EVOLUTION FROM STATUS THYMICOLYMPHATICUS. 

The Successive Phases and Their Treatment. 

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Medical literature for many years has sporadically produced a variety of glimpses into status thymicolymphaticus,—from the viewpoint of the pediatrist, or the internist or some other specialist who had become interested in the condition because of its bearing in his particular field. Warnings were always uttered as to the importance of its recognition for always did its presence modify symptomatology, treatment and prognosis. But never has any real attempt been made to trace the progress of status thymicolymphaticus through the developmental years to adult life and to mark its metamorphosed characteristics and the attempt of the individual to compensate for its disturbances. In the past ten years it has been my fortune to examine many hundred cases of status thymicolymphaticus in all stages of development including adult cases, in whom the early history gave indubitable evidence of such disturbance; and as a result of a more or less comprehensive study of these cases, certain general conclusions have been drawn which I shall attempt to present, together with the facts upon which they are based. 

Reviewing the general symptomatology of status thymicolymphaticus as a basis from which we shall proceed, I give hurriedly the outstanding features of this condition.

**Skeleton.**—Growth of skeleton is usually abnormal in that the various units are in disproportion—thorax too long for legs, and vice versa; hands and
feet too long for arms and legs; bony structure usually frail and rachitic evidences are frequently present. A maxillary torus is in evidence.

**Teeth.**—Almost invariably there is delay in permanent dentition with prominence in size of the central incisors of the upper jaw, with comparatively small lateral incisors, and canines that have lost, or rather not acquired the fanglike shape, but resemble the incisors in that they have a cutting edge. The molars appear very late.

**Joints.**—The tendons about the joints are loose and hence dislocations. Subluxations are frequent together with ability to produce marked contortions of the body. The extremities are like flails and the whole skeleton is of a loosely put together character. The apparently fixed joints, such as the sacroiliac, become partially movable and hence are the seat of intense backache on fatigue. Like conditions obtain in joints of the foot, and pes planus is the result.

**Skin.**—The skin is soft and velvety, covered with lanugo, frequently with a marked blush on the cheeks—a typical peaches and cream complexion. The bluish vessels are easily seen through the translucent skin.

**Hair.**—While lanugo covers the parts which would later be provided with secondary hairy growth, yet such later growth is very late in appearance. Axillary hair and pubic hair do not come in until long after the usual time for the arrival of puberty, and in the boy, beard and mustache are still later, and then very sparse. The growth on the head is, however, profuse.

**Genital system.**—In the boy there is usually retardation in growth of the genitals, and not only this, but the growth is of undifferentiated character, so that there is a fold of the scrotum which partially or even entirely surrounds the base of the penis, resembling the labia in the female. Occasionally, one or both testicles are undescended and there may be hypospadias. In the girl, the clitoris is usually disproportionately large, the menses come on late, and are delayed and irregular.

**Eyes.**—The pupils are usually large and mobile, the sclera, clear bluish white, and the vessels of the fundus are extremely thin in calibre, without engorgement of the veins.

**Endocrine glands.**—The thyroid shows no abnormalities in size, although it is usually underfunctioning; the thymus gland is present and large, even after the twelfth year. Percussion and roentgenography will confirm this. The picture should be made at the end of a long expiration. The adrenals are invariably deficient, both as to size and chromaffin content. Indeed, the chromaffin tissues throughout the body are deficient. The pituitary gland is usually small and is encased in a sella turcica which is small and enclosed by the chondrals. This fact is of great importance in the further history. The gonads are usually small and delayed in development and in differentiation.

**Vasomotor system.**—The blood vessels are of small calibre throughout the body, especially the aorta and the coronary arteries. The heart is small.

**Viscera.**—Frequently a tendency to splanchnotosis. Incontinence of urine; enuresis.

**Laboratory findings.**—Blood: red blood cells and hemoglobin usually normal; white cells show a marked relative lymphocytosis with a low polymorphonuclear count, which at times is as low as five per cent. Usually an eosinophilia is present. Blood sugar is usually low, .08 per cent., .060 per cent. Of importance is the carbon dioxide tension of the blood plasma, which is invariably low, minus forty-five to fifty per cent. The coagulation time is prolonged, often as long as fifteen minutes. The urine has a low specific gravity, and not infrequently shows the presence of acetone.

**General observations.**—From the foregoing, the symptoms exhibited by the patients are readily understood. These are fatigue and dyspnea on ex-
ertion; fainting attacks and collapse in critical situations; syncope and death in narcosis, fright and exhaustive demands. The symptoms depend upon the low chromaffin supply, the small bloodvessels, the low blood sugar and the tendency to acidosis. Death is not due, as has been thought, to pressure of the thymus on the trachea—or at any rate, only in the rarest cases, but is due to adrenal exhaustion. Urticaria, asthma, acidosis, enuresis, hay fever, circumscribed edema, arthritides, are all concomitants. Blood pressures are low, pulse pressure frequently down to 10 or 15 mm. The low adrenal efficiency gives a Sergent's line on stroking the skin of the abdomen.

From the general description, no matter what your field of work may be, you will all recognize cases that have come under your notice. These patients do not all die in growth or adolescence, nor do even a large number of them. What becomes of the survivors? How do they manage to maintain themselves in the struggle for existence? Do they constantly remain a prey to their deficiencies? These questions possibly can now be answered. The development and evolution out of status by the individual's intrinsic powers of compensation and adaptability form one of the most interesting chapters in modern medicine and their recognition will enormously aid us in our power to help hitherto obscure and apparently adventitious symptoms in our patient's progress, no matter what his ailment, no matter what our specialty.

The very first consideration in the difficulty of adaptation to environment of the status case is the outstanding fatigue. This, as has been said, is due to several factors—the adrenal insufficiency, the low blood sugar content, the low alkaline reserve and low blood and pulse pressures. If there were any possibility of overcoming these basic difficulties, a large measure of improvement would take place. But is there in the human economy any possibility of such autonomous regulation? If, for instance, splanchnic stimulation, such as is efficient in shock, were to occur, might the situation not be overcome? The stimulation of the splanchnics or the sympathetic system generally, depends for its effect largely upon an adrenalin reserve. This is wanting in the status cases. Stimulation by thyroid secretion also depends upon the sensitization of the neurovascular synapse by thyroid extract to the action of adrenalin. Again the same difficulty.

But there is one tissue which will produce the wherewithal, independent of adrenalin—to increase blood pressure and blood sugar content, and that is the pituitary body. Does increasing activity of the gland actually occur? For a reply we must go to our case histories. We find here two groups of status cases, one, by far the larger, in which the sella turcica on x ray examination is found to be small and enclosed; and the other in which the sella is presumably normal in size and conformation. The symptomatology in the two cases is different in important particulars, and it is the former group which is of interest to us now. In the small, enclosed sella group there is always associated with the fatigue states, headache. This headache is intratemporal in situation, of intense, painful boring, or pressure, or throbbing in character, and more or less periodical in its onset. Its periodicity is menstrual or seasonal; and yet it may be produced by any factor which will stimulate the pituitary gland. For instance, the ingestion of large quantities of carbohydrate food; cerebral hyperemia due to the intense cerebration of long continued worry or chagrin or mental effort; injections of anterior lobe pituitary extract; and similar stimulants. Just before the headaches begin, blood and pulse pressure are low in our cases, while during the headache period, both rise, as does the blood sugar content. After a year or two or three of such constantly recurring headaches, interesting data are available.
These are as follows:—Blood pressure, pulse pressure and blood sugar content are all on a higher level; there has been a rapid increase of skeletal growth; and an x ray of the skull shows a sella turcica that presents erosions and thereby an enlargement of its cavity. With these facts at our disposal, I believe that the conclusion is not very farfetched that pituitary hyperactivity has occurred and with it an amelioration of the asthenic symptoms. In other words, there has been a compensation process inaugurated automatically, which has served to overcome many of the symptoms of disability possessed by the status case. This compensatory process proceeds for years, the sella turcica becoming more and more eroded, the headaches gradually becoming less and less frequent, the skeletal growth, however, going on pace. Now, other symptoms of pituitary primary activity and other glandular activity secondarily, begin to present themselves. There is gonadal growth; undescended testicles come down; secondary hairy growth begins.

The young man that has reached this period of compensation gives somewhat the following picture. His age is twenty; he is six feet or more in height; his skin, while still smooth and velvety, has begun to look more rugged. The first hairs of mustache or beard are beginning to show themselves. His pubic hair, which has been for a few years scanty and feminine in its distribution, begins to encroach on the middle line of the abdomen towards the umbilicus. His joints are loose, subluxations of the mandible or of the carpal metacarpal joints being readily produced; he has the large central incisors of the upper jaw; a torus palatinus is evident—but he is getting to be more efficient in his study and in his play, and his fatigue is diminishing. He still has headaches, sometimes very severe. It is for this symptom that he sees the oculist, or the rhinologist or the internist or the neurologist. Careful inquiry into his developmental history will elicit many symptoms of the foregoing group, and he will be recognized as being in a transitional stage of compensation from an early status thymicolymphaticus. The rapid skeletal growth and the headaches will lead the careful clinician to examine the sella and the thymic region and there the telltale marks of his progress will be seen. At once it will be recognized that the extreme height and the headaches are simply the hallmarks of a purposeful compensatory process on the part of the pituitary gland to overcome the disabling characteristics of a status thymicolymphaticus, and are not disease symptoms in themselves. This is highly important to know both for purposes of treatment and for prognosis. As we watch his progress through the years, he goes on growing, though less and less in degree; his headaches come on only after undue fatigue or exertion; the thymic x ray shadow disappears; he may grow both mustache and beard; his blood pressure, pulse pressure, blood sugar content, coagulation time—all approach normal, and finally even his growth ceases. We have before us, a moderate giant, six feet two inches in height, who has finally matured, physically, psychically and sexually at the thirtieth year of life instead of at the twenty-first. He will always be conscious of some limitation to his physical possibilities, but will be able to survive in competition with his fellows. In other words, he has gone to cure through spontaneous compensation. Looking back over his career, the recognition of the milestones of his progress gives us the keynote of the treatment which we may accord his less fortunate brethren in their partial or complete failure to follow his trail. That keynote is the ability of the pituitary body to become hyperactive in order to compensate for the initial adrenal insufficiency. It is incumbent upon us, therefore, to recognize those cases that continue to exhibit various degrees of thymic disturbance in their later life and, secondly, to esti-
These patients, besides the original structural abnormalities described in the opening chapter, exhibit especially, a, fatigue, b, low blood and pulse pressures, c, low carbon dioxide tension of the blood plasma, d, long coagulation time, e, various vagotonic stigmata, such as visceroposis, hypermotility of stomach and intestine, urticaria and angioneurotic edema, cardiospasm, esophagospasm, high gastric acidity, anginoid attacks, attacks of syncope and so on. These symptoms are important in every field of medicine and play an extremely active part in each symptom complex. The danger lies in considering them as disease pictures in themselves and not as mere symptoms in a universal syndrome whose basis is a subinvolutied thymus gland, uncompensated. The recognition of continuations of the above intruding themselves into our patient’s complaints will make for more thorough diagnoses and more thorough basic rational treatment.

As we have seen that automatic compensation of a thymic state depends upon potential hyperactivity of the pituitary body, we must estimate this possibility by the very means as yet in our power, namely, the size of the sella turcica, and its freedom from complete enclosure. As before stated, the two large groups of our cases are separated on a basis of sella turcica conditions; the small enclosed sella giving rise to the pressure symptoms, with headache, growth, and gradual amelioration of the symptoms provided the sella become eroded and enlarged.

The normal sella group have at most only intratemporal pressure symptoms of a mild degree, but growth has been rapid and blood pressure, pulse pressure and blood sugar have gradually risen, and with this rise, a general improvement in the asthenia has taken place, and in a comparatively short time, our patient is normal and no longer interests us.

Furthermore, with a large, roomy sella from the very beginning, compensation may occur without any symptoms whatever and the case never comes to observation.

There is still another possibility, namely, that the small, enclosed sella will resist enlargement or that the pressure exerted within it is never sufficient to produce such enlargement. In either case, an inefficient pituitary activity leaves the patient at the mercy of his thymic subinvolution. At this point our therapy becomes effective.

Having decided then that our case presents the earmarks of an early thymic subinvolution, it is our function next to determine the phase of compensation at which the patient has arrived. An x ray examination of the chest and skull will help. The chest may still give evidence of a persistent thymus gland, although the absence of a thymic shadow is not necessarily proof of the absence of the thymus. The skull, however, will show a sella turcica of one of the following types:

- a, small enclosed, no erosions.
- b, small enclosed, with erosions.
- c, medium size, smooth wall, open between clinoids.
- d, medium size, eroded walls, or clinoids, or both.
- e, enlarged with evidences of extensive erosions.

Type a is of the noncompensating group of cases. This group requires constant treatment, probably throughout life.

Type b shows beginning compensatory enlargement, judged by the eroded walls of the sella, and requires treatment for the compensatory effort.

Type c is a normal sella which may or may not enclose a hyperactive gland, and in which treatment will depend upon the efficiency of the hyperactivity.

Type d is of normal size but has been made so by constant pressure, as witnessed by the marked erosions. In this group of cases there is usually a history of long continued, severe headache of migrainous character, intratemporal in situation and frequently of ophthalmoplegic type. This ophthalmoplegia depends upon the lateral encroachment of
the pituitary body to the cavernous sinus. The sinus conveys the third, fourth, sixth, and ophthalmic division of the fifth cranial nerve within its walls and pressure upon it, of the pituitary body will involve one or even all of these structures. Hence the symptomatology will include, during the headache, diplopia, strabismus, ptosis, pupillary abnormalities and so on. The radiologist will often report such a sella turcica as normal in size, without suggesting erosion, not recognizing that the normality in size is simply a transitional state from small to large. This is of importance to recognize.

Type e is the final state of a sella turcica in cases in which complete compensation may have taken place with gigantism, or acromegalic features, but with normal blood pressures and normal blood chemistry.

By means of these examinations, together with the patient's symptomatology, we can arrive at some conclusion as to his present whereabouts, in the progress to complete compensation. I divide the entire period of evolution into periods; first, the actual status of origin; second, the period of beginning compensation with beginning rapid growth, headaches and symptoms, both physical and psychical of an underdeveloped pituitary body; third, the period of enlargement of the sella turcica with a gradually decreasing fatigue, decreasing headaches, and a slowing down of growth; and fourth, the terminal period, in which the condition becomes fully compensated, with cessation of growth and of headache, and much moderation of fatigue.

The difficulties arising in each of these stages have been only lightly touched upon in the foregoing; but each period has a host of major and minor attributes that only a long experience will make familiar. I would like to mention here chiefly the mental disturbances with their concomitant behavioristic anomalies. During the second and third stages, namely, those of continuing compensation, the individual contending with his headaches and fatigue cannot give proper thought nor consecutive attention to the problems before him. As a result, he falls behind his more fortunate brothers in school and college and becomes backward in intellectual development. Realizing his inability to compete with them, he likewise separates himself from their company and their games, and becomes shut in. This leads to various psychic phenomena, with morbid thoughts and fears and a more or less depressive state supervenes. One curious condition which we have often seen in our patients at this stage, in those with small enclosed sella turcica, is a lack of inhibition which manifests itself in a variety of ways. They do and say the first thing their environment impels them to, without allowing judgment to enter until too late. Thus many of our patients are pathological liars, kleptomaniacs, moral inferiors and drug habitues. They always avoid obstacles by the means nearest at hand, and never by any chance either endeavor to overcome them, or make early provision against them.

When compensation is complete, however, or treatment is instituted early enough, many of them are improved in these regards as well as in the matter of their physical disabilities. A certain number of patients never compensate, the sella remains small and enclosed, and their lot is constant observation and treatment.

So that we see in the evolution from status thymicolymphaticus a series of stages involving a symptomatology which encroaches upon all fields of medicine from surgery to psychiatry. The tangential points are the ones that all of us must watch for, and once found and recognized, are the keystones to a complete understanding of the patient.

A knowledge of the dynamic process going on in our patients, and of the goal that the autonomic procedure is striving to attain, is the groundwork of our treatment. To recapitulate, the pituitary must do
additional work to increase blood sugar and blood pressure, for the adrenals are inefficient. Then the active thymus must be inhibited. The lack of differentiation in structure and gonadal characteristics of the thymus cases may be partially overcome by the administration of small doses of thyroid gland and of iodine. This is based upon recent investigations on the positive effect of thyroid gland and iodine upon differentiation in lower forms of life. The thyroid dosage should be low, one tenth grain daily; or of thyroxin, Kendall's product, a half milligram daily or on alternate days only. Iodine in one or two drop doses, well diluted, or in the form of sodium iodide, grains five, on alternate days will suffice. If the thymus remains large, it should be x rayed at periodical intervals, depending upon the urgency of the case. But the chief treatment must be directed to increasing the pituitary supply. In those cases in which the sella shows much erosion with gradually increasing efficiency on the part of the patient and a diminution of headache, no treatment at all is indicated. But where the effect of compensation is not apparent, the fatigue and headache persist, then pituitary medication is essential.

The correct administration of this product is extremely difficult to outline, for there are certain times when it increases the headache in individuals, and frequently, if continued without intermission, a gradually diminishing effect is seen. Personally, I begin with a quarter grain capsule of the whole gland, given once daily on an empty stomach. Frequently, after three or four days, the patient complains of pressure in the head, intratemporally. I then omit giving it for a day or more, and begin again. In girls, it is usually omitted a few days before the menstrual period, for it increased the headache usually present at that time in them. Gradually, with this small dose, conditions improve. If not, the amount is slowly increased, but given intermittently as before. Rarely do I exceed a daily dose of three or four grains. The patients, before very long, begin to feel the good effects of this treatment and become expert in their own cases, so that they can tell when and how much glandular extract to take. Stimulants of the sympathetic nervous system are efficient in tiding over especially severe periods of weakness. These include coffee, atropine in small doses, and alcohol in small doses. One might think that suprarenal gland extract or adrenalin would be of good effect. The former sometimes is of service in conjunction with pituitary feeding, but adrenalin usually is not. After ceasing the administration of adrenalin by mouth, the blood pressure usually falls below its former height. And when given hypodermically, the reaction is frequently bad and leads occasionally to syncope. Its effect is much like that of cocaine in these cases,—rapid adrenal exhaustion takes place due to intense stimulation of the splanchnics. Administration of alkalies—carbonate or bicarbonate of soda several times daily is of the greatest service in combating the low alkaline reserve.

Apart from active treatment, it is necessary to enjoin certain measures on our patients. They should not subject themselves to, 1, exercise, especially of a competitive nature, except in extreme moderation; 2, cold water bathing; 3, excessive ingestion of carbohydrates; 4, too intense application to any one task for a considerable period; 5, worry, anger or emotional strain; 6, narcosis, especially chloroform, cocaine or its derivatives. They should have air, sunshine, and much rest. Food should be taken frequently in moderate quantities. Adjuvants of all kinds will readily suggest themselves in the conduct of any one case and of course the special treatment involving any particular organ of little resistance must be carried out.¹

¹ Case histories belonging to the evolutionary stages may be found in a New Pluriglandular Compensatory Syndrome by Walter Timme. M. D., in Endocrinology, July-September, 1918, Volume 2.

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