THE ENDOCRINE CONTROL OF PHYSIOLOGICAL IMMUNE REACTIONS

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We may first define a "physiological immune reaction." This is the formation of an antibody to a protein that is normally present in the body tissues, otherwise known as "natural tissue antibodies" (NTA).

These antibodies are important factors that have functions to control growth, tissue repair and development of the young.

We might list the three stages of growth to illustrate the relationship of NTA to this activity:

1. Embryo, during which cell division is the major activity, encouraged by placental hormones, without which the normal control influences would inhibit such phenomena.

2. From birth to adolescence cell division (except of epithelial tissue) is blocked by NTA but cell growth is facilitated WITHIN THE ORGAN CAPSULE by cell cytotrophins there present, but cytotrophins that escape are eliminated by phagocyte activity under the control of NTA.

3. During and after adolescence the escaping cytotrophins are tagged by gonadal hormones for delivery to the gonadal destination where they become germinal components as genetic factors, chromosome blueprints as it were.

Stage 1 is stopped at birth by loss of placental influence, plus the inhibitory effect of thymus antibodies.

Stage 2 is stopped by gonadal hormones at adolescence which act to inhibit thymus as a part of their physiological job, unless the thymus is simply robbed of anything to do by the dispatching of cytotrophins to the gonad, with the end result of atrophy by disuse.

Among the other hormones of important influence is the thyroid, which appears to be essential to the release of cytotrophins from the cell nucleus.

Tadpoles under thyroxin influence turn into frogs so rapidly that they cannot grow normally, become housefly sized perfect dwarf frogs that in time grow to more normal dimensions. The blueprints are unfolded too fast for a normal rate of development. Contrarily, the human infant born with a defective thyroid is a dwarf unless fed exogenous thyroid hormone. His blueprints fail to unfold, so he remains relatively undeveloped.

The thymus and thyroid cooperate in disposing of excess cytotrophins by the thyroid acting to release adsorbed cytotrophins from connective tissue, which the thymus has earmarked for disposal by the creation of antibodies against said cytotrophins, which antibodies by combining with the cytotrophin make such cytotrophin the target for phagocyte pickup and disposal through the liver route. After the sex glands become active, the cytotrophins are earmarked by estrogen or androgen for delivery to the respective gonad, the surplus not thus used is also removed by the liver. That is, no doubt, how estrogens get into the bile.

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It is obvious that the thyroid is the primary instigator of the cycle we are observing. The thymus is the essential partner to provide a means of physiological removal of the end products of the thyroid action, which are physiologically hazardous unless properly disposed of. It is of great interest therefore, to hear from Dr. E. Schliephake of Germany who says: "I wish to state... that substances prepared from the thymus, administered either parenterally or orally, are able to remove in man all symptoms of the excessive function of the thyroid gland." (Deutsche Gesellschaft fuer innere Medizin, Verhandlungen, 57th Congress, 142-143, 1951)

He states that "For the last 15 years I have employed no other drugs but the products of the thymus in treating hyperthyroidism."

Therefore, we next must investigate the entire activity of the thyroid, now that we can interpret its various phases of activity in terms of simple physiological theory. It always has been known as a primary control organ, if for no other reason than its effect in regulating basal metabolism. Now this metabolic activity may be found to be simply the release of normal function otherwise held back or inhibited by lack of guidance from the cell determinants, blueprints, (cytotrophins) that cannot act until released or unwrapped by the thyroid hormone.

A proper analysis of thyroid function should illuminate the following facts:

1. The growth promoting effect of thyroid.
2. The relationship of thyroid to the specific dynamic action of amino acids and foods.
3. The role of iodine.
4. Relationship of S.D.A. to basal metabolism.
5. How thyroid interlinks with other endocrine activities.

We must assume that our reader has grasped the elements of "Protomorphology".* (If not, the reviews at the end of this commentary will acquaint him with the preliminary ideas.) For only through this hypothesis may we at this moment extend our concepts and elucidate a rational theory of operation of the thyroid, if not of all the endocrine mechanism.

We might start the observation of the cycle of action of the thyroid by noting the effect of thyroxine on the chromosome in the developing young. Without thyroxine there is a failure of the determinants (protomorphogens) to be released from the chromatin of the cell, and a consequent failure of the individual to properly unfold his normal characteristics. (No metamorphosis of the tadpole, no development of the cretin child.)

The sex hormones also release determinants, so we must distinguish the different activities. Estrogenic factors release the adsorbed determinant that has been taken up by connective tissue, that were thrown off by the cell during its normal dynamic activity, otherwise waste products. NOT the chromosome component at the moment. (But destined for that fate if the blood stream should carry them to the gonad.) The estrogen differs from the androgen in one important particular. It does not catalyze the tight wrapping of the determinant as does the androgen, so that only the male gonad can unwrap the (to it) highly valuable constituent needed to build the male sperm. Estrogen rather loosely wraps the determinant so that it can be used to promote somatic growth and repair at any point that it may be needed. (In gastric ulcer, the estrogen promotes healing, the androgen promotes the ulcer, by its isolation of the needed determinant, insuring its intact delivery to the

*PROTOMORPHOLOGY - Lee & Hanson - Lee Foundation, 1947 - $7.00

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male gonad for germ cell use.)

Estrogen thereby aids embryological growth, androgen makes such activity impossible. (Rapidly dividing cells create an excess of determinant, which androgens would convert to a deficiency by wrapping them into forms that only could be useful to the male gonad.)

This partnership between thyroid and estrogen is shown by the great increase of nitrogen elimination if thyroxine is administered during menstruation. (1) At this time the estrogen level is lowest, it apparently is needed to protect the determinants from the complete disintegration that the thyroxine will create if the proper cooperative factors are not present. That is why thyroxine is toxic to old people - after gonad recession, and when sex hormones are lacking to make use of the determinants.

The thyroid hormones are probably tripartite. The thyreoglobulin (the normal hormone) can be split into thyroxine and di-iodotyrosine. Both individually will promote the unfolding of the chromosome in the tadpole, but only the thyroxine will raise the basal metabolism. In addition to this dual hormone, the thyroid secretes a metabolic depressor, a negative thyroxine. (2)

It is obvious that all three of these hormones are required for a flexible controlling system. The Eskimo lacks the ability to secrete the anti-thyroxine (the cooling hormone), so has trouble adapting himself to warm climates.

This triple nature of the thyroid function will elucidate some of the riddles of thyroid reactions in clinical experience. Hyperthyroid patients are sometimes helped by thyroid administration. That is when they get the major effect from the particular fraction they need. The use of the right factors <u>alone</u> would be very much more successful.

(The most spectacular of endocrine discoveries have been made by taking apart the hormone complexes for this purpose.)

Here we might mention a fourth fraction of the dry preparations of the thyroid gland that has therapeutic merit, but not of hormone classification. It is the determinant in the thyroid cells that would, if present in the blood stream of a hypothyroid subject, act to promote gland growth, the Protomorphogen factor that might be properly termed THYROGEN. Most dessicated tissue preparations have too dilute a proportion of the determinant factor, it should be specially concentrated for best use. But there is no reasonable doubt but what it is this THYROGEN factor that has created the clinically superior reputation of dried thyroid over thyroxine for the hypothyroid patient. It would have the effect of promoting the regeneration of thyroid tissue and in time eliminate or at least reduce the therapeutic dosage.

One of the heretofore mysterious actions of the thyroid hormone is its delayed action on the basal metabolism. A dose of thyroxine will produce its peak effect on a basal metabolism in 8 to 10 days, no effect before three days, but the improvement in other ways such as mental quickening is apparent in one to four hours. (3)

To explain this we must refer to the phenomena of "Natural Tissue Antibody." Antibodies to his own tissues appear in the blood of the infant at 14 days of age. (Placental hormones blocked their appearance in intrauterine life.) These anti-

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bodies stop cell division in all but epithelial cells, except where compensatory development is produced by overload (the overload creating local inflammation and excess secretion of determinants from the cells, stimulating regeneration.)

The antigenic fraction of any tissue is its determinant fraction. As thyroxine alone can raise the metabolic rate, and only a response that depends upon antigenic effects is delayed, we must conclude that the metabolic stimulation is contingent upon the secondary reaction to the antibodies to natural tissue that are created at the instigation of the thyroxine. These antibodies promote the release of end products that in turn act to produce the metabolic reaction. (Probably amino acids). Until the new-born individual develops these antibodies, his metabolic rate is at a minimum. (4) Fourteen days after birth, the metabolic rate had increased 300-600%. It seems that it is during this period of low metabolic rate that the infant is susceptible to poisoning from nitrites, one part per million being known to cause fatal poisoning. (Usually due to chemical fertilizers seeping into well water and getting into the baby feeding formula.) (Nitrites are universally used to hold color in unrefrigerated meats.)

This 14-day timing must be kept in mind. In another 14 days a secondary antibody can be created towards the primary antibody, and in 28 days a full cycle be repeated. Most natural tissue antibodies, however, seem to be unaffected by this cycle; their level seems undisturbed except by thyroid control throughout life. Thyroid overactivity, however, is something that may be excited by various factors, with consequent disastrous events to the victim. One of these is the common cold. Its existence is dependent upon the release of histamine. Histamine is one of the tissue end products that is very toxic, can cause violent reactions of fever, pains and general illness. It is normally collected by phagocytes, wrapped up as blood platelets, and carried to the liver for disposal. A high blood sugar can add to the danger, it seems, by causing the collection of platelets in agglutinated deposits; and any factor that would release their histamine would be enhanced in its effect. (5) Such a factor is a dose of thyroxine. Or an exposure to cold that would incite an abnormal secretion of thyroxine. The effect would be delayed for 3 days. But in another case, the phagocytes may be just capable of holding their own against a flood of histamine. The chilling of even one leg or arm can then create a reaction felt in minutes instead of days later. Both situations often occur exactly like these hypothetical instances. Some people are relatively immune for a number of reasons. They may be low carbohydrate eaters, use no ice cream, soft drinks or candy. Or they might have a very good liver function, with a lot of the natural antihistamine factor otherwise known as anabolin, yakriton, or anti-pyrexin. Or their thyroid may be less sensitive to stimuli, and their delayed response never take place. (It is important to recall that the chilling slows phagocytic activities, the fever that occurs in most disease is one of the natural reactions of defense to stimulate phagocyte activity against any toxin, virus or microorganism that may be interfering with normal processes.) The bacterial involvement of the cold, the sore throat, etc. is just in all probability the accompaniment of lowered resistance to ever-present germs. Histamine cannot exist in the presence of much vitamin C, so the well-known protective effect of that vitamin is explained. (6) Also explained is the action of vitamin C in protecting test animals against lethal doses of thyroxine. (7)

The fever that accompanies this situation of acute histamine poisoning seems to be rather due to "pyrogens" that are normally inseparable from the tissue source histamine. These "pyrogens" are really protomorphogens, and they stimulate the temperature control center of the brain to increase the body temperature, creating a fever which has for its ovbious purpose the stimulation of phagocytic activity

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required to eliminate this offending pathological situation of scattered and dangerous determinants in the body fluids, mainly in the blood stream. (Bacterial protomorphogens can cause pyrogenic effects, are reviewed as "Endo toxins" in Vol. 16, P. 467, Annual Review of Physiology.)

An overdose of thyroid can have the identical effect of exposure to cold, by bringing on a fever after the 3 day delay above noted, that may not subside for a week.

The action is that of the histamine and its accompanying protomorphogens, released by the effect of the natural tissue antibodies, which in turn were formed by the antigenic effect of the protomorphogens released by the direct action of the thyroxine. That is why the immediate effect of thyroxine -- the mental stimulus, etc. is due to the increase of circulating protomorphogens. The secondary and delayed effect is the "anaphylactic" reaction. We may repeat the above comment, that in normal subjects, not overloaded with synthetic and refined carbohydrate foods, this anaphylactic reaction cannot occur, because the agglutinated platelet accumulations in the blood vessels will not be present. (Which carry the excess stores of the histamine-determinant aggregate.) (See reference on sludged blood.) (5)

The specific dynamic effect of foods seems to be the secondary effect of the foodstuff by its action in several ways. (a) By stimulating repair of tissue, the released determinants act on the temperature control center. (b) By the direct effect of determinants in the proteins of the food itself, on this center. (c) Iodine acts to cause the release of determinants, and acts on this center by such means. Iodine by the same token stimulates the formation of antibodies to both endogenous and exogenous proteins. This effect of iodine is in all probability the active circulating iodoproteins, formed from ingested iodine by the catalyzing effect of the anterior pituitary thyrotrophic hormone. (In the absence of this hormone, ingested iodine is very toxic, even iodized salt cannot be tolerated by such a patient.)

But the real specific dynamic action is dependent upon the presence of the anterior pituitary growth hormone. (8) "Thyrotrophic hormone can increase oxygen consumption, but cannot influence the specific dynamic action of ingested proteins."

Since the basic effect of the A.P. growth hormone is to stimulate mitosis (by catalyzing the synthesis of nucleoproteins), it acts at a strategic point in the life cycle. Cell mitosis is self-stimulating as mitotic activity releases more of the determinants that seem to act as the mainspring of life. The effect is like a self-energizing brake in reverse -- a self-energizing accelerator. The specific dynamic action cannot occur without the thyroid, or without various other factors. But here is the key control. "Thyroxin is the active principle of the thyroid." (9) It is secreted as such, but combines with blood proteins and is distributed to the tissues, where it combines with free protomorphogen. It ultimately is excreted by both bile and kidney route, in a combination not identifiable as thyroxin in bile, but may disassociate and be reabsorbed in gut. ("Maybe the iodine alone" is reclaimed.)

The thyroid gland has a limited ability to absorb iodine, it may be saturated in ten minutes after a dose of radioactive iodine.

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THYROID AND PAROTID RELATIVES

"The salivary glands deiodinate thyroxine and return the iodine to the thyroid gland as diiodotyrosine." (90% in 20 minutes in the rat.) (10)

This fact supports the hypothesis that the parotid gland accumulates protomorphogens (PMG) (determinants) and secretes them with saliva to influence conversion and assimilation of protein fractions of food. It is known that the amino acid content of the blood is increased by thyroxin (11) and that adenine and lysine are not utilized in hypothyroid states. (12)

It must be inferred that the thyroxine travels from the site of its action on absorbed tissue reserves of PMG to the parotid as an integral part of the wrapped PMG in transit, being removed from the assembly after arrival at the parotid destination, and returned to the thyroid as diiodotyrosine, where the thyroxin is regenerated.

Since thyroxine only acts to stimulate metabolism, this may well be done by the promotion of more free and active PMG in the tissue fluids. This hypothesis is supported by the fact that vitamin A, a PMG wrapper factor (with xanthine, cholesterol and vitamin E) administration decreases this effect of thyroxine, no doubt, by increasing the wrapper integrity or its "tightness." (13)

It is not impossible that the PMG dispensed by the parotid is one factor in this metabolic rise. The physiological action of the PMG alone is enough to explain this effect. There is a sound clinical basis for assuming that salivary assistance is indispensable in food digestion and assimilation. A patient with a blocked esophagus, who had to feed himself through a stomach "window" with a funnel, found that unless he first masticated his food with saliva, it was quite inadequate in nutritional effect. (14) Vitamin A may be an important accessory in this cycle by serving as a wrapping or protective factor for the PMG as described in "Protomorphology", its well known relation to growth promotion being concurrent with this idea. It has been shown that thyroxine itself does not act as a metabolic stimulant, but leaves something in the blood that has this effect. (15) This factor undoubtedly is the PMG.

The large chromosome of the salivary glands, and the fact that they are so biochemically similar to the testes that the mumps virus attacks them both exclusively, is further evidence of the probability of each being dispensers of protomorphogens, for two different but essential purposes.

Xanthine (paraxanthine) as a part of the PMG wrapper (with vitamins A, E, F and cholesterol) can also act as an antagonist to the effect of thyroxine as a stimulator of basal metabolism. (16) "Excess thyroxine can be neutralized by appropriate doses of paraxanthine and vice versa," (17) so the effect of wrapper-promoters of PMG is clearly consistent. It is quite probable that most cases of thyro-toxicosis are really states of deficiency of wrapper factors.

The common cold may be a related situation. A chilling of the body can stimulate a sudden secretion of thyroxine, a defensive reaction to the chill. This promotes a great release of improperly wrapped PMG, with the after-effect of toxicosis from released histamine and other irritant end-products of PMG. (Menkin's "necrosin", pyrexin, leucotaxine, leukopenin, exudin.) (18)

These toxins are all subject to sudden release by thyroxine, especially in sensitized subjects who have an excess of "natural tissue antibody" which is to say that their body fluids are charged with lytic enzymes that only need the offending

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antigen to let go with a typical anaphylactic reaction. Such an excess of natural tissue antibody is a common state referable to an unbalanced endocrine pattern in turn due to nutritional deficiencies, and in our day of "Rube Goldberg-Science" being commonly treated with Synthetic Anti-Histamines.

The physiological remedies are:

1. Natural vitamin complex A and C;
2. Antipyrexin (a liver extract) also known as Yakriton (Japanese) and Anabolin (Harrower), a natural antihistamine;
3. Cytotrophic factor of beef lung, a lung antigen (mucosa antigen) to lower the blood levels of the mucosa antibody;
4. Potassium Bicarbonate.

This hypothesis considers that the susceptible victim is allergic to his own tissues, particularly those that have been irritated repeatedly by previous attacks. (Respiratory mucosa) The factors are of variable importance in different individuals. The potassium alone often affords complete relief by restoring adrenal function, the adrenals are inhibited by potassium deficiency, AND the adrenals are part of the thyroid cycle, adrenal hormones regulate the antibody responses initiated by thyroid. It is probable that much cortisone is being given to patients who only need it because they cannot mobilize their own supplies because of potassium deficiency. They have a bank account but no check-book.

Recent reports show that kelp - a high potassium food - creates definite resistance to the common cold. (19)

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(16) Ann. Rev. Physiol. V, p. 430.
(17) "Vitamins in Medicine", Bicknell & Prescott, p. 611.
(18) "The Mechanism of Inflammation", Jasmin & Robert, Acta, Inc., p. 137, 1953.
(19) Lee Foundation Reprint #133.

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Reports like the following are now becoming more common in the literature:

A.M.A. Journal, 1-12-63, p. 171

"Adrenal Antibodies in Addison's Disease--R.M. Blizzard,
R.W. Chandler, M.A. Kyle, and W. Hung
Lancet 2:901 (Nov 3) 1962

Adrenal antibodies were measured in the serums of 30 patients with Addison's disease, using the Coons fluorescein technique. Antibodies were found in the serums of 16 patients with Addison's disease but not in the serums of patients with virilizing adrenal hyperplasia or Cushing's syndrome secondary to hyperplasia or tumor. Adrenal antibodies were not found in 28 patients with Hashimoto's thyroiditis. Adrenal antibodies were found in 4 patients who had hypoparathyroidism, but no apparent Addison's disease. Hypoparathyrodism and Addison's disease are known to occur concurrently. It is concluded that circulating antibodies to adrenal tissue are found in a large percentage of patients with Addison's disease and that Addison's disease is often an autoimmune disease. It is not known whether the antibodies measured are destructive or not."