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RESTORATION OF AGE-RELATED DECLINE IN IMMUNE CELL FUNCTION BY SUPPLEMENTATION WITH SELENIUM. M. Roy,[1] L. Kiremidjian-Schumacher,[1] H.I. Wishe,[1] M.W. Cohen,[1] and G. Stotzky[2] [1]New York University Dental Center, Basic Science Division, N.Y., N.Y. 10010 [2]New York University, Biology Department, N.Y., N.Y. 10003.

This study examined the effect of dietary (2.00 ppm for 8 weeks) supplementation with selenium (as sodium selenite) on the ability of lymphocytes from aged (24-month old), male, C57BL/6JNIA mice to respond to: 1) stimulation with mitogen (phyto-hemagglutinin) or alloantigen; 2) develop into cytotoxic effector cells; and 3) destroy tumor cells. Supplementation with selenium resulted in a significant increase in the ability of spleen lymphocytes from aged animals to undergo blastogenesis, as indicated by significantly higher amounts of nuclear incorporation of ^{3}H-thymidine after stimulation with mitogen. The dietary regimen abrogated the age-related deficiency of the cells to respond to stimulation by nuclear DNA synthesis and cell proliferation. Furthermore, populations of *in vivo*, alloantigen-activated lymphocytes, from Se-supplemented aged animals contained significantly higher numbers of cytotoxic lymphocytes which resulted in an enhanced capacity to destroy tumor cells. The significant increase in the number of cytotoxic effector cells within these activated T-lymphocyte populations was probably the result of an enhanced clonal proliferation of cytotoxic precursors cells, followed by the differentiation of greater numbers of cytotoxic effector cells. This effect occurred in the absence of changes in the ability of the cells to produce IL-2, which confirmed our earlier observation that dietary supplementation with selenium does not affect the production of IL-2. The data suggested that selenium abrogates the age-related defect in cell proliferation through an increase in the number of high affinity IL-2 receptors. (Supported by AICR grant 91A01)

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REPRODUCTIVE ACTIVITY OF ADULT MICE TREATED NEONATALLY WITH METHOXYCHLOR (TECHNICAL GRADE). W.J. Swartz and V.P. Eroschenko. Dept. of Anatomy, Louisiana State University Medical Center, New Orleans, LA 70112 and Dept. of Biological Sciences, University of Idaho, Moscow, ID 83844.

This study is designed to determine the ability of female mice, exposed neonatally to the pesticide methoxychlor, to mate, ovulate and become pregnant as adults. One-day-old female mice were exposed daily for 14 days to either sesame oil or 10 μg estradiol-17β (E) or 0.1, 0.5 or 1.0 mg MXC suspended in sesame oil. Three months later female mice were placed with males and checked daily for plugs. Mated mice were sacrificed 18 days following the appearance of a vaginal plug to evaluate pregnancy. Uteri were examined for the presence of fetuses and resorption sites. Ovaries were removed and prepared for histological evaluation and tabulation of corpora lutea. Mice from all three MXC-treated groups mated, whereas no E-treated mice did. With increasing dose of MXC there was a decrease in the number of pregnant animals observed at 18 days following mating. The mean number of live young was significantly reduced in the 0.5 and 1.0 mg MXC-treated groups with resorption sites found in most. Corpora lutea were significantly reduced in ovaries from these mice. It is concluded that neonatal exposure to MXC does not interfere with mating but does exert a significant effect on pregnancy. This may result from a significant decrease in the number of healthy oocytes ovulated and/or from a failure of the uterus to accept and retain the fertilized egg. (Supported by Grant 0H00835 Awarded by the National Institute for Occupational Safety and Health to W. J. S.).

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FOLATE REPLACEMENT IN ANTIBIOTIC-INDUCED INFERTILITY Durwood E. Neal, Jr., Karen L. Crotty, Alayne Kovicki, Robert A. May, and Dhruv Kumar Univ. Texas Med. Branch, Galveston, TX 77555-0540

A number of antibiotics have been shown to have an adverse effect on fertility. One of these, the sulfonamide group, has shown particular toxicity to the germinal epithelium, adversely affecting semen quality. Largely, these effects are directly related to the drug itself and are reversible when the agent is discontinued. This class of drugs is known to act by disrupting the folic acid pathway. Methods. Fifteen male Sprague-Dawley rats were used in three groups of five, treated by gastric gavage for 10 days. Group I received sulfamethoxazole (SMX) 20 mg/kg/d (with trimethoprim [tmp] 4 mg/kg/d), Group II received the same as Group I along with folate 0.014 mg/kg/d. Group III were treated with normal saline, as a control. The rats underwent a testicular aspirate on days 0, 11, and 56. These were submitted for flow cytometry to analyze the DNA content (ploidy) of the germinal epithelium. Results. A statistically different change was seen only in Group I (smx/tmp) on days 11 and 56 ($p=0.00025$ and $p=0.042$, respectively). The folate-treated animals and controls showed no change in the ploidy of the testicular aspirate. Conclusions. These results suggest that folate may obviate the adverse effects of smx/tmp on spermatogenesis and fertility.

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RETINOL IS REQUIRED FOR SUCCESSFUL GESTATION IN RATS. D. M. Wellik and H. F. DeLuca. Department of Biochemistry, University of Wisconsin-Madison, Madison, WI 53706.

In 1964, Thompson *et al.* demonstrated that vitamin A-deficient, retinoic acid-supported (VAD-RAS) rats require retinol to allow successful gestation. In confirmation, we have found that vitamin A-deficient, pregnant rats given retinoic acid daily will invariably resorb their fetuses around day 15 of gestation unless retinol is given. Retinol was found to be required no later than day 10 of gestation to prevent this resorption. Up to 500 µg of retinol administered on day 11 or later was not able to change the course of fetal resorption in these animals. Fetuses whose VAD-RAS mothers were given 2 µg of retinol on day 10 were macroscopically indistinguishable from fetuses taken from vitamin A-sufficient mothers when examined at day 20 of gestation, even though radiolabeled tracer experiments indicate that the administered retinol is mostly eliminated from the animal by day 16. This single dose of retinol allowed the birth of live young. Surprisingly, the neonates died minutes after birth from an apparent inability to acquire oxygen, suggesting an additional need for retinol later in gestation. These findings demonstrate that retinol is required for placental/fetal development by a mechanism not involving retinoic acid. This work was supported by an NIH grant #DK14881.

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LONG-TERM EFFECTS OF hGH AND/OR IGF-I ON GROWTH AND IGFBPS IN RATS. P. Mallett, P. J. Fielder, D. M. Mortensen, Y.W. Ma, R. C. Baxter*, and R. G. Clark (SPON: M. Cronin). Genentech Inc, S. SF., CA 94080; *Kolling Ins. Med. Res., ST Leonard's NSW 2065 Australia.

The effects of long-term insulin-like growth factor -I (IGF-I) and/or growth hormone (GH) treatment on body growth and the IGF/IGF binding protein (IGFBP)/Acid-Labile Subunit (ALS) axis have not been previously studied. Hypophysectomized (Hx) rats (100 g, 6-10/gp) receiving excipient (Hx), 200 µg/day of rhIGF-I(SC minipump infusion) or rhGH (SC qid injection), or both for 28 days, were weighed daily and bled on day 28. Serum IGF-I, IGFBP, and ALS, and the molecular size distribution (MSD) of IGFBP-3 following size-exclusion chromatography were measured. Data are means ± SEM. At day 28, weight gains were Hx (7±1 g), IGF-I (43±2 g), hGH (65±6 g), and hGH+IGF-I (94±7 g); the initial rapid growth response to IGF-I was not maintained during the last 14 days of the study. Serum IGF-I levels (hGH+IGF-I (492 ± 140) >IGF-I (322 ± 75) > hGH (85 ± 26) > Hx (39 ± 7) were not consistent with the growth responses. All three treatments increased serum IGFBP-3 levels comparably. However, IGF-I alone produced a unique MSD of IGFBP-3 (in the 200-300 KD and 44 KD MW ranges), compared to the other treatments or to normal rats (more IGFBP-3 in the 150 KD MW range). This may be due to rhGH, but not IGF-I, increasing ALS (measured by RIA) levels which are necessary for formation of the 150KD IGFBP-3 complex. Data suggest that therapies that induce a more normal IGF-I/IGFBP-3/ALS profile have greater long-term growth promoting activity.

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CIRCULATING INSULIN-LIKE GROWTH FACTOR-I DURING GROWTH AND AGING IN HORSES. R.A. CHRISTENSEN, K. MALINOWSKI, C.G. SCANES, AND H.D. HAFS. Dept. Animal Science, Rutgers University, New Brunswick, 08903.

A double antibody radioimmunoassay for Insulin-Like Growth Factor-I (IGF-I) was validated in horses in which plasma was incubated with 1 M diglycine-HCl at 37°C for 5 days to dissociate the IGF-I from its binding proteins. Plasma IGF-I (ng/ml) was measured from Standardbred females aged 0, 1, 7, and 14 days, 1, 2, 4, 6, and 9 months, and 5-10 and 16-21 years (n=6 to 18). Plasma IGF-I increased ($P \leq .05$) between days 0 and 7 and between days 7 and 14 (day 0, 267±33; day 14, 508±32) and remained high until 4 months. Plasma IGF-I decreased ($P \leq .05$) between 4 to 9 months and 5 to 10 years but no further at 16 to 21 years. In adult mares of eight different breeds ranging in size from miniatures to drafts, plasma IGF-I was not related with adult body size. ^{125}I-IGF-I ligand blot analysis of pooled plasma from Standardbred females revealed six potential binding proteins. We conclude that in female horses, plasma IGF-I changes during growth, particularly during the first 4 months of age. Furthermore, plasma IGF-I was not related to the mature body size of mares from different breeds. (Supported by the New Jersey Equine Research Initiative).

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ABSTRACTS

PART I

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