PUBERTAS PRECOX WITH ESPECIAL ATTENTION TO MENTALITY*

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Pubertas precox is a syndrome manifested by premature maturity, anatomically, physiologically, and often mentally, as a result of faulty metabolism induced, supposedly, by endocrine disturbances.

That this condition was recognized by the ancients is beyond doubt. For the first account of the condition recognizable as a clinical entity we must go back to Craterus, the brother of King Antigonus (1), who writes: "The subject was an infant, a young man, a mature man, an old man, was married and begat children and all in the space of seven years."

Pliny the elder, who lived in the reign of Vespasian, handed down the history of certain remarkable children; he states: "It is well known that there be some that naturally are never but a foot and a half high, others again somewhat longer, and to this height they came in three years, which is the full course of their age, and then die. We read, moreover, in the chronicles, that Salams, one Euthimenes, had a son who, in three years, grew to be three cubits or four and a half feet high, but he was in his gait slow and heavy, and in his wit as dull and blockish, howbeit in the time overgrown he was, and his voice changed to be great, and at three years he died suddenly of a general cramp" (2).

In 1747 Mead (3) presented before the Royal Society of London, a patient who was "remarkable for his bulk and height," and also for the external marks of puberty, which were first observed at the age of twelve months. At the age of five he had pthisis pulmonalis and died in a few months. "He had when dead the appearance of a venerable old man."

One of the first well observed cases was recorded over a century ago by Anthony White (4). He presented "Philip Howarth in whom signs of puberty commenced at an early age."

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The family history was negative, gestation was normal, and he was the ninth child born. At birth he had a full crop of hair; the sutures of his cranium were closed, but a slight fontenalle was palpable. At the end of the first year a change took place; his hair had grown to a great length, he grew pale and ugly in appearance. Small hairs appeared on his pubis; his testes and penis increased in size, and his voice altered. White, who was keenly interested in the lad, invited him to his home for further observation. He states: "On first view of the boy the manly character, strongly expressed, is extremely striking. His voice is like that of a young man of sixteen years and he can whistle very low tones; his laugh is loud. There was no hair on his chin, but steatomatous matter was present which usually makes its appearance preceding the growth of a beard. His teeth were spaced (how many not recorded); the nipples were prominent; no hair was visible in the axilla, but there was an odor emanating as that of an adult. His height was three feet, two inches and he weighed 47 pounds, i. e., at two years. At three years his height was three feet, four and a half inches and his weight was three stone, nine and a quarter pounds, or fifty-one and a quarter pounds." He was observed to have an understanding of a six-year-old child and, quoting this keen observer, "many of his observations and inquiries appeared to have been the result of mature reflection. It must, however, be observed that his general character was marked with a considerable mixture of childish playfulness. He was mild and not easily provoked to anger. When, however, his rage was excited, it was not expressed in the usual manner of children, but by the lowering of the eyebrows, the shaking of his head and with uplifted fist. He had a talent for music and sang with correctness."

The factor of hereditary transmission is apparent in the following two cases. Plumb (5) delivered a mature looking child whose facial appearance was feminine, and gave the impression of a delicate twelve-year-old child. Her external genitalia were developed as those of a child of seven to eight years, and her form was that of a fifteen-year-old girl. Her head was covered with thick, beautiful, brown curly hair which was three to four inches in length. There was no hair in the axilla. What was more remarkable was the beginning of menstruation when she was six weeks old. She menstruated for two and a half days

each month thereafter. At the time the case was recorded, she was ten months old and perfectly well. The child's clitoris was so long as to necessitate amputation. The parents of this child were both very vigorous sexually. Irion (6) reported a similar case in which menstruation first appeared seven days after birth; the patient showed the characteristic nervous phenomena when she skipped a period.

In the following case reported by Stone (7), there is a direct history of pubertas precox in the father. The subject when dressed gave the impression of a ten-year-old lad; he was actually four years old. When he disrobed, he looked the typical Infant Hercules, showing a fine physical development of a young man of 21. He was 4 feet, ¼ inch tall and weighed 70 pounds. His secondary sexual characteristics were fully developed. Mentally, the boy showed a lively intelligence; he was very talkative at home, but shy with strangers. His speech seemed to be imperfect. He was nearly always in good humor, but when angry settled his quarrels with old-fashioned "knock-down blows." The father, as mentioned above, was prematurely developed, and his first sexual indulgence occurred at the age of eight. He stated that between the age of ten and thirteen, "he was a better man than he has ever been since." Rogers also quoted a number of cases that showed the factor of heredity.

The direct causative factor of precocious puberty is hypersecretion of either the gonads, pineal gland or adrenal cortex, as indicated by hyperplasia or neoplastic development. That the pituitary and thyroid are also concerned, secondarily, however, is unquestionable. It will be necessary, therefore, to divide the cases of premature precocity into those that have acquired this syndrome through neoplasms and those due to hyperplastic states.

Ovarian Type. Rogers has collected 101 cases of pubertas precox; of these 81 subjects were females and 20 males. Of the 81 female cases, 73 appear to be due mostly to hyperovarianism. The cases of Krabbe (8), Wells (9), Lenz (10) and Bruno Wolff (11), were also of this type. Lenz's case was studied very carefully. He first saw the child when she was six and one-quarter years old. Menstruation had begun at 16 weeks. The secondary sex characteristics were those of a mature woman. She was shy and easily embarrassed. She went to school and was a good pupil.

She played with children of her own age and was childish in activity. She was again seen when twelve years old, when she appeared to be twenty-two. Her behavior was still childish, and extraordinarily shy. She was still playing with dolls. She cried pitifully when the other children teased her about her large breasts.

An instance of neoplasms of the ovary producing pubertas precox is recorded by Lucas (12). The little patient was seven years old and showed all the signs of genito-somatic maturity and early menses. A tumor of the ovary was diagnosed and after its removal all the signs of adolescence and menstruation disappeared. Blair Bell (13) quotes Roger Williams, who collected eleven cases of sexual precocity in female children, due to neoplasms of the ovary. However, one should not draw the conclusion from this that all ovarian tumors in young children necessarily lead to sexual precocity. There must be other factors entering into this mechanism.

To summarize the mental traits and habits in these ovarian cases, it can be said that none show mental precocity. In fact, the subjects are of a low mental type. They speak, play and act in accordance with their true age. The girl reported by Lenz (10) still played with her dolls, although she gave the physical impression of a girl of twenty-two. They learn well at school, but they show no "old-fashioned" way of thinking, as Krabbe (8) puts it. Neurath (14), who had a considerable opportunity to observe them, also comes to the conclusion that their psychic condition is not so far advanced as their physical. That some of these children put away their toys and become seclusive is to be ascribed to self-consciousness rather than to any mental maturity

Adrenal Cortex Types. The clinical picture differs here, according to whether the male or female is involved. When there occurs hyperplasia of the adrenals in the male, it tends to accentuated masculine precocity. When it occurs in the female it tends to change the female into the male type, and to give her the secondary sexual characteristics of the male.

In a case reported by Marchand (15), a girl was baptized as a male. As a result of a medico-legal examination, it was found that her body showed a spurious hermaphrodism with hair over face and body, and a clitoris as large as a penis. At autopsy

she showed hypertrophy of the adrenals, and particularly of the cortex.

Tumors of the Adrenal Cortex. Pitman (16) reported a girl of three who showed nothing child-like in either voice or manner. She often seemed idiotic, but aggressive. She showed bushy eyebrows and a moustache in addition to other male characteristics. A tumor of the adrenal cortex was found.

Bulloch and Sequeira (15) collected 12 cases of adrenal tumors. Ten were found in the female and two in the male. Orth (15) reported the case of a girl of 4½ years, who had so much hair on her face that she had to be shaved. The clitoris was the size of a small penis. She had a neoplasm of the right adrenal. In Dobbertson's (15) case, a girl had a mass of hair on her back. Glynn (17) reports the case of a girl of 7. She had the appearance of a young man, with a black silky beard, a moustache and whiskers.

These cases therefore show uniformly hypertrichosis of the male type. All manifest a large clitoris, which shows the tendency towards male sexuality, and all showed an absence of menstruation, with the exception of one case reported by Bulloch and Sequeira (15), in which menstruation appeared at the age of a little more than ten years. The appearance of menstruation at this time can hardly be classed, however, as precocious.

A case of adrenal origin in a boy of 5½ is reported by Linser (15). The physical development was that of from 16 to 18. Sex characteristics were of the male type. The pineal, pituitary and thyroid glands were found to be normal.

As regards mentality and habits in these cases, the literature is far from satisfactory. It indicates, however, that while they show some aggressiveness, in the main, their psychic condition is below par. Pitman states that his case showed idiocy; Bulloch and Sequeira and Colcott Fox (15) state that their cases showed a dullness of intellect. Glynn's patient was dull and apathetic; she took no interest in her surroundings and would answer questions only if they were frequently repeated.

Hypergonadal Condition in the Male. Sarchi (18) published a case that showed a malignant tumor of the left testicle. At 5, the testicle was as large as that of an adult. The boy grew rapidly, his voice grew to a deep bass, and hairs appeared on his genitals. At 9 years, he was 143 cm. in height and weighed 44

kilograms. The left testicle was removed and an alveolar carcinoma was shown. Four months after the removal, his beard disappeared, his voice again became child-like and his genitals were getting smaller. His sexual impulses, emissions and erections ceased. His character in general reverted to the childhood stage.

A case of hypergenitalism was reported by Strauch (19) of the Cook County Hospital. In this instance no anatomico-pathologic changes were found. No cerebral symptoms were present. No tumor of the pineal was suspected. The boy was 11½ years old and had previously shown mental retardation. His genitals, including the prostate and seminal vesicles, were developed as in an adult, but no spermatozoa were found. His voice was strikingly deep. As to his psychic condition and habits: He was irritable and nervous, and cried whenever his mouth had to be examined. He was stubborn, disobedient, troublesome and showed a resentful disposition towards other children. At home he played with boys younger than himself. There was no evidence of sexual shame, nor was there any visible propensity for the other sex. He could not count to more than five, and even then he had to be helped. His handwriting was not legible, nor could he write his own name without having a copy placed in front of him. He attended school for three years, and he could not execute a simple example of addition, nor did he remember his songs or prayers.

Morse (20) reports a boy of 23 months with genito-somatic precocity and delayed mentality. An X-ray examination of the skeletal system revealed the bony development of a 6½-year-old boy. No spermatozoa were found in the emissions. Woods (21) and Lopez (22) report cases that are of undoubted hypergonadal origin. Both subjects showed remarkable strength. The former was 6¾ years old and was nearly 5 feet tall. He was so mischievous and full of animal spirits that he had to be placed in an industrial school. It took three policemen to get him there. The latter subject was a colored boy of 3 years and ten months; he showed genito-somatic precocity and lifted a man of 140 pounds from the ground with ease. The case of Gilbert Breschet (23) should also be included here.

The mentality and habits in these cases show no precocity. In fact, the subjects are retarded and, according to Moreau (24), Hofacker (25), Hudoverning and Popovitz (26), Ziehn (27) and Neurath (14), may even show idiocy and imbecility. Neurath, who reported 27 cases of this type, is quoted by Strauch (19), that "in most cases there existed the psychic function of their infantile age."

Pineal Tumors. Neoplasms of the pineal gland have drawn attention to the subject of pubertas precox, as no other condition has. The opinion once prevailed that pineal tumors exist only in the male. This, however, has since been disproven. Baily and Jellife (28) collected and reported in an excellent paper 59 cases of pineal tumors, together with an additional case of their own, making 60 in all. Seventeen cases showed involvement up to the age of 16. Fourteen of these occurred in the male and three in the female.

There is this to be said in reference to tumors producing precocious puberty, that while the pineal tumors occur predominantly in the male, tumors of the adrenals as hypernephromata, occur five times oftener in the female.

I must agree with Gordon (29) that the histories of the recorded cases are inadequate, not only as regards pineal tumors, but all the subject matter herein discussed. The clinical observations are too meagre, often, for correct endocrine interpretation, and it seems the further back one goes the more illuminating and keener are the clinical observations of the writers.

The following cases of pineal tumors bear on our subject.

Aesterich and Slawyks (30) report a boy who was a still birth baby, as a result of forceps delivery, but who developed normally during the first year of life. Convulsive attacks then set in. At 3, this child, who was formerly bright, became strikingly quiet and shy and sat in the corner and cried. Genitosomatic precocity then became apparent. Mentally he was somewhat precocious,—what the Germans call "altklug." This boy displayed no onanism.

Von Frankl-Hochwart (31) reported a boy who, at three, grew with excessive rapidity and showed mental precocity. At 7 years, his precocity was astonishing. He pondered and discussed at length the immortality of the soul and the life after death. This case made such an impression on Dana and Berkely (32), that it led to the well-known feeding experiments on the mentally backward children in the New York Public Schools and to the experimental work at Vineland by Goddard (33). At autopsy, in the case mentioned, a teratoma of the pineal was found. In fact most of the tumors of the pineal are teratomas.

Baily and Jellife (28), who went into the mental study of their case much more than any of the other writers, state that the boy who was formerly bright in school work began to show a failing memory. He also grew more reserved and apathetic. He showed a tendency towards depression and cried often. The Zeihn test "revealed a lack of retention, with a marked slowing of all responses."

Gauderer (28) reports a boy of 12 who had a fixed expression, was apathetic and who answered questions slowly but clearly.

Raymond and Claude (30) report the case of a boy of 10, who was mentally apathetic and answered questions well, even slightly better than most boys of his age. His memory was good, but he showed a slight depression.

Kidd (30) reports the following cases, by Pellizzi and Machell. The first case of Pellizzi showed genito-somatic, together with mental precocity; the other case did not. The first subject, although only 2 years old, had seminal emissions that contained spermatozoa. Onanism was not present.

Machell reports two cases, one of which was interesting. This boy at 17 months had erections and emissions. In addition to his genito-somatic precocity, he showed marked mental precocity. At 44 months of age, he showed a disdain for the toys of small children. His habits bespoke an older boy. His manner was independent; he was perfectly self-possessed with strangers, and his answers to questions were given in a loud, bass, stentorian voice.

Kidd (30), although he wrote a thorough review of the literature, historical, clinical, experimental, etc., of the pineal, mentioned nothing concerning the mentality in pineal involvement.

From a comprehensive study of the literature, by which the various types of puberatas precox were classified, together with their respective mentalities, it can be said that mental precocity is non-existent, aside from its manifestation in the pineal type. In fact, there is in the major number a hypo-mental state, which gradually shades off into absolute idiocy. The subjects are in the main childish, and their mentality bespeaks their true age. In those cases, in which, through tumor growth, intracranial pressure is produced, various degrees of mental disorder arise, but such are scarcely germane to our discussion.

A trait common to all cases of precocity is the reserve, thoughtfulness, or quiet they manifest. They like to sit in a corner by themselves. Stanley Hall (34), in speaking of the psychic traits attending normal puberty, states that, "Inner absorption and reverie is one marked characteristic of this age and transition." This observation can, I believe, be applied to our cases, and is not in itself indicative of abnormality. Some writers believe that early sexual desire is a sign of mental precocity. This I believe is incorrect. It is purely an instinct.

DIAGNOSIS

To reach a diagnosis as to the particular gland involved primarily, and especially if there is any tendency towards readjust-

ment, one must: (1) have the cases under close clinical observation; (2) study their metabolism, particularly, as Blair Bell has advised, the calcium output, and (3) make Roentgen ray examinations for skeletal development and for the disappearance of the epiphyseal lines, as shown by Krabbe (8), Lenz (10) and Timme (35).

The approach to a correct diagnosis is somewhat difficult at present, in view of the fact that glandular structures that are seemingly antagonistic, produce nevertheless the common syndrome, precocious puberty. However, upon analysis there are always found some points of difference in respect to the particular gland involved.

Gonadal Type. In the female type due to hyper-ovarianism we always get early menstruation. This leads to excess calcium elimination, and therefore we find the subjects (if of pure ovarian type) always short in stature. If the skeletal system is examined by Roentgen ray, we find the epiphyses of the long bones closed. This fact is borne out clinically, that girls who menstruate early are usually short and those who menstruate late are tall. This tends to hold for races as well as individuals. Again the distribution of the hair is of the female type, as are the secondary sex characteristics, facies and form.

In the masculine gonadal type there is also short stature, concomitant with closed epiphyses, marked male secondary characteristics, deep voice, enlarged prostate and seminal vesicles and often emissions, either sterile or containing spermatozoa. What seems characteristic of this type is the marked physical strength manifested.

Adrenal Type. In the female we find marked hypertrichosis and secondary characteristics of the male type,—large clitoris, male facies and absence of menstruation. The case of Irion is an exception.

While we were always taught that the cortex of the adrenal has for its function the production of sex characteristics only, the work of Cramer (36) indicates that the cortex also participates in the production of adrenalin. The question of blood pressure should therefore be taken into account in a differential diagnosis.

The male adrenal type is difficult to differentiate from the gonadal except, perhaps, by their stature. Both types manifest accentuated male characteristics.

Pineal Types. In these the Roentgen plates should portray a shadow due to the acervalus cerebri, as a result of early involution, as shown by Boas, Scholtz (37) and Timme (38). Whether pure hyperplasia of this gland should give precocious puberty, as indicated by the work of McCord (39), Dana and Berkeley

(32), etc., or hypoplasia or recession of the gland according to Marburg, it is at present impossible to say.

Finally one may say that there are undoubtedly individuals living today, who were cases of pubertas precox, and undetected as such, who will undoubtedly live to a ripe old age. What takes place here is a compensatory readjustment of the excessive secretions by their antagonists, just as we see in the ultimate adjustment in the syndrome of thymus, pituitary and adrenal of Timme (35).

CONCLUSIONS

The literature as a whole supports the following conclusions.

1. Pubertas precox arises in certain individuals, whose progenitors show a particular type of endocrine imbalance.
2. The condition may arise in utero, or as a result of functionating rests, i. e., tumors, later in childhood, previous to puberty.
3. The entire internal glandular system is involved, but primarily the gonads, pineal and adrenal cortex.
4. Gonadal types predominate, then follow the pineal, and last, the cortico-adrenal.
5. Pineal types occur mostly in the male; cortico-adrenal and gonadal in the female.
6. Mental precocity is very rare and is found only in those in whom the pineal is primarily involved, and then only in the male.
7. The mentality in the other types is either unaffected or retarded.
8. The manifest mental precocity is of the child-like, imaginative form, and has no real substantial basis.
9. With early diagnosis in the hyperplastic type, readjustment can be aided materially by proper endocrine therapy.

BIBLIOGRAPHY

1. Greek translation, Phlegon de Mirabilia, Cap. xxxii; Cf. White (4), p. 277.
2. Pliny, Philemon Holland, translator, Book ii, Chapt. xvi. Cited by White (4).
3. Quoted from Anthony White (4).
4. White, Anthony: Historical account of Philip Howarth, a boy in whom signs of puberty commenced at an early age. Med. Chir. Trans. (London), 1809-11, **1-2,** 276-285.
5. Plumb, P. E.: Precocious menstruation; a unique case. N. Y. Med. J., 1897, **65,** 768.
6. Irion, J. W.: A case of precocious menstruation. Ibid., 1896, **64,** 227.

7. Stone, R. K.: Extraordinary precocity in the development of the male sexual organs and muscular system in a child of four years. Am. J. Med. Sc. (Phila), 1852, **24,** 561-564.
8. Krabbe, K. H.: Early synostosis of the epiphyses with dwarfism in pubertas precox. This Journal, 1919, **3,** 459-466.
9. Wells, G.: A remarkable case of early and continued menstruation. Maryland M. J. (Balt.), 1902, **45,** 440.
10. Lenz, J.: Vorzeitige Menstruation Geschlechtsreife und Entwickelung. Arch. f. Gynaek. (Berlin), 1913, **99,** 67-144.
11. Wolff, Bruno: Zur Kenntnis der Entwicklungsanomalien bei Infantilismus und bei vorzeitiger Geschlechtsreife. Arch. f. Gynaek. (Berlin), 1911, **94,** 542-579.
12. Lucas, R. C.: A case of tumor of the right ovary in a child of seven, associated with precocious puberty. Med. Press & Circ. (London), 1888, n. s. **45,** 459. Trans. Clin. Soc., Lond. 1888, **21,** 224.
13. Bell, W. Blair: The sex complex, Wm. Wood & Co., N. Y., 1916, p. 149.
14. Neurath, H.: Die vorzeitige Geschlechtsentwickelung, Ergebn. f. inner. Med. u. Kinderheilk., 1909, **4,** 41-81.
15. Bulloch, W. and Sequeira, J. H.: On the relation of the suprarenal capsules to the sexual organs. Trans. Path. Soc. Lond., 1905, **56,** 189-208.
16. Pitman, H. A.: General melasma and short hair over the entire body of a child of three years, with conversion of the left suprarenal capsule into a large malignant tumor; the external organs of generation resembling those of adult life. Lancet (Lond.), 1865, (i), 175.
17. Glynn, E. E.: The adrenal cortex; its rests and tumors, its relation to other ductless glands and especially to sex. Quart. J. Med. (Oxford), 1911-1912, **5,** 157-192, 1 pl.
18. Sacchi, E.: Di un caso di gigantismo infantile (pedomacrosomia) con tumore del testiculo. Arch. di ortop. (Milano), 1895, **12,** 305-318.
19. Strauch, A.: Sexual precocity in the male. Am. J. Dis. Child. (Chicago), 1918, **15,** 132.
20. Morse, J. L.: Case of abnormal physical and sexual development in an infant of two years, probably due to a tumor of the pineal gland. Arch. Pediat. (N. Y.), 1913, **30,** 179.
21. Woods, T.: An extraordinary case of early puberty in a boy. Lancet (Lond.), 1882, (ii), 337, 473.
22. Lopez, A.: Case of remarkable precocity in a male. Am. J. Med. Sc. (Phila.), 1843, **5,** 500.
23. Breschet, Gilbert: Description d' un enfant de trois ans offrant tous les signes de la puberté. Bull. Fac de Méd. de Paris, 1820-21, **7,** 98-111.
24. Moreau, J. L.: Fragment d' une notice sur un jeune homme de onze ans, chez lequel on observe tous les signes extérieurs de la virilité, accompagnés de l' accroissement extraordinaire d' un état pathologique du testicule. J. de Med. Chir. et Pharmacal. (Paris), 1806, **12,** 274-278.
25. Hofacker, C.: Ein seltener Fall von Frühreife mit Menstruatio praecox. Verhandl. d. Gesellsch. deutsch. Naturf. u. Aerzte, 1898, (Leipz.), 1899, **70,** Pt. 2, 2. Hefte., 182.
26. Hudoverning, C. and Popovits, U. P.: Gigantisme précoce avec développement précoce des organs génitaux. N. inconog. de la Salpêtrière (Paris), 1903, **16,** 181-192.

27. Ziehn: Fall von Gigantismus. Berlin. klin. Wchnschr., 1906, **43,** 1198-1199
28. Baily, P. and Jellife, S. E.: Tumors of the pineal body; with an account of the pineal syndrome, the report of a case of teratoma of the pineal and abstracts of all previously recorded cases of pineal tumors. Arch. Int. Med. (Chgo.), 1911, **8,** 851-880.
29. Gordon, M. B.: The role of the pineal in pediatrics. This Journal, 1919, **3,** 437-453.
30. Kidd, Leonard J.: The pineal body; a review. Med. Chronicle, (Manchester), 1912, **57,** 154-184.
31. von Fränkl-Hochwart, L.: Uber Diagnose der Zirbeldrüsentumoren. Wiener med. Wchnschr., 1910, **60,** 505-508.
32. Dana, C. L. and Berkely, W. N.: Functions of the pineal gland. Med. Rec. (N. Y.), 1913, **83,** 835.
33. Goddard, H. H.: The Vineland experiment with pineal gland extract. J. Am. M. Assn., (Chgo.), 1917, **68,** 1340.
34. Hall, G. Stanley: Adolescence; its psychology, etc., N. Y., 1904.
35. Timme, Walter: A new pluriglandular compensatory syndrome. This Journal, 1918, **2,** 209-240.
36. Cramer, W.: A histochemical method for the demonstration of adrenalin granules in the suprarenal glands. J. Physiol., (Lond.), 1918, **52,** viii-x; Abst., This Journal, 1919, **3,** 496.
37. Boas, E. P. and Scholtz, T.: Calcification in the pineal gland. Arch. Int. Med., (Chgo.), 1918, **21,** 66.
38. Timme, Walter: Progressive muscular dystrophy as an endocrine disease. Ibid., 1917, **19,** 79.
39. McCord, C. P.: The pineal gland. Trans. Am. Gyn. Soc., 1917; Surg. Gyn. and Obstet., (Chgo.), 1917, **25,** 250.
40. Horrax, Gilbert: Studies on the pineal gland; Arch. Int. Med., (Chgo.), 1916, **17,** 607, 637.