (8) support for the endocrine ecosystems, especially the frequently impaired thyroid-adrenal-pancreas trio.¹⁸ Such an approach has not been explored, and is the subject of the present report.

Direct Morphologic Assessment of Accelerated Oxidative Injury in Patients with Arrested Growth

We previously described our direct morphologic observations of oxidative phenomena in the circulating blood with high-resolution phase-contrast and darkfield microscopy.¹⁹⁻²⁰ In the present study, we extend those observations to children and adolescents with arrested growth. Specifically, we examined freshly prepared peripheral blood smears of the patients to evaluate the following: (1) the redox status of the blood and, hence of the whole body, by assessing the degree and extent of changes of oxidative coagulopathy and AA oxidopathy²¹; (2) the body burden of viruses, both in terms of chronic viral activation (by examination of the morphology and number of enlarged lymphocytes with increased nuclear size, convoluted nuclear membranes, and fine chromatin pattern) and evidence of acute infections (by the number and morphology of atypical, nucleolated, and transformed lymphocytes); (3) degree of bacteremia (direct observation) and the polymorphonuclear responses evoked by it (by the study of their maturity, motility and phagocytic activity morphology); (4) total blood burden of primordial life forms (PLFs, see pages 13-21 of this issue of the *Journal* for morphologic descriptions of such forms) indicating oxidative regression to primordial cellular ecology (ORPEC)¹⁰; and (5) presence or absence of motile parasite-like bodies.

Advanced changes of oxidative coagulopathy and AA oxidopathy, and a heavy population of PLFs were found in all five patients in this study whose growth was arrested by chemotherapy and/or other immunosuppressive therapies. All such patients required vigorous efforts to reduce the overall oxidative stress and to restore the integrity of the damaged bowel, blood and liver ecosystems. (See Tables 1-5 on pages of 10 and 11 for efficiency of

integrative plans for reducing the total burden of PLFs in the blood with an "anti-PLF" program (including antifungal drugs such as Nystatin and fluoconazol.)

FOUR PRINCIPLES OF INTEGRATIVE MEDICINE

At the Institute, all individualized management plans are founded on the following four previously established principles of integrative medicine: (1) The first principle is of ecologic integrity of the human body defined by modern science and technology that holds that no cause of human suffering may be sought in any individual biologic event, divorced from all the ecologic elements that affect the human condition in general and may exert influence on one or more organ that might draw the attention of the patient or the clinician (focus on the whole person rather than his diagnostic category)²³; (2) The second principle is of integration of all that is pertinent to the care of the individual patient without subservience to one or more schools of medical thought²; (3) The third principle is of empiricism that requires the clinician to prescribe all that is safe and effective regardless of whether the mechanism of action of the therapy is understood or not²³; (4) The fourth principle is of patient-clinician reciprocity that requires the clinician to actively seek guidance from the patient as she/he guides the patient (the clinician guides with knowledge and experience; the patient, with how her/his body responds to therapies employed.²⁵

In a companion article in this issue of the *Journal*, a microecologic-genetic model of illness based on oxidative regression to primordial cellular ecology (the ORPEC state) is presented.¹⁰ The molecular and cellular dynamics of the ORPEC state provide the scientific basis for the clinical model of The Pyramid of Trios of the Human Ecosystems described in that article and which guided formulations of plans for individual patients. Specifically, this model, schematically expressed on page 49 of this issue of the *Journal*, calls for a holistic view of *all the ecologic aspects* of health and diseases rather than be limited by any specific diagnostic label such as Crohn's disease or chemotherapy-induced arrested growth.

INTEGRATIVE MANAGEMENT PLAN FOR RESTORING ARRESTED GROWTH

This clinical outcome study was conducted as

an open trial and no attempt was made to narrowly define the management plans or to blind patients or any member of the team providing the care. Indeed, any attempt to set limits on the ecologic-integrative therapies employed or to establish placebo controls would have violated the spirit of integrative medicine. Furthermore, all such attempts would have been doomed to failure, since neither the clinicians nor the patients can be blinded to therapies such as those used for any length of time.

All patients in this study were managed with individualized, integrative plans for restoring arrested growth, and fostering the development of secondary sexual characteristics whenever applicable. Specifically, we focused on following: (1) weakened antioxidant defenses; (2) impaired digestive and absorptive functions; (3) inadequate hepatic detoxification of the xenobiotic and endogenous toxins; (4) clinical evidence of compromised enzymatic energy pathways (of Krebs' cycle and others); (5) damaged bowel, blood and liver ecosystems; (6) the "troubled trio" of thyroid, pancreas and adrenals; (7) food incompatibility reactions; (8) IgE-mediated mold and pollen allergy; (9) gentle, nongoal-oriented limbic exercise; (10) and stress, anxiety, and depression associated with chronic illness and growth arrested.

Details of such protocols have been described at length in several previous publications.²⁵⁻²⁷ The compositions of the oral nutrient and herbal formulations for restoring the damaged bowel, blood and liver ecosystems have been published.²⁸⁻³⁰ Compositions of the intramuscular and intravenous nutrient protocols used are given in Tables 1-3. Below, we include some brief comments about the components of our management program for the six patients in the present study.

1. Education

We recognized a special need to educate the patients and their parents in three specific areas:

(1) the four core principles of integrative medicine enunciated in the preceding section; (2) the scientific basis of the management plans that emphasize broad ecologic thinking rather than mere symptom suppression with pharmacologic agents; and (3) the oxidative phenomena that occur in the bowel, blood, and liver ecosystems, that jeopardize human antioxidant, enzymatic, and immune defenses. This was deemed essential for securing informed consents from

parents for prescribing "ecologic-integrative" therapies, including intramuscular and intravenous nutrient protocols. Under ordinary circumstances, this would have been a daunting task for any institution. However, for over a decade, the Institute staff has focused heavily on issues of patient education, and has prepared an extensive library of audio and videotapes, and books as well as organized seminars.²⁶⁻³⁰ The main components of our programs, the details of which have been published previously, included the following: (1) optimal hydration^{31,32}; (2) optimal breakfast to avoid swift glucose-insulin-adrenaline shifts (sugar roller coasters)³³; (3) proper food choices in the kitchen^{34,35}; (4) supplemental essential oils³⁶; (5) nutrient supplementations³⁷; (6) supportive herbal protocols for repairing damage to the bowel, blood and liver ecosystems³⁸; (7) two or three effortless, odorless bowel movements every day³⁹; (8) management of food incompatibility issues⁴⁰; (9) diagnosis and management of IgE-mediated inhalant allergy⁴¹; (10) meditative, noncompetitive, nongoal-directed limbic exercise.⁴²; and (11) effective methods of stress control.^{43,44}

2. Nutrition and Choices in the Kitchen

No attempt was made in this study to isolate the clinical benefits of individual foods, nutrient or herbal therapies. Rather, clinicians writing the nutritional plans for individual patients relied on their past clinical experience with the use of various types of diets and nutrient supplementation. Briefly, the subjects of the study were advised to: (1) drink 8-12 glasses of pure water with one-half teaspoon of sea salt (or herbal teas, but excluding carbonated drinks and black tea) to maintain optimal hydration; (2) one to one and one-half tablespoons of partially-hydrolyzed protein protocols containing 85-90% amino acids used to prevent undue stress on glucose-insulin dynamics (to avoid sugar roller coasters); (3) one or more tablespoons of one of the following cold-pressed oils: olive, flaxseed, sesame and pumpkin oils, to be taken cold with salad, uncooked vegetables or other cold foods; (4) avoid foods with oxidized, denatured fats; (5) frequently consume foods items such as ginger, onions, garlic and others that are empirically known to improve rheologic characteristics of blood; and (6) take prescribed amounts of vitamins, minerals, redox restorative substances (RRS), sulfhydryl restorative substances (SRS), and others. In general terms, nutrients were prescribed in the following daily dose ranges: (1) magnesium, 750 to 1,500 mg; (2) potassium, 150 to 300 mg; (3) taurine, 500 to 1,500 mg; (4) ascorbic acid, 500

to 1,500 mg; (5) vitamin B complex, 25 to 50 mg of thiamine, riboflavin, niacin, pantothenic acid, pyridoxin; (6) glutathione and N-acetylcysteine, 200 to 600 mg each; (7) methylsulfonylmethane and alpha lipoic acid, 100 to 200 mg each; (8) uyselenium, molybdenum, and chromium, each from 200 to 600 mcg; (9) zinc and copper, 25-50 and 2-5 mg respectively; and (10) freeze-dried probiotics such as *Bifidobacterium* and *Lactobacillus* in doses one to three billion organisms. The scientific basis and/or rationale for such prescriptions have been discussed.⁴⁵

3. Herbal Formulations

Herbal protocols for supporting battered bowel, blood, and liver ecologies were liberally prescribed for patients in this study as described previously.⁴⁶ The compositions of two commonly prescribed herbal protocols are given in tables 4 and 5. Compositions of ten other empirically used bowel protocols employed have been published.⁴⁵

4. Self-regulation

Children with arrested growth and secondary sexual development suffer from severe stress and self-esteem problems. We recognize that chronic, insidious adrenergic hyperactivity plays a critical role in the cause of clinical syndromes associated with arrested growth. IHDS Adolescents and parents of children were given training in effective previously described methods of self-regulation.^{43,44} Audiotapes for practice of such methods at home were provided to patients or their parents.

5. Limbic Exercise

Lack of physical exercise interferes significantly with growth and development. We are convinced that for improving physical fitness in adolescents with arrested growth, the Eastern methods of physical fitness that emphasize energy dynamics, fluidity and spontaneity of motion offer far superior results. Thus, our program focused on meditative, slow, sustained, noncompetitive and nongoal-oriented exercise that we designate limbic exercise.⁴² Specifically, our purpose was to help our patients free their bodies from the performance demands of their analytical mind.

Table 1. PEDIATRIC INTRAVENOUS PROTOCOL

Nutrient	Concentration= Volume	Amount
Vitamin C	500 mg/ml=10 ml	5 gm
Vitamin A	*=10 ml	3,300 IU
Vitamin D	"	200 IU
Vitamin E	"	10 IU
Biotin	"	60 mcg
Folic Acid	"	400 mcg
Niacinamide	"	40 mg
Riboflavin	"	3.6 mg
Thiamine	"	3 mg
Pantothenic Acid	250 mg/ml=1 ml	250 mg
Pyridoxine	100 mg/ml=1 ml	100 mg
Cyanocobalamine*	1,000 mcg-1.25 ml	1,250 mcg
Calcium Gly/Lac	10 mg/ml=7.5 ml	75 mg
Magnesium Sulfate	500 mg/ml=2 ml	1,000 mg

*Included in multivitamin formula

The above protocol was administered in 150 to 250 ml of Ringer's lactate over a period of 75 to 120 minutes. Following items were added to the infusion for improving the rheologic characteristics and to minimize the possibility of phlebitis: heparin, 2,000 units; lidocaine 2%, 1.5 ml; sodium bicarbonate, 0.75 mEq/ml.

Table 2. PEDIATRIC INTRAMUSCULAR PROTOCOL I

Nutrient	Concentration =Volume	Amount
Magnesium Sulfate	500 mg/ml= 0.75 m	375 mg
Calcium Gly/Lac	10 mg/ml= 1.5 ml	10 mg
Vitamin B ₁₂	10,000 mcg/ml= 0.1 ml	1,000 mcg
Vit B Complex	0.2 ml	*
Pantothenic Acid	250 mg/ml= 0.2 ml	50 mg
Pyridoxin	100 mg/ml= 0.2 ml	20 mcg
Zinc	5 mg/ml= 0.2 ml	1 mg
Molybdenum	25 mcg/ml= 0.2 ml	5 mcg
Selenium	40 mcg/ml= 0.2 ml	8 mcg
Multivitamin	0.2 ml	**

* Vitamin B complex includes the following per ml: thiamine, 100 mg, riboflavin, 2 mg; niacinamide 100 mg; dexpanthenol, 2 mg; pyridoxine, 2 mg. ** See Table 1 for amounts of components.

Table 3. PEDIATRIC INTRAMUSCLAR PROTOCOL II

Nutrient	Concentration =Volume	Amount
Magnesium sulfate	500 mg/ml=1. ml	500 mg
Calcium Gly/lac	10 mg/ml=2 ml	20 mg
Vitamin B ₁₂	10,000 mcg/ml= 0.1 ml	1,000 mg

Table 4. BOWEL ECOLOGY PROTOCOL #5

Par-Quing	150 mg.
Pau D'Arco	150 mg.
Beet root fiber	200 mg.
Gaur gum	100 mg.

Table 5. BOWEL ECOLOGY PROTOCOL #6

Echinacea	200 mg.
Goldenseal	150 mg.
Astragalus root	150 mg.
Burdock root	150 mg.

Doses: In general, both bowel protocols were prescribed in doses of two or three tablets daily.

CASE HISTORIES

Case 1

A 15-year-old with a four-year history of Crohn's disease presented with arrested growth and failure to develop secondary sexual characteristics. Her previous therapies at a New York university hospital included multiple courses of Asacol, antispasmodics, analgesics, and prednisone. Despite such therapies she continued to have frequent unformed stools (from six to twelve times a day) with intractable cramps and copious mucus. She lost weight progressively. The bowel lesions progressed as determined endoscopically

despite incremental doses of drugs. She was given nasogastric feeding and total parenteral nutrition with limited short-term benefits. Two years after the onset of her illness and after multiple hospitalizations, surgical resection of distal ileum and colon was advised. She was told by her physicians that "she will always be short." At that time the family brought her to the Institute for alternative treatment.

On the day of initial consultation, she weighed 55 pounds and measured 57 inches in height. She was a pale, emaciated young woman with severe and diffuse muscle wasting. She seemed exhausted and experienced visible difficulty just sitting up in the chair. Her face showed puffiness frequently seen in patients receiving long-term steroid therapy. Her pharynx was injected with copious mucoid exudate. Cervical nodes were fleshy and enlarged and measured up to 0.5 cms. Palpation of limb and torso muscles revealed multiple and localized areas of tenderness. Neck and shoulder muscles showed spasms. The examination of abdomen disclosed poorly delineated areas of deep tenderness, with most marked areas localized in the right lower quadrant. Salient laboratory data were as follows: WBC, 8,700; Hb, 10.2; T4 level was mildly elevated (13.3 ug/dL [range 4.5 to 12]); T3 1.05; TSH, 1.19. High levels of IgE antibodies with specificity for *Alternaria*, *Aspergillus*, *Fusarium*, *Candida*, *Hormodendrum* and five other molds as well as for several grasses, weeds, tress, and dust mite antigens. Examination of freshly prepared peripheral blood smears showed a score of 3.5 (scale 0 to 4+) for primordial life forms indicating an advanced stage of disruption of normal bowel flora (see page 7 of this issue of the *Journal* for morphologic descriptions of PLFs).

Intramuscular and Intravenous Nutrient Support

The individualized management plan included strong support for the antioxidant and enzyme defenses as well as for the bowel, blood, and liver ecosystems within the broad guidelines described later in the article. In addition, she received 11 injections of the intramuscular protocol and 19 infusions of the intravenous protocol over a period of twenty months.

Clinical Outcome

During the first 18 months of the program, she gained 4 1/2 inches in height and 26 pounds in weight (no gain in height or weight was observed during the first four months of the program). The use of steroids

and other drugs was discontinued after about nine months of instituting the integrative plan. She was symptom free except for occasional cramps and loose BM. Her disabling chronic fatigue was relieved. She felt well enough to attend a summer camp after nearly four years of absence from the camp. She began development of secondary sexual organs. Five weeks prior to completing the manuscript of this article, she reported her first menstrual cycle lasting for three days.

Case 2:

A pale, emaciated 16-year-old girl presented with a ten-year history of persistent and intractable Crohn's disease. She had received multiple courses of antibiotics and steroids, beginning with the first course administered to control acute colitis at the time of initial diagnosis established with a colonic biopsy. She had been on prednisone in doses of 30 to 5 mg during the preceding 18 months. The course of her illness was monitored with multiple endoscopies and colonic biopsies on six different occasions, which showed varying degrees of acute and chronic inflammation. The pharmacologic agents employed unsuccessfully during the intervening years included antispasmodic drugs, analgesics, and Azulfidine. Progressive digestive and absorptive dysfunctions were managed, again unsuccessfully, with "dietary management" that did not address issues of dysregulated sugar-insulin-adrenergic dynamics, food incompatibilities, mold allergy, and the consequent disruptions of the bowel, blood and liver ecosystems. Several months prior to her presentation, she developed stiffness and pain in multiple joints and erythematous lesions on both lower legs and feet that progressed to areas of tissue necrosis and ulceration, leading to the diagnosis of pyoderma gangrenosum. She received several additional courses of broad-spectrum antibiotic agents to control infections associated with ulcerative lesions of the skin.

On examination, she was obviously and severely malnourished, weighing 65 pounds and measuring 54 inches. Discrete and confluent lesions of pyoderma gangrenosum ranging in size from less than one centimeter to six centimeters and involving both lower legs and feet were observed. The ulceration of the skin and oozing of sanguinous discharge caused her socks and undergarments to stick to her skin in many areas. Small (0.2 to 1 cm) fleshy cervical nodes were palpated. There was no breast development. The pubic hairs were sparse. The salient laboratory data were as follow: WBC, 14,300; Hb, 9.3; MCH, 63; platelets 602,000; ferritin, 5.05 ng/ml; ANA, negative; T4 11.6

ug/dL; T-3 1.05; TSH, 3.7; 3+ PLFs, 3+ RBC clumping, and 2+ microclots seen with phase-contrast microscopy of peripheral blood; and markedly elevated levels of IgE antibodies with specificity for *Candida*, *Fusarium*, *Alternaria*, *Aspergillus*, *Cephalosporium*, *Epicoccum*, *Helminthosporium*, *Hormodendrum*, *Penicillium*, *Mucor*, dust mites, and a variety of grasses, trees and weeds.

Intramuscular and Intravenous Protocols

She received 21 weekly (or less frequently at some times due to scheduling difficulties) intravenous infusions over a period of 14 months.

Clinical Outcome

Her general condition improved steadily during the first four months of treatment. The use of steroids was discontinued. Her incapacitating chronic fatigue was relieved, and her skin ulcers healed. On most days, she was almost completely free of colitis symptoms. She began to develop secondary sexual characteristics (pubic hair and breasts), which had been arrested for almost two years. However no gain in height or weight was observed during that period and in the following three months. After that time, she began to grow, gaining 17 pounds in weight and two and one-half inches in height during the following 15 months. Prednisone was discontinued.

Case 3:

A 13-year-old pale, thin, poorly nourished boy presented with history of failure to gain weight and height during the preceding two years. He was 4' 2" tall and weighed 51 pounds. His face showed severe deformity caused by partial surgical absence and poor development of the left jawbone. Multiple facial scars were present on the left side of the face and upper neck. He had undergone multiple surgical procedures to resect the primary and recurrent poorly differentiated rhabdomyosarcoma of the left jaw region which had extended to involve pterygoid muscle. A CT scan at that time showed pulmonary metastases. He received postoperative radiotherapy followed by chemotherapy that included Cytosar, Adriamycin, Vincristine, and Actinomycin D. Severe malnourishment occurred during the prolonged period of chemotherapy resulting in arrested growth and failure to gain weight and height, precise details of which were not available. Seven years later, the tumor recurred in the neck as embryonal sarcoma and was treated with resection followed by additional chemotherapy comprising Ifosfamide, Carboplatin and Etoposide. The boy measured three

feet six inches in height at that time, and therapy with growth hormone was recommended by a child development specialist at a university hospital.

Local recurrence of the tumor about two years later was managed with additional courses of multiple drug chemotherapy. The boy had suffered severe malnourishment during the prolonged period of between two operations and multiple courses of chemotherapeutic agents. On examination, the left side of the face was markedly deformed by scar contracture, arrested growth of left mandible and poor development of left masseter and facial muscles. Skin was pale. The salient laboratory features were as follows: total IgE, 617 IU/mL; T4, 7.5ug/dL; T3, 0.85 uptake units; TSH, 2.33 uIU/mL; and low levels of IgE antibodies with specificity for *Alternaria*, *Aspergillus*, *Hormodendrum*, *Penicillium*, *Mucor*, and *Candida*, and extremely high levels of IgE antibodies with specificity for *D. farinea*. The values for CBC and chemistry profile were within the normal range.

Intramuscular and Intravenous Nutrient Protocols

The general integrated management plan for the patient was as described in the section on integrated management plan. Intravenous and intramuscular nutritional support included the following: (1) 16 infusions of Pediatric IV Protocol administered weekly or on alternate weeks, with some longer intervals necessitated by family's other commitments; and (2) 7 Pediatric IM Protocols given at times when IV infusion was not feasible due to a variety of reasons.

Clinical Outcome

No gain in height was recorded during the first four months of the management plan. After that the patient showed a two-and-one-half inch gain in height and 11 pounds in weight during the following five months. He felt much stronger with markedly improved appetite.

Case 4

A 6-year-old girl presented with arrested growth for a period of ten months. Left nephrectomy had been performed 21 months previously for Wilms' tumor with pulmonary metastases. She received radiotherapy followed by chemotherapy, including Adriamycin, Vincristine, Doxorubicin, and Actinomycin D. Fifteen months later she underwent stem cell transplant for recurrent Wilms' tumor following additional chemotherapy with Thiopeta and Cyclophosphamide. She developed septic shock which led to renal failure, hypertension, pneumothorax, and

gastroparesis. Four months later, she presented at the Institute with arrested growth and lack of any gain in height and weight for ten months. She had poor appetite and often complained of abdominal cramps and migratory arthralgia. Parents had noticed undue moodiness, nasal congestion, and episodes of urticaria.

Physical examination revealed a thin, pale, withdrawn, and poorly nourished child with a left nephrectomy scar and mild edema of lower lids. She weighed 30 pounds and measured 37.75 inches in height. Her skin was dry. She was noncommunicative. (Father's quote: "Her stubbornness saved her.") Pharynx was injected with copious mucus. Cervical nodes were enlarged (0.1 to 0.3 cm). Abdomen was distended with mild LLQ tenderness. The remainder of the physical examination was unremarkable. Some pertinent lab findings were as follows: WBC, 10,900; Hb, 14.1; lymphocyte count 35%; platelet count, 435,000; ANA, neg; thyroid profile low normal range. Allergen-specific IgE profile showed detectable antibodies with specificity for *Aspergillus*, *Alternaria*, *Candida*, *Cephalosporium*, *Mucor*, *Epicoccum*, and *Hormodendrum*, and other species. High-resolution phase-contrast and darkfield microscopy disclosed extensive oxidative erythrocyte membrane damage, about 30% damaged and/or nonmotile leukocytes, and a large population of primordial life forms (See companion article for descriptions of PLFs).

Intramuscular and Intravenous Protocols

An integrated oral nutritional and herbal program was instituted as described later in this article with focus on restoring damaged bowel, blood, and liver ecosystems. For intramuscular nutritional support, she was given 11 weekly injections of Pediatric IM Protocol as described in the section on integrative management plan.

Clinical Outcome

At the 14-week follow-up, the patient was playful and smiled often. Her color was pink and her skin was much less dry than at the initial visit. She weighed 32 pounds and measured 38.25 inches, showing a gain of two pounds in weight and one-half inch in height. (Mother's quote: "She is happy because she knows she needs new dresses. Her old dresses are short on her.")

Case 5

A malnourished 11-year-old boy presented with arrested development and failure to gain in height

and weight during the preceding year. He weighed 56 pounds and measured 49 inches. He gave a history of Glanzmann's thrombasthenia, prolonged bleeding time, multiple admissions for recurrent epistaxis, anemia and platelet transfusions. He had received aminocaproic acid (Amicar) intravenously in doses of 100 mg/kg and orally in doses of 500 mg twice daily intermittently for several years without significant clinical benefits. His hemoglobin levels fell as far down as 8.6 gm/dL and the platelet count below 8 K/uL. The laboratory profile during the last hospital admission showed the following salient values: Hb, 9.1 g/dL; WBC, 8.6 K/uL; MCV, 78.3 fL; platelet, 254 K/uL; reticulocyte count, 0.4%; pro-time 13.8 sec; APPT, 29.7 sec; potassium, 3.8 mmol/L; and creatinine, 0.4 mg/dL.

On physical examination, he seemed an intelligent but tired young boy. He looked pale and was evidently poorly nourished. He had an allergic facies and showed mild periorbital edema. No evidence of ecchymosis or soft tissue hematoma formation was seen. The pharynx was markedly injected with copious mucoid discharge. Small 0.2 to 0.4 cm fleshy cervical nodes were palpated. A small amount of purulent exudate was seen in the left ear. The examination of the heart, lungs, abdomen, and limbs was non-revealing. At the time of initial presentation, the relevant laboratory values were as follows: WBC, 8.7 K/uL; Hb, 9.6 g/dL; MCV, 72.6 fL; platelet, 273 K/uL; T4, 8.6 ug/dl; T3 uptake, 0.95 units; and TSH, 2.44 uU/mL. Micro-ELISA tests performed in view of history of inhalant allergy detected the presence of IgE antibodies with specificity for 17 molds (including *Candida*, *Alternaria*, *Aspergillus*, *Mucor*, *Epicoccum*, *Penicillium*, *Fusarium*, *Hormodendrum* and other species), and for house dust mites, and cat and dog epithelia.

Intravenous and Intramuscular Protocols

A broad, integrated management plan with focus on all issues of the bowel, blood and liver ecosystems as discussed in the section, on Integrative Management Plans was begun, including antigen immunotherapy for inhalant allergy as previously described. Intravenous nutrient protocol as outlined in Table 1 was administered weekly for seven weeks. Amicar was discontinued.

Clinical Outcome

During the short seven-week period of treatment, the boy gained three pounds in weight and grew one inch in height. He experienced no episodes of epistaxis. He felt stronger and seemed more playful.

No evidence of ecchymosis or soft tissues hematoma formation was observed. The left external ear canal was erythematous but devoid of any purulent exudate.

Case 6

A 13-year-old girl presented with a history of no gain in height during the preceding 15 months. She was a product of a normal pregnancy and delivery. Her birth weight was seven pounds and her developmental milestones had been normal; however, she was always the shortest person in her class. Her sister's height was 5' 3". Her past history was unremarkable except for inhalant allergy and asthma, which was well controlled with a bronchodilator.

Physical examination showed a short young lady who was 4' and 5-3/4' tall, and weighed 75 pounds. Her thyroid gland was palpable. Her breasts showed Tanner stage II development. Axillary hair was absent. Pubic hair was scant. An endocrinologic laboratory evaluation was nonrevealing, with normal thyroid and adrenal gland studies. Somatomedin level was low at 186 ng/mL (reference range, 261-1096). Growth hormone was low normal at 0.9 ng/mL (reference range, 0.0 to 10). The estimated skeletal age according to atlas of Greulich and Pyle was 10 to 11 years. Other laboratory values were as follows: WBC, 9,800/uL; Hb, 14 g/dL; platelets, 322,000/uL; cholesterol 210 mg/dL; uric acid, 2.4 mg/dL; liver and kidney chemistries within normal limits; 0-1+ PLFs and 0-1+ changes of oxidative coagulopathy in peripheral blood.

The use of growth hormone therapy was considered but not advised by a consulting endocrinologist. With informed consent of the patient and her parents, an integrated nutritional and immune management program (as outlined) was begun. She received 19 intravenous nutrient infusions during the following nine months.

Intramuscular And Intravenous Nutrient Support

She received 13 intravenous infusions on weekly basis with some interruptions due to a conflict with school activities.

Clinical Outcome

She gained three inches in the first five months, with an additional one and one-half inches during the following four months. Began to show secondary sexual development with enlargement of breasts and increase in pubic hair. She gained eleven pounds in weight Father's comments: "If she had 4 IVs

a month, she showed a growth spurt. If you're asking me, does it work, it does. You can quote me on it."

DISCUSSION

The literature of severe malnutrition and associated growth arrest is voluminous.⁴⁷⁻⁶¹ However, most, if not all, such literature focuses on "protein-energy malnutrition" and is limited to short-term efficacy, (or lack thereof), of total parenteral nutrition (TPN) based on wholly inadequate RDA notions of essential nutrient requirements. From the perspective of integrative medicine, such shortsightedness is astonishing. Even a cursory look at carbohydrate, protein and fat metabolism makes it amply evident that the macronutrients cannot be metabolized without the pivotal roles of vitamins and minerals. Beyond that there is the critical issue of optimal requirements for: (1) redox-restorative substances (RRS) such as vitamins C, A and E; taurine; minerals such as magnesium, potassium, zinc, selenium, molybdenum and chromium; and miscellaneous substances such as coenzyme Q-10; and (2) ample supplies of "sulfhydryl restorative" substances (SRS), such as glutathione, N-acetylcysteine, methylsulfonylmethane, and alpha lipoic acid, all of which carry sulfur and are essential for hepatic detoxification. Such substances are rarely, if ever, included in the prevailing TPN protocols. Not surprisingly, long-term results of TPN are poor.

It is well recognized that TPN is associated with sluggish bowel transit time, impaired mucosal integrity, bacterial translocation, diminished response, and hepatotoxicity.⁵⁵⁻⁶¹ The prevailing notion that mere gut atrophy during TPN results in bacterial translocation and attendant nutritional and immunologic deficits is simplistic. TPN-induced sympathetic activation compounds the ecologic disruption in the bowel. Again not surprisingly, the long-term results of TPN are poor.⁵⁶ and TPN worsens the condition rather than restores it. For those reasons, long-term TPN is not recommended to restore development and growth in cases of arrested growth secondary to chemotherapy, steroid administration, immunosuppressive regimens for autoimmune disorders, and digestive/malabsorptive disorders. Regrettably, almost all TPN literature fails to shed any light on the ecologic and immunologic aspects of a battered bowel, blood and liver ecosystems. Perhaps this should not be surprising since the 2170-page *Nelson Textbook of Pediatrics* does not even mention any of the above-mentioned issues.¹ It dismisses "Gastrointestinal Allergy Caused by Food" with less than a single page (1091) devoted to it.

Accelerated Oxidative Stress in Arrested Growth

In 1983, one of the authors (MA) proposed that spontaneity of oxidation in nature is the core pathogenetic mechanism of aging and *all* diseases.⁶² The notion that a single molecular phenomenon can serve as the core pathogenetic mechanism of injury in all diseases seems too simplistic to be plausible. However, extensive review of literature pertaining to oxidative phenomena in health and disease fails to uncover any evidence to the contrary.⁶³⁻⁶⁸ Beyond the general applicability of the principle of spontaneity of oxidation to children and adolescents with arrested growth, all the molecular and ecologic changes that may be expected to cause arrested growth may also be expected to augment oxidative stress in such patients. This indeed is the case. Our morphologic studies of oxidative stress in the peripheral blood of patients in this study document accelerated oxidative stress in children and adolescents with arrested growth. microscopy show changes of oxidative coagulopathy and AA oxidopathy (see page 34 of this issue of the *Journal* for descriptions of those oxidative phenomena). Some brief comments about the evidence of accelerated oxidative stress in inflammatory bowel disease are pertinent to the present discussion.

Several lines of evidence show that oxidative stress is accelerated and antioxidant defenses are decreased in the bowel tissue of patients with inflammatory bowel disease. Certain antioxidants have been shown to be beneficial for patients with inflammatory bowel disease.⁶⁹⁻⁷⁰ Sulfasalazine, the most commonly used drug for ulcerative colitis, Crohn's disease and other variants of inflammatory bowel disease, is a powerful free radical scavenger.^{71,72} Oxidative stress is accelerated and antioxidant defenses are decreased in colonic tissues in patients with inflammatory bowel disease.⁷³⁻⁸¹ Specifically, increased levels of oxidative species and oxidatively damaged proteins (as measured by protein carbonyls) are found in inflamed colonic mucosa.⁷⁸ Furthermore, activity of copper/zinc-containing superoxide dismutase in such tissues was diminished, and so were the concentrations of copper and zinc, minerals with antioxidant roles. By contrast, the amounts of iron, a mineral with pro-oxidant proclivity, were decreased.

The above-cited considerations of redox phenomena in the bowel are of paramount importance to children and adolescents with arrested growth, not only for a clearer understanding of the pathogenetic aspects of their disorders but also for therapeutic

imperatives. This explains why in formulating our management plans for subjects of this study, we focused so heavily on: (1) factors that allowed us to reduce the overall oxidative stress (as with self-regulation); (2) elimination or avoidance of foods that increase oxidative stress (as with allergic foods); (3) choices in the kitchen that prevent excessive oxidative stress; (4) liberal prescriptions of oral and injectable antioxidants; and (5) vigorous restoration of battered bowel, blood, and liver ecosystems, factors that powerfully feed the oxidative fires fanned by other elements.

Ecologic-Integrative Approach to Arrested Growth

In 1983, following his study of over 7,000 bowel biopsies as a hospital pathologist, one of the authors (MA) introduced the term "altered states of bowel ecology" to assert that the pathophysiology of the bowel could not be understood by the narrowly focused adherence to the prevailing pathologic or clinical classifications of bowel disorders.⁸² It was recognized that in almost all chronic bowel disorders, the full spectrum of the patient's illness cannot be attributed to any discrete and demonstrable morphologic lesions. Rather, the bowel is a dynamic, diverse, and delicate ecosystem, teeming with life and shrouded in biochemical mists of kaleidoscopic molecular mosaics. It is noteworthy that an estimated ten or more trillion microbes reside in the human ecosystem.

In 1995, the same author introduced the concept that circulating blood was also a dynamic, diverse, and delicate ecosystem sandwiched between the bowel and liver ecosystems.⁸³ Furthermore, the blood ecosystem is an open ecosystem with a free commerce with the bowel and liver ecosystems on its two sides of nutrient, oxidative species, organic acids such as tartaric that inhibit the Krebs' cycle, and bacterial and fungal toxins.⁸⁴

Extensive clinical experience with patients with severe chronic health disorders has convinced the authors that the narrowly-focused, reductionistic view of chronic diseases as discrete entities that exist without clear definable ecologic relationships with other ecosystems of the body is not valid. Notwithstanding the satisfactory short-term results obtained with drug regimens that employ an essentially blockade approach to managing chronic disorders (i.e. use of receptor and channel blocking drugs, immunosuppressants, enzyme inhibitors), such therapies yield very poor long-term

results. Such considerations have led us at the Institute to a medical philosophy that calls for a broad-based, ecologic-integrative management approach to clinical problems. Specifically, we hold that all patients must be managed with holistic and integrated protocols that reflect a sound ecologic thinking concerning human body ecosystems and an understanding of molecular relatedness of events that occur within those ecosystems. The scientific basis of that approach have been described in several previous publications.²³⁻³¹ (ABE monograph, RDA, and wolf). The essentials of that philosophy are schematically expressed as The Pyramid of trios of the Body Ecosystems on page 49 of this issue of the *Journal*. in the article. Note that the base trio of the Pyramid of Trios comprises bowel-blood-liver ecosystems in which are grounded all aspects of our restorative plans for patients with arrested growth.

Need for Strong Support for Antioxidant Defenses

Compared with healthy subjects, mucosal samples from patients with Crohn's disease exhibit evidence of increased oxidative stress and decreased antioxidant defenses. Specifically, in such tissues the levels of reactive oxidative species, oxidized proteins, and 8-hydroxyguanosine (a specific marker of DNA oxidation) are increased, while those of copper/zinc superoxide dismutase are decreased.⁷⁰

The issues of short-term and long-term safety of aggressive intravenous nutrient therapy such as those employed for the six subjects of this study are of paramount importance. Our decision to employ such therapies in pediatric patients was made after careful deliberation of all involved issues in light of our extensive experience with such therapies in adult patients with a broad range of nutritional, ecologic, autoimmune and degenerative disorders (over 75,000 intravenous nutrient infusions administered during a period of twelve years). A careful and prolonged clinical follow-up of over 5,000 adult patients given such therapies had failed to disclose appreciable short-term or long-term adverse effects that could be attributed to nutrient therapies. Only two exceptions to that experience involved two patients who developed transient elevations of transaminases that cleared within weeks after nutrient infusions were discontinued. Notwithstanding, such an extraordinary safety of intravenous and intramuscular nutrient therapies in adults, the nutrient infusions were administered to the first three subjects of this study (a boy with malignant

rhabdomyosarcoma and two girls with Crohn's colitis) only as part of our protocols for severe malnourishment caused by chemotherapy-related factors and malabsorption associated with Crohn's disease) only to control intractable symptomatology. The intravenous nutrients protocol was employed in the last two subjects because of encouraging clinical outcome observed with the total plans in the first three subjects. Thus, our use of intravenous and intramuscular nutrient protocols for adolescents is based on our empirical experience with adults.

We recognized that the issue of the clinical efficacy of our nutrient, herbal and intravenous therapies could not be assessed by the traditional double-blind cross-over studies. There were simply too many nutritional, digestive/absorptive, metabolic, ecologic and hormonal variables to carry on a pretense of a blinded and controlled study. Indeed, as we point out earlier, demands for blinded and controlled studies are simply irrelevant to open and true-to-life clinical outcome studies such as being reported here. (One might raise here the core issue of how scientific is the clinical research in which single pharmacologic agents are investigated as solo therapies with placebo controls for some months and reports of the efficacy are published. That is followed by the use of such drugs concurrently with two, three or more drugs for years without ever questioning the assumptions of safety and efficacy of such combination protocols.) As for the need for using a placebo, we wish to point out that a placebo can work only if the drug used has no chemical consequences at all. Otherwise, the drug will exert its chemical effects and reveal its identity). Those issues have been discussed at length by one of the authors in *RDA: Rats, Drugs and Assumptions*.⁸⁵

Herbal Protocols for Restoring Damaged Bowel, Blood and Liver Ecosystems

Herbology literature is replete with descriptions of empirical value of a host of herbs for reversing chronic bowel disorders. In 1986, one of the authors (MA) organized over fifty herbs in 18 herbal protocols to facilitate their use in clinical medicine.⁸⁶ The compositions and clinical uses of those protocols (including twelve "bowel protocols", three "cell protocols", three "liver protocols", and two "blood protocols" have been published.³⁴ We reiterate here that in the ecologic-integrative plans of management, the clinical use of herbal protocols is empirical. We emphasized certain foods empirically known to restore

altered states of the bowel, blood and liver ecosystems. Such foods included the following: daikon, turnips, burdock root, Chinese cabbage, green beans, shiitake mushrooms, green leafy vegetables, squashes, ginger, garlic, onions, turmeric, peppers, squashes, and others. Detailed descriptions of such foods have been published previously.⁸⁷

CONCLUSIONS

Restoration of growth in six children and adolescents with comprehensive, integrated plans that included oral nutrient and herbal protocols as well as intramuscular and intravenous nutrient formulations is reported. The need for broad ecologic thinking for managing such problems is emphasized. Specifically, the use of a global model, The Pyramid of Trios of the Body Ecosystems, is suggested. A review of relevant literature shows that other approaches, such as TPN and prolonged hormone therapies, are ineffective and have a significant potential for long-term adverse effects. The risk of hormone therapies for children and adolescents, as well as their future offspring remain unknown. fraught with undetermined future risk of adverse effects. The relatively short length of the follow-up in this study does not allow us to make any definitive statements about the long-term safety of intramuscular and intravenous nutrient protocols used in this study. However, our much larger experience with such nutrient protocols in adult patients extending over a decade suggests that the potential for adverse long-term effects in children is likely to be quite small, if any. Additional long-term studies are now in progress at the Institute to further evaluate efficacy and potential for adverse effects of injectable nutrient protocols.

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