

## ABSTRACTS

**Growth Hormone Reverses Aging****TREATMENT OF ADULTS WITH GROWTH HORMONE (GH) DEFICIENCY WITH RECOMBINANT HUMAN**

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In a double blind, cross-over placebo-controlled trial, we studied the effects of 26 weeks of replacement therapy with recombinant human GH on body composition, metabolic parameters, and well-being in 10 patients with adult-onset GH deficiency (GHD). All patients received appropriate thyroid, adrenal, and gonadal replacement therapy. The dose of recombinant human GH was 0.25-0.5 U/kg.week (0.013-0.026 mg/kg.day) and was administered sc daily at bedtime. One patient was withdrawn from the study because of edema and atrial fibrillation. Body composition was estimated with three independent methods: computed tomography, bioelectric impedance, and total body potassium combined with total body water assessments. The Comprehensive Psychological Rating Scale and the Symptom Check List-90 were used to assess any change in psychopathology. After 26 weeks of treatment, adipose tissue (AT) mass decreased 4.7 kg ( $P < 0.001$ ). Subcutaneous AT decreased by an average of 13%, whereas visceral AT was reduced by 30%. Muscle volume increased by 2.5 kg (5%;  $P < 0.05$ ). According to the four-compartment model derived from assessments of total body potassium and total body water, body cell mass and extracellular fluid volume increased significantly by 1.6 and 3.0 kg, whereas body fat decreased by 6.1 kg. Results obtained by the bioelectric impedance technique were similar. The mean ( $\pm$  SD) concentrations of insulin-like growth factor-I increased from 0.26 (0.06) at baseline to 2.56 (1.55) and 2.09 (1.03) kU/L after 6 and 26 weeks of treatment. Calcium and serum phosphate, osteocalcin, and procollagen-III concentrations were significantly higher, and intact PTH concentrations were reduced after 6 and 26 weeks of treatment, respectively. Total and free T3 concentrations were significantly increased after 6 and 26 weeks of treatment, whereas free T4 concentrations were reduced at 6 weeks, but after 26 weeks, free T4 concentrations had returned to pretreatment values. Finally, after 26 weeks of treatment, there was a decrease in the Comprehensive Psychological Rating Scale score ( $P < 0.05$ ). The results show that GH replacement in GHD adults results in marked alterations in body composition, fat distribution, and bone and mineral metabolism and reduces psychiatric symptoms. Finally, we conclude that the observed beneficial effects of replacement therapy with GH are of sufficient magnitude to consider treatment of GHD adults.

## GROWTH HORMONE VERSUS PLACEBO

Growth hormone versus placebo treatment for one year in growth hormone deficient adults: increase in exercise capacity and normalization of body composition

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**OBJECTIVE:** Studies with GH substitution in GH-deficient (GHD) adults lasting more than 6 months have so far been uncontrolled. End-points such as physical fitness and body composition may be subject to a considerable placebo effect which weakens the validity of open studies. We therefore tested GH (2 IU/m<sup>2</sup> per day) versus placebo treatment for 12 months.

**DESIGN:** Twenty-nine patients (mean age 45.5 +/- 2.0 years) with adult-onset GHD were studied in a double-blind, parallel design. Measurements of body composition by means of conventional anthropometry, bioelectrical impedance (BIA), CT scan and DEXA scan, exercise capacity, and isometric muscle strength were performed at baseline and after 12 months treatment. For body composition measurements a control group of 39 healthy, age and sex-matched subjects was included.

**RESULTS:** Sum of skinfolds (SKF) at 4 sites decreased significantly after GH treatment. Total body fat (TBF) as assessed by DEXA and BIA was elevated at baseline but normalized after GH. TBF assessed by SKF revealed significantly higher levels compared to DEXA and BIA, although all estimates intercorrelated closely. Visceral and subcutaneous abdominal fat decreased by 25 and 17%, respectively after GH (P 0.01) to levels no longer different from the control group. CT of the mid thigh revealed a significant reduction in fat tissue and a significant increase in muscle volume after GH treatment, both of which resulted in a normalization of the muscle: fat ratio (%) (placebo: 58:42 (baseline) vs 58:42 (12 months); GH: 66:34 (baseline) vs 72:28 (12 months) (P = 0.002); normal subjects: 67:33 (P 0.05 when compared to 12 months placebo data)). Total body resistance and resistance relative to muscle volume decreased significantly after GH treatment suggesting over-hydration as compared to normal subjects. Exercise capacity (kJ) increased significantly after GH treatment (placebo: 54.7 +/- 9.8 (baseline) vs 51.6 +/- 8.2 (12 months); GH: 64.9 +/- 13.3 (baseline) vs 73.5 +/- 13.6 (12 months) (P 0.05)). Isometric quadriceps strength increased after GH but no treatment effect could be detected owing to a small increase in the placebo group. Serum IGF-I levels (microgram/l) were low baseline and increased markedly after GH treatment to a level exceeding that of normal subjects (270 +/- 31 (12 months GH) vs 156 +/- 8 (normal subjects (P 0.01))). The levels of serum electrolytes and HbA1c remained unchanged. The number of adverse effects were higher in the GH group after 3 months, but not after 6 and 12 months.

**CONCLUSIONS:** (1) The reduction in excess visceral fat during GH substitution is pronounced and sustained; (2) beneficial effects on total body fat, muscle volume and physical fitness can be reproduced during prolonged placebo-controlled conditions; (3) uncontrolled data on muscle strength must be interpreted with caution; (4) a daily GH substitution dose of 2 IU/m<sup>2</sup> seems too high in many adult patients.

## EFFECTS OF LONG-TERM, LOW-DOSE GROWTH HORMONE THERAPY

Effects of long-term, low-dose growth hormone therapy  
on immune function and life expectancy of mice

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We have studied effects of long-term, low-dose growth hormone therapy on the immune function and life expectancy of Balb/c mice. Sixty male Balb/c mice were aged up to the time when they started showing signs of senescence and causal death (deaths started when they became 17 months old). The aged mice were divided into two groups of 26 mice each. One group received growth hormone (30 micrograms/mouse) subcutaneously twice a week for 13 weeks. The control group received an equal volume of saline for the same period. During this treatment period, 16 control mice died (61%) whereas only 2 of the hormone-treated mice died (7%). Four mice from each group were killed and immunological functions of splenocytes were evaluated. Hormone-treated mice had higher stimulation indices for pokeweed mitogen but not for Concanavalin-A. Total IgG production was decreased but IL-1, IL-2 and TNF production was increased. After a lag period of 4 weeks, growth hormone therapy was continued for another 6 weeks. One of the growth hormone treated mice died while the control group no longer existed. Splenocyte functions of the growth hormone treated mice were compared to those of young mice. The results showed no significant difference between cytokine production (IL-1, IL-2, TNF and IgG) in the young and the hormone treated groups. Stimulation induced by concanavalin-A and pokeweed mitogen however, was higher in the young group than the old group. The mortality curve obtained suggests that long-term low-dose growth hormone treatment prolongs life expectancy.

## EFFECTS OF HUMAN GROWTH HORMONE IN MEN OVER 60 YEARS OLD

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*N Engl J Med (UNITED STATES) Jul 5 1990, 323 (1) p1-6.*

**BACKGROUND.** The declining activity of the growth hormone-insulin-like growth factor I (IGF-I) axis with advancing age may contribute to the decrease in lean body mass and the increase in mass of adipose tissue that occur with aging.

**METHODS.** To test this hypothesis, we studied 21 healthy men from 61 to 81 years old who had plasma IGF-I concentrations of less than 350 U per liter during a six-month base-line period and a six-month treatment period that followed. During the treatment period, 12 men (group 1) received approximately 0.03 mg of biosynthetic human growth hormone per kilogram of body weight subcutaneously three times a week, and 9 men (group 2) received no treatment. Plasma IGF-I levels were measured monthly. At the end of each period we measured lean body mass, the mass of adipose tissue, skin thickness (epidermis plus dermis), and bone density at nine skeletal sites.

**RESULTS.** In group 1, the mean plasma IGF-I level rose into the youthful range of 500 to 1500 U per liter during treatment, whereas in group 2 it remained below 350 U per liter. The administration of human growth hormone for six months in group 1 was accompanied by an 8.8 percent increase in lean body mass, a 14.4 percent decrease in adipose-tissue mass, and a 1.6 percent increase in average lumbar vertebral bone density ( $P$  less than 0.05 in each instance). Skin thickness increased 7.1 percent ( $P = 0.07$ ). There was no significant change in the bone density of the radius or proximal femur. In group 2 there was no significant change in lean body mass, the mass of adipose tissue, skin thickness, or bone density during treatment.

**CONCLUSIONS.** Diminished secretion of growth hormone is responsible in part for the decrease of lean body mass, the expansion of adipose-tissue mass, and the thinning of the skin that occur in old age.

## SAME AND LIVER DISEASE

### ***Effects of oral S-adenosyl-L-methionine on hepatic glutathione in patients with liver disease***

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*Scand J Gastroenterol (NORWAY) May 1989, 24 (4) p407-15.*

S-Adenosyl-L-methionine (S-AMe) is a physiologic precursor of thiols and sulfurated compounds, which are known to be decreased in patients with liver disease. The effect of its administration on the hepatic glutathione content of liver patients was investigated. Four groups of subjects were selected: a) 9 patients with alcoholic liver disease treated with S-AMe (1.2 g/day orally for 6 months); b) 7 patients with non-alcoholic liver disease treated as above; c) 8 placebo-treated patients with alcoholic liver disease; and d) 15 normal subjects as a control group. Total and oxidized glutathione were assayed by high-performance liquid chromatography of liver biopsy specimens before and after the treatment period. In all patients pre-treatment hepatic glutathione was significantly decreased as compared with controls. S-AMe therapy resulted in a significant increase of hepatic glutathione levels both in patients with alcoholic and in those with non-alcoholic liver diseases as compared with placebo-treated patients. S-AMe may therefore exert an important role in reversing hepatic glutathione depletion in patients with liver disease.

***S-adenosyl-L-methionine synthetase and phospholipid methyltransferase are inhibited in human cirrhosis***

Duce AM; Ortiz P; Cabrero C; Mato JM *Metabolismo, Nutricion y Hormonas, Fundacion, Jimenez Diaz, Madrid, Spain. Hepatology (UNITED STATES) Jan-Feb 1988, 8 (1) p65-8.*

We have measured the activity S-adenosyl-L-methionine synthetase in liver biopsies from a group of controls (n = 17) and in 26 cirrhotics (12 alcoholic and 14 posthepatic). The activity of this enzyme was markedly reduced in the group of cirrhotics (285 +/- 32 pmoles per min per mg protein) when compared with that observed in controls (505 +/- 37 pmoles per min per mg protein). No differences in S-adenosyl-L-methionine synthetase was observed between both groups of cirrhotics. Similarly, a marked reduction in the activity phospholipid methyltransferase was also observed in liver biopsies from the same group of cirrhotics (105 +/- 12 pmoles per min per mg protein) when compared with the control subjects (241 +/- 13 pmoles per min per mg protein). Again, no difference in the activity of this enzyme was observed between both groups of cirrhotics. These results indicated a marked deficiency in the metabolism of S-adenosyl-L-methionine in cirrhosis.

**Reversal of extrahepatic membrane cholesterol deposition in patients with chronic liver diseases by S-adenosyl-L-methionine**

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*Clin Sci (Colch) (ENGLAND) Sep 1992, 83 (3) p353-6.*

1. S-Adenosyl-L-methionine is reported to improve serum liver function tests in chronic liver disease. Because liver disease is complicated by cholesterol deposition in hepatic and extrahepatic membranes, we have assessed whether oral administration of S-adenosyl-L-methionine to patients with hepatic disease can reverse the cholesterol enrichment of their erythrocytes. 2. The mean erythrocyte cholesterol-to-phospholipid molar ratio in 13 jaundiced patients was reduced 2 weeks after oral administration of S-adenosyl-L-methionine (from 0.874 +/- 0.112 to 0.844 +/- 0.102, P 0.05) with 10 of the patients (77%) showing a decrease. By contrast, only four of 11 untreated patients (36%) had a reduced erythrocyte cholesterol-to-phospholipid molar ratio after 2 weeks and the mean values did not differ. 3. The plasma and erythrocyte cholesterol-to-phospholipid molar ratios remained closely correlated ( $r = 0.77$ , P 0.01) before and after treatment, suggesting that S-adenosyl-L-methionine had not acted directly on the cells but rather had improved their lipoprotein milieu. Further support for this concept was provided by following one patient, who initially failed to respond, during an additional 3 weeks of S-adenosyl-L-methionine administration. The plasma cholesterol-to-phospholipid molar ratio fell steadily from week 1 to week 5 and was accompanied by a progressive decrease in the erythrocyte cholesterol-to-phospholipid molar ratio. Moreover, the initially suppressed acetylcholinesterase activity of the erythrocyte membranes returned towards normal during this period. 4. This preliminary study is the first evidence in jaundiced patients that a drug can help to reverse the deposition of cholesterol in an extrahepatic membrane.

***Prevention of S-adenosylmethionine of estrogen-induced hepatobiliary toxicity in susceptible women***

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Am J Gastroenterol (UNITED STATES) Oct 1988, 83 (10) p1098-102.

Women with past histories of intrahepatic cholestasis of pregnancy (ICP) exhibit a congenital exaggerated sensitivity to estrogens, which may express as abnormal hepatic reactivity to oral contraceptive intake and increased risk of developing gallbladder disease. Since previous investigations have shown that S-adenosylmethionine (S-AdoMet) is effective in antagonizing ICP, we wondered whether its administration to subjects with previous ICP could 1) protect them from a challenge with ethynylestradiol (EE) or 2) normalize the cholesterol saturation index (CSI).

To test the first hypothesis, six women volunteered to receive EE (0.1 mg/day orally for 1 wk) and, after 3 months, the same EE dose plus oral S-AdoMet (800 mg/day for 1 wk). EE significantly increased serum values of transaminases, conjugated bilirubin, and total bile acids with respect to basal values. In the rechallenge with EE plus S-AdoMet, liver function tests did not differ from basal levels and were significantly lower than the values obtained after EE. In the second experiment, we gave oral S-AdoMet (800 mg/day for 2 wk) to seven women with previous ICP who exhibited cholesterol supersaturation of duodenal bile.

Both subjects were nonpregnant and non-obese and had cholecystograms negative for gallstones. Bile CSI decreased from a basal value of  $1.35 \pm 0.07$  to  $0.98 \pm 0.08$  after S-AdoMet ( $p$  less than 0.01). These findings indicate that S-AdoMet protects women with previous ICP from EE-induced liver toxicity and normalizes bile CSI in the same subjects who secrete lithogenic bile. The data support the belief that S-AdoMet acts as a physiological antidote against estrogen hepatobiliary toxicity in susceptible women.

## GENOMIC ABNORMALITIES IN HEPATOCARCINOGENESIS-IMPLICATIONS FOR A CHEMO PREVENTIVE STRATEGY

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*Anticancer Res (GREECE) Sep-Oct 1993, 13 (5A) p1341-56.*

Carcinogenesis is a complex process characterized by the cumulative activation of various oncogenes and the inactivation of suppressor genes. Epigenetic mechanisms are also involved. Mutational activation of ras family genes occurs in most spontaneous or carcinogen-induced liver tumors, in susceptible mice, and less frequently in preneoplastic lesions. This suggests a pathogenetic role of these changes in hepatic carcinogenesis, in the mouse. Overexpression of various growth-related genes occurs in preneoplastic tissue during rat liver carcinogenesis, but mutational activation of proto oncogenes, notably of ras family genes, seems to be a late and rare event, while c-myc amplification is a late but frequent event in both rodent and human carcinogenesis. However, mutation of the suppressor p53 gene has been found in relatively early preneoplastic lesions in rat liver, and it may be frequently seen in human hepatocellular carcinomas. The possibility that this mutation is involved in the initiation stage of liver carcinogenesis is an attractive hypothesis which needs further evaluation. DNA hypomethylation is involved in carcinogenesis, but the mechanisms underlying this effect are still elusive. Hypomethylation of growth-related genes is associated with their overexpression and this could favor overgrowth of preneoplastic liver tissue. Decrease in S-adenosyl methionine/S-adenosylhomocysteine (SAM/SAH) ratio occurs in the liver of rats fed a methyl deficient diet, which is a carcinogenic treatment, and in preneoplastic liver tissue, developing in initiated/promoted rats fed an adequate diet. The role of low SAM/SAH ratio in carcinogenesis is substantiated by the tumor chemo preventive effect of lipotropic compounds. Treatment with exogenous SAM prevents the development of preneoplastic and neoplastic lesions in rat liver. This is associated with recovery of SAM/SAH ratio, DNA methylation and inhibition of growth-related gene expression. SAM effect on preneoplastic cell growth is abolished by 5-azacytidine, a hypomethylating agent, indicating the involvement of DNA methylation. The possibility that in SAM-treated rats, methylation and inhibition of the expression of growth-related genes is implicated in growth restraint is attractive and should be further evaluated. Modulation of rat liver carcinogenesis by influencing gene expression through DNA methylation or other epigenetic mechanisms could be a new approach to chemoprevention of these tumors.

## CORRELATION BETWEEN S-ADENOSYL-L-METHIONINE CONTENT AND PRODUCTION OF C-MYC,

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*Cancer Lett (IRELAND) Apr 29 1994, 79 (1) p9-16.*

Gamma-Glutamyltranspeptidase (GGT)-positive and glutathione S-transferase (placental-GST-P) positive foci were induced in male Wistar rats by initiation with diethylnitrosamine (DENa), followed by selection and phenobarbital (PB). GGT- and GST-P-positive foci occupied 20-46% and 27-68% of liver parenchyma, respectively, 5-9 weeks after initiation. A high DNA synthesis was found in GGT-positive foci. Decrease in S-adenosyl-L-methionine (SAM) level and SAM/S-adenosylhomocysteine (SAH) ratio, and overall DNA hypomethylation occurred in the liver during the development of enzyme altered foci (EAF). These parameters underwent very small and transient changes in the liver of uninitiated rats at the 5th week, when EAF occupied 0.7-1.4% of the liver. At the 9th week, high RNA transcripts of c-myc, c-Ha-ras, and c-Ki-ras were found in the liver of initiated rats, but not in that of uninitiated rats. Immunohistochemical evaluation of c-myc gene product showed overexpression in GST-P-positive cells. SAM treatment of initiated rats caused inhibition of EAF growth, recovery of SAM/SAH ratio and DNA methylation, and decrease in protooncogene expression proportional to the dose and length of treatment. Liver SAM/SAH ratio was positively correlated with DNA methylation, and negatively correlated with transcript levels of the three protooncogenes. Thus, decrease in SAM/SAH ratio and DNA hypomethylation are early features of hepatocarcinogenesis promotion in rats fed a diet containing adequate lipotrope amounts, paralleled by overexpression of growth-related genes and rapid growth. Re-establishment of a physiologic SAM level makes it possible to inhibit protooncogene expression and EAF growth and to prevent late liver lesion development.

## **METHYL GROUPS IN CARCINOGENESIS: EFFECTS ON DNA METHYLATION AND GENE EXPRESSION**

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*Cancer Res (UNITED STATES) Apr 1 1992, 52 (7 Suppl) p2071s-2077s.*

Lipotropic-deficient (methyl-deficient) diets cause fatty livers and increased liver-cell turnover and promote carcinogenesis in rodents. In rats prolonged intake of methyl-deficient diets results in liver tumor development. The mechanisms responsible for the cancer-promoting and carcinogenic properties of this deficiency remain unclear. The results of the experiments described here lend support to the hypothesis that intake of such a diet, by causing depletion of S-adenosylmethionine pools, results in DNA hypomethylation, which in turn leads to changes in expression of genes that may have key roles in regulation of growth. In livers of rats fed a severely methyl-deficient diet (MDD), lowered pools of S-adenosylmethionine and hypomethylated DNA were observed within 1 week. The extent of DNA hypomethylation increased when MDD was fed for longer periods. The decreases in overall levels of DNA methylation were accompanied by simultaneous alterations in gene expression, yielding patterns that closely resembled those reported to occur in livers of animals exposed to cancer-promoting chemicals and in hepatomas. Northern blot analysis of polyadenylated RNAs from livers of rats fed control or deficient diets showed that, after 1 week of MDD intake, there were large increases in levels of mRNAs for the c-myc and c-fos oncogenes, somewhat smaller increases in c-Ha-ras mRNA, and virtually no change in levels of c-Ki-ras mRNA. In contrast, mRNAs for epidermal growth factor receptor decreased significantly. The elevated levels of expression of the c-myc, c-fos, and c-Ha-ras genes were accompanied by selective changes in patterns of methylation within the sequences specifying these genes. Changes in DNA methylation and in gene expression induced in livers of rats fed MDD for 1 month were gradually reversed after restoration of an adequate diet. In hepatomas induced by prolonged dietary methyl deficiency, methylation patterns of c-Ki-ras and c-Ha-ras were abnormal. Although human diets are unlikely to be as severely methyl deficient as those used in these experiments, in some parts of the world intake of diets that are low in methionine and choline and contaminated with mycotoxins, such as aflatoxin, are common. Even in industrialized nations, deficiencies of folic acid and vitamin B12 are not uncommon and are exacerbated by some therapeutic agents and by substance abuse. Thus, it seems possible that interactions of diet and contaminants or drugs, by inducing changes in DNA methylation and aberrant gene expression, may contribute to cancer causation in humans.

## S-ADENOSYLMETHIONINE GENERATION AND PREVENTION OF ALCOHOLIC FATTY LIVER BY BETAINE

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*Alcohol (UNITED STATES) Nov-Dec 1994, 11 (6) p501-3.*

Earlier studies by other investigators have shown that S-adenosylmethionine (SAM) has the capacity to attenuate liver injury in experimental animals. In a recent study in this laboratory, it was shown that when supplemental dietary betaine was given to control and ethanol-fed rats at the level of 0.50% (W/V), SAM levels were doubled in the livers of control animals and increased fivefold in livers of ethanol-fed rats. The increased levels of SAM in the livers of ethanol-fed animals protected the livers from fatty infiltration due to ethanol feeding. In this study, an attempt was made to determine the minimum level of dietary betaine that protects against the fatty infiltration. Levels of betaine at 0.05%, 0.10%, 0.25%, and 0.50% in semiliquid control and alcohol diets were tested in rats for 30 days. When hepatic betaine, SAM, and triglyceride levels were determined, it was demonstrated that only the dietary level of betaine at 0.50% supplied enough hepatic betaine to generate the level of SAM that was required to protect against the alcoholic steatosis resulting from the dietary ethanol. These results suggest that betaine, when given in sufficient amounts, may be a promising therapeutic agent in the treatment of liver disease.

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