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GONADAL DYSFUNCTION AFTER NITROSOUREA CHEMOTHERAPY (CTX) FOR CHILDHOOD BRAIN TUMOURS.

We have shown that chemotherapy with nitrosoureas and not spinal irradiation is responsible for gonadal damage in our children treated for medulloblastoma (Ahmed et al, 1983). But the incidence and influence on pubertal development are unknown. 40 children(24M: 16F), who received a nitrosourea in 6 week cycles for 1-2yrs were followed for a mean of 4.8yrs (range 0.2-11). 29/29 entered or completed puberty spontaneously, and 7/7 commenced menses at appropriate ages. Testicular sizes, assessed at 17.5yrs and 5.9yrs from CTX (range 0.4-11), were inappropriately small for pubertal stage in 14/20 boys. Basal FSH was elevated in 16/24 and LH in 9/24, with normal testosterone levels in all. One male (19yrs), 7.2yrs from CTX, is azoospermic. Only 2/24, treated at 13.2 and 17.8yrs, have no evidence of testicular damage. For females, studied at 11.8yrs (range 3.6-25.9) and 4yrs from CTX, 5/16 had an elevated basal FSH. A further 5 had had raised FSH levels and 4 an exaggerated FSH response to GnRH, but the FSH levels in these girls had returned to normal at study. Only two, aged 12.2 and 14.4yrs at CTX, have consistently normal FSH levels after 8 and 9yrs respectively.

90% of those receiving nitrosourea showed gonadal damage; Steroidogenesis appears relatively spared and the children progress through puberty spontaneously. In males, there is no sign of recovery of the germinal epithelium (10yrs after CTX). In females, transient gonadal damage is more common.

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HEAD GROWTH AND GROWTH HORMONE (GH) THERAPY FOLLOWING CRANIAL IRRADIATION.

The occipito-frontal circumferences(OFC) of children, GH deficient following cranial irradiation, have been assessed before (n=38) and on completion of GH (n=15) or after a similar period of observation without GH (n=7). The changes in OFC were compared to those in treated idiopathic GH deficiency (n=14). Before GH, the latter had relative preservation of head size (mean OFC SDS -1) compared to their height deficit (height SDS -4.7), but showed catch-up head growth with GH (ΔOFC SDS +0.7, final mean OFC SDS -0.2). In contrast, before GH, irradiation patients had a normal OFC SDS (mean -0.1) with a height SDS of -1.7, though OFC SDS for those under 5yrs at irradiation (-0.6) was less than for those over 5yrs (+0.3, $p<0.05$). Over a similar period, all patients, who previously had received irradiation in the dosage range 2700-4750cGys, irrespective of the schedule or GH treatment, showed a decrease in OFC SDS (mean Δ -0.9). This was significantly different from the catch-up growth of the idiopathic group, and the expected head growth of normal children over a similar period.

Thus restricted head growth occurs in the years following cranial irradiation, and is unaffected by GH therapy. Earlier work has shown impaired intelligence may be a sequel to cranial irradiation, particularly in the younger child. The relationship between intellectual impairment and stunted head growth remains to be determined.

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BIOLOGICAL EFFECTS OF HUMAN PLACENTAL LACTOGEN (HPL) ON HUMAN FETAL EPIPHYSEAL CHONDROCYTES IN CULTURE.

The biological activity of HPL on human fetal epiphyseal chondrocytes in culture has been investigated by studying the capacity to stimulate chondrocyte proliferation in a chemically defined serum-free medium. Chondrocytes (70.000 cells/well) were incubated with HAM F-12 serum and antibiotic-free medium for 48 h. The medium was then aspirated and replaced by MCDB 104 serum and antibiotic-free medium with HPL (1-100 ng/ml). Cells were then incubated for 48 h, the last 24 h in the presence of ^{3}H-thymidine (5 uCi/ml). In each experiment five different wells were used for each HPL concentration and five as controls.

HPL (1-100 ng/ml) significnatly ($p<0.05$-0.01) stimulated ^{3}H-thymidine incorporation into chondrocytes from 20-40-week-old human fetuses of both sexes. This stimulation was 150±13.5 (m±DS) per 10 ng/ml, controls=100, n=8.

In conclusion, HPL stimulates human fetal epiphyseal chondrocyte proliferation in a serum-free medium and these results suggests that HPL may be involved in human fetal epiphyseal cartilage metabolism.

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STIMULATION OF CHONDROCYTE DNA SYNTHESIS BY JUVENILE CHRONIC ARTHRITIS SYNOVIAL FLUID

Synovial fluid from patients with juvenile chronic arthritis (JCA) was found to stimulate the DNA synthesis of rat epiphyseal chondrocytes in serum-free primary cultures in vitro. The effect was dose-dependent and more pronounced than that observed with newborn calf serum. The cloning efficiency and colony size of chondrocytes in soft agar colony cultures were also stimulated. JCA synovial fluid also contained interleukin-1 (IL-1) activity when tested in a murine thymocyte proliferation assay. AcA 54 gel filtration chromatography showed similar elution pattern of the chondrocyte stimulating activity and the IL-1 activity, indicating that IL-1 might act as a chondrocyte growth factor in vitro. This assumption was further supported by experiments demonstrating a dose-related stimulation of chondrocyte DNA synthesis by natural guinea pig macrophage-derived IL-1 and recombinant human IL-1. As it has been shown that the articular cavity is vascularly connected with nearby epiphyseal plates, our results might give one explanation for the stimulation of bone growth often seen in the affected limb in children with monoarthritis.

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THE SULFONYLUREA GLIBENCLAMIDE DIRECTLY STIMULATES GROWTH OF CHONDROCYTES.

Glibenclamide treatment of hypophysectomized rats augmented insulin, somatomedin, and skeletal growth. It is unknown if the sulfonylurea can directly enhance skeletal growth. Therefore chondrocytes from normal or hypophysectomized rats and from human nose septal cartilage were isolated and cultured in a semi-solid medium for 14 days at 37°C with or without glibenclamide. Colony formation was determined. Results: Colony formation (20-50 colonies) without glibenclamide was designated as 100% (M±SEM).

glibenclamide ng/ml	n	25	50	100
normal rats	12	111 ± 3%	124 ± 5%	136 ± 5%
hypox. rats	9	112 ± 2%	115 ± 3%	123 ± 3%
human septum	9	139 ± 17%	152 ±19%	145 ± 24%

Glibenclamide increased clonal growth. Cells from hypox. rats formed less colonies than cells from normal rats. Therefore chondrocytes from human nose septal cartilage were cultured with and without an IGF I-receptor antibody (IR-3, courtesy of Dr.S. Jacobs) in two dilutions: 1:50 and 1:1000. Glibenclamide (25-100 ng/ml) stimulated colony formation was completely blocked with both AK-dilutions, while in control experiments with 25 ng/ml IGF I, clonal growth was abolished with the IgF I-Ak dilution 1:50 but not 1:1000. Glibenclamide appears to be the first non-hormonal agent to augment growth of chondrocytes. The somatomedins may be involved in its action.

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EFFECTS OF THE SLOW RELEASE GNRH AGONIST DECAPEPTYL-DEPOT (DD) ON GROWTH AND BONE MATURATION IN CHILDREN WITH CENTRAL PRECOCIOUS PUBERTY (CPP).

In a multicentre study 76 patients with CPP were treated with DD, injected i.m. at 4-wk intervals. 18 Patients were on therapy for 6 mo, 42 for 12 mo or more. 24 Patients were previously treated with Buserelin (daily s.c.) or Cyproteronacetate (daily p.o.). DD was started at a mean chronol. age (CA) for girls (n=68) at 6.9 ± 1.9 yrs (mean ± sd) and for boys (n=8) at 6.5 ± 1.6 yrs; Bone age ((BA) (G & P) was 9.9 ± 2.0 and 11.0 ± 2.6 yrs resp. Growth velocity in boys (n=3)without pretreatment ranged between 12.5 - 14,3 cm/yr and decreased to 3.5 - 5.1 cm/yr after one year of therapy. In previously untreated girls the mean growth velocity decreased from 10.7 ± 3.5 (n=28) to 6.7 ± 2.8 (n=28) after 6 mo and further to 5.3 ± 2.5 cm/yr (n=20) after 12 mo. Δ BA/ΔCA (normal = 1.0) in the previously untreated patients was 1.15 ± 0.82 (n=19) before treatment, 0.95 ± 0.54 (n=29) after 6 mo and decreased to 0.67 ± 0.72 (n=25) after 12 mo. Adult height prediction (B & P) at start of therapy was 160.7 ± 11.6 cm in all girls and remained unchanged after 6 or 12 mo of DD; in boys the prediction increased from 168.0 ± 8.6 to 171.9 ± 10.3 cm after 12 mo. SM-C levels were increased for CA and not influenced by treatment (n=23). Androstenedione (Δ^4) basal level was 2.0 ± 1.4 nmol/l (n=21) and after 6 and 12 mo 1.2 ± 1.7 (n=20) and 1.1 ± 1.1 (n=16). DHEA-S levels did not change during DD. Clinical signs of pubic hair development decreased in boys but not in girls. In conclusion DD-treatment decreases growth velocity and bone maturation, resulting in an mean increase of adult height prognosis in boys , but not (yet) in girls.