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 explanations 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 μg/100 grams body weight, but was unaffected by doses as large as 2000 μg/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 (radioimmunoassay), 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 μg%), 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 μg%) and LH (1.3–3.0 μg%) levels were higher than those in male infants (FSH 4–10 μg%, $p < .01$; LH 0.5–2.0 μg%, $p < .01$). 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 μg%, LH 2.2–3.1 μg%) in males; female chimps had higher values (FSH 13–40 μg%, LH 2.2–6.1 μg%). Moreover the females showed day-to-day cyclicity 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

with periodic clinical examinations, nasopharyngeal cultures for *H. influenzae* and serum samples. *H. influenzae* strains were isolated from all at some time during the study; while 8 had type b, usually associated with clinical illness. One child had meningitis at 40 months; bacterial inhibitory substance (BIS) was present only during and immediately after the acute illness. Serum from 5 other patients had BIS within 3–4 weeks; in 2, BIS was temporary while in 3 it persisted until age 5. 11 other children had temporary BIS, 7 associated with nontype b strains and 4 without any relationship to isolations of *H. influenzae*. 18/20 of the children had BIS at some time, but it persisted until age 5 in 7/20.

Cord blood serum from 6/20 showed BIS which was lost by age 2 years in all but 2 patients.

The inhibitory effect was entirely removed from serum by adsorption with heavily encapsulated bacterial cells and partially removed by adsorption with PRP.

An increase in opsonizing antibody to type b was noted also in association with *H. influenzae* strains.

Response of children immunized with meningococcal group C and group A polysaccharides. MARTHA L. LEPOW, IRVING GOLDSCHNEIDER, and EMIL C. GOTSCHLICH. *Univ. of Connecticut Sch. of Med. Hartford, Conn., and Rockefeller Univ., N. Y., N. Y.*

To date 60 children ages 1 to 9 years have been immunized with 25 or 50 micrograms of highly purified meningococcal group-specific polysaccharide. Thirty children received the group C antigen and 30 the group A antigen by subcutaneous injection. Three immunized children developed local zones of transient erythema up to 1.8 cm. in diameter within 24 hours of injection. There were no local or systemic reactions.

Humoral antibodies were measured by bactericidal, immunofluorescence, hemagglutination and quantitative radioimmunoprecipitation assays. Complete antibody studies on 50 of the children showed that all responded within 3 weeks of immunization with the production of specific IgG, IgM and IgA antibodies against the C or A antigen in amounts comparable to those produced by immunized adults. Bactericidal and hemagglutinating antibodies were demonstrated. There was no advantage of the 50 microgram dose over the 25 microgram dose.

Previous studies with the meningococcal group C antigen in more than 40,000 military recruits has established the effectiveness of this immunization in preventing systemic meningococcal disease. On the basis of results of the current study, it appears that immunization of children with the meningococcal group A and C vaccines would be safe and immunologically efficacious in the age group tested.

Altered reactivity to respiratory syncytial virus: Description of atypical RSV illness and prospective four year follow-up of children previously immunized with an inactivated vaccine. JERRY J. ELLER, VINCENT A. FULGINITI, DANIEL C. PLUNKET, and OTTO F. SIEBER, JR. *U.S. Army Med. Research and Nutrition Lab., and Univ. of Colo. Med. Ctr., Denver, Colo.* (Intr. by Henry Kempe).

Beginning in July 1966, 424 children ranging from 6 months to 7 years of age were immunized. Mild RSV illness was documented to occur later upon natural exposure to the wild virus in all age groups. Nineteen children in the youngest age group immunized (6–23 mos) were hospitalized with an atypical illness due to RSV. Eleven were hospitalized in 1966–67, 6 in 1967–68, and 2 in 1968–69. Two children had recurrent atypical illness during separate years. The illness was characterized by high fever and pneumonia with marked bronchiolitic wheezing. Chest films showed prominent multi-segmental infiltrates usually in several lobes. Associated lung complications included: lobar atelectasis, pneumothorax, pneumomediastinum, pneumopericardium, subcutaneous emphysema, and pleural effusions. A diffuse maculopapular rash was present on the neck, trunk and proximal extremities of 8 (42%) vaccinees in contrast to 1 of 31 (3.2%) controls with hospitalized RSV illness ($\bar{X}^2 = 9.57$, $p < 0.01$). Of 9 hospitalized vaccinees available for prospective follow-up for 4 years from the time of immunization, 5 (55.6%) were diagnosed by allergists, independently of the investigators, as having either asthma (4) or allergic rhinitis (1). This was in contrast to a diagnosis of an atopic disorder made in 7 of 46 (15.2%) age-matched controls prospectively followed ($\bar{X}_c^2 = 5.01$, $p < 0.10$).

Studies on immunization with three types of combined viral vaccines. ROBERT E. WEIBEL, JOSEPH STOKES, JR., VICTOR M. VILLAREJOS, JORGE A. ARGUEDAS G, EUGENE B. BUYNAK, and MAURICE R. HILLEMAN. *Sch. of Med., Univ. of Pennsylvania, Philadelphia, Pa., Louisiana State Univ., International Ctr. for Med. Res. and Training, San Jose, Costa Rica, and Merck Inst. for Therapeutic Res., West Point, Pa.*

Combined lyophilized Moraten measles, Jeryl Lynn mumps, and HPV 77 duck rubella vaccines were administered by a single injection to 715 children ages 7 months to 7 years, and susceptible to these viruses. The geometric mean antibody responses to the triple vaccine were comparable to those obtained with monovalent vaccines. The antibody seroconversion rate was 96% to measles by hemagglutination-inhibition tests, 95% to mumps neutralization tests and 94% to rubella hemagglutination-inhibition tests. Clinical reactions to the triple vaccine were no greater than those following measles vaccine given alone. Arthralgia and arthritis were not reported during the 28 day recording period. In children combined measles-mumps-rubella vaccine provides a *safe, simple* and economical means of immunizing against these three diseases. Similar findings were obtained in tests in 375 seronegative children given combined measles-rubella vaccine and in 415 seronegative children given combined mumps-rubella vaccine.

Persistent joint symptoms associated with HPV-77DK12 rubella vaccine. SPOTSWOOD L. SPRUANCE, LAWRENCE E. KLOCK, JR., and CHARLES B. SMITH. *Univ of Utah Sch. of Med., Univ. of Utah Med. Ctr., Salt Lake City, Utah* (Intr. by Lowell Glasgow).

The incidence and duration of joint complications were investigated in 2989 children who received the HPV-77DK12 rubella vaccine. Two hundred eighty-seven (287) children experienced joint symptoms within 45 days after vaccination. Two hundred twenty-five (225) of these children were contacted 6 months later and three were found to have had recurrences of symptoms.

Histories, physical examinations, and serologic studies were conducted on 11 children, including three from the study group, who manifested recurrent joint symptoms 6–9 months after receiving the dog kidney rubella vaccine. In all cases the original and the recurrent symptoms were in the knees. Symptomatic episodes were 1–4 days in duration and were characterized by pain and limitation of knee extension. On examination of the knees, abnormalities were observed in 5 children. These included limi-