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A STUDY OF UNUSUAL ENDOCRINE DISTURBANCES; THEIR ASSOCIATED MYOPATHIES, ENDOCRINE BALANCE AND METABOLISM FINDINGS

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In a series of cases studied at the U. S. Army General Hospital No. 41, Fox Hills, Staten Island, N. Y., over a period of five months, such interesting manifestations were noted from an endocrinologic and myopathic standpoint, that their publication seems warranted.

REPORT OF CASES

CASE 1.—An advanced instance of polyglandular disturbance, characterized by a dystrophia adiposo-genitalis, precipitated by influenza, associated with a muscular dystrophy, and unusual reactions of the vegetative nervous system. A consideration of the endocrine balance and the metabolism findings is of unusual interest.

C. G., white, aged 27 years, was a motorman and rancher by prewar occupation. Habits: Alcoholic beverages indulged in moderately. Used tobacco. He smoked about a dozen cigarettes daily; a pipe occasionally.

Family History.—Father living and well; mother dead of unknown cause; no brothers or sisters. No history of tuberculosis; no nervous, mental or endocrinologic diseases in the family.

Previous History.—Pneumonia and measles in childhood. Mumps in February, 1918, unassociated with any testicular involvement. No venereal diseases.

Present Illness.—This dates its inception to an attack of influenza in July, 1918. At that time he was in bed one week, and suffered from pains in his bones, malaise and weakness. He states that his temperature reached 106 F. on a number of days, and he then was delirious.

In the latter part of July, 1918, he was returned to duty, stayed at the front about ten days and then was sent back to the hospital for a right-sided pleurisy, which had appeared during his initial attack of influenza. He remained in the hospital this time for seven weeks, suffering from a fibrinous pleurisy (right side). In October, 1918, he again returned to duty, remaining in that status until March, 1919.

During this period (October, 1918, to March, 1919) he noted the beginning of his present illness. Pain in the right chest appeared; weakness of the lower extremities even to the extent of falling, and sleepiness became manifest. At the same time, he noticed that his testicles were getting smaller and softer; that his skin and hair were getting dry and brittle, that his hips were broadening with peculiar deposits of fat, and that his breasts were getting larger, especially the right.

In March, 1919, he again entered the hospital where he remained until about May 1. These symptoms progressed, and, in addition, he noted a frequency of urination. In the beginning of the illness he lost about twenty pounds of

weight; then there followed an increase in weight which has continued ever since, until now he weighs 240 pounds.

In July, 1919, he was sent back to the United States. About this time, in addition to the definite progression of the other symptoms noted, a craving for sweets and a loss of erections, libido and ejaculatory reflex became evident; although prior to this time he was quite virile, there have since been but few erections or feelings of sexual desire. A change of voice (its pitch becoming raised) began at this time.

He has also noticed that his upper extremities have grown in length. An increased thirst has developed in the past few weeks.

Gastro-Intestinal: His appetite is rather capricious. Bowels: Normal. Vomiting: Of considerable frequency in the past six months. It is unassociated with abdominal pain or hematemesis. A "sour stomach" with gaseous

Fig. 1 (Case 1).—Dystrophia adiposogenitalis.

and acid eructations accompanies this symptom, together with a sense of fullness in the abdomen. There is no relation to the intake of food; the vomiting is aggravated by the acid eructations and alleviated by an empty stomach.

Genito-Urinary: No dysuria or hematuria. The sexual deficiencies have been mentioned. No history of enuresis.

Respiratory: No cough; no hemoptysis. Sharp and stabbing pain occurs in the right lower chest, at times. No history of epistaxis.

Cardiovascular: A considerable degree of shortness of breath is present. There is edema of the legs when he is up and about. Dizziness and a tendency toward syncope are likewise noted.

Central Nervous System: Headache is an insignificant symptom seldom complained of, and when present, is vertical in type. No complaints in the spheres of vision or hearing. A certain amount of emotional instability is complained of, manifested by his getting upset more easily than heretofore.

Skin: Shaving was begun at the age of 17 and resorted to once or twice a week until about a year ago. Since that time, the period between shav-

ings has increased considerably, until now it is hardly necessary. Many attacks of urticaria have occurred in the last few years.

Neurologic and General Physical Examination.—NEUROLOGIC: 1. Cranial nerves negative: Pupils equal, react fairly well to light and accommodation; they are fairly round in contour. The fundi and the fields of vision display no abnormality; no hemianopsia.

3. Reflexes: Knee jerks, right much diminished, left absent. Achilles tendon jerk, left much diminished, right absent. No Babinski, Oppenheim or no past-pointing.

2. Cerebellar functions: No adiadokokinesia; no manual or pedal ataxia; Chaddock phenomena; no ankle clonus. The middle and lower abdominal reflexes are present. The cremasteric reflexes are not always elicited; when they are, a diminution is noted.

4. Motor: Motor power is well preserved in the upper extremities. The muscles of the thigh, viz., quadriceps extensors, hamstrings, abductors and the glutei are considerably weakened, especially the abductors, the hamstrings, and the flexors of the thigh (pelvofemoral) are involved, whereas the inverters, evertors, flexors and extensors of the feet are fairly powerful. This stands in direct contrast to the fact that the legs are much thinner than the thighs (pseudohypertrophy of thighs?).

Fig. 2 (Case 1).—The genitalia.

Electrical Examination.—Examination was confined to three muscles on the left side, the tibialis anticus, gastrocnemius and quadriceps extensor. Faradic response was obtained in all three muscles; but it was weak and appeared only when the primary coil was completely covered. A quick galvanic response, without tetanus or reversal, was obtained from all three muscles; but the reaction did not start to appear until the current reached 15 milliamperes.

Examination with the Jones' condensor: A barely perceptible response was obtained with the following strength in microfarads, using 100 volts: Tibialis anticus, 0.02; gastrocnemius, 0.08; quadriceps extensor, 0.07.

In the control, a normal person, a response was obtained with 0.01 microfarad in all three muscles.

SUMMARY: Marked diminution of faradic and galvanic irritability. The reaction of degeneration is not present. A waddling gait is present, associated with lumbar lordosis.

Sensory: The appreciation of all forms of sensation seems slightly diminished on the left side, with the exception of the muscles and joint sense which seems to be well preserved on both sides. The sensory findings vary, and areas of anesthesia (touch) are found on the dorsum of the feet; pain appreciation,

heat and cold perception, however, are well preserved. Vibration sense is lost in both lower extremities. The sensory abnormalities disclosed are inconstant, and are definitely of a functional nature. Reexamination at intervals of months reveals no essential change in the sensory sphere.

6. Psychiatric examination reveals no abnormalities. The patient is neither depressed nor taciturn.

General Physical Examination.—The figure is of a feminine type. Deposits of fat are especially noted over the iliac regions and the buttocks, in the pubic region and on the lower abdomen. A collar of fat in the neck obscures the thyroid cartilages (pomum Adami); a questionable enlargement of the thyroid gland is present. Special deposits were noted on the outer aspects of both thighs and in the breasts. The breasts are notably large, the right being larger than the left (Fig. 1).

The skin is quite smooth, soft, pinkish and dry; its thinness, as determined by the hypodermic needle, deserves special mention. The skin is quite easily bruised. The face is beardless; the hair is dry and stiff. The configuration of the genital hairs is distinctly of a feminine type (Fig. 1). The hair in this region and in the axilla being quite sparse.

The testicles are quite small and atrophic; the scrotal folds surround the penis, like labia, being inserted laterally to the penis (Fig. 2).

Fig. 3 (Case 1).—The teeth.

The teeth are small; abnormal spacing is noted between the incisors; especially the lower central incisors. The upper central incisors are rather large. The canines simulate the incisors, and lack the fang form (Fig. 3).

The hands are large, but not unusually so.

With the exception of the bilateral genu recurvatum and genu valgum, and the marked lumbar lordosis, hyperextensibility is not found in any other joints.

Nose and Throat: Aside from deflection of the nasal septum to the right, no other nasal abnormalities found. The tonsils are moderately large; the pharynx is negative.

Ears: The ears reveal normal hearing, and are normal to labyrinthine (Bárány) tests.

Eyes: The pupils are usually dilated and react well to light and accommodation; on convergence, the left eye quite constantly fails (i. e., swings outward). Vision: Oct. 14, 1919, right, 20/30 plus; left, 20/30 plus; 1 degree esophoria. Ocular movements good in all directions. Fields show no defects in either eye. Outside of very slight blurring in the left disk margins, both fundi are negative. Conclusions: No ocular abnormalities noted. Feb. 9, 1920, vision was, right, 20/20; left, 20/20. No change since above examination. March 1 and March 20, 1920, perimetric examination to form and color was normal. June 5: Fundi and perimetric examination to form and color were normal.

Lungs: Normal.

Heart: The point of maximum intensity is not seen. The left border is 0.5 cm. outside the left nipple line; at the apex the first sound is heard rather weakly; a soft systolic murmur is heard at the apex, but it is not transmitted. The action of tryamin reveals a normal cardiac response.

Blood Pressure: Taken at intervals of two minutes.

Pulse	Blood Pressure	
	Systolic	Diastolic
90	122	80
90	122	82
90	120	85
94	120	84
90	122	85
90	122	84
94	122	84

Fig. 4 (Case 1).—Roentgenogram of the sella turcica.

When taken at intervals of one minute, the blood pressure was:

Systolic	Diastolic
122	85
122	85
122	84

Aside from a slight increase in the pulse rate, no other abnormalities are found.

Cyanosis is not noted in hands or feet. Edema of a moderate degree is found in the lower extremities, more especially after exertion.

Abdomen: No viscera are palpable. The markedly adipose pendulous abdominal wall has been mentioned; numerous striae are seen here as well as over the thigh. Rectal examination reveals an unusually small, firm prostate.

Glands: No special adenopathy.

Temperature: Records taken daily, every hour or two, for three weeks show a range between 98 F. in the morning and 99.4 F. in the afternoon. The afternoon and evening rise are quite constant.

LABORATORY DATA

	Feb. 9, 1920	Feb. 22, 1920	May, 1920
Erythrocytes	4,100,000	5,400,000	
Leukocytes	8,200	9,200	7,600
Hemoglobin, per cent.....	85	90	80
Differential Count:			
Small mononuclears, per cent.....	14	20	16
Large mononuclears, per cent.....	10	3	12
Polymorphonuclears, per cent.....	76	77	72

BLOOD CHEMISTRY *

Blood sugar (fasting stomach, March, 1920), 0.058 per cent.		
Blood sugar curve (May, 1920)	Blood Per Cent.	Urine
Fasting	0.078	None
One hour after taking 183.5 gm. glucose.....	0.140	None
Two hours afterward.....	0.104	None

Blood sugar curve (August, 1920): Determined four months later when the patient was gaining weight rapidly, having attained 250 pounds.

	Per Cent.
Fasting	0.133
One half hour after taking 183.5 gm. of glucose.....	0.238
Two hours afterward.....	0.312
Three hours afterward.....	0.232

(* These determinations were made in the laboratory of Dr. George Draper.)

Urea nitrogen: 15.4 mg. per 100 c.c. of blood (May, 1920).
 Blood creatinin: 1.97 mg. per 100 c.c. of blood (March, 1920).
 Blood creatinin: 1.4 mg. per 100 c.c. of blood (May, 1920).
 Blood creatin: 4.1 mg. per 100 c.c. of blood (May, 1920).
 Blood uric acids: 2.3 mg. per 100 c.c. of blood (May, 1920).
 Blood calcium: 11.7 mg. per 100 c.c. of blood (April, 1920).
 Blood carbon dioxide: 62.4 volume per cent.
 Blood Wassermann reaction was negative Oct. 17, 1919, and Feb. 10, 1920.
 Bleeding time: 2 minutes.
 Coagulation time: 4½ minutes.

FECES

March 1, 1920: Mucus, negative; muscle fibers, few striated and nonstriated fibers present; fat, moderate; starch, negative.

March 3, 1920: After the ingestion of 200 gm. fat in the form of butter, the color was dark brown; consistence, hard; mucus, negative; blood, free (occult), negative; muscle fiber, none; fat, moderate amount; no appreciable increase of this substance over that found on previous examination; starch, negative.

STOMACH CONTENTS

Oct. 21, 1919	March 5, 1920
Free hydrochloric acid, negative	27
Occult blood, negative	Negative
Total acidity	59

SPINAL FLUID

Pressure, normal; transparency, clear; cell count, two; globulin, negative; Wassermann, negative; colloidal gold curve, normal for preliminary and final curves.

URINE

Numerous urine examinations were made at varying intervals. They all revealed:

Amber color; clear; acid; specific gravity varying between 1.010 and 1.030, with an average of about 1.022; albumin, negative; sugar negative; acetone, negative. Casts were not found at any time. The average output of eight twenty-four-hour observations was 1,300 c.c. with a range of from 750 to 1,900 c.c. Phenolphthalein showed 25 per cent. output for the first hour; 40 per cent. for the second hour; total, 65 per cent. Total nitrogen, 11.7 gm.; uric acid, 0.47 gm.; urinary creatin, 0.09 gm.; urinary creatinin, 1.4 gm.

Sugar Tolerance Test (Alimentary Glycosuria).—No glycosuria after 100 gm. glucose, after 183 gm. glucose, after 100 gm. glucose with 1 c.c. of 1:1,000 epinephrin solution, hypodermically, nor after 150 gm. glucose with 1 c.c. of 1:1,000 epinephrin, hypodermically.

Pathology.—A specimen of muscle removed from the biceps of the right thigh showed on gross examination a distinct pallor. Histologic examination "does not appear to show any pathologic change of importance. There is some fatty infiltration, but the muscle bundles themselves do not exhibit any evidence of degeneration or other lesion of significance." (Dr. K. M. Vogel.) These findings indicate very strongly the early stages of muscle dystrophy.

ROENTGEN-RAY FINDINGS

Chest.—Aug. 12, 1919: Apices clear. Moderate amount of peribronchial infiltration on both sides, especially right base.

Heart.—Oct. 5, 1919: Transverse diameter of the heart shadow measures 14 cm. and does not show a definite enlargement, except in the regions of the auricles, and is the type of heart shadow noted in mitral insufficiency.

Head.—October 5: There is noted a deep sella turcica with rather long anterior clinoid process. No other irregularity or deformity noted in the bones of skull. (Fig. 4.)

February, 1920: Lateral stereo of head shows no evidence of pathology about sella turcica. The mastoids are clearly shown and are negative, as to bone pathology. Anteroposterior and lateral views show large frontal sinuses which are clear. Ethmoids and antra are clear. There is a shadow which appears to be a spur on right side of septum.

June 24, 1920: No further change in sella turcica is noted.

Bones.—March 2, 1920: The epiphyses of the lower end of tibia have united, but the epiphyseal line is still evident. This is seen in 90 per cent. of individuals of his age. All other joints taken are negative. A good portion of the shafts of the bones are shown, and also are negative.

Stomach.—March 2: Fluoroscopic examination shows the stomach normal in size and position. Peristalsis active and stomach begins emptying very quickly. Pylorus in midline; no filling defect noted in stomach. The duodenal bulb appears normal. Plate examination confirms fluoroscopic. There is no six-hour retention. The bowel has begun emptying in twenty-four hours and there is still some barium in large intestine in forty-eight hours. No abnormality is noted in the large intestine. Roentgen-ray findings are negative except for a hyperperistalsis in the stomach. Pineal shadow suggestive; thymus shadow absent.

MEASUREMENTS OF PATIENT

	Cm.
Total length	176.5
Circumference of head.....	57.5
Circumference of chest (at level of nipples).....	101
Circumference of abdomen (at umbilicus).....	112.5
Sternoclavicular junction to anterior superior spine of ilium.....	39
Anterior superior spine to internal malleolus.....	93
Anterior superior spine to upper border of patella.....	48
Acromion to styloid process of radius.....	62.5
Acromion to tip of olecranon.....	34
Distance between acromion processes.....	42
Distance between iliac spines.....	25
Spanwidth	192
Penis	5.5
Testes	2.5 × 1
Thigh, right	63
Thigh, left	63
Calf, right	35
Calf, left	35.5
Arm, right	34
Arm, left	32.5
Torso-leg ratio	39/93 or 0.42

EPINEPHRIN TEST (GOETSCH'S)

	Pulse	Blood Pressure		Symptoms and Signs
		Systolic	Diastolic	
Before administration	96	122	90	
Epinephrin, 0.5 c.c., 1:1,000 solution, hypodermically:				
7 min. later.....	104	136	88	Patient complains of nervousness. Has moderate tremor of hands.
10 min. later.....	104	140	84	Tremor and throbbing of vessels and palpitation of heart marked. Patient feels nervous and "shaky."
16 min. later.....	108	140	88	Tremor, palpitation and nervousness marked.
24 min. later.....	108	142	88	Marked tremor, etc.
30 min. later.....	102	145	100	Symptoms as above.
35 min. later.....	104	150	95	Marked palpitation, tremor, nervousness, pallor. Respiration 22.
60 min. later.....	112	165	90	Marked tremor, palpitation, throbbing of vessels. First sound at apex sharp with loud systolic murmur.
1 hr. and 30 min. later.....	110	145	88	Tremor, palpitation, throbbing and nervousness marked.
2 hr. and 10 min. later.....	120	135	88	Palpitation and throbbing of vessels still fairly marked. Patient still complains of nervousness.

EPINEPHRIN TEST

	Pulse	Blood Pressure		Respiration	Symptoms and Signs
		Systolic	Diastolic		
Before administration	82	112	90	24	
Epinephrin, 1 c.c., 1:1,000 solution, hypodermically:					
10 min. after.....	100	148	85	29	"Feels nervous," the outstretched hands show considerable tremor; the face is somewhat blanched. Cardiac palpitation.
20 min. later.....	100	140	80	35	Tremor marked; considerable cardiac palpitation, with pulsation of neck vessels. Definite pallor.

EPINEPHRIN TEST AND OBSERVATION OF SERGENT'S WHITE LINE
(WHITE ADRENAL LINE)

	Pulse	Blood Pressure		Symptoms and Signs
		Systolic	Diastolic	
Before administration	80	120	80	
Epinephrin, 1 c.c., 1:1,000 solution, hypodermically:				
5 min. later.....	104	140	80	Tremor fairly marked. Heart thumping, palpitation marked, patient moderately pale, respiration rapid; pa- tient complains of feeling very nervous. <i>Disappear- ance of white adrenal line.</i>
10 min. later.....	112	140	80	<i>White adrenal line gradually reappearing, and becoming more marked.</i> Marked tremor, palpitation of heart, nervousness continuing.
15 min. later.....	112	145	80	<i>White adrenal line well marked, notwithstanding a maintenance of the height- ened blood pressure.</i> Tre- mor, etc., still marked.
25 min. later.....	115	140	80	<i>White adrenal line still marked. Blood pressure still high.</i>
30 min. later.....	112	135	78	White adrenal line still marked; blood pressure fall- ing; tremor, palpitation, nervousness, still present.

The interest in the above observations attaches to the rapid disappearance of the pure white adrenal line, as described by Sergeant, following the administration of epinephrin, and to its rapid reappearance in the face of the sustained increased blood pressure.

The length of time during which the blood pressure (systolic) remained elevated is quite unusual, as is also the persistence of the nervous and cardiac phenomena.

From the above observation it would seem that the presence of the white line depends on factors other than lowered blood pressure.

TYRAMIN AND OBSERVATIONS ON WHITE ADRENAL LINE

	Pulse	Blood Pressure		Symptoms and Signs
		Systolic	Diastolic	
Tyramin, 60 mg., hypodermically....	..	...	..	White adrenal line present.
5 min. later.....	80	140	78	White line just as marked as before drug's administra- tion.
10 min. later.....	80	145	80	Intensity of white line same.
15 min. later.....	64	130	80	Intensity of white line just as marked.

	Pulse	Blood Pressure Systolic Diastolic	Respira- tion	Symptoms and Signs
Before administration of 80 mg. tyramin, hypo- dermically	100	130 90	40	White line present
5 min. later.....	64	180 105	70	White line unchanged
10 min. later.....	68	186 104	78	White line unchanged
20 min. later.....	80	170 100	62	Temperature, 98.4 F.; white line unchanged

This again demonstrates the persistency of a marked line in the presence of an increased blood pressure, brought about by tyramin.

PITUITARY EXTRACT AND OBSERVATIONS ON WHITE ADRENAL LINE

	Pulse	Blood Pressure Systolic Diastolic	Symptoms and Signs
Pituitary extract, 1 c.c., hypodermi- cally, at 11 a. m.....			White adrenal line well marked.
5 min. later.....	..		White line has disappeared.
10 min. later.....	..		White line still not visible.
15 min. later.....	..		White line still not visible.
20 min. later.....	80	110 75	White line barely visible.
25 min. later.....	..		White line has appeared again faintly.
			Patient complains of cramps in abdomen, and desire to defecate. Defecation oc- curred.
Pituitary extract, 1 c.c., hypodermi- cally, at 2 p. m.			
1 min. later.....	..		White line present (xx).
2 min. later.....	..		White line present.
5 min. later.....	..		White line has disappeared.
10 min. later.....	84	110 70	White line has disappeared.
15 min. later.....	..		White line beginning to ap- pear. (Desire to defecate.) Patient complaining of cramps in abdomen.
20 min. later.....	..		White line faint.

PITUITRIN TEST

	Pulse	Blood Pressure Systolic Diastolic	Symptoms and Signs
Before administration pituitary ex- tract 1 c.c.....	84	120 90	
5 min. later.....	100 Small volume	120 90	Patient pale. Feels sleepy. Desire to defecate and urinate present. Cramps in abdomen.
10 min. later.....	96 Small volume	120 90	
15 min. later.....	96 Small volume	120 90	Movement of bowels oc- curred.

ATROPIN TEST

	Pulse	Blood Pressure		Respira- tion	Symptoms and Signs
		Systolic	Diastolic		
Before administration.....	80-84	122-126	80	16	
After administration $\frac{1}{75}$ gr., hypodermically, given at 9:15 p. m.					
9:25 p. m.....	68	112	70	22	Pupils dilating; dryness of mucous membrane begin- ning.
9:45 p. m.....	80	116	90	44	Considerable dryness of mouth, tongue and pharynx; pupils dilating further; feels hot; face flushed.
10:15 p. m.....	90	135	100	48	Marked dryness complained of, producing distress. Pupils widely dilated. Re- spiratory rate increasing further.
10:30 p. m.....	88	135	100	45	Same as 10:15 p. m.
10:45 p. m.....	96	135	90	90	Respiratory rate notably in- creased. Face flushed; skin and mucous mem- brane quite dry.
11:00 p. m.....	82	135	85	70	Mucous membrane of mouth not quite so dry; pupils still widely dilated.
11:15 p. m.....	80	135	90	38	Respiration less rapid; mu- cous membrane of mouth and pharynx not so dry. Face less flushed.

PILOCARPIN TEST (1)

	Pulse	Blood Pressure		Respira- tion	Symptoms and Signs
		Systolic	Diastolic		
Before administration	100	120	90	28	Skin dry.
Administration of 0.008 gm., hypodermically:					
15 min. later.....	100	134	98	30	Moderate salivation; skin dry. A desire to defecate is present.
30 min. later.....	110	134	98	40	Moderate salivation; skin moderately moist.
45 min. later.....	110	130	95	50	Quite marked salivation and moisture of skin; axilla quite moist; temp. 98.6 F.
1 hour later.....	118	135	100	48	Salivation less marked. Skin less moist; desire to uri- nate present.

PILOCARPIN TEST (2)

	Pulse	Blood Pressure		Symptoms and Signs
		Systolic	Diastolic	
Before administration	90	120	85	
Pilocarpin, 0.0065 gm., hypodermically:				
5 min. later.....	90	120	85	
10 min. later.....	96	120	80	Moderate salivation; slight sweating.
20 min. later.....	100	124	80	Quite marked salivation; moderate sweating, slight flushing of cheeks.
30 min. later.....	..	...	..	White line of Sergent well marked.
30 min. later.....	100	124	80	Rather marked salivation, skin moist. Patient urinated three times during action of the drug. Patient expectorated about three ounces of saliva.

ERGOTIN TEST

	Pulse	Blood Pressure		Symptoms and Signs
		Systolic	Diastolic	
Before administration	84	124	80	
Ergotin, $\frac{1}{40}$ gr., hypodermically:				
5 min. later.....	88	122	80	
15 min. later.....	88	122	80	No special signs or symptoms noted.

PHYSOSTIGMIN (ESERIN) TEST

	Pulse	Respiration	Symptoms and Signs
Before administration	92	34	
Physostigmin, $\frac{1}{50}$ grain:			
15 min. later.....	96	36	Outside of slight headache and slight salivation, no gastro-intestinal effects were noted during the hour following the giving of this drug. Blood pressure readings showed no change.

ASCHNER'S PHENOMENON (OCULOCARDIAC REFLEX)

Pulse, 72: Slight increase to 84. Winking reflex, 13 per minute. Loewi's phenomenon (epinephrin instillation in conjunctival sac). Negative.

GOETSCH'S SKIN TEST

This test was markedly positive. A large central area of blanching surrounded by a peripheral zone of reddening lasted from four to five hours. In the blanched area there was the characteristic goose flesh formation.

In view of the surprisingly high respiratory rates gotten in response to the injection of some of the foregoing drugs, it was decided to determine how much of a psychic factor entered into this peculiarity. Accordingly, 1 c.c. of sterile water was injected subcutaneously. Soon after the respiratory rate rose from 24 to 46. In view of this, the high respiratory rates recorded in the foregoing observations must be discounted considerably.

CUSHING'S THERMO-REACTION

An attempt was made to determine the effect of pituitary extract injections on the temperature; injections were made on six successive occasions. A rise to 99.8 and 99.2 F. occurred on two occasions; the other four injections produced no reaction.

TABLE 1.—SYMPATHICOTONIA

	Case 1	Case 2	Case 3
1. Mydriasis.....	Positive	Positive	Negative
2. Paralysis of accommodation.....	Negative	?	Negative
3. Dryness of eyeball.....	Negative	Negative	Negative
4. Infrequency of winking.....	Negative	Positive (slight)	Positive
5. Dryness of mouth.....	Negative	Negative	Negative
6. Low gastric acidity.....	Negative	Negative	Negative
7. Increased gastric secretion.....	Positive	Negative	Negative
8. Lessened intestinal tonus.....	Negative	Negative	Positive ?
9. Constipation.....	Negative	Negative	Negative
10. Faulty convergence of eyes.....	Positive	Positive	Negative
11. Wide eyeslits.....	Positive	Negative	Negative
12. Exophthalmos.....	Negative	Negative	Negative
13. Tachycardia.....	Positive (slight)	Positive (slight)	Negative
14. High blood pressure.....	Slight	Positive (slight)	Negative
15. Vasoconstriction.....	Positive	Negative (slight)	Negative
16. Relaxation of detrusor of bladder (incontinence).....	Negative	Negative	Negative
17. Urticaria.....	Positive (history)	Negative	Negative
18. Atony of stomach.....	Negative	Positive	Positive
19. Gastroparesis.....	Negative	Positive	Negative
20. No dermatographia.....	Positive	Slight	Negative
21. Tonsils small and atrophied.....	Negative	Positive	Negative
22. Gag reflex marked.....	Positive	Negative	Negative
23. Eosinopenia.....	Positive	Positive	Positive
24. Tachypnea with dyspnea not affected by atropin, i. e., rate not lowered by atropin.....	Positive	Negative	Negative
25. Dry hands and feet.....	Positive	Negative	Negative
26. Ashner's phenomenon (oculocardiac reflex) produces no change in pulse.....	Positive	Negative	Negative
27. Steatorrhea.....	Negative	Negative	Negative
28. Lowered carbohydrate tolerance before and after epinephrin administration.....	Negative	Negative	Negative
29. Pilocarpin causes no salivation.....	Negative	Positive	Negative
30. Loewi's test positive.....	Negative		Negative
31. Reaction to epinephrin.....	Positive (marked)	Negative	Negative
32. Pituitary extract.....	Fairly marked peripheral constriction; movement of bowels		Same
33. Reaction to ergotin.....	Slight		Slight
34. Tyramin.....	Marked reaction		Slight reaction

BASAL METABOLISM

1. *March 27, 1920.*—Calories per sq. meter per hour, 29.3. Variation, minus 26. per cent.¹
 2. *April 15, 1920.*—Calories per sq. meter per hour, 35.6. Variation minus 10 per cent.
Antuitrin (extract of anterior lobe of hypophysis, Parke, Davis & Co.) 1 c.c. was now given hypodermically; 15 minutes after the basal metabolism revealed: Calories per sq. meter per hour, 36.6. Variation, minus 7 per cent.; 45 minutes after: Calories per sq. meter per hour, 34.5. Variation, minus 13 per cent.

The patient was suffering from a rather severe rhinitis and pharyngitis, the temperature ranging from 99.5 to 100, while these determinations of April 15, 1920, were being obtained.

3. *May 6, 1920.*—Basal metabolism determinations with patient on 1 c.c. of antuitrin (Parke, Davis & Co.) by hypodermic, three times daily, for a period of two weeks, together with capsules of orchic extract, 5 grains, three times daily, revealed: Calories per sq. meter per hour, 33.7. Variation, minus 14.5 per cent.

1. Determination made by Dr. B. Sanger, department of metabolism, Presbyterian Hospital. The determinations of April 15 and May 6 were made by Dr. H. E. Marks, department of metabolism, College of Physicians and Surgeons (Columbia University).

COMMENT

Owing to the patient's irregular respiratory excursion, the basal metabolism findings were obtained with difficulty. Such variations, as may be ascribed to respiratory irregularity probably do not amount to more than 4 or 6 per cent. In general, it may be said, that the basal metabolism is lowered, that a decrease is from minus 10 to minus 26 per cent. Administration of antuitrin hypodermically caused little, if any, change, other than the slight rise from minus 10 to minus 7 per cent., either when given *directly* before the basal metabolism determination, or when administered steadily with orchic extract for weeks prior to the determination. In other words, neither a single dose nor the cumulative effects of many doses of antuitrin seemed to alter the basal metabolism.¹

It seems not unlikely that the nasopharyngeal infection present during the second series of metabolism determinations produced a slight rise. Interpreted in the light of the polyglandular disturbance, the lowering of the basal metabolism indicates that the hypopituitarism present is of much greater intensity than the hyperthyroidism.

PROGRESS NOTES

During the period of observation (six months) certain important additional facts were noted: (1) a marked susceptibility to infection; (2) the gradual development of a slight weakness of the shoulder group of muscles; (3) periods of somnolence; (4) a continuance of gain in weight until 250 pounds were attained in August, 1920; (5) an indolent reaction of the tissues in healing, with relation to the wound in the thigh, through which a specimen of muscle was obtained.

TREATMENT

After a week of thyroid tablets, 0.065 gm., three times a day, dizziness, tachycardia (120), tremor and weakness appeared.

At another hospital, the patient was given whole gland hypophysis (Armour and Co.) over a period of three months. No improvement was noted. In fact, the patient thought he became worse, i. e., his weakness increased. No reduction of weight occurred during this time.

Various combinations of gland products were given in a variety of ways with no real improvement. Extract of whole pituitary gland (Armour and Co.) from 0.33 to 0.66 gm., three times a day, by mouth, with ampoules of antuitrin (Parke, Davis and Co.), 1 c.c., two, and then three, times a day, subcutaneously, together with orchic extract (Armour and Co.), 1 gm. a day

1. It is interesting to note that some very recent investigators² likewise noted no effect on basal metabolism from powdered anterior lobe hypophysis by mouth or extract of posterior lobe hypophysis and pars intermedia subcutaneously in a group of similar cases.

2. Snell, A. M.; Ford, F., and Rowntree, L. G.: Studies in Basal Metabolism, J. A. M. A. **75**:515 (Aug. 21) 1920.

by mouth, were given over a period of months without beneficial effect. Owing to the patient's sensitiveness to epinephrin and pituitary extract (posterior lobe hypophysis), the hypodermic administration of these drugs in doses as low as 0.18 c.c. each, three times a day, had to be discontinued.

The vomiting was well controlled by extract of belladonna, 1.2 c.c. five times a day, combined with bismuth subcarbonate, 0.66 gm. and sodium bicarbonate, 1.2 gm., four times a day.

Tincture of digitalis, in the usual dosages, was quite effective in relieving the edema of the legs.

DISCUSSION

1. *The Endocrine Balance.*—While there is no doubt that the picture presented is one of dystrophia adiposogenitalis, it is difficult to differentiate between the hypophysial and pure or primary genital forms of this disorder. Although there is very little evidence on which to involve the hypophysis, namely, no roentgen-ray changes in the sella turcica, no signs of intracranial pressure, no polyuria, no subnormal temperature, and no blood changes (such as eosinophilia, lymphocytosis, low hemoglobin, as noted by Falta³), yet, the lowering of the basal metabolism possibly favors pituitary participation as against the pure gonadal or eunuchoid type.⁴ The persistently open epiphyses of eunuchoidism are not found here, but as the onset of this affection occurred after epiphysial closure (i. e. after puberty), this differential point is of no avail.

It has been suggested⁵ that two other gland disturbances may possibly produce this syndrome, namely, (1) an involvement of the suprarenal cortex; (2) the activity of ovarian rests.

Concerning the former, it may be said that a deficiency of the suprarenal cortex may well affect the genital status and the growth of the body and hair, but we have been unable to find sufficient evidence to postulate such involvement; the same is true of ovarian rests.

Of no little interest is the participation of the other ductless glands in this syndrome. Hyperthyroidism is evidenced by the increased tone of the vegetative nervous system, by the questionable enlargement of the gland, the epinephrin sensitiveness (the pronounced Goetsch test), the increased temperature and pulse rate, and, of most importance, the response to thyroid gland feeding (see Chart 1, Fig. 15). Of especial significance is the increased temperature, for uncomplicated hypopituitarism is accompanied by a *hypothermia*.

As for the gonadal participation, pronounced atrophy of the gonads is quite evident.

3. Falta, W.: *The Ductless Glandular Diseases*, Ed. 2, Philadelphia, P. Blakiston's Son & Co., 1916.

4. Falta states "many more investigations are necessary" in reference to this differential point.

5. Timme, W.: Personal communication.

For involvement of the pineal gland, we have the suggestive roentgen-ray shadow and the muscular dystrophy.⁶

Since we regard the white line of Sergeant as being a very doubtful sign of hypoadrenia,⁷ and with no other certain evidence of deficient suprarenal secretion, the participation of this gland seems very doubtful.

Claude and Gougerot⁸ have considered a somewhat allied clinical syndrome some years ago under the caption of "Insuffisance pluriglandulaire endocrinienne," in which an instance of thyro-suprarenal-testicular deficiency was described.

Von Dziembowski⁹ reports a case of dystrophia adiposogenitalis with muscular dystrophy in a young man of the same age with findings very similar to those here presented.

2. Muscle Dystrophy.—The relationship of the muscular dystrophies to endocrine disturbance was emphasized of late by W. Timme⁶ and by Janney, Goodhart and Isaacson.¹⁰ These authors have reviewed the literature on this subject. Timme emphasizes the rôle of the pineal gland; Janney and his co-workers note a polyglandular involvement in which the thyroid, hypophysis, gonads, pineal and supra-adrenals participate.

The latter workers have also drawn attention to the creatin—creatinin and sugar metabolism. In their series of dystrophy case, they found a marked decrease in the urinary preformed creatinin, the abnormal presence of creatin in the urine, low blood creatinin values with a normal amount of creatin in the blood, a hypoglycemia and a delay in the utilization of sugar.

In the case recorded above, there was a normal blood creatin, and the abnormal presence of creatin in the urine. The creatinin in the blood and urine is in normal amounts. This may be due to the limited extent of the dystrophy present in this case at the present time, with the preservation of a good deal of normal muscle function especially in the upper extremities. There is definite hypoglycemia,¹¹ and a delayed utilization curve present.¹²

In this connection the cardiac weakness manifested by this patient since the onset of the illness may be due to a cardiac involvement in

6. Timme, W.: Progressive Muscular Atrophy as an Endocrine Disease, *Arch. Int. Med.* **19**:79 (Jan.) 1917.

7. Kay, W. E., and Brock, S.: The White Adrenal Line (Sergeant): Its Clinical Significance, *Am. J. M. Sc.*, to be published.

8. Claude, H., and Gougerot, H.: Insuffisance pluriglandulaire endocrinienne, *J. de physiol. et path. gen.*, June, 1908.

9. Von Dziembowski, S.: Dystrophia Adiposo-genitalis mit Myopathie, *Deutsch. med. Wchnschr.* **43**:654, 1917.

10. Janney, N. W.; Goodhart, S. P., and Isaacson, V. I.: The Endocrine Origin of Muscular Dystrophy, *Arch. Int. Med.* **21**:188 (Feb.) 1918.

11. See blood sugar determination of March and May, 1920.

12. See blood sugar determination of August, 1920.

the dystrophic process, a point recently emphasized by Goodhart and Globus.¹³

3. *The Vegetative Nervous System.*—The reactions on the part of the vegetative nervous system indicate a marked hyperirritability, which is predominantly sympathicotonic as evidenced by the pronounced sensitiveness to epinephrin and to the other tests indicative of sympathetic dominance (Tables 1 and 2).

The significant disappearance of the white adrenal line (Sergeant) following the administration of epinephrin, with its rapid reappearance deserves mention, the more so as the reappearance of the line occurred while the other manifestations of epinephrin action were still in marked evidence (tremor, cardiovascular symptoms and elevated blood pressure). This fact, as well as other investigations which are now being made on the white line, lead us to hesitate in accepting the alleged dependence of this phenomenon upon a state of hypo-adrenia.

4. *Complicating Infections.*—A noteworthy feature of the case is the patient's susceptibility and reaction to infection. While under observation he has had numerous nasopharyngeal and respiratory infections. In an attack of follicular tonsillitis the pulse rose to 160, respirations to 50, and the temperature to 105 F., remaining thus for forty-eight hours; periods of delirium accompanied the infection. *This indicates a distinct lack of immunity bodies.* The response to infection also reveals certain sympathicotonic characteristics in the symptomatology.

At this point the relationship of influenza to the production of this dysglandular disturbance may be considered. We believe that this individual had always been of the hypopituitary type, that the predisposition to a glandular dyscrasia was latent, and that the severe infection merely served to upset the balance to such a degree as to bring about the marked changes described.

CASE 2.—A polyglandular syndrome on a definitely hereditary basis, in which a hyperfunctioning of the thymus and suprarenal glands counterbalances a hypopituitary state. Of especial interest are the physical manifestations, the increased muscular power, the roentgen-ray and laboratory findings. Attention is directed to the remarkable contrast offered between this case and Case 1.

M. C., white, 20 years of age; prewar occupation, laborer. Habits: Negative for alcoholic excesses and drug addiction.

Family History.—Father, paternal grandmother and aunt are very stout, short in stature and possess a convergent strabismus similar to that shown by the patient. The father suffers from "asthma and rheumatism." Mother is small and thin; she has been operated on for gallbladder disease. Brothers:

13. Goodhart, S. P., and Globus, J. H.: On the Nature of Muscular Dystrophies, with a Report of Changes in Cardiac Muscle in Two Cases, *Neurol. Bull.* 1:386, 1918.

none. Sisters: one, living and well; she resembles the mother but not the father nor the patient.

Personal History.—He has had measles and influenza; the latter disease kept him in bed about two weeks. No gunshot wounds or other casualties. No venereal infection.

Present History.—The patient was sent to the hospital for mental observation, because of numerous escapades, and infractions of military regulations.

Gastro-Intestinal: Appetite voracious; does not care for candy or sweets. Vomiting, none. No gaseous or acid eructations. Bowels: Four or five movements a day.

Fig. 5 (Case 2).—Dystrophia adiposogenitalis.

Respiratory: No cough; no hemoptysis; no pain in the chest. Epistaxis, seldom.

Nervous System: Headache at times, located in forehead above the eyes; a dull pain getting better as the day progresses, inconstantly present, and sometimes absent for weeks. No especial nervousness; no dizziness; no fainting; no convulsive seizures.

Cardiovascular: Somewhat short winded, getting out of breath on running; no swelling of the feet; no palpitation of heart; no precordial pain.

Genito-Urinary System: Urinates about six times per day. No nocturia; no dysuria; no hematuria; no enuresis. Libido is apparently much diminished; states he entertains no feeling of sexual desire; nocturnal emissions absent. No history of coitus or homosexual practices.

Physical Examination.—The patient is of a short, stout build (Fig. 5), weighing about 180 pounds. The fat distribution is of an adiposogenitalis nature being noted especially in the breasts, lower abdomen, pubic regions and over the iliae. The skin over the abdomen and face is fine, smooth and silky. The breasts show a marked areolae formation.

Hair: The pubic hairs reveal a horizontal upper border simulating the female type. The hair is sparse over the abdomen, face and axillae; the hair on the face is limited to the chin and upper lip, being of the lanugo variety. The hair of the head and eyebrows is rather profuse; that over the lower back, buttock and thighs is considerable in amount, fine in texture and rather sharply delimited from the hairless parts above. Shaving is resorted to twice a week.

A definite degree of pigmentation is noted, especially about the waist and in the axillae.

The patient perspires very profusely.

Fig. 6 (Case 2).—The teeth.

Teeth: The teeth are definitely abnormal. In the upper row, the two central incisors are large; the left lateral incisor is erupted behind the left upper canine. The right upper canine is quite small and resembles an incisor. The lower incisors are irregularly erupted and stunted in growth. The first molars have a fang-like contour. Many cavities of small and large size and some pyorrhea alveolaris are present (Fig. 6).

Genitalia: Testicles are of medium size, situated near the external inguinal ring. The penis is normal in size and in power of erection.

Heart: The left border percusses out one inch beyond the nipple line; rate slow (80 per minute); rhythm regular. A soft systolic murmur is heard over the aortic area; it is not transmitted.

Blood Vessels: Negative.

Thyroid: Not enlarged.

Lungs: Slight dulness right base. No other abnormalities.

Abdomen: Negative.

Glandular and Osseous System: Negative.

Neurologic Examination.—1. Cranial Nerves: Eyes: Right affected with a convergent squint. Pupils: equal, round, regular in contour and reacting to direct and consensual light stimulation. There is some restriction of the field of vision of the right eye incident to the strabismus. No cranial nerve palsy.

2. Motor: *An unusual degree of muscle strength is exhibited by this individual.* He is able to lift and carry very heavy objects, seemingly out of

proportion to his height and general stature. (This capacity has influenced his choice of occupation. He has always worked at very laborious tasks as freight handling, etc.) No tremor is present.

3. Sensory: No abnormalities.

4. Reflexes: Normal; no abnormal reflexes.

5. Equilibration: Normal. No ataxia. No adiadosokinesis.

Psychiatric Examination.—This reveals a definite degree of mental deficiency, with the emotivity, suggestibility, and irresponsibility of a child.

ROENTGEN-RAY EXAMINATION

Chest.—Anteroposterior stereoroentgenogram (Fig. 7) shows a marked retraction in the right lateral aspect where there is a considerable thickening of the pleura; the costophrenic angles are clear. The upper mediastinum

Fig. 7 (Case 2).—Roentgenogram of the chest.

reveals a distinct thymus shadow. The right lung shows considerable clouding of apex. The bronchial trunks reveal considerable thickening. The left lung is negative. The apex does not give the impression of activity. The heart shadow appears moderately enlarged to the left.

Hands.—Anteroposterior view reveals the tapering form to the fingers and the small tufts characteristic of hypopituitarism (Fig. 8). The stereoroentgenogram of wrist joint, including carpus and metacarpus, shows that the epiphysis of the lower ends of the radius and ulna are not united firmly. There is an area of rarefaction at the proximal end of the second metacarpal bone on both sides. The femora and knee joints are negative.

Head.—The lateral stereoroentgenogram reveals a sella turcica which is quite shallow; anterior clinoid processes, which are shortened and blunted.

and a posterior wall seemingly eroded; the posterior clinoid processes are shortened and indistinct (Fig. 9).

Gastro-Intestinal Tract.—Fluoroscopic examination shows a slightly dilated stomach with lower border on level of crest of ilium. Stomach was hypotonic but began emptying in ten minutes. Emptied in midline. Examination of duodenum negative. The two and one-half and six hour plates each shows retention in the stomach. The six hour plate showed that the barium had passed entirely through the small intestines and was then present in the large bowel and rectum. The appendix was visualized in the twenty-four and forty-eight hour plates. The large intestines appear to be entirely empty in forty-eight hours.

Fig. 8 (Case 2).—Roentgenogram of the fingers of hypopituitarism.

The roentgen-ray findings in this case show that patient has a hypotonic stomach; hypertonic small intestines; a residual appendix. The large intestines empty in the normal time.

PHARMACOLOGIC TESTS (VEGETATIVE NERVOUS SYSTEM)

Pituitary Extract	Pulse	Blood Pressure	Symptoms
Before administration . . .	85	120-65	
Pituitrin, 1 c.c., hypodermically:			
15 min. later.....	84	125-85	Patient pale; no white line; slight red line.
25 min. later.....	84	120-80	Patient pale; no other symptoms; slight red line. Temp. 98.8 F.
40 min. later.....	80	127-80	Patient still slightly pale; no other symptoms; slight red line.

ATROPIN TEST

	Pulse	Blood Pressure Systolic Diastolic	Symptoms and Signs
Before administration	80	122 55	
Atropin sulphate, $\frac{1}{50}$ grain, hypodermically:			
10 min. later.....	80	120 70	Moderate dryness of mouth; pupils dilated; white line present, of moderate intensity.
20 min. later.....	90	115 65	Patient complains of dryness of mouth; no other symptoms; no flushing; extreme dryness; respiration, 35.
30 min. later.....	84	118 65	Mouth moderately dry; white line of moderate intensity; no especial symptoms or signs; oculocardiac reflex (Aschner's phenomenon) negative, i. e., no change in pulse; 90 to 86; pupils dilated.
1 hour later.....	80	122 60	Moderate dryness of mouth; slight dryness of skin; respiration, 26.
Before administration	85	135 60	
Atropin, $\frac{1}{100}$ grain:			
5 min. later.....	90	128 75	No symptoms.
7 min. later.....	90	130 70	No symptoms.
17 min. later.....	86	134 70	White line present, of moderate intensity on light pressure; red line on moderately deep pressure; no symptoms.
30 min. later.....	84	130 80	Slight dryness; white line present, of moderate intensity; red line of moderate intensity intermixed with white line on deeper pressure.
40 min. later.....	88	130 70	Slight dryness.

PILOCARPIN TEST

	Pulse	Blood Pressure Systolic Diastolic	Symptoms and Signs
Before administration	88	138 40	White line present.
Pilocarpin, $\frac{1}{40}$ grain, hypodermically.			
10 min. later.....	88	138 40	Patient feels warm; salivation and perspiration moderate in degree.
25 min. later.....	88	138 40	Face flushed; moderate perspiration and salivation; marked red line not hitherto noted; white line present on light pressure, but diminished in intensity.
35 min. later.....	94	134 36	Slight salivation and perspiration; red line not nearly as marked; a mixture of red and white is obtained; white line of moderate intensity.

EPINEPHRIN TEST

	Pulse	(Blood Systolic	Pressure Diastolic	Symptoms and Signs
Before administration (10 min.)....	88	130	55	
Before administration (3 min.)....	86	132	60	
Epinephrin, 1 c.c., 1:1,000 solution, hypodermically.				
8 min. later.....	80	136	45	No especial symptoms.
20 min. later.....	82	138	45	Moderate palpitation of heart and throbbing of vessels; white line present; no especial subjective signs.
25 min. later.....	88	134	60	Quite marked palpitation and throbbing of vessels; no tremor; no subjective symptoms.
35 min. later.....	80	137	30	Palpitation and throbbing less marked; white line much diminished (hardly pres- ent); patient has "goose flesh" formation.
50 min. later.....	80	136	35	Still moderate throbbing of vessels; white line almost disappeared; red line pres- ent (no "goose flesh"); pa- tient makes no complaint of symptoms.

MEASUREMENTS OF PATIENT

	Cm.
Total length	160.5
Circumference of head.....	53
Circumference of chest (at level of nipples).....	99
Circumference of abdomen (at umbilicus).....	99
Sternoclavicular junction to anterior superior spine.....	42
Anterior superior spine to internal malleolus.....	84
Anterior superior spine to upper border of patella.....	39.5
Acromion to styloid process of radius.....	49
Acromion to tip of olecranon.....	30.5
Distance between acromion processes.....	38
Distance between iliac spines.....	25
Span width	164.5
Penis (length).....	9.5
Testes, approximately	4 × 2.5
Thigh, left	54.5
Thigh, right	54.5
Calf, left	33
Calf, right	33
Arm, left	29
Arm, right	29.5
Torso-leg ratio	½ or .5

LABORATORY DATA

BLOOD

	April, 1920	May, 1920
Erythrocytes	3,968,000	4,980,000
Hemoglobin, per cent.....	85	90
Leukocytes	10,200	9,700
Polymorphonuclears, per cent.....	72	72
Small mononuclears, per cent.....	22	16
Large mononuclears, per cent.....	4	12
Transitionals, per cent.....	2	..
Wassermann negative.		

BLOOD SUGAR CURVE

	Blood Per cent.	Urine
Fasting	0.100	None
One hour after taking 132 gm. of glucose.....	0.108	None
Two hours after taking 132 gm. of glucose.....	0.121	Very faint trace

CARBON DIOXID TENSION

65.5 volumes per cent.

GASTRIC CONTENTS

Total acidity	70
Combined acids	6
Free hydrochloric acid.....	34
Combined hydrochloric acid....	30
Lactic acid	Neg.

FECES

Color	Brown
Consistency	Soft
Mucus	None
Occult blood	Trace
Fat	Large amount
Starch	None
Muscle fibers	Few

SUGAR TOLERANCE

Glucose, 200 and 250 gm., on fasting stomach, produces no glycosuria in the four hourly specimens taken following its administration.

URINE

The urine is of an amber color; turbid; acid; specific gravity about 1.030; negative for albumin and sugar, and on microscopic examination.

BASAL METABOLISM

Seventy-one and eight-tenths calories per hour; 40.3 calories per square meter per hour. Variation: plus 2 per cent. Essentially normal basal metabolism.

TABLE 2.—VAGOTONIA

	Case 1	Case 2	Case 3
1. Myosis.....	Negative	Negative	Moderate
2. Epiphora.....	Slight	Negative	Negative
3. Hyperhidrosis.....	Negative	Negative	Negative
4. Frequency of winking.....	Negative	Negative	Negative
5. Salivation.....	Negative	Negative	Negative
6. Gastric hyperacidity.....	Positive	Positive	Negative
7. Arrest of gastric secretion.....	Negative	Negative	Negative
8. Vomiting.....	Positive	Negative	Negative
9. Diarrhea (8 to 10 times).....	Negative	Positive	Negative
10. Gastric hypertonia.....	Positive	Negative	Negative
11. Spastic colon.....	Negative	Negative	Negative
12. Enophthalmos.....	Negative	Positive	Positive
13. Bradycardia.....	Negative	Negative	Positive
14. Low blood pressure.....	Negative	Negative	Positive
15. Asthmatic seizures.....	Negative	Negative	Negative
16. Esophagism.....	Negative	Negative	Negative
17. Mucous colitis.....	Negative	Negative	Negative
18. Dermatographia.....	Negative	Positive	Positive
19. Status thymicolympathicus.....	Negative	Negative	Negative
20. Absent gag reflex.....	Negative	Positive	Positive
21. Eosinophilia.....	Negative	Negative	Negative
22. Pulsus irregularis respiratorius which disappears with atropin.....	Negative	Positive	Positive
23. Clammy hands and feet.....	Negative	Negative	Negative
24. Priapism.....	Negative	Negative	Negative
25. Oculocardiac reflex.....	Negative	Positive	Positive
26. Increased fat tolerance.....	Positive	Positive ?	Positive
27. Increased carbohydrate tolerance before and after epinephrin.....	Positive	Positive	Positive
28. Salivation induced by pilocarpin.....	Positive	Negative	Positive
29. Reaction to atropin.....	Positive	Negative	Negative

DISCUSSION

1. *Endocrine Balance.*—*Suprarenal:* Hyperfunction of this gland is evidenced by the peculiar hairiness of the individual, slightly increased blood pressure, the increased muscular strength and possibly by the cardiac hypertrophy. The pigmentation noted might well be interpreted as having been deposited during a phase of hypoadrenia, either before the establishment of the present balance, or during upsets incident to infections.

Thymus: The definite thymus shadow indicates participation of this gland.

Pituitary: The peculiar adiposity, the shallow sella turcica, the increased sugar tolerance (evidenced especially in the alimentary tests) bespeak a definite hypopituitarism.

2. *Muscle Function.*—An increased muscle strength is noted, which, as has been mentioned, is out of proportion to his height and stature. In Case 1, which stands in peculiar contrast to this case, a muscular dystrophy was noted. While this case occurs in an individual in whom a distinct hereditary tendency may be traced, the first patient has no ascertainable hereditary basis.

Fig. 9 (Case 2).—Roentgenogram of the sella turcica.

It is difficult, if not impossible, in the present state of our knowledge, to explain satisfactorily the increased muscle strength of the one and the dystrophy of the other—to apportion to this or that gland even its relative importance, or to ascribe to any one gland, definite relationships to muscle function.

This uncertainty is enhanced not only by the multiplicity of glands playing a part, but also by the fact that complicated, subtle compensatory mechanisms are at work tending to establish a balance—attempting a restoration of normal function.

Fig. 10 (Case 3).—The relaxation difficulty in myotonia congenita. The facial expression is indicative of concentrated effort.

It is beside the purpose of this report to enter into the highly theoretical possibilities deducible.

3. *Basal Metabolism*.—That a balance is struck in this disturbance of the endocrine system is again demonstrated by the essentially normal basal metabolism determination.

4. *Psyche*.—The mental deficiency and inadequate personality reactions present are dependent not on the endocrine dyscrasia but rather on a basic developmental and hereditary defect which involves the psyche on the one hand, and the glands of internal secretion and physical make-up (namely, congenital squint) on the other.

Fig. 11.—The normal and myotonic myogram. 1. The curve in myotonia congenita (Case 3). 2. The time markings in one-tenth second. 3. The normal curve. The downstroke represents contraction; the upstroke relaxation. The same amount of electrical stimulation was used in the myotonic as in the normal control.

CASE 3.—An instance of myotonia congenita associated with definite endocrine disturbances. A polyglandular syndrome involving a thyroparathyroid gonad deficiency on a probable hereditary basis is described.

R. L., aged 23 years, laborer. Habits: Tobacco and alcohol used in moderation. Drugs: None.

Family History.—Father living; suffering from cataract; mother living and well. Sisters: three, living and well. No history of epileptic seizures, psychiatric disorders, or any other diseases obtainable. No history of any muscular disorders.

Previous History.—Measles, scarlet fever and varicella in childhood. No venereal diseases.

Present Illness.—Ever since the age of 7 the patient has been subject to seizures, in which a tremor "comes on him." He then falls unconscious (?). He has never hurt himself in falling nor has he bitten his tongue, lip or cheek.

No involuntary passage of urine or feces has occurred. The seizures are of variable duration. On recovery he does not know his whereabouts and is confused. No feeling of fatigue or headache follow the seizures. They are infrequent in occurrence, sometimes being years apart.

Fig. 12 (Case 3).—Dystrophia adiposogenitalis.

Ever since he can remember he has noted a peculiar difficulty in relaxing the grip muscles of his hands after grasping an object.

Gastro-Intestinal: Appetite good; no craving for sweets. Bowels: Two movements a day. No vomiting; slight gaseous eructations; no pyrosis.

Genito-Urinary: No dysuria or hematuria. No nocturia; no enuresis. Libido: definitely diminished as long as he can remember; he has never had sexual intercourse. No nocturnal emissions.

Respiratory: No cough, no epistaxis.

Cardiovascular: No shortness of breath, precordial pain, or distress. No easy fatigability; no edema of the legs.

Central Nervous System: No headache unless emotionally upset.

Skin: Shaves about two or three times a week although beard is ill-developed. Urticaria: None.

Neurologic and General Physical Examination.—No abnormalities in sensory, reflex or cranial nerve sphere.

Motor: A remarkable myotonia of the so-called myotonia congenita type (Thomsen's disease) is present; especially the grip muscles of the hand are involved making the relaxation of the grip a slow, difficult movement (Fig 10). This preponderating power of the flexors produces a position of the hand very similar to the accoucheur's hand of tetany, especially in the performance of fine movements (such as buttoning the shirt). The mechanical irritability of the muscles of the entire body is quite elevated, remarkable depressions being noted when muscles are mechanically stimulated; the muscle response on mechanical stimulation reveals a sustained plateau of contraction followed by a slow relaxation. This myotonic response is well marked in the tongue, and at times individual facial muscles may be made to undergo slow contraction.

Fig. 13 (Case 3).—The teeth.

In the lower extremities the myotonia produces some slight stiffness in the performance of quick movements, such as rapid squatting movements. While fibrillary twitchings are noted after mechanical stimulation, they are not nearly as marked as the myotonic depression. A greater degree of myotonia was noticed when the patient concentrated all his attention on his muscular efforts.

No Trousseau or true Chvostek phenomenon obtained.

Electrical Examination.—Faradic examination: As compared with controls, a stronger current was required to contract the muscles of the upper limbs. The reaction is definitely slower than normal, and is associated with a persistence of the contraction after removal of the current (myotonic reaction, Fig. 11).

Galvanic Examination: Normal quick response; KCC greater than ACC. Cerebellar Functions: Normal.

Psychiatric Examination reveals a definite mental deficiency, associated with a very labile emotional state. The suggestibility and lack of inhibition characteristic of the child are in marked evidence. Inability to remain in one place or concentrate on a given task is also characteristic. No other psychic abnormalities.

General Physical Examination.—The facies of the patient is that of a cretin, with a wide nasal bridge, thick lips, a mouth that is habitually open,

a large tongue which is slightly bifid. The eyes have a mongolian slant, and are somewhat deep-set with narrow apertures. A low forehead, quadrangular head and large mouth are noted (Fig. 12). The thyroid gland is definitely enlarged (isthmus and lateral lobes).

The hair of the head is dry and has a markedly convex curve at the forehead margin. The hair on the thighs and in the axillae is moderate in amount, but sparse on the trunk.

The skin and subcutaneous tissue are quite thick, as is very evident on attempts to draw blood or give a hypodermic injection. Dryness of the skin is also a feature.

While the penis is of normal size, the testes are distinctly undersized. The simulation of the labia minora by the scrotal folds is lacking. The pubic hairs are profuse and of a male type.

Fig. 14 (Case 3).—Roentgenogram of sella turcica.

Examination of the teeth reveals upper central incisors which are very large in size; the lower incisors are normal. The lower and upper incisors do not approximate when the jaws are closed, the upper jaw protruding slightly. An elliptical area exists between the upper and lower incisors when the jaws are closed, in addition to the prognathism of the upper jaw. The canines are not fang-like and resemble the incisors. A marked pyorrhea alveolaris is present (Fig. 13). A high palatal arch is noted.

No hyperextensibility of the joints is present.

No adiposogenitalis type of fat distribution.

The terminal phalanges are definitely thickened, the nails are somewhat incurved.

Nose and Throat Examination: Except for a small spur on the left side of the septum, and a hypertrophied right inferior turbinate, the nose is normal.

The tonsils are slightly enlarged.

Hearing is normal in both ears. The labyrinthine reactions (Bárány) are normal although sluggish.

Eyes: Vision: right, 20/40; left, 20/40. Ocular movements good; right pupil larger, both pupils active to light and accommodation. Esophoria, 3 degrees. Right hyperphoria, 1 degree. Under homatropin: right, 20/70—100, axis 180 degrees; equals 20/50; left, 20/50—50, with plus 100, axis 90 degrees; equals 20/50. Both fundi negative. Perimetric examinations to form and color is normal. A compound myopia is present.

Lungs: Normal.

Heart: Normal.

Blood Pressure Observations: taken at 2 minute intervals:

Systolic	Diastolic
100	66
97	66
99	66
100	68
100	68

The pulse has been notably slow ranging in rate from 48 to 84, usually being in the sixties; a marked respiratory (sinus) arrhythmia is present. There is no edema or cyanosis.

Abdomen: No viscera palpable. Rectal examination reveals prostate flat, small, moderately firm.

Glands: No special adenopathy noted.

Temperature Observations: A definite subnormal temperature, ranging between 97 F. in the morning and 98 F. in the afternoon has been observed daily for weeks.

MEASUREMENTS OF PATIENT

	Cm.
Total length	165
Circumference of head.....	55
Circumference of chest (at level of nipples).....	87.5
Circumference of abdomen (at umbilicus).....	77
Sterno-clavicular junction to anterior superior spine.....	39
Anterior superior spine to internal malleolus.....	82
Anterior superior spine to upper border of patella.....	41.5
Acromion to styloid process of radius.....	51.5
Acromion to tip of olecranon.....	29.5
Distance between acromion processes.....	36
Distance between iliac spines.....	24.5
Span width	168
Penis	12
Testes	2 × 1.5
Thigh, right	49.5
Thigh, left	49.5
Calf, right	33
Calf, left	33.5
Arm, right	27.5
Arm, left	27.5
Torso-leg ratio	39/82 or .47

LABORATORY DATA

BLOOD

	Feb. 11, 1920	May, 1920
Erythrocytes	4,200,000	4,320,000
Leukocytes	6,700	8,500
Hemoglobin, per cent.....	90	80
Differential count:		
Small mononuclears, per cent.....	22	16
Large mononuclears, per cent.....	8	13
Polymorphonuclears, per cent.....	70	71

BLOOD CHEMISTRY

Blood sugar (fasting stomach), 0.106 per cent. (106 mg. per 100 c.c. of blood).
 Blood sugar (116.9 gm. of glucose given), 0.136 per cent. (136 gm. per 100 c.c. of blood).
 Blood urea: 40 mg. per 100 c.c. of blood.
 Blood creatinin: 1.875 mg. per 100 c.c. of blood.
 Blood calcium: 10.6 mg. per 100 c.c. of blood (Dr. K. M. Vogel).
 Blood carbon dioxide: 62.4 volume per cent.
 Blood Wassermann reaction negative Jan. 8, 1920. and Feb. 12, 1920.
 Bleeding time: 2 minutes.
 Coagulation time: 6 minutes.

FECES

March 1, 1920: Color, brown; consistence, medium; mucus, negative; blood, negative; muscle fiber, striated and nonstriated present; fat, present; starch, negative.

March 3, 1920: After the ingestion of 200 gm. fat in the form of butter: Color, brown; consistence, medium; mucous, negative; blood, negative; muscle fiber, none found; fat, present. No appreciable increase over that found on previous examination. Starch, negative.

STOMACH CONTENTS

	Feb. 28, 1920	March 1, 1920
Total acidity	18	34
Combined acidity	3	4
Free hydrochloric acid.....	0	12
Combined hydrochloric acid.....	10	18
Lactic acid	Faint trace	Negative
Blood (gross and occult).....	Negative	Negative

SPINAL FLUID

Pressure, normal; transparency, slight admixture of blood (technic); cell count, normal, discounting presence of blood; globulin, no material increase; Wassermann, negative. Colloidal gold test, normal curve for preliminary and final curves.

URINE

Numerous urine examinations made at varying intervals revealed: Amber; clear; acid, with a specific gravity varying between 1.026 and 1.036; albumin, sugar, acetone and casts were not found in any of the examinations. No polyuria. Phenolsulphonphthalein showed 45 per cent. output for first hour, 25 per cent. output for second hour, a total of 70 per cent.

SUGAR TOLERANCE TEST (ALIMENTARY GLYCOSURIA)

No glycosuria after 100 gm. glucose, after 180 gm. and after 200 gm. glucose (given in 430 c.c. of milk equaling 30 gm. of lactose).

No glycosuria in the first hour, after 230 gm. glucose (with 1 c.c. of 1:1,000 solution epinephrin given one-half hour later). Glycosuria very positive two hours later; glycosuria less positive three hours after that; glycosuria still less positive four hours later.

After three weeks of thyroid gland feeding (from 6 to 9 grains a day), 100 gm. glucose were given in the morning with no thyroid gland tablets; no glycosuria resulted. On the following morning, 3 grains thyroid gland was given by mouth, followed by 100 gm. glucose in one-half hour; a very faint trace of sugar was noted in the urine collected, following the above procedure.

BASAL METABOLISM

Calories per square meter per hour, 39.9. Variation plus 1 per cent.

ROENTGEN-RAY EXAMINATION

No abnormalities noted in bones and joints; all epiphyses are firmly united.

Fluoroscopic examination shows a rather large stomach with its lower border one inch below the intercostal line. It is slightly hypotonic with no filling defect apparent. The duodenal cap appears to have a filling defect which is inconstant. The ileum is pulled over slightly to the right of the median line. There is no six hours retention. The twenty-four hour plate reveals the barium still in the cecum. The forty-eight hour plate reveals an almost empty intestine. Roentgen findings suggest a large slightly hypotonic stomach with probably periduodenal adhesions; in addition there appears to be some pericecal adhesions.

The chest reveals a slight broadening of the mediastinal shadow (thymus?).

Examination of the skull reveals a small sella turcica with a posterior clinoid process which is definitely thickened. A suggestive pineal shadow is found (Fig. 14).

Hands: The tuft of the left thumb is considerably smaller than that of the right; the other tufts are equal in size, but slightly smaller than usually seen.

ATROPIN TEST

	Pulse	(Blood Pressure— Systolic Diastolic)	Respira- tion	Symptoms and signs
Before administration	44	105 60	20	Pulse shows marked respira- tory arrhythmia.
Administration of $\frac{1}{15}$ grain				
20 min. later.....	44	90 60	20	No dryness of mucous mem- brane; respiratory arrhyth- mia less marked.
30 min. later.....	48	95 65	20	Slight dryness of tongue; respiratory arrhythmia al- most entirely disappeared.
45 min. later.....	54	95 70	20	Moderate dryness of tongue.
1 hour later.....	56	102 65	20	Same.

ERGOTIN TEST

	Pulse	(Blood Pressure— Systolic Diastolic)	Signs and Symptoms
Before administration	64	100 70	
Ergotin, $\frac{1}{40}$ grain.....	..		No reaction was noted fol- lowing this drug.

ESERIN TEST

	Pulse	(Blood Pressure— Systolic Diastolic)	
Before administration	72	105 70	
Eserin, $\frac{1}{50}$ grain			

Following the administration of this drug, no gastro-intestinal effects were noted, the only reaction was slight headache.

PILOCARPIN TEST

	Pulse	(Blood Pressure— Systolic Diastolic)	Respira- tion	Symptoms and Signs
Before administration	58	100 60	22	
Administration of 0.008 gm.				
10 min. after.....	70	90 55	22	Feels warm; face consider- ably flushed; slight perspi- ration.
18 min. after.....	60	100 60	22	Face moderately flushed; considerable perspiration; moderate salivation; a feel- ing of warmth noted; re- spiratory arrhythmia un- changed.
24 min. after.....	62	100 60	22	Feels cooler; moderate per- spiration; slight salivation; desire to urinate present.
30 min. after.....	62	100 60	22	Feels cool; no salivation; perspiration much less, slight on forehead; face less flushed; temperature, 97.4 F.

PILOCARPIN TEST (REPEATED)

	Pulse	Systolic (Blood Pressure)	Diastolic	Signs and Symptoms
Before administration	60	100	65	
Pilocarpin, 1/10 grain				
10 min. after.....	60	96	60	Moderate flushing of face; slight salivation and moisture of skin; complains of headache.
15 min. later.....	60	100	60	Skin moderately moist, moderate salivation.
25 min. later.....	60	100	60	Face moderately flushed, skin moist, salivation fairly marked.
30 min. later.....	..	..	..	Skin moist, salivation fairly marked; patient exhibited psychic changes after administration of drug; began to cry and stated he was worried over his mother; said he was "bursting with sorrow."

EPINEPHRIN TEST

	Pulse	Systolic (Blood Pressure)	Diastolic	Respiration	Signs and Symptoms
Before administration	58	102	70	16	Considerable respiratory arrhythmia.
1 c.c. of 1:1,000 solution hypodermically					
10 min. later.....	52	102	70	15	No tremor no general reaction.

PITUITARY TEST

	Pulse	Systolic (Blood Pressure)	Diastolic	Signs and Symptoms
Before administration	64	100	70	
Pituitrin, 1 c.c.				
5 min. later.....	64	100	70	
10 min. later.....	64	100	70	Patient pale; desires to urinate.
20 min. later.....	64	100	70	Desire for defecation present; movement of bowels occurred.

Thermo-reaction (Cushing) negative, i. e., no rise in temperature after injection of pituitrin (1 c.c.).

TYRAMIN

	Pulse	Systolic (Blood Pressure)	Diastolic	
Before administration	54	100	60	
Tyramin, 60 mg.				
5 min. later.....	40	110	64	
12 min. later.....	44	105	60	Blood pressure rise very slight

Narrow slits; enophthalmos; tendency toward myosis; gag reflex lessened. Oculocardiac phenomenon positive pulse, 64, slowed to 48. Winking infrequent. Epinephrin into conjunctival sac, negative. Goetsch's test (intracutaneous injection of epinephrin) negative.

DISCUSSION

1. *The Endocrine Balance.*—The cretin facies, the enlargement of the thyroid gland, the subnormal temperature, the increased sugar tolerance, the thick skin, the hypotonic vegetative nervous system, and the insensitiveness to large amounts of thyroid gland feeding, are conclusive evidences of a hypothyroidism.

The testicular atrophy reveals the gonadal deficiency.

The parathyroid involvement is suggested by the myotonia (see below) in this connection the occurrence of double cataract in the father at the age of 48 might be construed as a parathyroid defect.

The rôle of the thymus is uncertain.

2. *Myotonia Congenita.*—The association of this remarkable motor disorder with endocrine disturbances has been noted before. W. Falta writes of this relationship under diseases of the parathyroid gland and

Fig. 15.—The response to ascending doses of thyroid gland (Harrower's test).

notes the presence of myotonia in certain cases of tetany; he states that "just those animals in whom thyroid and parathyroids have been removed show these manifestations," i. e. myotonia. Steinert,¹⁴ speaking of the closely allied myotonia atrophica, emphasizes the atrophy of the testicles and impotence in his cases.

It will be noted that the myotonia in this instance is associated with a very definite thyrogonadal deficiency.

14. Steinert: Ueber das klinische und anatomische Bild des Muskelschwunds des Myotoniker, Deutsch. Ztschr. f. Nervenhe. **37**:58, 1909.

Certain American authors have likewise called attention to the dependence of this myopathy on endocrine disturbances.¹⁵

3. *Metabolism*.—The essentially normal basal metabolism again demonstrates the fact that the hypothyroidism is compensated for by the activity of the other glands and possibly through the agency of other mechanisms less understood.

As for the calcium metabolism, we have not had the facilities at hand to estimate this, with the detail with which Rosenbloom and Cohoe¹⁶ have accomplished it. These authors concluded from their studies that a "loss of calcium may play a part in the production of the symptoms of myotonia congenita."

The increased sugar tolerance is noted in the alimentary tests. Of interest is the reduction of sugar tolerance with the consequent appearance of a slight glycosuria after the oral administration of three grains of thyroid gland (see laboratory data); this seems to show in a conclusive way the dependence of increased sugar tolerance upon thyroid deficiency in this case.

4. *The Psyche*.—The mental deficiency and inadequate personality reactions present in this case point again to a basic hereditary developmental defect which affects both the psyche and ductless glands.

THERAPEUSIS

For over a period of one month he was given first 6 grains and then 9 grains of thyroid gland a day, together with $\frac{1}{10}$ grain parathyroid gland, three times a day, and potassium iodid, 5 minims, three times a day. Under such therapy there was no appreciable change in the myotonia. Hoffmann (quoted by Falta), in a case of myotonia associated with tetany, noted the disappearance of the myotonia on the administration of thyroid gland and its reappearance after withdrawal, while the tetanic symptoms were not affected.

There was an increased psychomotor activity—purely a quantitative increase, however; the same psychic abnormalities (childish behavior, emotional instability and irresponsibility) were still in evidence. He stated that he had some difficulty in getting asleep, and that he felt warm at night. No tremor, tachycardia, loss of weight or diarrhea occurred, nor were there any changes noted in the configuration of the thyroid gland. A coryza due to the iodid necessitated a discontinuance of this drug for a time.

15. McCouch, G. P., and Ludlum, S. D. W.: Is Myopathy Related to Disorders of Internal Secretion? *Med. Rec.* **39**:1042, 1916.

16. Rosenbloom, J., and Cohoe, B. A.: Clinical and Metabolism Studies in a Case of Myotonia Congenita-Thomsen's Disease, *Arch. Int. Med.* **14**:263 (Aug.) 1914.

CONCLUSIONS

1. Three unusual cases are presented in detail, in each of which remarkable endocrinopathies are associated with unusual manifestations in the muscular system.

2. Attention is directed to the endocrine balance, the sugar and the basal metabolism.

3. It is shown that the basal metabolism is the result of the sum total activities (in part compensatory), of the various ductless glands. In polyglandular disorders, such as those described, the basal metabolism does not reflect the degree of participation of any individual gland.

4. In two cases a congenital developmental defect is postulated as the cause of both the endocrine deficiencies and the psychic disorders.

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