We have studied six infants and young children with hyperthyroidism whose clinical course differs from the few reports of others. Neonatal and early childhood hyperthyroidism are usually thought of as separate, rare, and transient disorders seldom requiring long term treatment. 1) Our cases have not been transient: 2) they have occurred in families with a high incidence of adult Graves disease.

Four were born with Graves disease. Three continue to be hyperthyroid at ages 1, 5, and 6 years. Two developed Graves disease at ages 3 and 8 years and continue on anti-thyroid medication. Graves disease occurred in five of the six mothers and was apparent during gestation in four. The sixth mother, mother of a neonatal case, has never had overt Graves disease, but female members of four generations have had Graves disease. In all six kindreds there was a direct maternal line of affected patients for two or more generations.

Selected families were studied for the presence of latent thyroid disease using measurements of thyroid hormonal iodine. Some were screened for thyroid markers: PTC tasting and circulating thyroid antibodies. A rare unsuspected case was detected, but no thyroid marker pattern developed.

The occurrence of Graves disease in the very young in families with a high incidence of Graves disease suggests a hereditary factor. No goitrogens or use of medications were common to the families. We suggest that there is biologic unity between neonatal, early childhood and adult Graves disease. This unity is best explained by the presence of an autosomal dominant determinant with a predilection for the female.

Inhibition of masculine differentiation in male rat fetuses by two candidates for active-site-directed-irreversible (ASDI) inhibitors of 17α hydroxylase and C_{17-20} lyase. ALLEN S. GOLDMAN. *Children's Hosp. of Philadelphia, Philadelphia, Pa.*

ASDI inhibitors stoichiometrically bind to enzyme active-sites, have a high degree of "lock and key" specificity, cannot be removed from the active site by dilution and should have few side effects. Two synthetic steroids selected as ASDI candidates, 17β -ureidoandrosta-1,4-dien-3-one and 16β -bromo- 5α -pregnan- 3β , 17α -diol-11,20-dione were found to inhibit the conversion of pregnenolone or progesterone to testosterone by adult rat testicular microsomes specifically at the level of both 17α hydroxylase and C_{17-20} lyase. When administered to pregnant rats at 30mg/kg daily from day 13 to day 21 each inhibitor significantly blocked penis formation in male offspring by reducing anogenital distance from 3.69 ± 0.24 mm. (control) to 3.26 ± 0.22 (17β -ureide) and 3.32 ± 0.23 mm. (16β -bromide). Testosterone production in vitro by experimental testes was only 25% of that of controls with either pregnenolone or progesterone as substrates. Abnormal accumulations of progesterone and 17-hydroxyprogesterone were present in incubations of experimental testes. Female fetuses and maternal and fetal adrenal size and steroid synthesis were unaffected. Each inhibitor obliterated C_{19} steroid excretion in urines and feces of adult female rats as analyzed by gas-liquid chromatography and mass spectrometry. Thus, these inhibitors appear to block sex hormone without affecting glucocorticoid synthesis in adult and fetal rats.

Rapid diagnosis of congenital adrenal hyperplasia (CAH) by plasma steroid determinations. ROBERT C. FRANKS. *Univ. of Texas Med. Sch. at San Antonio, San Antonio, Tex.* (Intr. by Michael J. Sweeney).

A semi-quantitative method for steroid determinations in a 0.5

ml plasma sample has been evaluated for the rapid (4-6 hr) diagnosis of CAH. Pet ether, benzene and methylene chloride extracts of plasma are quantitated by competitive protein binding using 17-hydroxyprogesterone (17-OHP), 11-deoxycortisol (cmpd S), and cortisol standards, respectively, for comparison. The observed plasma steroid concentrations are expressed as a ratio of "17-OHP" + "cmpd S" to "cortisol" since comparison of ratios, rather than absolute values, has been found to differentiate normals from patients more clearly.

Plasma samples have been obtained from six normal children aged 4 days-7 yrs following administration of ACTH, from six adults with 11-hydroxylation impaired by the administration of metyrapone, and from three children aged 11 mos, 6 yrs and 8 years with CAH due to deficient 21-hydroxylation (five samples). The ratios of "17-OHP" + "cmpd S" to "cortisol" for the respective groups have been determined:

	Range	Mean	1SD
Normals after ACTH	0.15-0.25	0.20	0.03
Normals after metyrapone	1.30-3.20	2.04	0.67
CAH	2.13-6.36	3.66	1.60

These preliminary results suggest usefulness of the procedure for rapidly ascertaining the presence or absence of the common variants of CAH, although further data from both normals and patients will be required for confirmation.

Urinary steroidal patterns in the adrenogenital syndrome. ALFRED M. BONGIOVANNI, WALTER R. EBERLIN, THOMAS MOSHANG, and HERBERT L. VALLET. *Univ. of Pennsylvania and Children's Hosp. of Philadelphia, Pa.*

The urinary steroidal pattern was reviewed in 7 cases of 21-hydroxylase deficiency (21-H) and 3 of 3β -hydroxysteroid dehydrogenase deficiency (3β -D). These were compared with 3 normals and 1 adrenal tumor of similar age. Pregnanetriol not only predominates in the urine of those with 21-H deficiency over Δ^5 -pregnene- 3β , 17α , 21α -triol but in no instance did the latter substance exceed 0.9 mg./day and the ratio was 50:1 or greater. In 3β -D deficiency although pregnanetriol was found in each (in one case 34.6 mg./day) there was great elevation of pregnanetriol and the ratio was 2:1 or less. In one experiment 17-hydroxypregnenolone administered to a normal volunteer was converted exclusively into pregnanetriol. It is proposed that in 3β -D deficiency there may be peripheral conversion to pregnanetriol and careful measurement of these two triols can differentiate the two conditions. In addition pregnanetriolone was not found in 3β -D deficiency but was present in the 21-H deficiency and several steroids present in and peculiar to 3β -D deficiency were not found in 21-H deficiency. Gas chromatography was employed in these studies. The earlier hypothesis from this laboratory that pregnanetriol in 3β -D deficiency might represent a double defect no longer appears valid. (Drs. Maria I. New and Frederic M. Kenny kindly supplied specimens from 2 established cases)

Familial primary aldosteronism with delayed glucocorticoid responsiveness: A new syndrome? G. S. GIEBINK, R. W. GOTLIN, F. H. KATZ, and E. G. BIGLIERI (Intr. by H. K. Silver). *Univ. of Colo. Med. Ctr., VAH, Denver, Colo. and U. of Calif., San Francisco, Calif.*

Two brothers, ages 7 and 9, with systolic and diastolic hyper-

tension; normal growth; absence of virilism; hypokalemic alkalosis; elevated urinary aldosterone (UA), tetrahydroaldosterone (THA), tetrahydrocorticosterone; low plasma renin activity (PRA); and high plasma aldosterone (PA) were studied. Mild elevation of urinary 17-ketosteroids (KS) and marked elevation of 17-ketogenic steroids (KGS) was noted intermittently in both boys. Plasma cortisol (F) was low-normal in the older and normal in the younger subject. Spironolactone in the younger corrected the hypokalemic alkalosis without lowering the BP. Dexamethasone therapy, 8 mg/day for one week, also corrected the hypokalemia and lowered the BP within the first week in both subjects; correction has been sustained for four months with prednisone, 5 mg/day in the older and 2.5 mg/day in the younger subject. THA remained elevated but PRA became normal during the first 2 weeks of treatment. THA and UA fell to normal levels and F was suppressed by the fourth week, but KS and KGS remained intermittently elevated. The unique features in these cases are: a.) occurrence in male siblings; b.) lack of biochemical data supporting a complete or partial 11, 17, or 21-hydroxylase deficiency; c.) rapid fall in BP elevation and rapid correction of PRA and PA abnormalities with large doses of glucocorticoids; d.) delayed fall of THA excretion and e.) persistent elevation of KGS and KS. The findings of a generalized adrenocortical hyperactivity not totally suppressed by glucocorticoid therapy are consistent with adrenocortical adenomata.

FSH induction of sensitivity to LH: One mechanism for control of puberty. WILLIAM D. ODELL, RONALD S. SWERDLOFF, and HOWARD S. JACOBS. *UCLA Sch. of Medicine, Harbor Gen. Hosp., Torrance, Calif.*

It is postulated that the immature hypothalamic-pituitary unit is more sensitive to inhibition by gonadal steroids and that sexual maturation results from a decrease in this sensitivity. However, we have reported separately that in the male rat there is no difference in threshold dose of testosterone for feedback inhibition of LH and FSH at the time of sexual maturation. We now wish to report data in the female rat which provides a possible alternate explanation for puberty. These data indicate that the immature ovary is insensitive to LH stimulation and that this sensitivity is restored by FSH treatment. Hypothalamic-pituitary sensitivity to feedback suppression was tested as in the male. To study ovarian sensitivity to gonadotropin stimulation, immature (21 days) and mature (87 days) females were hypophysectomized. Five days later graded doses of LH (NIH-P7) were administered. Since only LH was administered, specificity of response was not important. Uterine weight increased in mature animals by all doses over 5 $\mu\text{g}/100$ grams body weight, but was unaffected by doses as large as 2000 $\mu\text{g}/100$ grams body weight in immatures. Sensitivity to LH in immatures could be made equal to matures by pre-treatment with FSH. When a constant dose of LH was administered with graded doses of FSH, a dose response to the LH effects was observed. The threshold dose of FSH for ovarian weight increase was similar in matures and immatures and uterine sensitivity to estrogen also was similar. Thus in the female rat FSH induces LH responsiveness of the gonad which in turn results in sexual maturation.

The pituitary-gonadal axis in the female child during infancy and at puberty. JEREMY S. D. WINTER and CHARLES FAIMAN. *Univ. of Manitoba and Children's Hosp. of Winnipeg, Manitoba, Canada.* (Intr. by James C. Haworth).

Serum FSH and LH (radioimmunoassay), estradiol (radioim-

munoassay), and testosterone (competitive protein-binding) were studied in 120 healthy females aged 0-20 years, and correlated with physical development. Prepubertal girls (4-9 years) showed low levels of FSH (6-12 μg LER-907%), LH (0.5-2.5 $\mu\text{g}\%$), estradiol (<1 ng%) and testosterone (<20 ng%). Puberty (thelarche and pubarche) was accompanied by a rise in all these variables, reaching adult levels by age 14-16. The earliest hormonal change (age 9-11) was a rise in serum FSH, together with estradiol and testosterone; serum LH rose later (around age 12). These data resemble our previous findings in males. In 0-2 year old females, serum FSH (8-40 $\mu\text{g}\%$) and LH (1.3-3.0 $\mu\text{g}\%$) levels were higher than those in male infants (FSH 4-10 $\mu\text{g}\%$, $p < .01$; LH 0.5-2.0 $\mu\text{g}\%$, $p < .01$). Female FSH and LH levels diminished from age 0-8 years, while in boys these values increased slightly during this time. Estradiol and testosterone levels were not elevated in infancy. Serial determinations of FSH and LH in infant chimpanzees demonstrated similar constant low values (FSH 5-9 $\mu\text{g}\%$, LH 2.2-3.1 $\mu\text{g}\%$ in males; female chimps had higher values (FSH 13-40 $\mu\text{g}\%$, LH 2.2-6.1 $\mu\text{g}\%$). Moreover the females showed day-to-day cyclicality of varying amplitude (with 6-14 day periodicity). This sex difference in hypothalamo-pituitary function in infancy possibly represents an effect of differing intra-uterine exposure to endogenous androgen. This is the first demonstration of an endocrine sex difference in primates prior to puberty.

INFECTIOUS DISEASE

Acquisition of type-specific antibodies following exposure to *Hemophilus influenzae* b meningitis. G. PETER, S. GREENFIELD, V. M. HOWIE, and D. H. SMITH. *Children's Hosp. Med. Ctr. and Beth Israel Hosp., Boston, Mass.*

Type-specific antibodies (Ab) to *Hemophilus influenzae*, b (H. i.) are believed to confer protection against invasive infections by this organism. The rising incidence of Ab with age is generally cited to explain the decreasing incidence of H. i., b infections after age 3 yrs., but the antigenic experience responsible for eliciting Ab has not been defined. To investigate this question the incidence of hemagglutinating and bactericidal Ab among 4 groups of children was examined. (1) In a Day Care Center in which a 2 yr. old girl developed H. i., b meningitis, 7 of 8 of her classmates demonstrated markedly elevated Ab titers. H. i., b was cultured from the nasopharynx of only 3 of the 8 and this carriage was transient in 2 of 3 cases. In contrast, Ab titers were observed in (2) only 5 of 28 control children (2-4 yrs. old); (3) only 2 of 7 children with culture proven H. i., b otitis media; and (4) only 5 of 17 children (<4 yrs. old) hospitalized with H. i., b meningitis, epiglottitis, or arthritis. These data suggest that acquisition of type-specific antibodies correlates more closely with intense exposure to H. i., infection than with clinically significant *Hemophilus influenzae* infection.

Studies of children with natural infections with *H. influenzae* antibacterial serological test vs. type B. SARAH H. SELL and RICHARD B. JOHNSTON, JR. (Intr. by David T. Karzon). *Vanderbilt Univ. Sch. of Med., Nashville, Tenn., and Univ. of Ala., Birmingham, Ala.*

Polyribose phosphate (PRP) antigen from *H. influenzae*, type b, is available for clinical trials for prevention of serious infections, such as septicemia and meningitis. It is therefore critical to document bacteriological and serological events in natural infections. 20 normal children were followed from birth through 5 years