A R T I C L E

Thyroid: Therapies, Confusion, and Fraud

I. Respiratory defect

Broda Barnes, more than 60 years ago, summed up the major effects of hypothyroidism on health very neatly when he pointed out that if hypothyroid people don't die young from infectious diseases, such as tuberculosis, they die a little later from cancer or heart disease. He did his PhD research at the University of Chicago, just a few years after Otto Warburg, in Germany, had demonstrated the role of a "respiratory defect" in cancer. At the time Barnes was doing his research, hypothyroidism was diagnosed on the basis of a low basal metabolic rate, meaning that only a small amount of oxygen was needed to sustain life. This deficiency of oxygen consumption involved the same enzyme system that Warburg was studying in cancer cells.

Barnes experimented on rabbits, and found that when their thyroid glands were removed, they developed atherosclerosis, just as hypothyroid people did. By the mid-1930s, it was generally known that hypothyroidism causes the cholesterol level in the blood to increase; hypercholesterolemia was a diagnostic sign of hypothyroidism. Administering a thyroid supplement, blood cholesterol came down to normal exactly as the basal metabolic rate came up to the normal rate. The biology of atherosclerotic heart disease was basically solved before the second world war.

Many other diseases are now known to be caused by respiratory defects. Inflammation, stress, immunodeficiency, autoimmunity, developmental and degenerative diseases, and aging, all involve significantly abnormal oxidative processes. Just brief oxygen deprivation triggers processes that lead to lipid peroxidation, producing a chain of other oxidative reactions when oxygen is restored. The only effective way to stop lipid peroxidation is to restore normal respiration.

Now that dozens of diseases are known to involve defective respiration, the idea of thyroid's extremely broad range of actions is becoming easier to accept.

II. 50 years of fraud

Until the second world war, hypothyroidism was diagnosed on the basis of BMR (basal metabolic rate) and a large group of signs and symptoms. In the late 1940s, promotion of the (biologically inappropriate) PBI (protein-bound iodine) blood test in the U.S. led to the concept that only 5% of the population were hypothyroid, and that the 40% identified by "obsolete" methods were either normal, or suffered from other problems such as sloth and gluttony, or "genetic susceptibility" to disease. During the same period, thyroxine became available, and in healthy young men it acted "like the thyroid hormone." Older practitioners recognized that it was not metabolically the same as the traditional thyroid substance, especially for women and seriously hypothyroid patients, but marketing, and its influence on medical education, led to the false idea that the

standard Armour thyroid USP wasn't properly standardized, and that certain thyroxine products were; despite the fact that both of these were shown to be false.

By the 1960s, the PBI test was proven to be irrelevant to the diagnosis of hypothyroidism, but the doctrine of 5% hypothyroidism in the populaton became the basis for establishing the norms for biologically meaningful tests when they were introduced.

Meanwhile, the practice of measuring serum iodine, and equating it with "thyroxine the thyroid hormone," led to the practice of examining only the iodine content of the putative glandular material that was offered for sale as thyroid USP. This led to the substitution of materials such as iodinated casein for desiccated thyroid in the products sold as thyroid USP. The US FDA refused to take action, because they held that a material's iodine content was enough to identify it as "thyroid USP." In this culture of misunderstanding and misrepresentation, the mistaken idea of hypothyroidism's low incidence in the population led to the acceptance of dangerously high TSH (thyroid stimulating hormone) activity as "normal." Just as excessive FSH (follicle stimulating hormone) has been shown to have a role in ovarian cancer, excessive stimulation by TSH produces disorganization in the thyroid gland.

III. Tests & the "free hormone hypothesis"

After radioactive iodine became available, many physicians would administer a dose, and then scan the body with a Geiger counter, to see if it was being concentrated in the thyroid gland. If a person had been eating iodine-rich food (and iodine was used in bread as a preservative/dough condition, and was present in other foods as an accidental contaminant), they would already be over saturated with iodine, and the gland would fail to concentrate the iodine. The test can find some types of metastatic thyroid cancer, but the test generally wasn't used for that purpose. Another expensive and entertaining test has been the thyrotropin release hormone (TRH) test, to see if the pituitary responds to it by increasing TSH production. A recent study concluded that "TRH test gives many misleading results and has an elevated cost/benefit ratio as compared with the characteristic combination of low thyroxinemia and non-elevated TSH." (Bakiri, Ann. Endocr (Paris) 1999), but the technological drama, cost, and danger (Dokmetas, et al., J Endocrinol Invest 1999 Oct; 22(9): 698-700) of this test is going to make it stay popular for a long time. If the special value of the test is to diagnose a pituitary abnormality, it seems intuitively obvious that overstimulating the pituitary might not be a good idea (e.g., it could cause a tumor to grow).

Everything else being equal, as they say, looking at the amount of thyroxine and TSH in the blood can be informative. The problem is that it's just a matter of faith that "everything else" is going to be equal. The exceptions to the "rule" regarding normal ranges for thyroxine and TSH have formed the basis for some theories about "the genetics of thyroid resistance," but others have pointed out that, when a few other things are taken into account, abnormal numbers for T4, T3, TSH, can be variously explained.

The actual quantity of T3, the active thyroid hormone, in the blood can be measured with reasonable accuracy (using radioimmunoassay, RIA), and this single test corresponds better to the metabolic rate and other meaningful biological responses than other standard tests do. But still, this is only a statistical correspondence, and it doesn't indicate that any particular number is right for a particular individual.

Sometimes, a test called the RT3U, or resin T3 uptake, is used, along with a measurement of thyroxine. A certain amount of radioactive T3 is added to a sample of serum, and then an adsorbent material is exposed to the mixture of serum and radioactive T3. The amount of radioactivity that sticks to the resin is called the T3 uptake. The lab report then gives a number called T7, or free thyroxine index. The closer this procedure is examined, the sillier it looks, and it looks pretty silly on its face.. The idea that the added radioactive T3 that sticks to a piece of resin will correspond to "free thyroxine," is in itself odd, but the really interesting question is, what do they mean by "free thyroxine"? Thyroxine is a fairly hydrophobic (insoluble in water) substance, that will associate with proteins, cells, and lipoproteins in the blood, rather than dissolving in the water. Although the Merck Index describes it as "insoluble in water,"

it does contain some polar groups that, in the right (industrial or laboratory) conditions, can make it slightly water soluble. This makes it a little different from progesterone, which is simply and thoroughly insoluble in water, though the term "free hormone" is often applied to progesterone, as it is to thyroid. In the case of progesterone, the term "free progesterone" can be traced to experiments in which serum containing progesterone (bound to proteins) is separated by a (dialysis) membrane from a solution of similar proteins which contain no progesterone. Progesterone "dissolves in" the substance of the membrane, and the serum proteins, which also tend to associate with the membrane, are so large that they don't pass through it. On the other side, proteins coming in contact with the membrane pick up some progesterone. The progesterone that passes through is called "free progesterone," but from that experiment, which gives no information on the nature of the interactions between progesterone and the dialysis membrane, or about its interactions with the proteins, or the proteins' interactions with the membrane, nothing is revealed about the reasons for the transmission or exchange of a certain amount of progesterone. Nevertheless, that type of experiment is used to interpret what happens in the body, where there is nothing that corresponds to the experimental set-up, except that some progesterone is associated with some protein.

The idea that the "free hormone" is the active form has been tested in a few situations, and in the case of the thyroid hormone, it is clearly not true for the brain, and some other organs. The protein-bound hormone is, in these cases, the active form; the associations between the "free hormone" and the biological processes and diseases will be completely false, if they are ignoring the active forms of the hormone in favor of the less active forms. The conclusions will be false, as they are when T4 is measured, and T3 ignored. Thyroid-dependent processes will appear to be independent of the level of thyroid hormone; hypothyroidism could be caller hyperthyroidism.

Although progesterone is more fat soluble than cortisol and the thyroid hormones, the behavior of progesterone in the blood illustrates some of the problems that have to be considered for interpreting thyroid physiology. When red cells are broken up, they are found to contain progesterone at about twice the concentration of the serum. In the serum, 40 to 80% of the progesterone is probably carried on albumin. (Albumin easily delivers its progesterone load into tissues.) Progesterone, like cholesterol, can be carried on/in the lipoproteins, in moderate quantities. This leaves a very small fraction to be bound to the "steroid binding globulin." Anyone who has tried to dissolve progesterone in various solvents and mixtures knows that it takes just a tiny amount of water in a solvent to make progesterone precipitate from solution as crystals; its solubility in water is essentially zero. "Free" progesterone would seem to mean progesterone not attached to proteins or dissolved in red blood cells or lipoproteins, and this would be zero. The tests that purport to measure free progesterone are measuring something, but not the progesterone in the watery fraction of the serum.

The thyroid hormones associate with three types of simple proteins in the serum: Transthyretin (prealbumin), thyroid binding globulin, and albumin. A very significant amount is also associated with various serum lipoproteins, including HDL, LDL, and VLDL (very low density lipoproteins). A very large portion of the thyroid in the blood is associated with the red blood cells. When red cells were incubated in a medium containing serum albumin, with the cells at roughly the concentration found in the blood, they retained T3 at a concentration 13.5 times higher than that of the medium. In a larger amount of medium, their concentration of T3 was 50 times higher than the medium's. When laboratories measure the hormones in the serum only, they have already thrown out about 95% of the thyroid hormone that the blood contained.

The T3 was found to be strongly associated with the cells' cytoplasmic proteins, but to move rapidly between the proteins inside the cells and other proteins outside the cells.

When people speak of hormones travelling "on" the red blood cells, rather than "in" them, it is a concession to the doctrine of the impenetrable membrane barrier.

Much more T3 bound to albumin is taken up by the liver than the small amount identified in vitro as free T3 (Terasaki, et al., 1987). The specific

binding of T3 to albumin alters the protein's electrical properties, changing the way the albumin interacts with cells and other proteins. (Albumin becomes electrically more positive when it binds the hormone; this would make the albumin enter cells more easily. Giving up its T3 to the cell, it would become more negative, making it tend to leave the cell.) This active role of albumin in helping cells take up T3 might account for its increased uptake by the red cells when there were fewer cells in proportion to the albumin medium. This could also account for the favorable prognosis associated with higher levels of serum albumin in various sicknesses.

When T3 is attached chemically (covalently, permanently) to the outside of red blood cells, apparently preventing its entry into other cells, the presence of these red cells produces reactions in other cells that are the same as some of those produced by the supposedly "free hormone." If T3 attached to whole cells can exert its hormonal action, why should we think of the hormone bound to proteins as being unable to affect cells? The idea of measuring the "free hormone" is that it supposedly represents the biologically active hormone, but in fact it is easier to measure the biological effects than it is to measure this hypothetical entity. Who cares how many angels might be dancing on the head of a pin, if the pin is effective in keeping your shirt closed?

IV. Events in the tissues

Besides the effects of commercial deception, confusion about thyroid has resulted from some biological clichés. The idea of a "barrier membrane" around cells is an assumption that has affected most people studying cell physiology, and its effects can be seen in nearly all of the thousands of publications on the functions of thyroid hormones. According to this idea, people have described a cell as resembling a droplet of a watery solution, enclosed in an oily bag which separates the internal solution from the external watery solution. The cliché is sustained only by neglecting the fact that proteins have a great affinity for fats, and fats for proteins; even soluble proteins, such as serum albumin, often have interiors that are extremely fat-loving. Since the structural proteins that make up the framework of a cell aren't "dissolved in water" (they used to be called "the insoluble proteins"), the lipophilic phase isn't limited to an ultramicroscopically thin surface, but actually constitutes the bulk of the cell.

Molecular geneticists like to trace their science from a 1944 experiment that was done by Avery., et al. Avery's group knew about an earlier experiment, that had demonstrated that when dead bacteria were added to living bacteria, the traits of the dead bacteria appeared in the living bacteria. Avery's group extracted DNA from the dead bacteria, and showed that adding it to living bacteria transferred the traits of the dead organisms to the living.

In the 1930s and 1940s, the movement of huge molecules such as proteins and nucleic acids into cells and out of cells wasn't a big deal; people observed it happening, and wrote about it. But in the 1940s the idea of the barrier membrane began gaining strength, and by the 1960s nothing was able to get into cells without authorization. At present, I doubt that any molecular geneticist would dream of doing a gene transplant without a "vector" to carry it across the membrane barrier.

Since big molecules are supposed to be excluded from cells, it's only the "free hormone" which can find its specific port of entry into the cell, where another cliché says it must travel into the nucleus, to react with a specific site to activate the specific genes through which its effects will be expressed.

I don't know of any hormone that acts that way. Thyroid, progesterone, and estrogen have many immediate effects that change the cell's functions long before genes could be activated.

Transthyretin, carrying the thyroid hormone, enters the cell's mitochondria and nucleus (Azimova, et al., 1984, 1985). In the nucleus, it immediately causes generalized changes in the structure of chromosomes, as if preparing the cell for major adaptive changes. Respiratory activation is immediate in the mitochondria, but as respiration is stimulated, everything in the cell responds, including the genes that support respiratory metabolism. When the membrane people have to talk about the entry of large molecules into cells, they use terms

such as "endocytosis" and "translocases," that incorporate the assumption of the barrier. But people who actually investigate the problem generally find that "diffusion," "codiffusion," and absorption describe the situation adequately (e.g., B.A. Luxon, 1997; McLeese and Eales, 1996). "Active transport" and "membrane pumps" are ideas that seem necessary to people who haven't studied the complex forces that operate at phase boundaries, such as the boundary between a cell and its environment.

V. Therapy

Years ago it was reported that Armour thyroid, U.S.P., released T3 and T4, when digested, in a ratio of 1:3, and that people who used it had much higher ratios of T3 to T4 in their serum, than people who took only thyroxine. The argument was made that thyroxine was superior to thyroid U.S.P., without explaining the significance of the fact that healthy people who weren't taking any thyroid supplement had higher T3:T4 ratios than the people who took thyroxine, or that our own thyroid gland releases a high ratio of T3 to T4. The fact that the T3 is being used faster than T4, removing it from the blood more quickly than it enters from the thyroid gland itself, hasn't been discussed in the journals, possibly because it would support the view that a natural glandular balance was more appropriate to supplement than pure thyroxine.

The serum's high ratio of T4 to T3 is a pitifully poor argument to justify the use of thyroxine instead of a product that resembles the proportion of these substances secreted by a healthy thyroid gland, or maintained inside cells. About 30 years ago, when many people still thought of thyroxine as "the thryoid hormone," someone was making the argument that "the thyroid hormone" must work exclusively as an activator of genes, since most of the organ slices he tested didn't increase their oxygen consumption when it was added. In fact, the addition of thyroxine to brain slices suppressed their respiration by 6% during the experiment. Since most T3 is produced from T4 in the liver, not in the brain, I think that experiment had great significance, despite the ignorant interpretation of the author. An excess of thyroxine, in a tissue that doesn't convert it rapidly to T3, has an antithyroid action. (See Goumaz, et al, 1987.) This happens in many women who are given thyroxine; as their dose is increased, their symptoms get worse.

The brain concentrates T3 from the serum, and may have a concentration 6 times higher than the serum (Goumaz, et al., 1987), and it can achieve a higher concentration of T3 than T4. It takes up and concentrates T3, while tending to expel T4. Reverse T3 (rT3) doesn't have much ability to enter the brain, but increased T4 can cause it to be produced in the brain. These observations suggest to me that the blood's T3:T4 ratio would be very "brain favorable" if it approached more closely to the ratio formed in the thyroid gland, and secreted into the blood. Although most synthetic combination thyroid products now use a ratio of four T4 to one T3, many people feel that their memory and thinking are clearer when they take a ratio of about three to one. More active metabolism probably keeps the blood ratio of T3 to T4 relatively high, with the liver consuming T4 at about the same rate that T3 is used.

Since T3 has a short half life, it should be taken frequently. If the liver isn't producing a noticeable amount of T3, it is usually helpful to take a few micorgrams per hour. Since it restores respiration and metabolic efficiency very quickly, it isn't usually necessary to take it every hour or two, but until normal temperature and pulse have been achieved and stabilized, sometimes it's necessary to take it four or more times during the day. T4 acts by being changed to T3, so it tends to accumulate in the body, and on a given dose, usually reaches a steady concentration after about two weeks.

An effective way to use supplements is to take a combination T4-T3 dose, e.g., 40 mcg of T4 and 10 mcg of T3 once a day, and to use a few mcg of T3 at other times in the day. Keeping a 14-day chart of pulse rate and temperature allows you to see whether the dose is producing the desired response. If the figures aren't increasing at all after a few days, the dose can be increased, until a gradual daily increment can be seen, moving toward the goal at the rate of about 1/14 per day

VI. Diagnosis

In the absence of commercial techniques that reflect thyroid physiology realistically, there is no valid alternative to diagnosis based on the known physiological indicators of hypothyroidism and hyperthyroidism. The failure to treat sick people because of one or another blood test that indicates "normal thyroid function," or the destruction of patients' healthy thyroid glands because one of the tests indicates hyperthyroidism, isn't acceptable just because it's the professional standard, and is enforced by benighted state licensing boards.

Toward the end of the twentieth century, there has been considerable discussion of "evidence-based medicine." Good judgment requires good information, but there are forces that would over-rule individual judgment as to whether published information is applicable to certain patients. In an atmosphere that sanctions prescribing estrogen or insulin without evidence of an estrogen deficiency or insulin deficiency, but that penalizes practitioners who prescribe thyroid to correct symptoms, the published "evidence" is necessarily heavily biased. In this context, "meta-analysis" becomes a tool of authoritarianism, replacing the use of judgment with the improper use of statistical analysis.

Unless someone can demonstrate the scientific invalidity of the methods used to diagnose hypothyroidism up to 1945, then they constitute the best present evidence for evaluating hypothyroidism, because all of the blood tests that have been used since 1950 have been.shown to be, at best, very crude and conceptually inappropriate methods.

Thomas H. McGavack's 1951 book, The Thyroid, was representative of the earlier approach to the study of thyroid physiology. Familiarity with the different effects of abnormal thyroid function under different conditions, at different ages, and the effects of gender, were standard parts of medical education that had disappeared by the end of the century. Arthritis, irregularities of growth, wasting, obesity, a variety of abnormalities of the hair and skin, carotenemia, amenorrhea, tendency to miscarry, infertility in males and females, insomnia or somnolence, emphysema, various heart diseases, psychosis, dementia, poor memory, anxiety, cold extremities, anemia, and many other problems were known reasons to suspect hypothyroidism. If the physician didn't have a device for measuring oxygen consumption, estimated calorie intake could provide supporting evidence. The Achilles' tendon reflex was another simple objective measurement with a very strong correlation to the basal metabolic rate. Skin electrical resistance, or whole body impedance wasn't widely accepted, though it had considerable scientific validity.

A therapeutic trial was the final test of the validity of the diagnosis: If the patient's symptoms disappeared as his temperature and pulse rate and food intake were normalized, the diagnostic hypothesis was confirmed. It was common to begin therapy with one or two grains of thyroid, and to adjust the dose according to the patient's response. Whatever objective indicator was used, whether it was basal metabolic rate, or serum cholesterol. or core temperature, or reflex relaxation rate, a simple chart would graphically indicate the rate of recovery toward normal health.

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into the cytoplasm of target cells. Electron microscopic autoradiography revealed that blood serum TBPA is localized in ribosomes of target cells as well as in mitochondria, lipid droplets and Golgi complex. Negligible amounts of the translocated TBPA is localized in lysosomes of the cells insensitive to thyroid hormones (spleen macrophages). Study of T4- and T3-binding proteins from rat liver cytoplasm demonstrated that one of them has the antigenic determinants common with those of TBPA. It was shown autoimmunoradiographically that the structure of TBPA is not altered during its translocation.

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Radioimmunoprecipitation with monospecific antibodies against TBPA revealed that this protein also the antigenic determinants common with those of TBPA. The in vivo translocation of 125I-TBPA into submitochondrial fractions was studied. The analysis of densitograms of submitochondrial protein fraction showed that both TBPA and hormones are localized in the same protein fractions. Electron microscopic autoradiography demonstrated that 125I-TBPA enters the cytoplasm through the external membrane and is localized on the internal mitochondrial membrane and matrix.

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