Staff Meeting Bulletin
Hospitals of the » » »
University of Minnesota

Congenital Hyperplasia of the Adrenals

Volume XV | Friday, October 8, 1943 | Number 2

STAFF MEETING BULLETIN
HOSPITALS OF THE . . .
UNIVERSITY OF MINNESOTA

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INDEX

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William A. O'Brien, M.D.

I. LAST WEEK

Date: October 1, 1943

Place: Recreation Room
Powell Hall

Time: 12:15 to 12:45 p.m.

Program: Hospitals' Report
1941 - 1943
R. M. Amberg

Movie: "Yellow Fever Control"

Attendance: 73

Alice Carlson,
Record Librarian

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II. MEETINGS

1. ANATOMY SEMINAR

Saturday, October 9, 1943, 11:30 a.m.
Room 226, Institute of Anatomy.

"Effect of Retrograde Degeneration of Neuroactivity"

Berry Campbell

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2. THE MINNESOTA PATHOLOGICAL SOCIETY

University of Minnesota Medical School
Medical Science Amphitheatre

Tuesday, October 19, 1943, 8:00 p.m.

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"Malaria"

Dr. L. T. Coggeshall
Ann Arbor, Michigan

Annual Address

- - -

III. ANNOUNCEMENTS

1. WAR CHEST

The Powell Hall nursing students are selling carnival tickets for their war chest effort. The funds will go to:

World Student Service Fund
Twin City Community Chest
U.S.O.
China Relief
Russian Relief
Army-Navy Relief
S.W.E.C.C. (Student War Effort Cooperative Committee)
Campus Red Cross Activities
War Discussion Group
Student Speakers' Bureau
First Aid Training
Foreign Student Fund
Christian Fellowship League

The local campus goal is $4,000. The carnival tickets cost $0.25. The carnival will be held October 16, at 8:00 p.m. The Navy Dance Band will play for dancing. Please help our students to achieve their goal.

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IV. MINNEAPOLIS SURGICAL SOCIETY

Minneapolis Surgical Society met Thursday, October 7, 8:00 p.m. in Hennepin County Club Rooms. Program: "Injuries of the Urinary Tract" by Theodore Sweetser. Discussion by W. D. White. "Parathyroid Tumors," by Carl Rice, discussion, Martin Nordland. "Soap and Water Preparation of Lacerated Wounds" by Roscoe Webb.

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V. JOHN B. AND MARY R. MARKLE FOUNDATION LECTURE

Tuesday, October 19, 2:00 p.m., Medical Sciences Amphitheatre.

"Tropical Medicine"
Major General James C. Magee

Note: Same Date as Pathology Lecture.

VI. CONGENITAL HYPERPLASIA OF THE ADRENALS

T. E. Bratrud
Willis H. Thompson

This report presents 6 cases of congenital hyperplasia of the adrenals occurring in new born and older infants together with a 7th probable case, that of an adult female external pseudohermaphrodite in whom a carcinoma of the hyperplastic adrenal cortex developed. The pertinent literature and reports are reviewed.

The pathogenesis of congenital adrenal hyperplasia is of interest since the hyperplasia begins early in embryonic life, probably as early as the 9th or 10th week of development.[11] An androgenic phase of development of the adrenals has been noted in the normally developing embryo by Broster and Vines, Sudis and others.[11,93] This phase is well seen in the adrenals of the male embryo from the 9th to the 18th week of development and in the female embryo from the 11th to the 15th week. During this period the developing adrenal cortex exhibits a strongly positive Ponceau-Fuchsin staining reaction which is said to indicate androgen secretory activity on the part of these cells. Normally this androgenic phase disappears to return as a sparsely scattered and irregular staining reaction in the adrenal cortex in about 25% of adults. This staining reaction is seen in microsections of adrenals fixed in bichromate solutions and stained with one of the various acid fuchsin stains such as Ponceau Fuchsin, Masson Trichrome or Acid Fuchsin. It appears in the form of brilliantly red staining granules in the cytoplasm of the cortical cells, often in the form of large coalescent masses of fuchsinophilic material which may fill the cytoplasm of the cells. In cases of adrenal hyperplasia this staining reaction remains markedly positive and correlates with histologic and gross evidence of marked hyperplasia of the adrenal cortex together with endocrinologic changes and marked increase in the urinary excretion of androgenic substances such as the 17-ketosteroids. The disease appears to be one of persistence of "androgenic phase" accompanied by extreme hyperplasia of androgenic secreting cells which grow so extensively as to cause marked enlargement of the adrenals and complete replacement of the cortex. The excessive elaboration of androgens brings about an abnormal embryologic development of the female generative organs (female external pseudohermaphroditism). In males no abnormalities are present at birth but puberty praecox develops at an early age together with macrogenitosomia and marked changes in skeletal and muscular development. These latter changes also occur in the females and make their appearance at a similarly early age. Their development is such as to render females more and more male-like in body form and secondary sex characters. A third possibility occurs in either male or female, namely, adrenocortical insufficiency or Addison's disease. This may be present at birth or develop in infancy or childhood. This syndrome is one of insufficiency of the adrenal cortex produced by a crowding out of the normal electrolyte regulating hormone (or cortical hormone) secreting cells by the androgenic cells making up the hyperplasia.

CLINICAL FEATURES OF CONGENITAL ADRENAL HYPERPLASIA

1. Macrogenitosomia and precocious puberty.

In the male there is usually little or no evident change at birth. Within a few months macrogenitosomia signs appear and precocious puberty starts to develop. External genitals undergo enlargement, particularly the penis, and pubic hair appears. The child shows signs of precocious skeletal and muscular development with accelerated ossification of bones. At a few years of age the external genitals may be of the usual puberty type or even those of an adult. Pubic hair is abundant and generally there is an adult, male-type distribution. The body may be of the "Infantile Hercules" type with marked muscular development. The larynx is enlarged and the voice is deep. The

epiphyses may be closed by the time of usual puberty. The body is then dwarfed in height, though markedly muscular.

2. Female External Pseudohermaphroditism.

The classification of Creevy[105] is utilized. (The sex stated is determined by the gonas, external or internal denoting the genitals differing in sexual character from the gonad).

The abnormalities are present at birth and the child is more frequently called male than female because of the presence of a phallus and scrotum. The phallus is ventrally curved and hypospadic. The scrotum is cryptorchid and consists of lateral masses with a deep median cleft. A penoscrotal, hypospadias is present, this being the orifice of the urogenital sinus. Macrogenitosomia precox appears with the child developing more and more like a male. Hair distribution, voice, skeletal-muscular systems, and genitals develop similarly to those in group 1. The phallus remains ventrally curved though enlarged and resembles a small penis. In adulthood the patient appears completely masculine and has a deep voice and a large larynx, a heavy beard and mustache. The body development is markedly masculine and may be of the "Hercules Type."

3. Adrenocortical Insufficiency or Addison's disease.

The child may be a female external pseudohermaphrodite and, if so, an aid in the diagnosis is present. The common clinical picture is one of poor nursing, regurgitation of feedings, diarrhea and dehydration shortly after birth. The dehydration is accompanied by a fall in serum sodium concentration and a rise in serum potassium. The picture is often like that of congenital pyloric stenosis and surgical exploration was done on a number of the cases in the literature. The neonatal weight loss is excessive and progressive. Vomiting and diarrhea continue. The dehydration may be rapidly progressive and terminate in profound hemoconcentration and death in from a few days to a few months after birth. Fever is frequently present.

If the child survives for a period of several months there may be a progressive pigmentation of the skin over the entire body, often first noticed in the areolae. Profound reaction may occur to infection, of even the mildest sort, such as vaccination.

Hormonal Alterations

Urinary assay of androgens reveals increased amounts of 17-ketosteroids in the urine, often the levels being high. Talbot et al[94] report the total 17-ketosteroids to be elevated in hyperplasia as they also are in adrenocortical carcinoma. However, fractional determinations of the aopha and beta, alcoholic and non-alcoholic 17-ketosteroids differentiates cases of carcinoma from hyperplasia in their experience. Chiefly the beta forms are greatly increased in cases of adrenocortical carcinoma, whereas they are normal or slightly elevated in cases of hyperplasia.

Young, Broster and Vines, Talbot, Wilkins, Thelander, Butler, Cahill and a number of others have reported increased urinary excretion of androgens in cases of hyperplasia or carcinoma of the adrenals. Genetis and Bronstein and several others have reported increased urinary outputs of pregnandiol glucuronidate in cases of hyperplasia. There are several reports of extraction of hyperplastic adrenals or adrenal carcinomas for androgens, in which increased amounts were found in the tissue. Dehydroisoandrosterone is reported by some authors as being the substance composing up to 70% of the active hormonal substances present in the ruine in cases of adrenocortical carcinoma. In one of our cases, Samuels has isolated some androgenic substances of the 3-ketosteroid group from our extract of the adrenal tissue.

These 3 possible syndromes of the disease overlap and occur concurrently making the clinical picture difficult as to diagnosis. With this in mind the following cases are presented, each of which exhibits one or more of the 3 syndromes.

CASE REPORTS

Case 1.

Full term infant of normal parents, age 26 and 27, birth weight 7 pounds 11 ounces. One sibling - 28 months - was well. Shortly after birth exhibited mental lethargy, nursed poorly and regurgitated part of the feedings but was sent home at 10 days. She remained a feeding problem, became more lethargic, nursed poorly, had a poor appetite, exhibited diarrhea, vomiting, dehydration and purplish discoloration of the skin. After 4 days she was returned to the hospital in a state of near-coma with profound dehydration and hemoconcentration. Hemoglobin was 150% and blood urea nitrogen 80 mg.%. For 4 weeks she was given fluids parontorally in addition to regular feedings. Weight loss, poor appetite and difficulty in feeding continued until the child weighed 6 pounds 5 ounces. When given saline hypodermoclysis improvement was noted. Pitressin given intramuscularly and nasally afforded no benefit. Desoxycorticosterone acetate in a dosage of 0.5 cc. produced a weight gain of 1 pound 4 ounces in 4 days, mental alertness, improved feeding and progressive decrease in regurgitation. Brownish pigmentation of the skin developed soon after birth and after a pertussis inoculation vomiting developed which continued for a week, together with rapid evacuation of food in the stools when feedings were forced. From 36 days of age on she was given 2-5mg. of cortate i.m. daily with salt water 2 hours before meals. On the 66th day of life the hemoglobin was 90%. Advanced ossification of the bones, rapid body growth, progressive enlargement of a penis-like phallus and marked muscular development appeared. Urinary androgen output was increased and features of progressive Addison's disease appeared, with brownish pigmentation of the skin, relapse on withdrawal of cortate and severe reaction to infection or vaccination.

The child was admitted to the University Hospitals at age of 6 months, because of an upper respiratory infection of 1 week's duration. Weight was 8540 gm., length 68 cm., head circumference 43 cm. and chest 43.5 cm. The child was well developed and muscular, of good body turgor but presented a generalized brownish pigmentation of the skin. The genitalia externally consisted of a large penis-like phallus, possessing a penoscrotal hypospadias ventrally as well as a urethral orifice at the urinary meatus, and a bifid cryptorchid scrotum, having prominent lateral masses and a deep median raphe. The laboratory studies without withdrawing cortin therapy revealed the blood counts, hemoglobin, urinalysis are essentially normal with normal chloride, sodium, and potassium, and glucose tolerance tests. Urinary androgen excretion was 2.61 mg/24 hrs and estrogens 0.238 mg./24 hrs. X-rays of the wrists revealed evidence of advanced ossification with well developed carpal centers, possessing 2 centers of ossification, presence of the distal radial epiphysis, early signs of the distal ulnar epiphysis and appearance of the phalangeal and metacarpal epiphyses. Four centers were also present in the tarsa. Convalescence was uneventful, and the child was sent home.

The next admission was at another hospital on 10/17/42 at 18 months of age. Restlessness and vomiting had appeared the evening before, followed by accelerated wheezing respirations at midnight. Examination disclosed consolidation of the right lower lobe. Dyspnea became marked and the respirations gradually increased. The white cell count was 23,000 and the temperature 99. Type 4 pneumococcus was isolated from the sputum and x-ray of the chest revealed biateral bronchopneumonia. The pneumonia progressed rapidly in spite of sulfonamide therapy, cyanosis developing at noon, a rapid, weak pulse appearing at 8 p.m. and becoming imperceptible at 11 p.m. The temperature was elevated to 106 degrees and the child expired at 1 a.m. on 10/18/42.

Autopsy was performed on 10/18/42 approximately 12 hours after death. The body was that of an unusually well developed, well nourished, white, male-appearing child measuring 33.75 inches in length and weighing approximately 30 pounds. The musculature was unusually well developed, the body being of the "infantile hercules" type. The skin

presented a bronzed pigmentation over the entire body, not unlike the appearance of a deep sun tan. More deeply pigmented areas were present over the axillae, perineum and groin. The pubic hair was black, coarse in texture and measured 2 inches in length, short, brown hair being present over the legs and forearms. The musculature of the pectoral and pelvic girdles, thighs, calves, arms and forearms were well developed and prominent.

The external genitals consisted of a rather large phallus, 2.5 x 2 x 3 cm. in size, having a penoscrotal hypospadias and a urinary meatus at the tip of the well formed glans, prepuce and foreskin, a body and shaft with a marked ventral curvature, and a cryptorchid, bifid scrotum with a deep sagittal cleft and prominent, wrinkled, lateral masses.

The serous cavities revealed no abnormalities. The heart weighed 60 grams and was somewhat enlarged for an average child of 18 months. The right lung weighed 175 gms., the left 130 gms. On section they presented an extensive bronchopneumonia involving portions of all five lobes, that of the right lower being almost of lobar type, 90% of its substance being consolidated and resembling red hepatization.

The Spleen weighed 45 gms. On section there were prominent follicles and moderate congestion. The Liver weighed 447 gms., on section revealing a moderate congestion. The gall bladder, bile ducts and gastrointestinal tract presented no abnormalities. The Pancreas weighed 30 gms., showing no abnormality.

The ADRENALS weighed 35 grams together. They measured 5.5 x 3 x 2 cm. and 5 x 3 x 1.5 cm., were dark brown in color, deeply pigmented and presented extendively convoluted surfaces. Deep sulci and large gyri were present. On section the thick cortex was yellowish in color and the thin medulla a deep brown. Kidneys weighed 30 gms. each, on section presenting moderate congestion. A 6 mm. adrenal rest, appearing similar to the adrenal cortex, was present in the peripelvic fat of the right kidney and a similar adrenal rest was present at the tip of each broad ligament in the inguinal canals.

The external and internal generative organs presented the characteristic abnormalities of female external pseudohermaphroditism (Creevy, 105). Uterus tubes and ovaries, were present internally with a vagina which opened into the prostatic urethra, a prostate being present about the base of the bladder. The opening of the vagina and urethra forming a persistent urogenital sinus externally was at the hypospadic orifice on the ventral surface of the base of the penis at the penoscrotal juncture. The uterus measured 35 mm. from the tip of its small cervix to the top of the fundus. The uterine cavity was rather large and possessed horns which communicated with fallopian tubes, the latter measuring 5 cm. in length, 2-3 mm. in diameter and having patent lumens. Round ligaments were present which measured 7 cm. in length and ended in the loose connective tissue of the bifid scrotum, after passing through the inguinal canals. A small 5 mm. adrenal rest was present at the end of each. The ovaries were located in their usual position. They measured 15 x 4.5 x 3.3 mm. and each possessed a mesovarium. The vagina measured 4 x 1 cm. and its opening into the prostatic urethra was a small, slit-like orifice located at the verumontanum. Two tiny ejaculatory ducts were present which admitted the tip of the probe for a distance of about 2 mm. each. No seminal vesicles or vasa deferentia could be found. The prostate measured 18 x 20 x 13 mm. and possessed prominent lateral lobes. The tip of the prostatic urethra was surrounded by the proximal ends of well developed corpora cavernosa which were attached to the under surface of the pubic rami. The urethra proceeded through a well developed corpus spongiosum to open largely at the hypospadic orifice but a patent urethra could be demonstrated throughout the shaft of the penis-like phallus. A probe could be passed through from the bladder to the urethral meatus of the glans. The phallus was ventrally curved and possessed a corpus spongiosum and corpora cavernosa with a prominent glans.

The corpora measured 7 cm. in length. The bifid scrotum contained loose connective tissue and fat but no testes.

The thymus weighed 50 grams but on section presented no unusual features. The thyroid, larynx, pharynx, parathyroids and trachea appeared norma. The mesenteric lymph nodes were large and prominent, measuring up to 1.5 cm. in diameter. Three large ileocolic nodes measured 2.5 x 2 x 1 cm. The brain revealed a mild vascular congestion. Miscroscopic examination of the brain by A.B. Baker revealed essentially negative findings. The hypophysis, after fixation, trimming and removal of stalk weighed 0.130 gm. (average at 6 month and minimum at 18 mo. of age). Microscopic examination by A.T. Rasmussen revealed some findings consistent with Addison's Disease. Few typical basophiles were present, many being indistinctly granular, greatly swollen and containing many small and large vacuoles along with an enlargement of each Golgi apparatus. The acidophiles seemed to be reduced in number and their cytoplasm was reduced to little or nothing.

Microscopic examination: The lungs revealed a severe, confluent bronchopneumonia in 4 lobes and a lobar pneumonia in the right lower. The spleen revealed acute splenitis and the liver and kidneys moderate congestion. The thyroid, parathyroids, pancreas, thymus, aorta and scrotum revealed nothing of note. The appendix, stomach and duodenum showed a prominence of lymphoid follicles and the lymph nodes revealed a suggestion of benign hyperplasia. Section of the adrenals revealed a marked hyperplasia of what appeared to be cortex. Large cortical convolutions with deep sulci and large gyri were present and little or no medulla could be found. The zona glomerulosa was thin and in most places but 4-6 cells in thickness. A thin layer of cells (30-40 at a maximum) resembled zona fasciculata, located just beneath the glomerulosa, but this layer was absent in many places and completely replaced by androgenic cells. Arrangement of the fasciculata was in parallel columns while that of the androgenic cells, occupying the greater part of the adrenals, was irregularly branching and anastamosing cords. Often they appeared to be isolated islands and nests. The latter were irregularly cuboid shaped, large in size and deeply eosin staining. They continued in most places from one side of the convolution, across the midline where medulla should be, to the other side, making up fully 75% of the bulk of the cortical convolutions. With special stains (Masson's trichrome, Ponceau fuchsin or Kull's) the androgenic cells stained a brilliant red, their cytoplasm being filled with fuchsinophilic granules and masses of granules which appeared to be conglomerations of mitochondria. The remainder of the cytoplasm took a light bluish or pinkish stain, the nuclei staining blue, the nucleoli red and the cell membranes blue or green. The skin revealed considerable deposits of melanin pigment i in the basal layers of the epidermis. The prostate possessed a fibromuscular str stroma and well formed glands. A small ejaculatory duct was seen in a section taken from near the verumontanum. The cervix possessed a smooth muscle wall and glands filled with mucin. The ovaries contained numerous developing follicles.

This case is presented in detail because it is the first in the literature with proven adrenocortical insufficiency, congenital adrenal hyperplasia and female external pseudohermaphroditism. The case was studied in detail by Dr. Thompson from birth until death. The final diagnoses were: 1. Congenital Adrenal Hyperplasia, 2. Female External pseudohermaphroditism 3. Infantile Addison's Disease of Adrenocortical Insufficiency 4. Lobar and Bronchopneumonia 5. Acute splenitis and probable septicemia.

The next six cases are briefly tabulated (see table 1). Cases 2 and 4 were males with congenital hyperplasia of the adrenals and a clinical picture of adrenocortical insufficiency. Cases 3,5,6 and 7 were female external pseudohermaphrodites, all save 7 presenting a picture of infantile Addison's disease or adrenocortical insufficiency. Case #7 presented the features of an adult female external pseudohermaphrodite

with congenital adrenal hyperplasia. Body growth was stunted in length though skeletal and muscular development was markedly male-like. A beard and moustache required daily shaving and the voice had been male-like since childhood. A carcinoma of the cortex of one adrenal developed and the patient died post-operatively. Unfortunately autopsy was not permitted. Examination of the patient before and during operation revealed the characteristic abnormalities of this disease, however, and the opposite adrenal was enlarged to palpation. Sections of the intact adrenal attached to the tumor reveal evidence of the congenital type of hyperplasia. This case then is believed to be an example of cortical carcinoma developing in a hyperplastic adrenal. The association between adrenocortical adenoma or carcinoma and hyperplasia is significant in the literature.

	CLINICAL PICTURE	AUTOPSY & GENERATIVE ORGANS	ADRENALS
Case 2* Full term lusty male Sibling of case 3. CONGENITAL HYPERPLASIA OF ADRENALS with ACUTE NEONATAL ADRENOCORTICAL INSUFFICIENCY	Listless and drowzy. Fed poorly. Weight loss of 1 lb. in 4 days. Regurgitation of feedings, anorexia, vomiting & progressive weight loss, dehydration & death on 15th day of life.	Internal organs essentially normal. Prostate large - 18x14x12 m.m.. Sex organs normal male internal and external.	Large, dark brown adrenals. Weight 19.6 gms. together Large cortical convolutions and deep sulci with large gyri. Yellowish cortex and brownish medulla. SECTIONS: 22x8 & 30x8 m.m. marked cortical hyperplasia with thin zona glomerulosa and fasciculata. Thick androgenic zone occupying 75% of convolutions. Some involution present. Sparse medulla. Positive fuchsinophile stains (Ponceau etc.)
Case 3# Full term, lusty child. Deep transverse arrest and forceps delivery. SIBLING OF CASE 2. FEMALE EXTERNAL PSEUDO-HERMAPHRODITE with CONGENITAL ADRENAL HYPERPLASIA AND PROBABLE NEONATAL ADRENOCORTICAL INSUFFICIENCY.	Moderate anemia after birth. Fever of 102° with Pyelitis on 7th day. Reappeared on 22nd day. Fed poorly, dehydration and no weight gain. Cyanosis & death on 42nd day of life.	Patchy bronchopneumonia. Pyelitis. Uterus, tubes & ovaries internally with vagina opening into posterior urethra. Small prostate at base of bladder. Phallus "penis-like" and ventrally curved. Lateral scrotal masses and perineal hypospadias (orifice of urogenital sinus). No testes.	Large, dark brown adrenals. 20.4 gms. together. Marked hyperplasia of androgenic zone filling large convolutions. Thin glomerulosa and fasciculata. Some invoution of inner and androgenic zone. Positive fuchsinophilic stains (Ponceau etc.) 3-ketosteroids isolated from adrenal tissue by Dr. Samuels.

* Case 2- Dr. E.F. Robb, Abbott Hospital
# Case 3- Drs. E.F. Robb and John Haugen, Abbott Hospital
Cases 2, 3, and 4 autopsied by Dr. R.W. Koucky, specimens available for study through his kind cooperation.

	CLINICAL PICTURE	AUTOPSY & GENERATIVE ORGANS	ADRENALS
Case 4* Full term, lusty male CONGENITAL ADRENAL HYPERPLASIA with INFANTILE ADDISON'S DISEASE.	Projectile emesis of feedings at 11 days. Dehydration, emaciation & pallor at 25 days. Only 150 gm. weight gain at 1 month with pigmentation of nipples, skin about ears & extremities. Some response to Cortate for 1 month. Laparotomy failed to reveal evidence of pyloric stenosis. Cyanosis and convulsions & death at $5\frac{1}{2}$ months.	Dusky, pigmented skin. Bronchopneumonia (slight) Normal male genitalia, Internal and External.	Large adrenals (19.6 gms. together) Dark brown color. Large convolutions with deep sulci & large gyri. Marked hyperplasia of androgenic zone, filling convolutions neath a thin glomerulosa and fasciculata. Tiny islets of medulla. Fuchsin stains positive (Ponceau etc.)
Case 5 University Hospitals Full term infant. CONGENITAL ADRENAL HYPERPLASIA with FEMALE EXT. PSEUDO-HERMAPHRODITISM and probable ADRENO-CORTICAL INSUFFICIENCY.	Picture of pylorospasm with repeated emesis after feedings, progressive dehydration and malnutrition. Cyanotic spells and death at age of $5\frac{1}{2}$ months.	Penis-like phallus with perineal hypospadias and empty later scrotal masses. Uterus, tubes & ovaries internally with vagina opening into urethra. Otherwise negative autopsy. "Pylorospasm and malnutrition."	Large adrenals, weight not given. Slides available reveal marked hyperplasia of androgenic cells which replace most of the cortex. Thin glomerulosa and little fasciculata recognizable. Positive fuchsin staining reaction (Ponceau, etc.)

* Case 4- Drs. E.D. Anderson and O.S. Wyatt, Abbott Hospital

CASE	CLINICAL PICTURE	AUTOPSY & GENERATIVE ORGANS	ADRENALS
Case 6. Ancker Hospital Full term infant. CONGENITAL ADRENAL HYPERPLASIA with FEMALE EXT. PSEUDO-HERMAPHRODITISM & probable ADRENOCORTICAL INSUFFICIENCY.	Vomiting of all feedings at age 3 weeks with dehydration, weight loss and diarrhea. Picpure of pyloric stenosis. Death at age 6 weeks.	Penis-like phallus with perineal hypospadias and empty lateral scrotal masses with deep median cleft. Uterus, tubes and ovaries int. with vagina opening into urethra.	"Adrenals large." Sections obtained show block 31 x 9 mm. Little or no glomerulosa or fasciculata. Marked hyperplasia of androgenic cells with positive fuchsin staining reactions. (Ponceau, Kull's, Masson's, etc.)
Case 7. FEMALE EXTERNAL PSEUDOHERMAPHRODITE Age 32 years. Genital abnormalities noted at birth. Mother sheltered her and prevented studies of her condition. CARCINOMA OF RIGHT ADRENAL CORTEX and PROBABLE BILATERAL CONGENITAL ADRENAL HYPERPLASIA. No autopsy.	Abnormality of genitals noted at birth. Early pubescence of male type with male voice and male hair distribution. Stocky, muscular build, male breasts, pigmented nipples, bronzed skin, frontal baldness. Beard and mustache required daily shaving. 25 lb. weight loss in 2 months. Large mass in right upper abdomen displacing the kidney on x-ray.	OPERATIVE FINDINGS and genital organs. Uterus size of tip of fifth finger, string-like tubes, pea sized ovaries. Probable tiny vagina. Opposite adrenal enlarged. Large 1,250 gram tumor of right adrenal removed together with kidney. Post-operative death. Clitoris the size of a thumb. No vaginal orifice seen externally.	Large, incompletely encapsulated adreno-cortical carcinoma. Remaining portions of right adrenal show evidence of marked hyperplasia of androgenic zone with a thin normal cortex composed of zona glomerulosa and zona fasciculata (lipoid vacuolated cells). Thick androgenic zone surrounding the capsule of the tumor. Positive fuchsin staining reactions.

Case 8. Is under study. Female external pseudohemophiodite, age 17 years. Pubertas praecox and macrogenitosomia present at age 6. Laparotomy then disclosed uterus, tubes, ovaries, vagina internally. Body configuration is now male - marked muscular development, a beard, and deep voice, urinary androgen, assay several months ago by Dr. Samuels disclosed 75 mg. of 17-ketosteroids per 24 hours. Fractional determinations revealed no rise in beta 17-ketosteroids. Partial adrenolectomy is contemplated at the present time. (Case of Dr. Theo. Sweetser).

CASES COLLECTED FROM THE LITERATURE

1. Female External Pseudohermaphroditism:

Otto-1816-(76), Bouillaud and Manec-1833-(9), de Crecchio-1865-(102), Heppner-1870-(48), Ogstone-1872-(74)- 3 cases, Marchand-1891-(66), Krokiewicz-1896-(58), Engelhardt-1900-(30), Fibiger-1905-(31)-3 cases, Neugebauer (98), Auvray and Pfeffel-1911-(4), Friedlander-1903-(35), Koch-1909-(56), Rossle-1910 85), Berry Hart-1914-(8), Fraenkel-1914-(34), Kustner-1913-(59), Maicher-1923-(65), Tilp-1913-(95), Quinby-1916-(80), Stahr-1923-(92), Loser and Israel-1923-(64)- 2 cases, Scabell-1923-(87),- 2 cases, Wereschinski-1924-(100), Priesel-1931-(79), Orel and Priesel-1929-31-(75,79)- 2 cases, Creevy-1933-(106), O'Farrell-1935-(73)- 3 cases, Zaudy-1936-(104), Jacobziner and Gorfinkel-1936-(53)- 3 cases, Bayer and Lang-1934-(5) - 2 cases, Bosselmann-1937-(10)- 2 cases, Mozkowicz- 1935-(71)- 4 cases (1 that of Feldman-1926), Polzer and Priesel-1937-(78)- 2 cases, Broster and Vines-1933-(11)- and 1938- 5 cases, Young-1937-(102, 103)- 9 cases, Richardson and Doll-1939-(83), Shepardson-1936-(89), Jones-1938-(54), Carlisle and Geiger-1938-(19), Miller and Kenny-1938-40-(69), Sisk and Cornwell-1941-(91), Charvat and Kodicek-1938-(20), Albert,M.-1941-(2), Rollins-1940-(105), Finkler-1941-(32), Channis-1942-(107), Genitis and Bronstein-1942-(84), 3 cases.

2. Males with adrenal hyperplasia:

Schwalbe-Pagel-1929-(88), Dietrich and Sigmund-1931-(25), Scabell-1923-(87), Orel and Priesel-1929-31-(75, 79), Jacobziner and Gorfinkel-1936-(53), Le Marquand-1932-(60), di Ruggiero and Jolly-1938-(27), Dijkhuizen and Behr-1938-(26)- 5 cases (one case of Harmer's), Broster and Vines-1933-(11), Butler, Ross and Talbot-1939-(15), Thelander and Cholffin-1941-(106), Wilkins et al-1940-(101), Talbot et al-1942-(94).

3. Male pseudohermaphroditism with adrenal hyperplasia or large adrenal rests:

Brutschy-1920-(13), Krabbe-1924-(57), Von Gierke-1928-(97), Healey and Guy-1931-(47), Broster and Vines-1938-(11),- 3 cases, Mittasch-1920-(70).

- - -

Table 2

Table of Cases Collected from Literature

(In these 78 cases I have been able to study the reports and definitely able to classify as the external type. Neugebauer[98] collected over a thousand cases of all types of pseudohermaphroditism in 1905 but few of these could be definitely classified because of incomplete reports.

FEMALE EXTERNAL PSEUDOHERMAPHRODITISM
78 cases

Autopsies (Proven congenital adrenal hyperplasia)	39
Operations (Proven congenital adrenal hyperplasia)	10
X-ray with peri-renal air insufflation (both adrenals markedly enlarged)	2
Total female external pseudohermaphroditism with proven congenital adrenal hyperplasia	51
Genital abnormalities characteristic but adrenals not explored	22
Adrenal biopsies (Cortical adenoma?)	2
Autopsies before year 1900. No note as to adrenals	3
Female external pseudohermaphroditism, adrenal hyperplasia not proven. (Either not explored, or not examined adequately)	27

Total with personally reported cases:	
Female external pseudohermaphroditism with proven congenital adrenal hyperplasia	55
Female external pseudohermaphroditism, adrenal hyperplasia not proven	28
TOTAL cases Female External Pseudohermaphroditism	83
Total Males with Adrenal Hyperplasia	14
Clinical picture of adrenocortical insufficiency	10
Proven adrenocortical insufficiency (Case of Wilkins et al - proven adrenal hyperplasia)	1
Male pseudohermaphroditism and adrenal hyperplasia (Brutschy, Von Gierke and Healey and Guy)	3

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Table 3

Total Males and Females with proven congenital adrenal hyperplasia	69
Macrogenitosomia praecox and proven adrenocortical insufficiency (Butler and Thelander) (Probable adrenal hyperplasia, clinical)	2
Female external pseudohermaphroditism with proven adrenocortical insufficiency and proven adrenal hyperplasia (Case report #1)	1
Female external pseudohermaphroditism with proven adrenal hyperplasia and clinical adrenocortical insufficiency	5
Precocious puberty in males with probable adrenal hyperplasia	3
Total cases with clinical adrenocortical insufficiency	19
Total cases with clinical adrenocortical insufficiency and proven adrenal hyperplasia	17
Total cases collected from the literature	105
Total cases personally reported	7
Total cases reviewed or personally reported	112

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Of the cases reported 4 were female external pseudohermaphrodites and two were males. All presented clinical features of adrenocortical insufficiency and all revealed marked adrenal hyperplasia at autopsy. In case 1 the adrenocortical insufficiency was proven, urinary androgen excretion was increased and special stains disclosed a markedly positive fuchsinophilic staining reaction in the hyperplastic adrenal corticies. The hyperplastic adrenals from case 2 were dessicated and extracted for chemical and endocrinologic study by Dr. Samuels of the Department of Physiology and Biochemistry. Analysis so far has revealed considerable amounts of hormonal substances of the nature of the 3-ketosteroids (the testosterone group).

These case reports bring the total number of reported cases of female external pseudohermaphroditism to 83, of which 55 are proven instances of adrenal hyperplasia. The total number of case reports of macrogenitosomia praecox, precocious puberty and infantile or neonatal adrenocortical insufficiency occurring in males is raised to 17, of which 11 were autopsied and proven to be instances of adrenal hyperplasia. Of these 2 groups there is but 1 case in which (1 male and 1 female external pseudohermaphrodite) in whom the infantile Addisonian syndrome was proven and the adrenal hyperplasia also proven by autopsy. Wilkins'[101] case was the proven example in the male and Dr. Thompson's case that in the female

pseudohermaphrodite. In Wilkins' case extraction of the adrenals for androgens revealed their presence in abnormally large amounts and urinary androgen assay revealed increased urinary androgen excretion.

In 5 cases of proven adrenal hyperplasia with female external pseudohermaphroditism there was a clinical picture of adrenocortical insufficiency. In 3 cases of precocious puberty in males with macrogenitosomia praecox there was a similar clinical picture. Two cases are reported (Thelander[106] and Butler[15]) of macrogenitosomia praecox in males with a proven clinical picture of Addison's disease. These 2 cases were alive at the time of the reports and were being maintained on cortate or salt in the diet. A total of 19 cases exhibited the clinical picture of adrenocortical insufficiency or Addison's disease. Three cases of male pseudohermaphroditism were found in the literature, in which adrenal hyperplasia was present.

In all cases reported thus far, where the adrenals were adequately studied (by operative exploration or hemiadrenalectomy, or cases autopsied and the adrenals closely examined) they were found to be the site of a marked, bilateral hyperplasia. Those cases studied properly with Ponceau-fuchsin stain or other fuchsin stains revealed the presence of this staining reaction in the hyperplastic adrenals. Those which were studied for urinary excretion of androgens revealed an increased output of 17-ketosteroids. Some revealed increased urinary assays of pregnandiol as well. In those cases where the adrenals were dessicated and extracted for androgens they were found to be present in large amounts.

The condition of female external pseudohermaphroditism seems to be a specific one, always associated with congenital hyperplasia of the adrenals. A number of these cases develop the infantile or neonatal Addisonian syndrome, apparently due to a replacement of normal adrenal cortex by androgenic cells. In males the picture may be the Addisonian syndrome or a syndrome of hypergenitalism with macrogenitosomia and precocious puberty. In a number the two occurred together, either preceding the other.

DEVELOPMENT AND INVOLUTION OF THE ADRENALS

The adrenal cortex develops from the celomic epithelium on the medial side of the wolffian ridge and the medulla develops from the ectoderma; tissue which also gives rise to the sympathetic ganglion cells. The two are separate organs in fishes while in man they are united, the medulla growing into the cortex early in embryonic development. The adrenals first appear in an embryo of 6 m.m., being definite organs at the 8 m.m. stage. Masses of celomic epithelial cells enlarge and fuse, developing into a pair of rounded cell masses situated on the medial side of the wolffian ridges. The cortex is rather large at 12 mm. and in the 15-18 mm. stages strands of sympathochromaffin cells can be seen growing into the medial sides of the cortex. The chromaffin reaction soon appears and the cortical cells soon contain lipoid droplets. At 3 months the zona glomerulosa is a slender outer zone beneath which is a wide cell mass consisting of a larger, inner fetal zone and an outer, primitive adult cortex. The inner, fetal zone involutes soon after birth, leaving the adult cortex to differentiate into its 3 zone by the first year or two of life.

Broster and Vines[11] have investigated the adrenals of more than 80 fetuses and embryos ranging in age from 7 to 40 weeks. Sudds[93] has examined the adrenals of 6 fetuses from 6 to 20 weeks of age. I have been able to obtain the adrenals from 4 fetuses, 9 to 17 weeks in age, and have studied the involution of the cortex in an additional 25 selected prematures, stillborns and young infants. From the 9th to the 20th weeks of embryonic life in the male and from the 11th to the 15th weeks in the female the developing adrenal cortex stains intensely with the fuchsin stains, the cortical cells being filled with cytoplasmic granules that are deeply fuchsinophilic. This is known as an "androgenic phase" in the development of

the adrenals. This androgenic phase corresponds with the time of appearance and development of certain other structures. The external genitalia exhibit sexual differentiation by the 11th or 12th week, this process beginning by the 8th week. The indifferent sex gland appears at 5½ weeks, the testis becoming dfined by 6 weeks, about the same time as the adrenals are recognizable as definite organs. The ovary is defined by the 7th or 8th week. Interstitial cells are recognizable in the testes by about the 9th week, the fuchsinophilic cells appearing in the male adrenal at about the same time and in the female adrenal about 2 weeks later. Vines[11] found this fuchsinophilic reaction to disappear by the 15th week in the female and the 20th week in the male. He also noted the appearance of the hypophysis as a solid gland by the 12th to 14th week and was able to distinguish acidophiles and basophiles by the 13th-15th week. He suggests a relationship between the appearance of the basophiles of the hypophysis and the disappearance of the fuchsinophiles from the adrenals. The persistence of this androgenic phase is likely to be the beginning of the development of congenital adrenal hyperplasia.

The involution of the adrenal cortex after birth is of interest in this connection. This unusual process was described by Thomas[96] and by Elliot and Armour[29] in 1911. Lewis and Pappenheimer[62] reinvestigated the process several years later and Benner[7] fully reinvestigated the problem in 1940. At birth the greater portion of the cortex consists of fetal zone and but a small layer of medulla is present. Within the first 10-12 days there is a marked degeneration of the inner part of the cortex. The fetal zone is reduced in thickness from 4 times that of the outer layer at birth to 2 times its thickness. At 5 weeks the 2 are of equal thickness while at 3 months the fetal zone is 1/4 the thickness of the outer cortex and at 1 year it has practically disappeared. By the end of the first year the zona glomerulosa and zona fasciculata are well seen and an early reticularis. By the 3rd year the adrenal appears essentially as it does in adulthood. Benner found the following average normal weights for the adrenals: 1 year- 4.7 gm., 2 years - 5.8 gm., 3½ years- 6.9 gm., 5 years- 8.0 gm., and 11 years- 9.3 gm. The average normal weight of the adult adrenals is 10-12 grams, the average weight at birth being 3.5 gms.

SIGNIFICANCE OF THE FUCHSINOPHILIC STAINING REACTION

The presence of this staining reaction in the adrenals in cases of adrenal hyperplasia and in adrenocortical carcinomas correlates with the increased urinary androgen excretion as well as with the clinical picture of endocrine dysfunction. It also correlates with the finding of increased amounts of 17-ketosteroids and other androgenic substances in extracts of the diseased adrenals. Goormaghtigh[39] and Sudds[93] believe this staining reaction to be of importance. Broster and Vines are of a similar opinion. Goormaghtigh believes it to indicate androgen secretory activity. He was one of the first to study this staining reaction and he described its presence in a juxta-medullary zone of cells in the adrenals of a certain number of adult humans (1922 - Doctorate Thesis). He believed this zone to be the residue of the fetal zone in the adult and forecast the similar staining of adrenocortical carcinomas.

Sudds found that sections of the adrenals from routine autopsies revealed approximately 25% to have groups of fuchsinophilic cells scattered through the cortex. Broster and Vines, Sudds, Goormaghtigh, Cahill,[17] Wilkins, Young, Richardson and Doll and others have reported the staining reaction as being positive in cases of adrenocortical carcinoma or hyperplasia. By and large in the cases reported this staining reaction has been positive where it has been used and properly carried out. On all 7 cases reported here it has been positive. On 4 carcinomas of adrenal cortex studied here recently the stain has been positive. In 1 of the carcinomas and 1 of the hyperplasias studies were done which revealed increased urinary excretion of androgens. A number of other neoplasms have been examined for this staining reaction and

found to be negative. In Adrenals from 30 new-borns and children the reaction has been negative. In 30 routine autopsies on adults the adrenals revealed a few small collections of fuchsinophilic cells in 7 cases.

This staining reaction is not specific for adrenals. Secretory activity of other body cells and tissues produces this staining reaction. The pancreas presents fine collections of fuchsinophilic granules in its acinar cells. Corpora lutea also show a positive staining reaction and the acidophiles of the hypophysis stain positively. Erythrocytes and muscle tissue frequently stain positively. In most cells the staining reaction appears to be due to an affinity of mitochondria for the stain. As the mitochondria enlarge and coalesce the fuchsinophilic masses become large, filling the cytoplasm. In the case of erythrocytes the hemoglobin often takes up the stain, as does the sarcoplasm of the muscle cells occasionally.

EXPERIMENTAL PSEUDOHERMAPHRODITISM IN ANIMALS

Hain[44], Dantchakoff[23], Greene and Ivy[41], Hamilton[46], and others have experimentally produced a condition of female external pseudohermaphroditism in animals by the injection of androgens. Testosterone was mainly used, being injected in varied dosage into pregnant rats and guinea pigs. They obtained a large number of cases of this anomalous situation when relatively large doses were used throughout the latter 1/2 to 1/3 of pregnancy. The abnormalities of the genitalia are almost exact counterparts of those seen in humans. In some animals the masculinization went so far as to produce masculinizationof the female gonad with persistence of portions of the rete testis and medullary tubules in the ovaries.

The production of the anomalies is apparently by stimulation of the Wolffian duct system and urogenital sinus in the female, towards the development of male structures. Some repression of the Mullerian duct system also occurs.

SUMMARY AND CONCLUSIONS

1. Eighty three cases of female external pseudohermaphroditism are studied, 78 of which were collected from the literature and 6 personally reported. The existence of adrenal hyperplasia was proven in 55 cases. All cases with adequate adrenal studies revealed hyperplasia. This abnormality appears to be a specific one, nearly always associated with adrenal hyperplasia.

2. Fourteen cases of congenital adrenal hyperplasia in males have been studied, 12 from literature and 2 personally reported. Early in neonatal or infantile periods they manifest macrogenitosomia praecox and precocious puberty. Three cases were encountered in the literature in which male pseudohermaphroditism was associated with adrenal hyperplasia. It is possible that a more complete reversal of genital organs was produced by the hyperplasia.

3. In 19 of the cases, males and females with congenital adrenal hyperplasia, a third syndrome occurred, neonatal adrenocortical insufficiency or infantile Addison's disease.

4. The common pathologic entity is congenital hyperplasia of the adrenals, the etiology of which is obscure.

5. One male case and 1 female case were, in addition, proven examples of adrenocortical insufficiency. Hormone studies in each revealed increased urinary excretion of androgens. Microscopically the fuchsinophilic cells replaced almost all of the normal cortex. This replacement is thought to be responsible for the adrenocortical insufficiency.

6. The fuchsin stains though not specific seem to indicate the presence of androgen secretory activity in the adrenals.

7. Experimental evidence exists to support the theory that the abnormalities of female external pseudohermaphroditism are brought about by the excessive secretion of androgens during embryonic development.

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VII. GOSSIP

Operation of the University on a continuous basis takes from the fall opening of school some of its special glamour. In spite of this change, fall is the traditional time to commence the school year. Our exercises, Freshman Week and the opening convocation are relics of the day when commencement was really observed at the opening of the school year and not the end. The past summer continues to linger in our memories as the victory gardeners have their day. Gossip concerning tomatoes has been the leading conversational topic. A recent trip East showed it to be in first place in Buffalo, Detroit, Chicago, and Milwaukee. An extraordinary number of persons learned that a tomato vine can produce a lot of excitement and work for the average household. Earlier canning efforts were largely confined to orthodox attempts at preserving tomatoes in various sized pieces. Later on the artists began to perform with special varieties of juice, chutney, chili sauce, and catsup. Green tomatoes are now having their day, with the highlight of the season a green tomato pie and (Meade and Johnson's) Hamilton's green tomato pickle, which requires a three-gallon crock, a box of builders' lime, powdered alum, and ginger for various soakings before the sweet or sour fluids are applied. In Milwaukee the tomato people were not quite as well represented as those who grew egg plants. Apparently this is another form of garden culture which does things for people. Speaking of fall the annual migration of the field mice families has begun. Those of us who live on the edge of town have had our peace disturbed by whole families moving in through open doors and windows. They are simple creatures, easily caught in ordinary ways. A string of traps will usually produce quick results. The children have the houses filled with glass jars containing caterpillars in various stages of animation. A caterpillar devouring this favorite leaf is one of nature's greatest spectacles. The acorns are again plentiful this year after several years of scarcity. One year the trees were perfectly bare which caused the squirrels to leave enmasse and only a few have returned. The football season which started out to be just another one of those things has quickly assumed interesting proportions. In spite of easy opposition from Missouri and Nebraska with resultant high scores many young players of promise will display their wares this year. In many respects the season should be more interesting than last year largely because of the uncertainty in the caliber of the opposition and the uncertainty of our own strength. The Center for Continuation Study is completely occupied by an Army group. Last year was our outstanding year in number of courses, attendance and interest. This year promised to be even better until this change occurred. Efforts were made this summer to locate living and learning space in a hotel. The Hennepin County Medical Society has kindly offered its quarters as a meeting place for downtown groups. It is planned to continue the program, but it is unfortunate in times like these that our civilian professional groups are deprived of the opportunity to keep in touch with their University. The program details will be announced shortly. The Surgeon General's Course in Laboratory Technique for Army officers was completed the latter part of September. The group was made up of both medical and sanitary corps representatives from various parts of the United States. Some were chemists, others bacteriologists, one pathologist, and the others were physicians. As usual Dr. Riley's course in Parasitology was given special mention. Dr. Riley's course is one of the finest expositions in this field. Individuals who should know, insist that even the Army medical school is not able to offer better laboratory material. It is a shame this unit is not utilized by the Army and Navy to better advantage. Other subjects in the Army Officers' course included hematology, bacteriology, serology, pathology, chemistry and laboratory practice. This type of course has now been discontinued. Speaking of tropical medicine, Wesley W. Spink made an interesting trip to Central America this summer to study the clinical aspects of tropical medicine. He is full of his subject as usual and brought back many unusual observations. Since it was learned he was a member of the Penicillin group he has been besieged by requests for the drug. Penicillin which costs $25,000 a pound to produce is handed out sparingly...