73 F. HANEFELD[+], L. BALLOWITZ[+], W. HESS[+] (intr. by H. HELGE), Dept. Pediat. Free University Berlin, Increased kernicterus rate in homozygous Gunn rats after application of different antibiotics.

The frequency of kernicterus following the administration of different antimicrobial drugs was studied in homozygous infant Gunn rats. Survival rate, weight gain, serum bilirubin and cerebral/cerebellar weight were measured. Kernicterus was studied in the cerebella of the animals by grading the loss of Purkinje cells using histochemical methods for the demonstration of oxydative enzymes (NADH-Tetrazolium reductase; LDH). Some gentamycin preparations containing great amounts of the stabilizer benzylalcohol produce a decrease in serum bilirubin levels to 5o % of the baseline concentration of 7-9 mg%. At the same time there is a marked increase in frequency and severity of kernicterus in these animals. Gentamycin without stabilizer had no such effect.
Semi synthetic penicillins (oxacillin, cloxacillin, flucloxacillin, ampicillin, carbenicillin) had only little effect on serum bilirubin levels when given as single injection. The rate of kernicterus in homozygous Gunn rats was enhanced only when a combination of several semi synthetic penicillins was given. The changes of bilirubin concentrations and the rate of kernicterus observed in our experiments are the result of the displacement of bilirubin from its binding site to albumin. This can be produced by the stabilizer (benzylalcohol) or by the drug itself (semi synthetic penicillins). Unbound (free) bilirubin is shifted into the brain immediately, where it can produce kernicterus.

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Pharmacokinetics of cyproterone acetate (CA). Preliminary investigations in adults using a sensitive radioimmunoassay (RIA).

CA has been used in the treatment of precocious puberty (pp). In most patients regression of secondary sex characteristics and deceleration of skeletal maturation can be achieved with 1oo mg/m^2 daily in 3 or 4 doses. Occasional therapeutic failures have been attributed to irregular administration or temporary malabsorption of the drug. For the evaluation of CA efficacy and the control of therapy knowledge about CA plasma concentrations is required. Therefore, a specific RIA for CA was developed[++]. The assay is done using diluted plasma (sensitivity: 10ng/ml; accuracy: 98%; intra- and interassay coefficients of variation: 5 and 1o%). There are no significant crossreactions with adrenal or gonadal steroids. CA-kinetics were investigated in 4 adult male volunteers after short- and longterm administration. After a single 25 or 5o mg oral dose CA plasma concentration rose quickly, reaching peak levels (17o-32o ng/ml) after 2-4 hrs. During one week of treatment with 25 mg CA 3 (I) or 4 times (II) per day the 8 o'clock plasma concentrations gradually attained levels of 25o (I) and 45o (II) ng/ml At this time the diurnal variations measured at 2 hr intervals ranged between 21o and 315 ng/ml (I) or 43o and 56o ng/ml (II). Plasma testosterone was reduced below 2 ng/ml in both. Studies in children with pp will have to find out the minimal CA plasma levels that guarantee permanent suppression of clinical symptoms.

++ B.NIEUWEBOER, in preparation.

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Inhibition of normal male sex differentiation in male offspring of rabbits actively immunized against testosterone (T) before pregnancy.

Mature female rabbits immunized with T-3-BSA developed highly specific antisera against T. Animals with the highest antibody titres revealed elevated plasma T-levels up to 2 000 ng/dl (normal: 15 ng/dl). Nevertheless, mating was successful and pregnancy uncomplicated. Immediately after normal delivery, the newborns were bled and fixed in Bouin's solution. In all neonatal plasma samples high concentrations of antibodies against T were found with identical characteristics as in the maternal plasma. T-levels were excessively elevated: up to 2 500 ng/dl in females and up to 25 000 ng/dl in males (normal: 20 ng/dl). Histological examination, however, revealed normal sex differentiation in the females, but inhibited male sex differentiation in the males: partial retrogression of Wolffian duct derivatives, absence of prostatic glands, feminized phallus with reduced corpus fibrosum, and marked hypospadias; testicular differentiation was normal, Müllerian ducts were absent. Our experiments indicate that hormones essential for normal fetal development can be neutralized in the fetus by their respective antibodies raised in the mother.

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Serum androgen levels and in vitro metabolism of 4-androstene-3,17-dione in skin from boys with hypospadias.
Hypospadias is an expression of a defective masculinization of the male fetus. Ethiological factors may include impaired synthesis of androgenic hormones, or unresponsiveness of the target organs. 5α-reductase deficienty leading to a relative lack of 5α-dihydrotestosterone has been suggested to be the cause of some forms of hypospadias. Skin biopsies were taken from the prepuce, axilla and arm during operation for hypospadias or phimosis(controls). Serum levels of LH, FSH and steroid hormones were measured by radioimmunoassay after chromatography of the steroids. The in vitro metabolism of 4(1, 2-^{3}H)-androstene-3,17-dione by skin from the different locations obtained from 10 controls and 12 boys with hypospadias, age 1-6 years, was investigated. No difference in 5α-reductase activity was found between hypospadias and controls. Hypospadic boys in age group 10-14 years showed higher LH-levels, and in age group 1-14 years lower 5α-dihydrotestosterone levels in blood compaired to controls. No differences were found in the concentration of testosterone, 4-androstene-3,17-dione, estradiol, FSH or testosterone binding globulin. These findings may indicate that some boys with hypospadias have impaired responsiveness to gonadotrophin. This needs confirmation in a larger series of adult men with hypospadias.

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PRENATAL LH-DEFICIENCY AS POSSIBLE CAUSE OF MALE PSEUDOHERMAPHRODITISM, HYPOSPADIAS, HYPOGENITALISM AND CRYPTORCHIDISM.

Some boys with gonadotropin (Gn) deficiency have hypogenitalism (very small penis). In some patients with cryptorchidism LHRH stimulated LH is low while FSH is high or normal (our experience and Canlorbe et al. 1974). The following two observations suggest that fetal LH is not only important for genital growth and testicular descent, but also for genital differentiation. Patient 1 is a girl aged 10 with ambiguous genitalia, XY karyotype, inguinal testes and no pregnantriol and testosterone response to HCG. LHRH stimulated LH was low and remained low 1 week and 6 months after bilateral castration while FSH increased to very high levels as seen in agonadal subjects. Patient 2 is a male adolescent with mild hypospadias, bilateral cryptorchidism, XY karyotype and Gn deficiency with anosmia (Kallmann syndrome). - In the male rabbit, fetal Gn deficiency produced by decapitation prior to or during genital differentiation results in female genitalia or hypospadias (Jost 1951). So far it has been assumed that in the human fetus, testosterone secreted by the Leydig cells and responsible for the differentiation of the male genitalia is not controlled by the fetal Gn as in the rabbit but rather by HCG, and that the fetal Gn take over their control of testicular function only after the period of genital differentiation. The experience presented here suggests that this concept may be wrong and that prenatal hypothalamo-pituitary disorders with LH deficiency may cause male pseudohermaphroditism, hypospadias, hypogenitalism and cryptorchidism, depending on the severity and timing of the deficiency.

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Impaired interauterine gonadotropin secretion as an etiological component of cryptorchidism.

In the electronmicroscope, atrophy of the Leydig cells was a predominant feature of 14 biopsies of cryptorchial testes from infants operated before the age of 12 months. In order to elucidate the pathogenesis leading to this atrophy mice were injected on the 14th day of pregnancy with 5 mg oestradiol. This resulted in cryptorchidism of the fetus and an atrophy of the Leydig cells similar to that observed in children with undescended testes in the first year of life. Weight and testosterone content of the testes was compared between treated and untreated mice on the 1st day after delivery and 7 and 14 months later. The mean testosterone content in newborn controls was 0.20 ng/testis, as compared to 0.13 ng/testis in treated animals. Similarily in animals treated, 7 and 14 months after birth the mean testosterone concentration was diminished 19 ng/testis (control 72,5 ng/testis). Thus a permanent impairment of Leydig cell function suggests disturbance in the gonadotropin system. Simultaneous administration of HCG and oestrogen at the 14th day of pregnancy prevented atrophy of Leydig cells in newborn animals. If impaired intrauterine gonadotropin secretion proves to be the main cause of cryptorchidism, a prologued treatment could favourably affect the testicular function.