author—or in five out of fifty if we include a case presented later at a meeting of the Dermatological Section of the Royal Medical Society—was there a history of tuberculosis in the patient's family, and in but a single instance did the patient himself present signs of tuberculosis.

The observations of Wende, Graham Little and my own more recent study have quite convinced me that the so-called erythema elevatum diutinum of Crocker is simply a clinical variety of granuloma annulare; histologically, there is no essential difference between the two affections.

As to the essential nature of this curious malady, little or nothing definite is known. The objection which has been made to the name "granuloma annulare" that it is not a granuloma, is apparently supported by its histopathology, which is much more that of a connective-tissue neoplasm than of a granuloma. Some observers, it is true, have found plasma and giant-cells, usually in very small numbers, but this finding is decidedly the exception rather than the rule. Halle thinks it a chronic inflammation of the middle and deep portions of the corium, while Dalla Favera believes it dependent wholly and alone on the blood-vessels; none of these views, however, explain in the least the peculiarities of the neoplasm. My own belief is that it is an affection *sui generis*, not related, so far as our present imperfect knowledge permits us to form an opinion, to any other. As to its etiology we cannot furnish even a reasonable conjecture.

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ABSTRACT OF DISCUSSION

DR. CHARLES J. WHITE, Boston: One case of granuloma annulare which I had the pleasure of studying proved rebellious to many sorts of medication, but yielded to the Roentgen-ray treatment, unfortunately, however, only to recur in a few weeks.

DR. A. RAVOGLI, Cincinnati: I have never seen a case of typical granuloma annulare in this country. I can recall a few cases in Italy; in those the lesions were typical, being limited to the hands and the fingers, in form of rings, near the joints, and giving rise to no itching nor other discomfort. I am inclined to regard this eruption as a localized lichen planus rather than to associate it with lupus erythematosus, tuberculosis or sarcoid. It is exceedingly stubborn, and I know of no remedy that will permanently relieve it. The Roentgen ray may hide it for a time, but there are cases in which it may aggravate the trouble.

DR. FRANK E. SIMPSON, Chicago: I have seen one case of this affection with Dr. Joseph Zeisler, which disappeared, apparently permanently, under the use of carbon dioxid snow.

DR. FRANK W. GREGOR, Indianapolis: Before listening to Dr. Hartzell's paper, I had almost come to the conclusion that granuloma annulare was not a dermatologic entity. Of two cases I can recall that were regarded as examples of this affection, one proved to be a case of syphilis; the other a case of lichen ruber planus in which I was subsequently able to demonstrate the typical lesions of that disease on the buccal mucous membrane.

DR. RICHARD L. SUTTON, Kansas City: I have under my care a case of granuloma annulare in a girl, 2½ years old, who instead of improving under Roentgen-ray treatment, grew distinctly worse. I then tried the carbon dioxid snow, without knowing that Dr. Simpson had previously employed it in this affection. The results apparently, were very good, but it is still too early to make any definite statement concerning the final outcome.

DR. M. B. HARTZELL, Philadelphia: Of course, an experience with only two cases does not prove very much. In one the lesions disappeared absolutely and did not return. It should be borne in mind, however, that these lesions sometimes dis-

appear spontaneously, but in this instance it followed so promptly after the use of the Roentgen ray that the patient could but attribute it to the treatment. These lesions show a certain predilection for the neighborhood of the joints. The eruption is most common in children, and occurs most frequently on the hands, particularly about the knuckles. As to its relationship to tuberculosis, I think that is a purely gratuitous assumption which is entirely negated by the histologic picture. To repeat, I regard it as a disease *sui generis*.

THE PINEAL GLAND IN RELATION TO SOMATIC, SEXUAL AND MENTAL DEVELOPMENT *

CAREY PRATT McCORD, M.D.

DETROIT

From tumors involving the pineal gland, two distinct systems of symptoms and signs ensue, the neurologic and the metabolic. The neurologic manifestations arise from the encroachment of the neoplasm on the intracranial contents and are indications of changes in pressure, in placement and of destruction of tissue. Such changes are the consequence of pineal tumors at any age of the patient; but in pineal tumors appearing in prepuberal life a second group of changes arise, the metabolic. These metabolic alterations are referable to disturbance in the gland's secretory function. Apparently only in young males is this syndrome complete.¹ It consists of (1) early sexual development evidenced in the enlarged sex organs, pubic hair, general body hair, early changes in voice; (2) precocious mental development evidenced in the maturity of thought and speech, and (3) general body overgrowth to the extent that a child of 5 or 6 years may have the appearance of a child of 11 or 12.

A case reported by Machell² presents these changes in a striking manner. The patient was a boy less than 6 years old at the time of the publication. At the age of 5 months there was pubic hair, erections at 17 months, emissions at 30 months. The patient's weight was 7½ pounds above normal at 4 months of age, 12 pounds in excess at 8 months, 20 pounds in excess at 3 years. When the patient was 44 months old, his height was 8½ inches above normal for a child of that age. At 48 months the circumference of the head was over 2 inches in excess of normal. The voice was a deep bass. Mental precocity was very marked and the general bearing and language was that of a much older person.

On account of the difficulties attending experimentation on this vestigial organ, the clinical findings with subsequent necropsy records have been the prime factor in the formulation of the prevailing ideas as to this gland's functions. The conception of this gland's function, however, has in part been developed from laboratory studies, notably from the results concomitant to the extirpation of the organ. This has been attempted frequently, but the situation of the gland is such that in the greater number of instances death followed the operative procedure, from hemorrhage or injury to the vermis or the occipital lobes. By operating on a large number of animals some workers have had a few animals survive. No changes attended the

* Read before the Section on Pathology and Physiology at the Sixty-Fifth Annual Session of the American Medical Association, Atlantic City, N. J., June, 1914.

1. For review of clinical cases see Bailey, Pearce, and Jelliffe, Smith Ely: Tumors of the Pineal Body, Arch. Int. Med., December, 1911, p. 851. For Physiology and Anatomy, see Vincent Swale: Internal Secretion and Ductless Glands, 1912.

2. Abstract taken from Medical Chronicle, 1912, lvii, 154.

removal of the gland by Biedl,³ Dandy⁴ and Exner and Boese,⁵ but Foa⁶ ablating the gland in chicks and Sarteschi⁷ in young rabbits and puppies report the production of the precocious macrogenitosomatic syndrome.

The publications growing out of these several clinical and laboratory studies have given rise to conceptions of this organ and its functions that may be thus epitomized:

The pineal body (epiphysis cerebri), probably the remains of a parietal eye, is situated just beneath the splenium of the corpus callosum, resting on the anterior quadrigeminate bodies, and is attached by its base to the habenular commissure. The gland varies in size, shape and pigmentation and does not stand in any proportional relation to the size of the brain or size of the body. The pineal body contains glandular elements, but these are few and not well defined. The greatest postnatal development is in the first years of life, and as far as is known the gland is only functionally active in the prepuberal life. On the assumption that tumors destroy the gland and deprive the body of the substances generated by it, the function of the gland is generally described as retarding and holding in abeyance too rapid development in childhood, of the body, mind and sexual characteristics. When precocity in development appears in conjunction with pineal tumors, it is attributed to lack of glandular secretion.

Below are recorded some findings from experimental work that are entirely in accord with the results obtained by Dana and Berkeley.⁸ Contrary to the view that precocious development is due to pineal deficiency (hypopinealism) the same precocity in development has been brought about by the oral administration of pineal gland tissue.

EXPERIMENTAL DATA

The general plan of work entailed in this study has been to feed to very young animals minute quantities of pineal tissue and to record the weight changes, sexual differences, and in the case of dogs increased mentality, over control animals maintained under otherwise identical conditions. One hundred and ten guinea-pigs, eighteen puppies, fourteen adult dogs and sixteen chicks have been under observation.

Fresh pineal glands from cattle have been employed. These were in part from veal, in part from young adults approximating 3 years, and in part from the general run of cattle from the abattoirs. The glands averaged in weight (on weighing sixty glands) 2.14 grains. There were in the many thousand glands making up the several pounds that have been used, marked variations in size, shape and melanopigment. This pigment, which was present in a high percentage of glands, involves chiefly the encapsulating tissue.

For feeding experiments the glands were prepared for permanent use in the following manner: The fresh glands were rinsed free of blood and stripped of adherent tissue. They were ground to a fine paste in the Latapie grinder, and without drying, the paste was admixed with milk-sugar in such quantity that $\frac{1}{2}$ grain milk-sugar represented 10 mg. pineal tissue. The mass was made into $\frac{1}{2}$ -grain tablets and quickly dried at room temperature.

Early in the work it was apparent that the more striking results were being obtained from the animals

fed with pineal substance from cattle not having reached adult life. Efforts were then made to establish quantitatively the activity and the identity of the various experimental lots of pineal preparations by employing the methods commonly used in testing the activity of endocrinous derivatives. Although certain cardiovascular changes regularly follow the intravenous administration of pineal extracts to dogs, the extent of these changes is not a measure of the activity of the gland as a stimulator of growth.

On the hypothesis that precocious development is due to hypopinealism, the first work was done in anticipation that feeding would retard development and prolong the presexual life. This was begun on two chicks incubated in the laboratory. Beginning at the age of two days one was fed 10 mg. veal pineal tissue, three times weekly, the other (and in all cases of controls) was fed a blank tablet of milk-sugar. The difference in growth should be noted (Table 1).

Fig. 1.—Position, relations and relative size of the pineal gland. Taken from beef 3 years of age.

TABLE 1.—RESULTS OF FEEDING PINEAL GLAND TO CHICKS

	Third Week, gm.	Sixth Week, gm.	Ninth Week, gm.	Twelfth Week, gm.
Pineal	219.5	557.7	895	925
Control	92.5	286.5	550	700
Difference	127.0	271.2	345	225

The striking disproportion in size and the marked skeletal overgrowth making the large chick very awkward in his movements, soon made these chicks a laboratory curiosity, but the small number and the different sex did not justify any inference as to the influence of the pineal feeding. The results, however, were so striking that at once work was instituted in a more extensive way.

A lot of fifty guinea-pigs in the second week of life was selected and divided into test and control groups. The test pigs were fed daily 10 mg. veal pineal tissue. The controls were fed a $\frac{1}{2}$ -grain milk-sugar tablet.

3. Biedl: *Innere Sekretion*, 1910.

4. Dandy, cited by Cushing: *Pituitary Gland and Its Disorders*, p. 283.

5. Exner and Boese: *Deutsch. Ztschr. f. Chir.*, 1910, cvii, 182.

6. Foa: *Arch. Ital. de Biol.*, 1912, lvii, 233.

7. Sarteschi: *Pathologia*, 1913, p. 707.

8. Dana and Berkeley: *Med. Rec.*, N. Y., 1913, lxxxiii, 835.

Other conditions for the two lots were identical. The results obtained are given in Table 2.

TABLE 2.—RESULTS OF FEEDING PINEAL GLAND TO YOUNG GUINEA-PIGS

Control, 25 Pigs Average Initial Weight, 201.2 gm. Age, 2 Weeks			Pineal, 25 Pigs Average Initial Weight, 204.3 gm. Age, 2 Weeks		
Weeks	Aver. Wt. gm.	Gain gm.	Weeks	Aver. Wt. gm.	Gain gm.
1	198.7	—2.5	1	213.2	8.9
2	220	21.3	2	236.8	23.6
3	226.8	6.8	3	247.6	10.8
4	251	24.2	4	273.2	25.6
5	265.3	14.3	5	299.9	26.7
6	265.7	0.4	6	311.1	11.2
7	292.2	26.5	7	338	26.9
8	306	13.8	8	361.4	23.4
9	316.3	10.8	9	365.5	4.1
10	356.5	40.3	10	410.8	45.3
Average weight at end of tenth week.....356.6 gm.			Average weight at end of tenth week.....410.8 gm.		
Average initial weight...201.2 gm.			Average initial weight...204.3 gm.		
Average gain.....155.4 gm.			Average gain.....206.5 gm.		
Gain, per cent.....77.0			Gain, per cent.....100.0		

Excess gain of pineals over controls, 23 per cent.

This excess in weight of pineal-fed guinea-pigs over their controls is a symmetrical overgrowth. There is some increased adipose tissue, but this is generally distributed and not localized in any one region of the body. At no time has it been possible to continue this excessive growth above normal adult size. As the animals approach adult size the pineal feeding is less effective and after full maturity is attained is without effect. There has been no tendency to gigantism.

As a step toward determining the metabolic differences, quantitative urinalyses were made on twenty-four-hour composite samples of urine from the two groups.⁹ With proper regard for the numerous other factors that might vitiate the results obtained from urinalyses, there is a suggestive difference in the two urines as may be seen in the summary given in Table 3.

TABLE 3.—SUMMARY OF ANALYSIS OF URINES

	Pineal	Control
Total volume collected (24 hours)	187 c.c.	160 c.c.
Specific gravity (15.5 C.)	1.016	1.019
	Per Cent.	Per Cent.
Total solids	2.51	3.02
Water	97.49	96.98
Total mineral matter	1.21	1.37
Total nitrogen	0.628	0.872
Total creatinin	0.018	0.025
Phosphoric acid (as P ₂ O ₅)	0.065	0.043
Calcium	0.016	0.018
Magnesium	0.020	0.018
Alkalinity (as Na ₂ CO ₃)	0.053	0.037

Chicks.—A lot of fourteen chicks was secured at the age of one week. At so early an age sex could not be determined and the lot was divided into test and control groups without knowledge as to grouping by sex. The test chicks were placed on veal pineal tissue for one week with a resultant greater growth than controls. For the next four weeks they were fed pineal tissue from old cattle, without gaining. On being placed on the original veal preparation the test chicks again grew in excess over controls.

Dogs.—The eighteen dogs employed represent four litters. Infection of these puppies with distemper

interfered seriously with the weight charts of these animals. So long as infections could be kept out of the animal quarters, the test animals outgrew the controls, but the wasting from infections interfered seriously with average results over prolonged periods. It was in connection with puppies that some differences in intelligence were observed. No great import is attached to these observations, but it was noted that the pineal-fed dogs were about one month ahead of the others in their habits. They were the first to learn to lap milk, the first to respond to a call, the first to be able to find their way back to the kennel. When work on these animals was discontinued, only the pineal-fed animals were in demand as pets, and those choosing them did so without any knowledge as to differences in feeding. Of much more importance as regards increased intelligence are the favorable results reported by Berkeley,¹⁰ who administered pineal tissue to mentally defective children and performed Binet tests as a criterion of mental advancement.

Precocious Sexual Development.—A group of forty-eight guinea-pigs was divided into test and control lots. There was an equal number of males and females in each lot, but the males and females were separated. The test pigs were fed veal pineal tissue in 10 mg.

Fig. 2.—Effect on growth of feeding pineal-gland tissue to chicks. The larger chick was fed 10 mg. pineal tissue three times weekly.

amounts daily. Feeding was begun when the animals were 2 weeks old and continued for nine weeks. The males and females of each group were then placed together in breeding-pens. As a measure of any difference in sexual development it was thought desirable to note the date of birth of young in the two lots. As the end of the approximate gestation period approached, these animals were observed as to the date of giving birth to young. All except two of the pineal-fed pigs gave birth to young before the first of the controls.† Fourteen days elapsed between the birth of young of the first pineal-fed pig and the first control pig. In all cases the young were normal and in no wise different from any other young pigs.

COMMENT AND SUMMARY

In the foregoing records of experiments, it may be observed that some of the changes generally attributed to deficiency of pineal secretion may be produced by

10. Berkeley: Med. Rec., New York, 1914, lxxxv, 85, 513.

† In a second series of fifty guinea-pigs observed as to sexual differences, the males and females have been kept together from birth. Some of the females to whom pineal gland tissue has been fed have already given birth to young and many others are within the last ten days of gestation. With the exception of one pig, the control animals evince no signs of pregnancy.

9. I am under obligations to Mr. Lewis Davis for these analyses.

supplying an added amount of pineal substance. In an effort to reduce to rationality these identical findings derived from two opposing sources, the so-called destructive neoplasms of the pineal gland on the one hand, and the feeding of the gland on the other, there arise two possibilities: First, this syndrome may appear from disrupting the general endocrinous balance from either increasing or decreasing the amount of pineal secretion available for the body's use. These secondary changes in the other endocrinous glands are now in the course of investigation. Second, the cells of the neoplasms involving the pineal gland may retain some of the metabolic and other functional characteristics of the normal pineal cell from which they were derived, and the peculiar body, sexual and mental changes in patients with such tumors are all manifestations of increased rather than decreased pineal activity. One of the most frequently occurring lesions of the pineal is the adenoma, and there is abundant evidence that at times cells of adenoma functionate after the manner of the cells from which they arise. In adenoma of the liver in cases reported by Weber,¹¹ Rolleston,¹² Wheeler¹³ and Ribbert,¹⁴ distinct bile secretion by tumor-cells has been pointed out. Ribbert established that the bile present in such tumors was not the bile of icterus from necrotic liver-tissue by demonstrating that the scirrhous encapsulating tissue was free from bile-stain and that the bile was confined to the liver-like cells of the active tumor. In at least

Fig. 3.—Effect on growth of guinea-pigs produced by feeding pineal-gland tissue. Control pigs to left, test pigs to right.

one case, a metastasis in the lung from the liver secreted bile. In this connection it is significant that the functioning glandular cells of typical thyroid structure have been found in thyroid metastases in bone-tissue. Furthermore, in myeloma of the bone-marrow the cytoplasm¹⁵ of the tumor-cells contain the granules that characterize normal myelocytes, that is, the tumor to a certain extent assumes the function of the bone-marrow. All considered, it is perceived that functional activity of tumor-cells is *not* infrequent. Germane to the present contention is the statement by Hinds Howell¹⁶ in describing the characteristics of the cells of the pineal tumors of his three cases. He says:

A noteworthy feature is the similarity of these tumor-cells in many instances to those of the normal pineal gland.

The results of this work lead me to the conclusion that the administration of minute quantities of pineal tissue from young animals to young animals stimulates rapid growth of the body, but not beyond normal size. Also there are less well-established indications of precocity of mental and sexual development.

EXPERIMENTS ON THE CURATIVE VALUE OF THE INTRASPINAL ADMINIS- TRATION OF TETANUS ANTITOXIN *

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AND

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While tetanus antitoxin has proved most efficacious in the prevention of tetanus, its employment as a curative agent has been much less successful. This failure to produce more uniformly good results is chiefly due to its too late administration. Insufficient dosage and the use of the subcutaneous method have also been important factors. While the subcutaneous use of antitoxin, which at first was the usual method employed, may prove of value in large doses given within the first few hours after the onset of symptoms, nevertheless it frequently fails because of slow absorption and the time required to reach the tissues of the central nervous system. In the light of our present knowledge, this method can be justified only by an inability of the physician, for one reason or another, to give an intraspinal or an intravenous injection. The latter method is being more and more recommended, and when employed before the disease has made too much headway has given much better results than the subcutaneous.

From time to time since 1903, single cases or small series of cases have been reported in which the antitoxin has been given intraspinally. Thus Neugebauer¹ in 1905 reported forty-three cases from Continental and American sources with a mortality of twenty-two, or 51 per cent., and also three patients treated by him of whom two recovered. Many of these patients received also intravenous or subcutaneous injections or both. The results seemed to some observers to be better than when other methods were used without intraspinal dosage, but on the whole, this method of treatment has not made much headway. Experimental proof of the greater value of the intraspinal method has not until very recently been at all convincing. Permin of Copenhagen, working on rabbits and dogs, showed that local tetanus could be prevented by the simultaneous injection of tetanus toxin intramuscularly and a dose of antitoxin given in the spine, whereas with the same dose of antitoxin given intravenously, local tetanus occurred. Four hours after the giving of the toxin neither method of preventing the occurrence of local tetanus was efficacious, and when nine hours were allowed to elapse between the giving of toxin and antitoxin, the animals could not be saved.

The following series of experiments was undertaken with the object of determining to what extent tetanus antitoxin given in the spine has greater curative power, when the disease is actually established, than when given in the circulation. The comparative ineffectiveness of subcutaneous injections of tetanus antitoxin in developed cases is incidentally brought out. The use of guinea-pigs for this purpose has not been recorded so far as we know. They possess, however, a marked susceptibility to tetanus together with comparative freedom from intercurrent diseases and a certain

11. Weber: Proc. Roy. Soc. Med. (Path. Sec.), 1910, iii, 147.

12. Rolleston: Diseases of the Liver, 1905.

13. Wheeler: Guy's Hosp. Rep., 1909, lxiii, 225.

14. Ribbert: Deutsch. med. Wchnschr., 1909, xxxv, 1507.

15. Weber and Ledingham: Proc. Roy. Soc. Med. (Path. Sec.), 1909, ii, 206.

16. Howell, Hinds: Proc. Roy. Soc. Med. (Neurolog. Sec.), 1910, iii, 65.

* From the Research Laboratory, Department of Health, New York City.

1. Neugebauer: Wiener klin. Wchnschr., 1905, xviii, 450.