

GENERAL MEDICAL ASPECTS OF ENDOCRINOLOGY

WITH A FEW REMARKS CONCERNING SOME OF THE NEWER
HORMONES

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The following brief review of a few of the interesting features of hyper and hypothyroidism, and hyper and hypoparathyroidism is presented from a clinical standpoint.

Let us consider first some problems in the diagnosis of thyroid disorders.

Three conditions which commonly offer resistance to accurate diagnosis of thyroid disorders are (1) hyperthyroidism in remission, (2) neurocirculatory asthenia, and (3) hyperthyroidism masked as heart disease.

HYPERTHYROIDISM

In recent years, the indiscriminate use of iodine has increased tremendously the difficulty of accurate diagnosis of thyroid disorders. Patients with hyperthyroidism are frequently seen who have been taking Lugol's solution for several weeks, and at the time they present themselves for examination they may have very few symptoms or signs of hyperthyroidism remaining and the metabolism may be normal.

The essential factor in the diagnosis of hyperthyroidism in the case of such a remission is a painstaking history. Usually there is a characteristic onset of the condition with an increasing sense of stimulation warmth, hyperhidrosis, forceful tachycardia, tremor, loss of weight in spite of a good appetite, and distinct improvement after taking iodine. Histories of patients with diabetes or tuberculosis may bear a superficial resemblance to those of patients with hyperthyroidism except for improvement on taking iodine in the case of the latter.

The most important finding from the physical examination is the general appearance of the patient. He is alert, he is apprehensive, the eyes have a brilliant stare, skin is flushed and perhaps a mild hostility may be noted. A similar appearance may be seen in hypertension and at times in beginning psychosis.

The general physical findings may be scanty. A goiter is usually present which may be solid, suggesting diffuse hyperplasia. Mild

tachycardia may persist. There may be slight cardiac enlargement and usually the heart sounds have a peculiar loudness. The systolic blood pressure often is raised. Exophthalmos is usually absent in the early cases. Occasionally there is a residual tremor and the fine moist texture of the skin may be maintained.

In short, when the history is characteristic of hyperthyroidism, the appearance of the patient is suggestive, and the cardiovascular signs consistent, especially if improvement has been noted following the use of iodine, even though the basal metabolism is repeatedly normal, hyperthyroidism is still present. In such a case thyroidectomy should be performed.

NEUROCIRCULATORY ASTHENIA

Neurocirculatory asthenia is probably misdiagnosed hyperthyroidism more frequently than any other disease. The syndrome is seen usually in individuals under thirty years of age and is characterized chiefly by fatigue, nervousness and vasomotor disturbances.

It is easy to visualize the young woman of twenty whose general appearance as she sits in the consulting room suggests exhaustion. She complains that she is weak and nervous, that she has palpitation on the slightest exertion or even when at rest. She may have been losing weight. She believes a goiter is responsible for these symptoms.

It is often stated that in such a patient nervousness, tachycardia, tremor, hyperhidrosis, weight loss, and goiter are present and indeed the basal metabolism (especially the first estimation) may be elevated. From such a simple statement of facts the conclusion often is arrived at that such a patient has hyperthyroidism. The symptoms and signs, however, must be more critically considered.

The nervousness has probably been present for a long period with slight change, and the appearance of the patient is suggestive of exhaustion. The tachycardia is extremely variable and may change markedly on deep breathing, on ocular pressure, on forceful flexure of the trunk (the so-called Erben's phenomenon) or even on forceful convergence of the eyes (Ruggeri's sign). Tremor is usually coarse.

Hyperhidrosis is present chiefly in the extremities and is associated with coldness. Loss of weight is usually associated with a poor appetite. Goiter, if present, is commonly of the diffuse, soft, so-called colloid type.

In cases of neurocirculatory asthenia the pupils are frequently dilated and may show hippus or positive visero-ocular reflex.

The impressive points in such a case are (1) the prominence of fatigue in the clinical picture, (2) the variability of the pulse rate, and (3) the coldness of the extremities. In such patients even though several metabolism tests may show a rate of plus 16 or plus 20 per cent no hyperthyroidism is present and I know of no type of patient to whom thyroidectomy may do more damage. It is true that in nearly all cases repeated metabolism tests may show a rate falling to normal but this may occur also in mild hyperthyroidism if the patient is at rest.

HYPERTHYROIDISM MASKED AS HEART DISEASE

Hyperthyroidism is often misdiagnosed heart disease and patients frequently go about for years with a diagnosis of rheumatic or arteriosclerotic heart disease, with auricular fibrillation or myocardial degeneration, because in cases of mild hyperthyroidism of long standing the cardiac symptoms and signs frequently overshadow all others until they are lost sight of.

In all cases of auricular fibrillation the possibility of the presence of a goiter should be borne in mind as a cause, and in all cases of myocardial damage in which a goiter is present, the existence of the goiter should never be dismissed lightly as a possible cause of such damage, although other signs of hyperthyroidism may not be evident. The so-called "goiter heart" is enlarged to the left, there is increased force and amplitude to the apex beat and the sounds are peculiarly loud. Usually a systolic, non-transmitted, apical murmur is present and perhaps a systolic murmur may be heard at the base. Sometimes a systolic vibration may be felt. A diastolic thrill or murmur is never present. Tachycardia and elevation of the systolic blood pressure may or may not be present.

The history is often suggestive of hyperthyroidism but this may be indefinite. There is no history of rheumatism. Here again the general appearance of stimulation, staring and alertness is important. A goiter is usually present and if the condition is suspected and the basal metabolism is persistently elevated the diagnosis is easy. Not infrequently, however, the basal metabolic rate may be normal in such cases at the time of observation. Such patients are greatly improved by thyroidectomy.

HYPOTHYROIDISM

Let me remind you that hypothyroidism is not necessarily present in all cases in which a low metabolic rate is present. Hypo-

metabolism may occur in chronic exhaustion from various causes, in arthritis, in pituitary disorders, etc.

The results of treatment for this condition would seem to indicate that the diagnosis should be made by a careful correlation of symptoms, signs and metabolic studies.

Hypothyroidism is of especial interest to ophthalmologists, because it is so often associated with ocular muscle imbalance.

Hypothyroidism can seldom be diagnosed by the appearance of the patient. The patient usually complains of lack of energy and endurance, or as he terms it "lack of pep." He may have noted nervousness, coldness, diminished mental alertness and drowsiness or some loss of memory.

Careful questioning may be necessary to reveal further facts. The patient may have noted dryness of the skin and hair, brittleness of the nails, or slight edema especially about the eyes. Paresthesia in hands and feet is frequently noted.

In 100 non-operative cases analyzed recently there was a gain in weight in only 43 per cent, bradycardia in only 39 per cent and a temperature below 98 in 26 per cent.

In the presence of typical symptoms of hypothyroidism a diagnosis may be established although the metabolic rate is not below minus 10. On the other hand, the metabolism may be as low as minus 30 and no hypothyroidism be present. A basal metabolic rate of less than minus 25 per cent, however, is probably due to either thyroid or pituitary disease. In cases in which the diagnosis is questionable a thorough trial of thyroid feeding may be useful. The average dose is 2 grains of desiccated thyroid or 10 grains of the whole gland per day.

Four interesting and common laboratory findings in the presence of hypothyroidism are given below:

(1) Carbohydrate tolerance may be so increased that to produce alimentary glycosuria is practically impossible. Increased tolerance was found in 45 per cent of 20 cases in this series.

(2) Low gastric acidity is often present. Hydrochloric acid was absent one hour after an Ewald test meal in 16 cases of a total of 45, i.e., 35 per cent.

(3) Lymphocytosis of 40 per cent or over occurs in about 30 per cent of cases.

(4) Electrocardiogram showed low amplitude with flat T waves in 16 cases in 58 or 27 per cent. This does not seem to be caused by previous myocardial damage since the amplitude may be made normal on administration of thyroid extract.

CHRONIC POSTOPERATIVE TETANY

In connection with hypoparathyroidism let us consider only chronic postoperative tetany which is due to the removal or destruction of the majority of the parathyroids. The occurrence of this condition may be unavoidable even when standard operative technique is used.

Chronic tetany is characterized by a decrease in serum calcium, a retention of phosphates, intermittent attacks of muscle spasm, and in some cases trophic changes.

The serum calcium is reduced from a normal content of 10 mg. per 100 c.c. to below 9 mg. In some chronic cases the serum calcium has been known to fall to 5.3 mg. per 100 c.c. in the presence of very slight symptoms of tetany. The phosphates rise from a high normal of 4.5 mg. per 100 c.c. to 5 or above.

In many cases the symptoms are for the most part latent; mild paresthesia of hands or feet may be present but may go unmentioned for years.

In other cases more pronounced symptoms appear at the menses, during infection or in exhaustion. In the latent stage Chvostek's sign is usually present. No case has been seen in which Trousseau's and Erb's signs were not present.

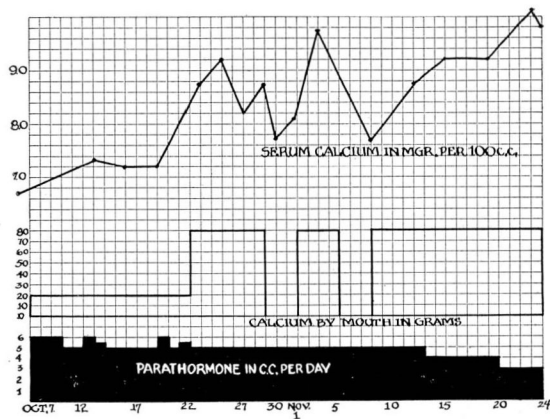
An acute attack of tetany is usually preceded by paresthesia in hands or feet; fibrillary twitching and ciliary spasm may occur, then carpo-pedal spasm, hypersensitiveness is present in the extremities; there is spasm of the facial muscles with circumoral pallor; hyperpnoea, laryngeal spasm with stridor, and abdominal pain are noted, and in extreme cases all muscles may be involved. Obviously, motor, sensory, and sympathetic nerves are all involved.

In some cases tetany may occur with extreme suddenness, producing generalized convulsions, usually tonic, but nevertheless frequently mistaken for grand mal. In other cases muscle spasm increases so slowly that walking is interfered with and Parkinson's disease may be closely simulated. Temporary psychoses may occur. The general nutrition of the tissues is poor, the color often sallow, the teeth may be loose, the nails may become chalky white and fall out, and diffuse lenticular haziness may progress to cataract.

The most important reason for thorough treatment of chronic tetany is the prevention of cataract. The patients become so tolerant of low calcium that symptoms are no guide and blood studies must be used.

The most important factor in the treatment of chronic tetany is the giving of large enough doses of calcium. Calcium lactate

powder in doses as large as two heaping teaspoonfuls three to four times per day is usually sufficient. If this amount produces diarrhea, calcium carbonate may be substituted. If calcium alone is not sufficient, lactose in doses of one or two teaspoonfuls three or four times a day should be added, which will help to lower the blood phosphates. If this amount produces diarrhea the dose should be lessened. Milk is useful as it contains both calcium and lactose. Ultra-violet light is helpful. The usual doses of viosterol are of doubtful value. Parathormone may be necessary rarely. In acute cases 5 to 10 c.c. of a 5 or 10 per cent solution of calcium chloride may be necessary. It is best given by the gravity method preceded and followed by saline. Parathyroid administered by mouth has been practically useless in my cases.

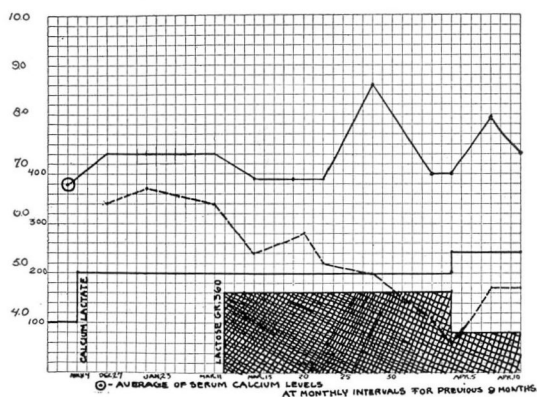


Author's Note — In Chart I "Calcium by mouth in grams" should read "Calcium by mouth in grains."

Chart I represents a case of chronic parathyroid tetany and illustrates the value of large doses of calcium by mouth. The upper line represents the total serum calcium which varies from below 7 mg. per 100 c.c. to above 10 mg. per 100 c.c. The lines in the middle of the chart represent the dose of calcium lactate in grains by mouth per day. The lower portion of the chart which is blocked represents the amount of parathormone in c.c. per day. At first the patient was receiving 20 grains of calcium per day and 5 and 6 c.c. of parathormone. The blood calcium varied about 7 mg. per 100 c.c. On October 22nd the parathormone dosage was not changed but the dose of calcium was increased to 80 grains per day. A marked increase in serum calcium followed. When the dose of calcium was decreased the serum calcium fell but rose again when the calcium was increased to the same dose on November 1st. When it was

discontinued, on the 5th day of November the serum calcium again fell but after November 19th it continued to rise following the administration of calcium even though the parathormone was lessened. Subsequently this patient's symptoms were completely relieved by doses of calcium lactate amounting to between 200 and 250 grains per day without the administration of any parathormone.

Chart II represents another case of chronic parathyroid tetany and illustrates the value of lactose in the case of patients in whom the administration of large doses of calcium lactate alone is not sufficient to control the symptoms of tetany. The upper line repre-



sents serum calcium in mg. per 100 c.c. The interrupted line represents the inorganic phosphate of the whole blood in mg. per 100 c.c. The straight black line represents the amount of calcium lactate given by mouth in grains per day and the cross-hatching represents the amount of lactose given by mouth per day. The upper line represents serum calcium; the circle represents the average serum calcium over a nine months' period. The patient was receiving 100 grains of calcium lactate by mouth per day. Between November 12th and March 11th she was taking 200 grains of calcium lactate by mouth per day. During this time the blood phosphates were measured and are reported in the chart. On March 11th in addition to the previous medication lactose powder was given in doses of 120 grains three times a day. It will be noted that the blood phosphates fell following the administration of lactose. During this time the patient's condition very materially improved. The blood calcium was not raised except in the case of the one peak which is unexplained. On April 3rd the dose of lactose was lessened to 180 grains per day and the blood phosphates rose somewhat although they were still within normal limits.

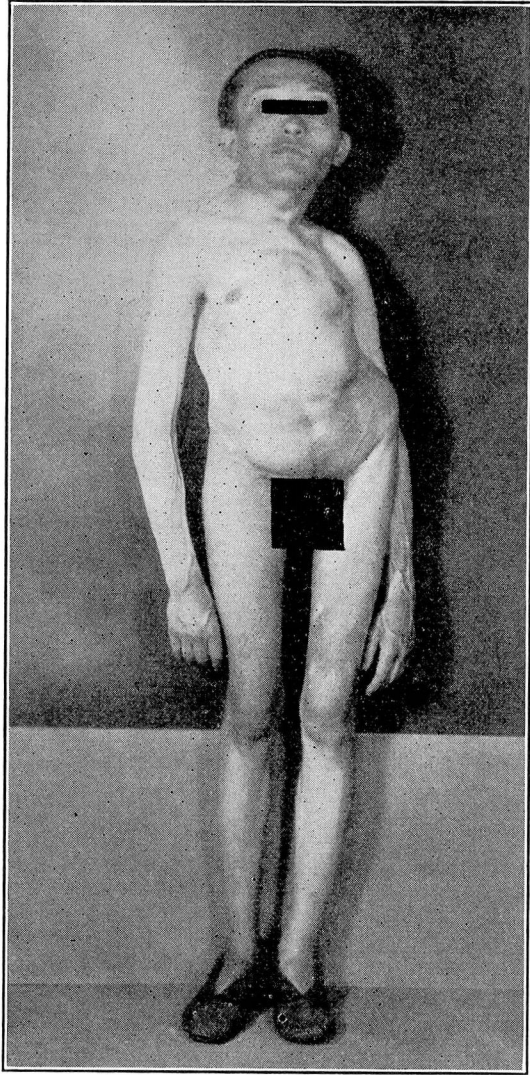


Fig. 1. Photograph showing deformity caused by multiple lesions. The presence of tumors in the left ilium and left maxilla is obvious. Marked deformity of the spine is noticeable and a large tumor is present in the right scapula.

HYPERPARATHYROIDISM

Hyperparathyroidism is a syndrome which is characterized by an increase in serum calcium, a decrease in inorganic phosphates, muscular atonia, general decalcification of bones, and multiple bone lesions. The bone lesions are identical with those known as osteitis

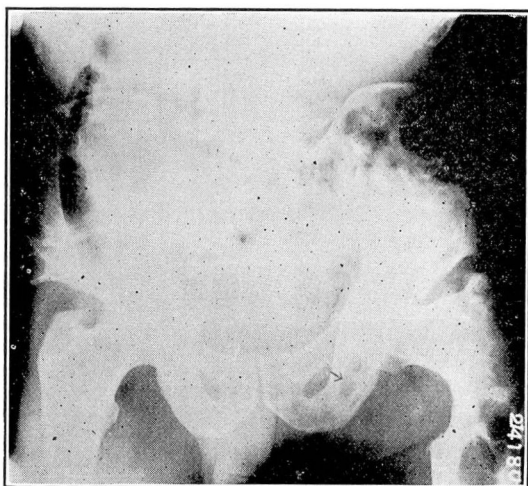


Fig. 2. Roentgenogram of the pelvis showing the distribution of the lesions present. Areas of rarefaction and cyst formation are seen, especially in the left pubis and ischium, and the left femur and ilium.

fibrosa cystica of the generalized type. There is also diffuse rarefaction affecting all the bones.

The first cases of this type to be reported were all associated with tumor of the parathyroids but more recently cases have appeared in which there is apparently functional overactivity. Usually the serum calcium in such cases is well above 12 mg. and the blood phosphates below 2 mg. per 100 c.c. In cases of long standing this is apparently not always true. This is to be expected since experimental evidence shows that one large dose of parathyroid extract may produce a marked hypercalcemia but if repeated doses are used the calcium may gradually fall to within normal range and the bones become decalcified.

CASE REPORT

A man 31 years of age came to the Clinic with a history of bone lesions which had been known to be present since he was 13 years of age. These lesions involved the skull, vertebrae, sternum, ribs, pelvis and long bones. They were painful and caused much loss of sleep. Fractures were frequent. The serum calcium was above 12 mg. Blood phosphates totaled about 2 mg. X-ray examination of the bones showed the presence of typical osteitis fibrosa cystica. The calcium balance was negative and the blood phosphatase, which is the recently discovered enzyme in the blood which has to do with bone formation and destruction,¹ was increased to ten times the normal.

Parathyroidectomy was performed and one hypertrophied gland removed. The calcium dropped to normal, blood phosphates rose, phosphatase was decreased to one-third of its original value, the pain in the bones disappeared, strength increased, and no fractures have occurred in a year.

SOME OF THE NEWER HORMONES

Time will not permit us to consider the pituitary gland but let me remind you of a few facts in connection with some of the more recently discovered hormones. The Aschheim-Zondek² test for pregnancy is an important recent advance. As you know, not only an ovarian but also a pituitary hormone appears in the urine in pregnancy. Due to the presence of pituitary hormone, injection of such urine into young test mice produces changes in their ovaries within 100 hours or less which allow of the diagnosis of pregnancy. The result of this test is accurate in at least 98 per cent of cases — more accurate than the Wassermann reaction and probably the most dependable biological test. In the Friedman³ test similar changes are seen in the ovaries of rabbits after intravenous injection of pregnancy urine. The Mazer-Hoffman⁴ test for pregnancy depends on the fact that pregnancy urine, due to the presence of theelin, produces oestrus when injected into castrated female mice.

Folliculin, the follicular hormone of Allen and Doisy,^{5, 6, 7} is on the market under the names of amniotin, estrogen and theelin. Folliculin occurs in urine, amniotic fluid and blood in pregnancy and will produce oestrus changes in castrated animals. Its clinical value is not yet known.

Cortin, so named by Hartman,⁸ is the active principle of the adrenal cortex. It has recently been described by Swingle and Pfiffner.⁹ Its potency is proved by the fact that it keeps adrenalectomized cats alive for an indefinite period or will bring them from coma to normalcy. Its activity clinically in Addison's disease has been confirmed by Rowntree¹⁰ and others. Recently Roy McCullagh¹¹ has produced this material in the laboratories of the Cleveland Clinic. It was found to be potent experimentally and in one case in which I tested its action clinically it appeared active although the results obtained were not as striking as those reported by Rowntree.¹⁰

The male sex hormone may be produced from testes by the method used by Koch and Gallagher.¹² Funk and Harrow¹³ have described a method for obtaining it from the urine of young men and animals. Roy McCullagh could not corroborate the work of Funk and Harrow, but working with a different method he found this sub-

stance to be present. The hormone is tested on capons. As is well known, the combs and wattles of castrated young roosters shrink to a very small size. Injection of the male sex hormone in such birds causes these shrunken appendages to grow rapidly. At present we are making a test of the material but are not prepared to make any statements as to its clinical value.

The luteinizing hormone² of the anterior lobe of the pituitary gland may also be obtained from the urine. This substance causes the formation of corpora lutea in the ovary and is apparently active clinically. It lessens menstrual bleeding and evidence is quickly accumulating which indicates that this may be the means of a physiological control of menorrhagia.

Emmenin has recently been described by Collip¹⁴ who believes it originates in the placenta. It is apparently active when given by mouth and causes stimulation of sexual development. Its origin is still debated as it has several properties suggesting its possible origin in the pituitary. Attempts are being made at present to determine its clinical application.

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