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PETER BENT BRIGHAM HOSPITAL

DEFECTS IN MEMBRANOUS BONES, EXOPHTHALMOS AND DIABETES INSIPIDUS; AN UNUSUAL SYNDROME OF DYSPITUITARISM

THE case that I am going to show appears to be almost unique, and is reported primarily for the rarity of occurrence of the extraordinary defects in the skull bones, which, with the associated exophthalmos and diabetes insipidus, makes a truly remarkable clinical picture. The diabetes insipidus and its reaction to pituitary substance make certain a causal relation between a functional derangement of the pituitary gland and the increased urinary output. The fact that the only 2 additional cases with similar skull defects which I have been able to find reported in the literature had evidence of disturbed pituitary function makes it probable that the bone changes, too, owe their origin to dyspituitarism. Hence in discussing this case we are calling attention to an effect of pituitary change not generally recognized. Finally, this case has given the opportunity to make observations on the effects of pituitary substance given in various ways.

The patient, A. S., Med. No. 7945, a little girl aged five years, was admitted to the Peter Bent Brigham Hospital on January 24, 1918, referred by Dr. Thomas E. Lilly, of Shirley, Mass. She remained under observation in the hospital for six months. Her history is as follows:

Family History.—Father, mother, and one brother are living and well. The brother, who is three and a half years old, is

normal in every way according to the father's statement. The mother has had no miscarriages. The father has had some rheumatism for about a year. The father and mother are both troubled with pain in their backs. There is no family history of cancer, diabetes, gout, tuberculosis, hemophilia, arthritis, or diseases of the circulatory, respiratory, digestive, renal, nervous, or muscular systems.

Habits.—Two to three cups of coffee daily. No tea, alcohol, tobacco, or drugs.

Past History.—The patient was born in Shirley, Massachusetts, of Austrian parents, and has lived in Massachusetts all her life. She is the first child, and was born at full term after forceps delivery. Her birth weight is not known, but she was of medium size and was breast fed for one year. During this time she grew normally, getting her teeth at the normal time, and had no symptoms of rickets. She had mumps three to four months ago. There have been no other acute illnesses.

Injuries.—None.

Operations.—None.

Head.—For two years she has had pain in her head (see *Present Illness*). No trauma to head. *Eyes:* No failing vision or glasses. Her eyes occasionally become reddened and pain her much of the time. *Ears:* For two years her hearing has been getting poorer. No pain in ears, discharge, or tinnitus. *Nose:* Not subject to head colds. No discharge or epistaxis. She breathes through her mouth all the time. *Teeth:* Her first teeth came in all right, but when she was three years old they began to decay. Several of her second set are now through (see *Present Illness*). *Throat:* No tonsillitis, sore throat, or hoarseness. Her mouth, especially around the teeth, has been sore much of the time for two years (see *Present Illness*).

Cardiorespiratory.—No pain in the chest, no palpitation, dyspnea, cough, sputum, hemoptysis, night-sweats, chills, fever, or edema.

Gastro-intestinal.—Her appetite is rather poor, but she eats something three times a day. For two years she has had an enormous thirst. Her bowels have been somewhat irregular,

for which Castoria has been used. A movement was obtained almost every day. No nausea, gas, vomiting, hematemesis, distress, colic, icterus, diarrhea, bloody, tarry, or clay-colored stools.

Genito-urinary.—For almost two years she has been passing her urine about every hour—from 1 to 2 glassfuls at a time. Her intake is about 9 quarts in twenty-four hours. Three months ago she had a little pain on urination for a short time. No hematuria, pyuria, smoky urine, retention, or incontinence. No history or symptoms of syphilis or gonorrhea.

Neuromuscular.—The patient sleeps well. She is of a quiet disposition, not nervous. No vertigo, fainting, twitching, spasms, anesthesia, paresthesia, ataxia, girdle, or shooting pains in the muscles or joints. Her memory is good and her disposition agreeable. Her father says she learns things quickly, talks well, and walks normally. She plays with other children some, but less than a child normally does.

Weight.—For the past year she has weighed about 43 pounds, which is the most she has every weighed.

Present Illness.—According to the father's statement, the patient was well and normal in every way until she was three years old. At that time her teeth began to decay and become loose and her gums became swollen and tender. No other symptoms were noted. Her mouth continued to be sore, and at the age of three and a half years the right eye became prominent, and she began to drink more water and pass her urine more frequently. These symptoms gradually increased in intensity until both eyes were markedly protruding, and she was drinking 9 quarts of water a day and urinating every hour. She has complained of more or less constant pain in her head for two years. Her hearing has gradually become poorer. Her father thinks she has had no disturbance of vision and she has had no vomiting. For four or five months she complained of a little pain in her back and three months ago she had a little dysuria for a short time. At times her feet and hands become hot and sweaty. (History obtained through father who speaks little English.)

Physical Examination.—The patient is poorly developed and nourished, lying quietly in bed and apparently fully conscious. *Skull:* Symmetric. Over the whole skull, but most marked over the posterior portion, are numerous small, smooth irregularities. Both fontanels are closed. In the right frontoparietal region and in the left parieto-temporal region are two irregular areas, each measuring 8 cm. in its greatest extent, which feel soft as compared

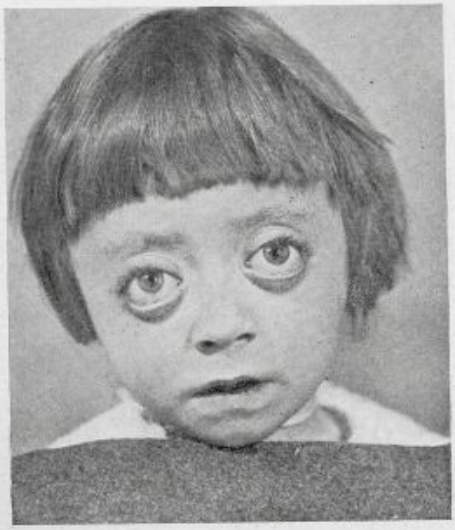

Fig. 178.—Front view of head showing the exophthalmos causing a wide aperture between the eyelids.

with the surrounding portions of the skull. Two similar smaller areas are also present in the left frontal region and on the forehead just above the nose. Both pulsate with each heart-beat and bulge when the patient cries; otherwise there is no bulging. The circumference of the head in its greatest diameter is 50 cm. No areas of tenderness. *Scalp:* Clean and free from scars. The veins over the frontal portion are prominent. *Hair:* Brown, fairly abundant, and of fine texture. The *face* gives no evidence

of suffering. It is somewhat triangular in shape with a prominent forehead. The bridge of the nose and the area directly above it are full, rounded, and shiny. The veins of the forehead are prominent and the skin around the inner canthi is cyanotic. The *skin* is rather pale, of fine texture, normal temperature, and without eruptions or pigment. It is under normal tension and neither dry nor moist. *Eyes:* The pupils are equal, regular, and react to light and accommodation. The scleræ are blue. There

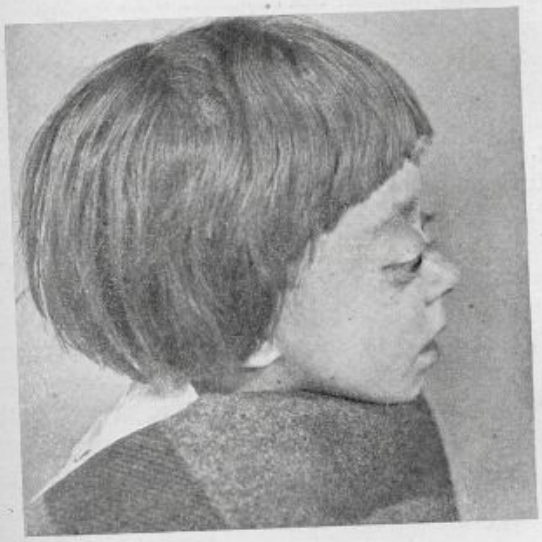

Fig. 179.—Lateral view of head showing prominence of eyeball.

is a slight lacrimation. No photophobia, diplopia, nystagmus, or palsies. There is a very marked degree of exophthalmos (Figs. 178, 179) and lidlag (Von Graefe's sign). The eyes can be held in convergence (no Möbius' sign). The conjunctivæ are rather pale. The eyes are definitely tender. No gross disturbance of vision. No glasses worn. No edema of the lids. Both lids are somewhat reddened, are thin, and the vessels stand out prominently. This condition is slightly more marked on the right. *Ophthalmoscopic examination* is not satisfactory. The

inner margins of the disks are blurred, the outer margins distinct and raised. The veins are tortuous and prominent. *Ears:* The patient hears if one talks in a loud tone. A watch held against either ear is apparently not heard. (The child is very diffident, so this test of hearing is probably not accurate, and later on there was no evidence of deafness. H. A. C.) No stigmata, tophi, or discharge. Mastoid processes not enlarged; no mastoid tenderness. *Nose:* Both inferior turbinates are thickened and the patient breathes through her mouth all the time. No discharge. *Mouth:* The breath is slightly foul. No ulcerations, exudate, or pigment. *Lips:* Of good color and without herpes, ulcerations, or fissures. *Teeth:* The second set of central incisors are through. Several of the other teeth are loose and some are missing. There are a few cavities. All are ill kept. *Gums:* Retracted around part of the teeth and ulcerated, as though about to bleed. Pus can be expressed from along several of them, and the gums in places are coated with a thick, dirty brown exudate. No leadline. *Tongue:* Heavily coated with a light brown coat. The papillæ show up prominently. The tongue is protruded in the median line without tremor. No mucous patches or scars. *Tonsils:* Not seen. *Pharynx:* Covered with the same dirty brown exudate as that on the tongue and gums. Palate and reflexes normal. *Larynx:* The voice is of good quality. *Neck:* No enlargement of thyroid. No palpable lymph-glands. Small pulsations are visible in the cervical vessels. The patient holds her head slightly bent forward and objects to having it lifted or turned sideways. No tracheal tug.

Thorax.—Symmetric and expands equally on both sides. It is of normal size and shape. Respiration regular, of moderate depth, and 28 per minute. Pulsations are visible over most of the precordium.

Heart.—Apex impulse felt in the fourth space in nipple line. It is regular, forceful, and felt over a large area. The right border is 2 cm. and the left 6 cm. from the midsternal line. A systolic thrill is felt over the whole precordium. The first sound is loud and ringing in character. No murmurs. P^2 is greater than A^2. No thrills or murmurs over the aortic arch.

Vessels.—Radial pulses regular, equal, synchronous, 116 per minute. The vessel walls are not felt.

Blood-pressure.—Systolic 90, diastolic 50.

Lung.—Tactile fremitus is normally transmitted. No areas of dulness. No changes in voice or breath sounds. No râles. Lower borders of lungs at ninth thoracic spine.

Abdomen.—Full, symmetric, tympanitic. Fecal material can be felt in the descending colon. No pulsations, tenderness, or spasm. Respiratory movements are plainly visible. No herniæ or fluid. Reflexes present.

Liver.—Dulness extends from the fifth rib to 1 cm. below the costal margin. The edge is felt and is sharp and not tender.

Gall-bladder, spleen, and *kidneys* not felt. No costovertebral tenderness.

Genitalia.—Normal.

Rectal examination not made.

Lymphatic glands of pea size are palpated in both groins. None felt in the neck, axillæ, or epitrochlear regions.

Bones.—The spine shows no scoliosis, lordosis, rigidity, or tenderness. No other bones than the skull, as already noted, show any exostoses, irregularities, or tenderness.

Extremities.—*Arms* show no involuntary, athetoid, or choreiform movements. The muscles are poorly developed. No tremor or clubbing of the fingers. The nails are not remarkable. The biceps and radioperiosteal reflexes are obtained, but not the triceps.

Legs.—No varicosities, scars, or ulcers. Knee-jerks and Achilles' reflexes and plantar reflexes obtained. No Babinski, Oppenheim, ankle-clonus, or Kernig's sign. Romberg and gait not tested. (Subsequently the gait seen to be normal.) No edema. The knees are large.

Skin.—No areas of anesthesia, paresthesia, or hyperesthesia.

The Wassermann test on the blood-serum was negative. Study of the stools was negative. Blood examination showed a red blood-cell count of 5,200,000 and a white cell count that ranged between 6600 and 12,600, with an occasional rise to 14,100; 15,600, and 20,100. The differential count on admission

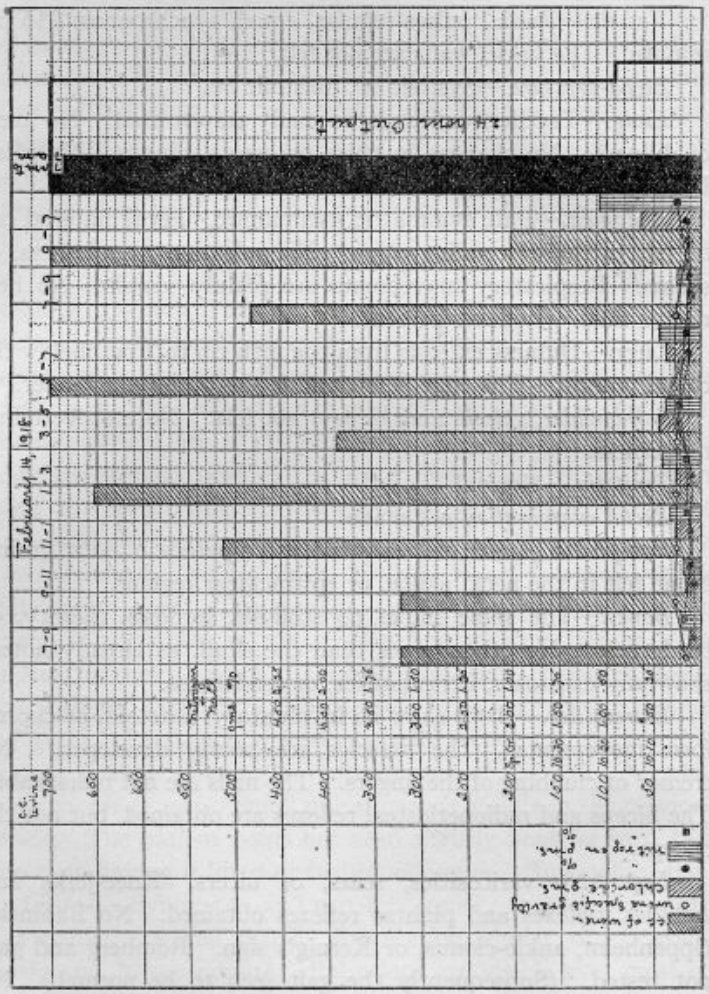

Fig. 180.—Two-hour renal test showing fixation of specific gravity and percentage concentration of sodium chlorid and nitrogen during period of polyuria. Columns indicate amounts of urine in cubic centimeters and of sodium chlorid and nitrogen in grams; each series of three corresponding to a period of urine collection. The circle indicates the specific gravity; the dot, percentage concentration of sodium chlorid; the square, percentage concentration of nitrogen. Black columns at the right indicate the night amount of urine; uninked columns indicate day amount of urine.

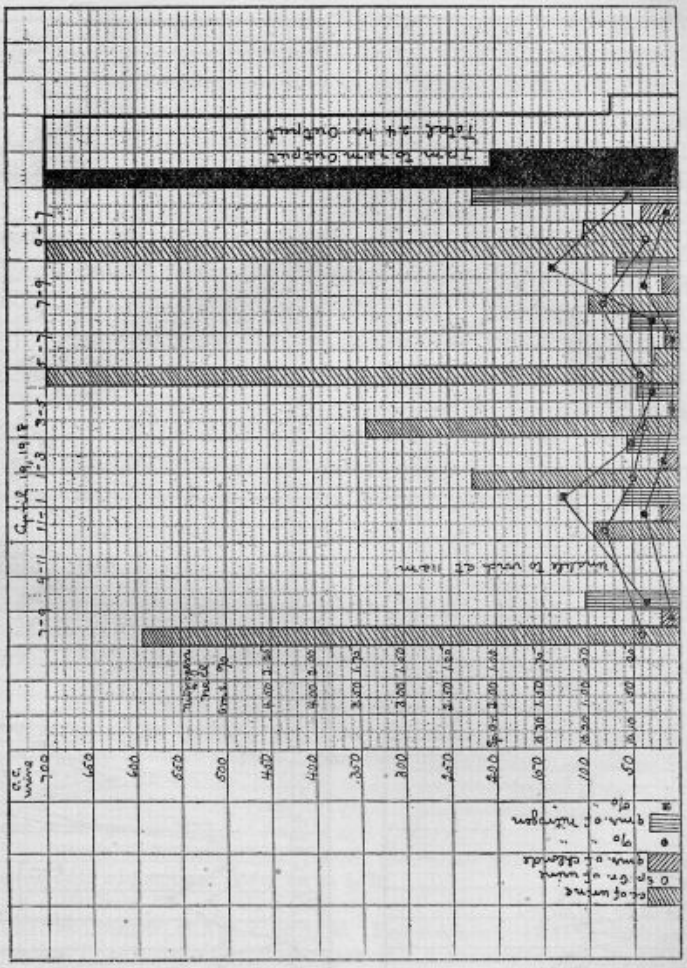

Fig. 181.—Two-hour renal test showing absence of fixation of specific gravity and percentage concentration of sodium chlorid and nitrogen during a period of normal urinary output while the patient was under influence of pituitary substance given subcutaneously. For explanation of the chart see legend under Fig. 180.

showed polymorphonuclear cells 30 per cent., lymphocytes 45 per cent., large mononuclears 23 per cent., and eosinophils 2 per

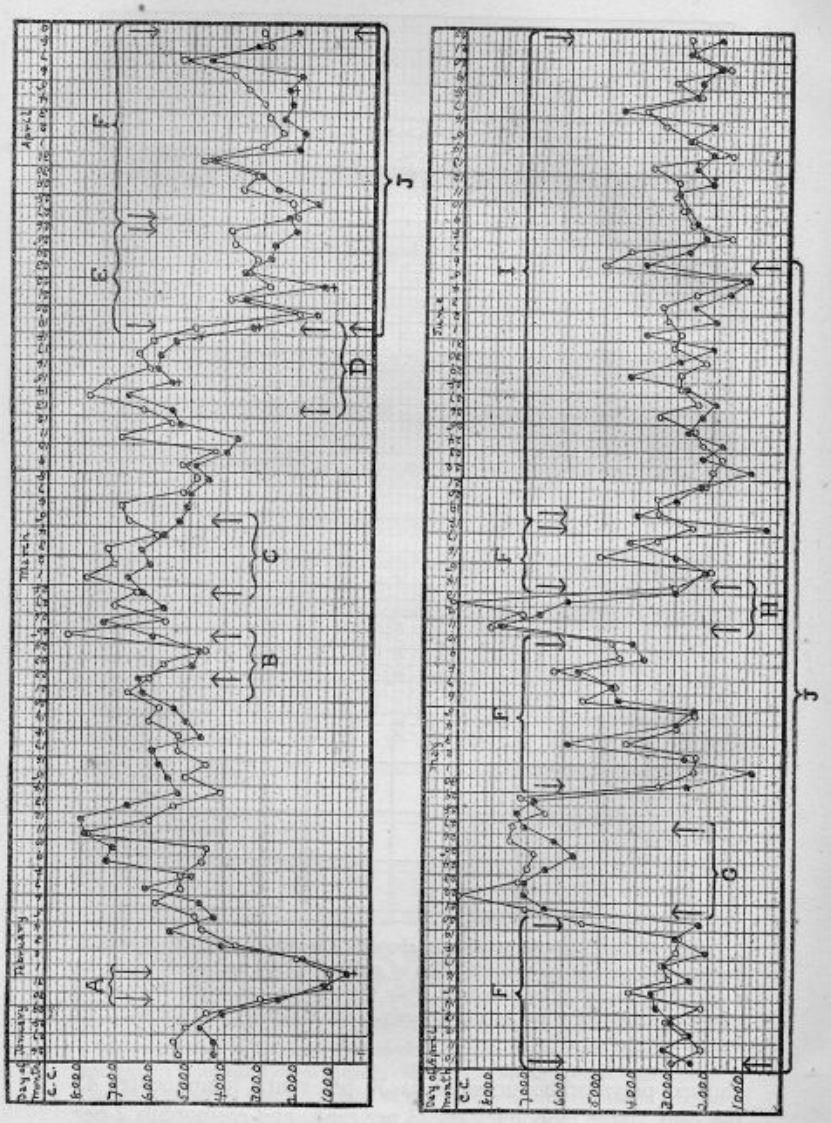

Fig. 182.

cent. The urine was normal except for the low specific gravity during the periods when there was a polyuria. The specific gravity then ranged from 1001 to 1004. Under the influence of pituitary substance, when the amount decreased, the specific gravity of the twenty-four-hour specimen rose to 1008 or 1010. On February 14th, during a period of polyuria with an output of 5250 c.c., a two-hour renal test was made as shown by the accompanying chart (Fig. 180). On April 19th, with a decreased output under the influence of pituitary substance, the output of urine amounting to 2900 c.c., a two-hour test (Fig. 181), in contrast to the first one, shows a very considerable ability to concentrate, as represented by a specific gravity varying from 1007 to 1016, a percentage concentration of sodium chlorid varying between 0.02 and 0.19 per cent., and a percentage concentration of nitrogen varying between 0.13 and 0.69 per cent., as shown in the chart; in other words, a normal picture. In the table

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Fig. 182.—Showing fluid intake and urinary output for each twenty-four hours. Letters and arrows refer to pituitary substance given in various ways as indicated below:

A. Pituitrin, 4 drops subcutaneously three times a day. Begun at 3 P. M. on 1/30 and stopped at 6 P. M. on 2/1.

B. Dried pituitary gland, 0.1 gram three times a day in gumdrops dissolved in the mouth. Begun at 8 A. M. on 2/22 and stopped at 8 A. M. on 2/25.

C. Dried pituitary gland, 0.1 gram three times a day in gumdrops dissolved in the mouth. Begun at 8 A. M. on 2/28 and stopped at 4 P. M. on 3/5.

D. Powdered pituitary gland, 0.1 gram in suppositories four times a day. Began at 12 noon on 3/13 and stopped at 4 P. M. on 3/19.

E. Pituitrin, 0.25 c.c. subcutaneously three times a day. Begun at 8.45 P. M. on 3/19 and stopped at 8 P. M. on 3/26.

F. Pituitrin, 0.5 c.c. subcutaneously twice a day. Begun at 10 A. M. on 3/27 and stopped at 6 P. M. on 4/20. Begun again at 12.35 on 4/30 and stopped at 10 A. M. on 5/10. Begun again at 6 P. M. on 5/14 and stopped at 10 A. M. on 5/18.

G. Pituitrin suppositories containing 1 c.c. of pituitrin four times a day. Begun at 9.20 A. M. on 4/21 and stopped at 8 P. M. on 4/27.

H. 2 c.c. pituitrin in 200 c.c. of salt solution per rectum twice a day. Begun at 6 P. M. on 5/10 and stopped at 10 A. M. on 5/14.

I. Pituitrin, 0.75 c.c. subcutaneously twice a day. Begun at 6 P. M. on 5/18 and stopped on discharge on 6/22.

J. Powdered pituitary extract by mouth, 0.1 gram four times a day. Begun at 8.45 P. M. on 3/19 and stopped at 12 noon on 6/6.

on page 871 appears the excretion of sodium chlorid and nitrogen from day to day.

The excretion of urine in relation to dosage with pituitary substance was of much interest. Figure 182 shows this graphically. The solid dot represents the urine output for each twenty-four hours; the circle, the fluid intake. The arrows show the time of beginning and ending dosage with pituitary substance. The letters in reference to the key show the form of pituitary substance, dosage, and mode of giving. It is evident in the chart that at *A*, *E*, *F*, and *I* there is a definite decrease in urine output and fluid intake. At those periods the patient received pituitrin (Parke Davis & Co.), a liquid extract of pituitary gland, given subcutaneously in varying dosage. In contrast, gland substance taken by mouth and swallowed, *J*; gland substance mixed in gumdrops and allowed to dissolve slowly in the mouth for local absorption, *B* and *C*; and gland extract (pituitrin, Parke Davis & Co.) in salt solution introduced per rectum, *H*, or in the form of suppositories, *D* and *G*, all failed to have any appreciable effect on the excretion of urine. At no time during the patient's stay was her fluid intake limited; she had free access to water and the fluid intake was such as her sense of thirst dictated. These tests show that pituitary gland substance, in liquid form, introduced subcutaneously, had a striking effect on urine excretion, decreasing it to normal if sufficient gland substance was used, whereas other ways of giving gland substance had a negligible effect. The action of gland substance absorbed from the subcutaneous tissue was temporary, and better effects were obtained by more frequent dosage than by larger doses given at longer intervals. As we shall see later, the quite long-continued use of pituitary substance in this case had no demonstrable effect on the bone defects.

Two determinations of basal metabolism were made on this patient for us by Miss E. H. Tompkins in the Hospital Respiration Laboratory. Her results were as follows: March 11, 1918: Height, 101.3 cm.; weight, 12.5 kg.; buccal temperature, 99.0° F.; blood-pressure—systolic 80, diastolic 50.

	Period I.	Period II.	Average.
Pulse	131	130	131
Respiratory quotient	0.78	0.78	0.78
Calories per square meter per hour	57.9	55.4	56.7

March 29, 1918: Height, 101.6 cm.; weight, 12.7 kg.; buccal temperature, 99.8° F.; Blood-pressure—systolic 85, diastolic 50.

	Period I.	Period II.	Average.
Pulse	119	127	123
Respiratory quotient	0.81	0.82	0.82
Calories per square meter per hour	53.2	56.0	54.6

Miss Tompkins' interpretation of the results appear in the following notes:

March 11, 1918: "As yet I can find no standard metabolism for children below eight years of age. At that age it is 54 calories per square meter per hour. From eight to fifteen years the standard metabolism of females changed 3.5 calories per square meter per hour for each year. Assuming the same rate from five to eight years (a very uncertain assumption) the standard for five years of age would be 61 calories per square meter per hour. In this case the child's metabolism would be: Period I = —5 per cent.; Period II = —9 per cent.; Average = —7 per cent. It is worthy of note that the child's pulse was much higher during the determination than it runs on the ward."

March 29, 1918: "Metabolism percentage from normal, with the same uncertainty in the standard used, as is noted upon the determination of March 11th: Period I = —13 per cent.; Period II = —8 per cent.; Average = —11 per cent. Here also the pulse runs higher than upon the wards."

It would seem from these reports that no great departure of basal metabolism from the average normal was present. Apparently there is a moderate decrease in activity of metabolism. This would be in complete accord with our usual findings in adults with disturbances of pituitary function, but owing to the uncertainty as to a normal value for such a child it can be regarded quite as much as an essentially normal value of no diagnostic significance.

The most remarkable feature in this case is the truly ex-

traordinary picture revealed by *x*-rays. A number of plates were made during the six months' observation; several times stereoscopic plates were taken. Rather than giving a description of these individual plates a composite description of the group will be attempted. Fortunately, a year before admission (February 22, 1917) she came to the hospital and skull plates were made. These showed at that time a similar, though slightly less extensive process.

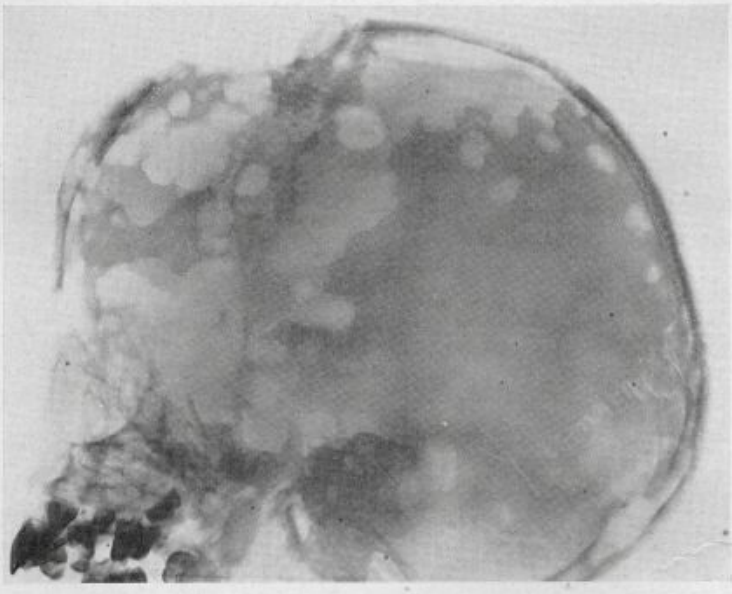

Fig. 183.—*x*-Ray of skull showing bone defects: lateral view.

The striking thing in a complete Roentgen ray study of the skeleton is the very extensive defects in the skull bones, slight but similar changes in the flat bones of the pelvis, and a quite normal appearance and normal stage of ossification and development of all other bones in the body. The defects in the skull caused an appearance which can be best described by comparing them to the irregular holes in a bit of moth-eaten flannel or the appearance of a pasteboard box gnawed full of holes by mice (Figs. 183, 184).

As seen in the lateral view (Fig. 183), the most extensive defects are in the anterior half of the skull. Of the frontal bone, particularly the lateral portions, only irregular rather narrow septa of bone are left between the large islands of entire bone disappearance. In a similar way the orbital plates of the

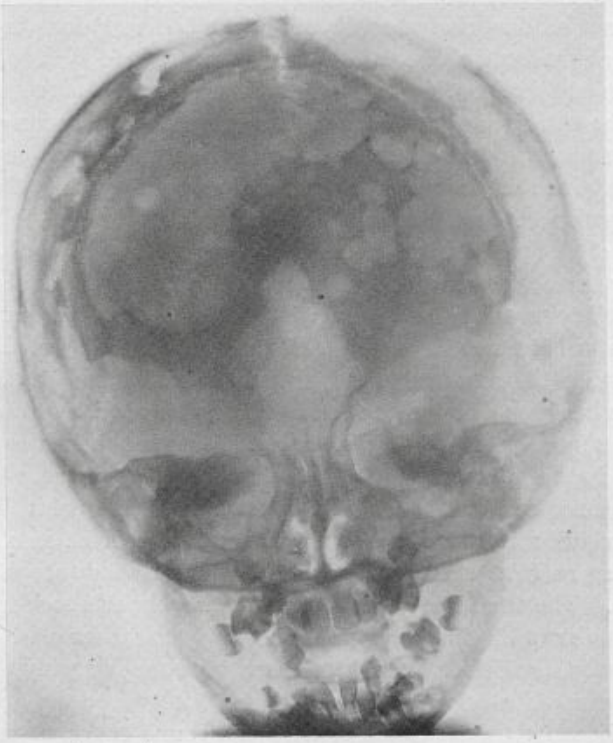

Fig. 184.—*x*-Ray of skull showing bone defects: frontal view.

frontal bone have largely disappeared, so that there is little bony support remaining for the eyeballs. In the parietal bones there are extensive defects in the vertex portions, whereas in the lateral portions of the parietal bones there are only a few round defects, measuring from 1 to 2 cm. in diameter. In the occipital bone only three small circular defects are present.

Viewed in the anteroposterior direction (Fig. 184) the very extensive defects in the frontal bones are very evident, as is also the irregularity in the orbits of the eye. The best idea of the character of the skull defects is obtained from stereoscopic plates, from which it is perfectly clear that the defects represent a complete loss of all bone substance capable of throwing any distinct shadow characteristic of bone. The variations in density at different places in the bones when seen in the ordinary plates are due to the fact that in some places there are defects on the two sides of the skull in line with each other, whereas in other places the defect on one side of the skull is opposite to a place where intact bone remains on the opposite side. Almost everywhere the margins of the defects are sharply cut, as if the line of demarcation between no bone and fairly normal bone is a very sharp one. Only here and there do the edges show a ragged appearance, indicating points where small projecting portions of bone remain intact. This picture may be due to the fact that the inner table at this point remains and the outer table has been dissolved or destroyed, or vice versa. At certain points in the stereoscopic plate it is evident that there are small round defects or cavities in the substance of the bone, with a thin inner and outer table still intact, and at one point in the lateral view the thin inner and outer tables can be seen projecting as faint shadows beyond the general substance of the bone. The character of the round defects of small size seems to be similar to the character of the large irregular defects. About none of these defects does the surrounding bone show any thickening or other evidence of proliferation, and where the defects do not exist the structure of the bone seems entirely normal. The sella turcica seems somewhat enlarged and slightly flattened, and in the stereoscopic view it looks as if there is a defect in the base of the skull very close to, if not continuous with, the sella turcica.

Plates taken at different times show very slight variations in the picture. On February 22, 1917, the defects were evidently less numerous and less extensive than on January 30, 1918. The last plates taken, those of June 10, 1918, after six months'

stay in the hospital and treatment with various forms of pituitary substance, show no change apparently of progression or retrogression in the defects as contrasted with the picture of January, 1918. All the other bones in the skeleton, except the pelvic bones, show no change whatever. In this bone in the lower half of the ilium there is slight irregular rarefaction suggesting small incomplete defects roughly circular in character, similar to what is seen in the skull, only very much less marked, and in the anterior portion of the ischium near the acetabulum there is also slight irregularity in the density, suggesting loss of substance.

DISCUSSION

A careful search of the literature revealed but one report of a similar condition. Schüller, in the Fortschritte auf der Gebiete der Roentgenstrahlen, 1915–16, xxiii, 12, under the title "Uber eigenartige Schädeldefekte in Jugendalter," describes 2 cases observed by him in Vienna. In these, *x*-rays of the skull show the same condition as described above in my case. His description is as follows:

CASE I.—"Boy of sixteen years, with normal family history. Except for measles the patient was well in the first years of childhood. He went through four classes in the Volksschule successfully. Since that time he has not grown any more. Three months ago the patient noticed that his left eye was more prominent than the right. Since then a slight inflammation of the left eye has been present. There has never been any headache, dizziness, vomiting, or decreased vision. Recently there has been double vision in looking to the side, affecting mostly distant objects. They stand either parallel or leaning toward each other. In January, 1913 the patient was 137.5 cm. high and weighed 39.5 kilos. Panniculus adiposus richly developed. Cheeks fat. On both sides of the neck above the clavicle are fatty tumors. Also in the thorax there is much fat and the abdomen is fatty. Arms and legs also are fatty. No abnormal findings in the internal organs. No symptoms of tuberculosis or syphilis. The genitals are small and completely infantile. The

right lobe of the thyroid is slightly larger than the left, but not abnormal. Skull dolichocephalic. Forehead is short and somewhat narrow. Over the left eyebrow the skull is somewhat sensitive. The face is asymmetric. The left half appears prominent and seems as if swollen. The left eye projects about 8 mm. beyond the right. Movements of the left eyeball unaffected. Nystagmus on looking to the side. In the fundus of the left eye the veins have dilated without pulsation. The fundus is normal.

"At different places in the Roentgen ray plate the left half of the skull shows clearing of the bone shadow corresponding to extensive ulceration of the skull. The greatest defect is in the region of the left parietal bone near the midline. This defect shows an irregular, nearly square form, diameter 3 to 5 cm. From the posterior lower corner of this defect goes a narrow horn-like, half-moon, curved process. The edges of the defect are sharp. The central part of the defect appears brighter than the periphery. Further defects are found in the region of the left frontal bone and in the region of the occiput. The walls of the left orbit do not appear changed as compared with the right. The sella is small. The dorsum sellæ is intact. Reflexes are normal. There can be no doubt that the combination of dystrophia adiposogenitalis and protrusion of the eye can be explained on the assumption of a tumor at the base of the brain. Other things suggest pressure. The suggestion is made that the tumor is an angioma of the dura or of the skull bone."

CASE II.—"Four-year-old girl who when one and a half years old had whooping-cough. When two years old she suddenly developed left-sided exophthalmos. At that time the physician who saw the child demonstrated a defect in the skull roof. Some months later a right-sided exophthalmos suddenly appeared. In October, 1913 the child was small and slender. Skin and mucous membranes were pale. Microscopic and Wassermann study of the blood was negative. Internal organs and neurologic examination was unimportant. There was no glandular swelling; no remains of any previous rickets. Intelli-

gence of the child seemed well developed. There were markedly increased thirst and polyuria, up to 8 liters daily. The child's head is of normal size and oval shape. The growth of hair is very sparse. Extensive portions of the scalp are free of hair. Both eyes show a high-grade exophthalmos. Vision amounts to at least 6/20. On both sides there is temporal pallor of the optic nerve. On palpation the skull shows several defects of different extent. They are partly oval, partly oblong. The edges of the defects are sharp and firm. Where the defects exist one feels the pulsations of the brain, but the membranous covering of the defect does not bulge, but seems slightly sunken. *x*-Ray of the skull shows very plainly the defects. They appear both in the transverse and sagittal picture as an entirely peculiar map-like spotting of the *x*-ray shadow. Only a relatively small part of the skull shadow corresponds to the normal bone thickness. Within very extensive regions one sees different sized and differently formed clear places. These are partly light gray and in part completely lack the ordinary darkening or shadow of bone. The former correspond to skull defects without any on the opposite side, so that, on the defect on one side, a bone shadow is projected from the opposite side. The latter are defects which overlie defects on the opposite side. The edges of the defects are completely sharp. When the defects appear in profile the edges have a funnel form, so that the defect in the lamina externa is greater than in the lamina interna. The skull between the defects seems entirely normal. Also in the region of the base of the skull extensive defects are recognized. The well-known contour of the upper edge of the orbit is completely lacking on both sides. The orbital roof appears almost completely eroded. The sella turcica is markedly changed. Only the dorsum sellæ is present. The anterior part of the floor of the sella is greatly deepened. The destruction of the roof of the orbit explains the exophthalmos. In January, 1914 the symptoms had not changed. The defects in the skull plainly were smaller. *x*-Rays taken of the pelvis at this time showed a round defect about the size of a five-crown piece in the right ilium and also a spindle-like thickening in the upper part of the

right femur (healed fracture)." Reproductions of *x*-rays of the skull of this patient are almost identical with those of my patient.

Schüller goes on to say, "The explanation of this case is very difficult. The history makes it plain that it is not a congenital, but an acquired, disease of the skeleton. The clinical observation shows that the process is capable of regression. Most probably it is a primary bone disease in the sense of a system disease of the skeleton. One might think of a disturbance of the centers of ossification brought about through a disease of the glands of internal secretion. Diabetes insipidus occurs most frequently in affections of the hypophysis. The erosion of the sella turcica, demonstrable in the *x*-ray, might be caused by a tumor of the hypophysis region. The defects of the roof of the skull and of the ilium are, however, not explicable on the assumption of pressure from a hypophysis tumor. Experimental observations on the results of the extirpation of the hypophysis in young animals have shown that disturbance in bone development occurs in the sense of calcium poverty, so that the bones may show holes and suffer fractures. Also disturbance of the formation of the teeth could be brought into line with a disturbance in the hypophysis. We can make a presumptive diagnosis of anomaly of the skeleton as the result of disease of the hypophysis."

In some cases of muscular dystrophy, as pointed out by Janney and his co-workers (The Endocrine Origin of Muscular Dystrophy, Janney, Goodhart, and Isaacson, Arch. of Int. Med., 1918, xxi, 185) and by others, atrophic changes occur in the skull bones somewhat similar to those found in my case and in the 2 cases of Schüller. In muscular dystrophy, however, the bone changes are by far less extensive. In their cases the following changes in the skull bones were noted. *Case II:* "The roentgenographic examination shows small spots of bone absorption scattered throughout the upper portion of the cranium." *Case III:* "The roentgenographic examination shows very marked bone rarefaction in the skull, evidently in the tabula interna, simulating strongly the convolutions of the brain."

Case IV: "Roentgenographic examination shows several small irregular spots of bone absorption scattered through the parietals and frontals." It is of particular interest that Janney and his associates are maintaining in this paper the thesis that muscular dystrophy is closely associated with disturbance in glands of internal secretion, and in one of their cases there was evidence of a causative connection between dyspituitarism and muscular dystrophy.

The only condition in which I have seen any resemblance to the bone picture of the case here reported, and that only a partial one, is multiple myeloma. With this condition the skull and other flat bones often show in the Roentgen ray scattered round or oval defects due to tumor growth. In these cases I have never seen any large irregular bone defects. In multiple myeloma palpation usually reveals a nodule where the Roentgen ray shows the larger bone defects, so the resemblance is but a superficial one.

Syphilis might cause somewhat similar bone defects from gumma formation. Schufeldt (Amer. Jour. of Syphilis, 1918, xi, 462) pictures a skull with most extensive destruction of bone from a negro of twenty-four, without further statement other than that "eventually the fact became known to me that this negro had died from tertiary syphilis." Adami and Nicholls (The Principles of Pathology, Lea & Febiger, Philadelphia, 1909, Vol. II, p. 1029, Figs. 289, 290) give a figure of a somewhat similar skull labeled "periostitis with destructive inflammation (osteoporosis) affecting the frontal and temporal bones supposedly due to syphilis." In syphilis, however, breaking down of the gumma and later scar formation in the scalp are to be expected. In my case no evidence exists of any previous local inflammatory condition, and the patient's blood Wassermann was negative.

Craniotabes in rickets occasionally shows thinning and defects in the skull bones, but there was nothing in our case suggestive of rickets. Osteoporosis congenita presents some similarity, but this is an ill-defined clinical group whose nature is too little understood to throw any light on this patient, and I

have found no cases described under this heading very similar to the case here reported.

That a disturbance in the secretion of the pituitary gland is responsible for the defects in the flat bones in this case is a hypothesis that has considerable support. The coexistence of diabetes insipidus controlled by subcutaneous injections of pituitary substance is strong evidence of a disturbed pituitary function. Motzfeldt (Boston Med. and Surg. Jour., 1916, clxxiv, 644; Jour. Exp. Med., 1917, xxv, 153) and others have shown by clinical and experimental observations that there is a relation between diabetes insipidus and deficient pituitary function, as Motzfeldt expresses it, "lowered activity of the posterior lobe of the pituitary body." In the only 2 cases similar to mine that I can find reported (Schüller, loc. cit.) evidence of pituitary disturbance was noted, in one an adiposogenital dystrophy, in the other diabetes insipidus, as in my case. In such an unusual disturbance as is represented by the bony defects in these 3 cases it could hardly be a coincidence that there existed in each evidence of disturbance in the function of the pituitary gland. Rather does it seem highly probable that the bony defects are caused in some way by change in the pituitary gland, changes as to whose exact nature we have no evidence from the study of these cases.

SUMMARY

A case is presented where in a girl of five there occurred the symptom-complex of very extensive defects in the skull bones, exophthalmos, and diabetes insipidus. Only 2 other cases of this condition could be found in the literature. Diabetes insipidus suggests that the symptom-complex is due to a disturbance of pituitary function. Both of the other 2 reported cases showed evidence of disturbed pituitary function. In the case here reported pituitary extract controlled the polyuria when given subcutaneously. Other methods of introducing pituitary substance had no effect on the polyuria. No method of giving pituitary substance had any effect on the bone defects or the exophthalmos.

TABLE I

Date.	Volume of urine.	NaCl		Nitrogen	
		Per cent.	Grams.	Per cent.	Grams.
February					
7	6210	.03	1.86	.08	4.97
8	4885	.05	2.44	.05	2.44
9	7360	.03	2.21	.06	4.42
10	7260	.03	2.18	.06	4.36
11	7930	.01	.79	.04	3.17
12	8000+	.06	4.80	.05	4.00
13	6712	.02	1.34	.05	3.36
14		Two-hour renal test.			
15	5535	.04	2.21	.08	4.43
March					
22	1380	.13	1.79	.28	3.87
23	3556	.05	1.78	.12	4.27
24	2380	.13	3.09	.21	5.00
25	2670	.06	1.60	.17	4.54
26	2157	.11	2.37	.20	4.31
27	2382	.09	2.14	.14	3.33
28	1580	.14	2.21	.35	5.53
29	3050	.07	2.14	.15	4.58
30	3174+	.06	1.90+	.12	3.81+
31	4350	.07	3.05	.06	2.61
April					
1	2045	.15	3.07	.23	4.70
2	1961	.11	2.16	.25	4.90
3	2528	.15	3.79	.21	5.31
4	2268	.11	2.49	.23	5.22
5	2335	.11	2.57	.22	5.14
6	2025	.3	2.63	.20	4.05
7	4530	.06	2.72	.12	5.44
8	3215	.16	5.14	.23	7.39
9	2165	.17	3.68	.26	5.63
10	2412	.14	3.38	.24	5.79
11	3220	.12	3.86	.21	6.76
12	2551	.16	4.08	.20	5.10
13	3122+	.12	3.75+	.19	5.94
14	3445	.08	2.76	.20	6.89
15	3580	.08	2.86	.18	6.44
16	2495	.08	2.00	.17	4.24
17	3205	.08	2.56	.15	4.81
18	2068	.05	1.03	.22	4.55
19		Two-hour renal test.			