

Overview

The relationship between iodine intake, thyroid hormones and breast cancer has engaged the interest of clinicians for well over 50 years. Within the past thirty years diverse experimental observations examining (1) the autoregulatory mechanism in the thyroid, (2) the dynamic control of pituitary derived prolactin in patients with fibrocystic breast disease and (2) aqueous iodine chemistry, have provided a mechanistic basis that for the variety of epidemiological, non-clinical and clinical observations related to iodine intake and mammary tissue.

The thyroid needs a mechanism to protect itself from chronic exposure to high levels of iodine. Observations from a variety of different laboratories indicate that the enzyme peroxidase catalyzes the formation of iodinated polyunsaturated fatty acids, such as arachidonic acid and docosahexaenoic acids, instead of tyrosine at elevated concentrations of iodide. Several of the iodinated lipids formed by peroxidase have been shown to exhibit a broad antiproliferative effect. Iodolactones have been shown to inhibit the production of inositol phosphates induced by epidermal growth factor (EGF); the hydrogen peroxide production by NADPH oxidases; and adenylyl cyclase. Several leading researchers in this field believe that the antiproliferative activity of iodolactones and iodoaldehydes mediate thyroid autoregulation. These iodolipids should be able to be formed in other tissues of the body.

The formation of these iodinated lipids is reasonable based upon the enzymology of peroxidase and aqueous iodine chemistry. The mechanism of the enzyme peroxidase has been studied for close to 100 years. Between 1940 and 1990 many teams of expert enzymologists around the world attempted to identify how peroxidase catalyzes the formation of thyroid hormones. Despite thousands of published studies we cannot identify a discrete set of experiments that unequivocally identify the mechanistic pathway for thyroid hormone synthesis. An overlooked factor that probably contributes to this difficulty is the characteristics of the oxidized iodide. Hatch¹ developed the first complete set of equations that describe the behavior of the I_2 species in an aqueous environment. In the 1980s Gottardi developed a computer program that solves the nonlinear equations describing this equilibrium. It is clear from Gottardi's studies that oxidized iodide species do not behave in a linear manner.^{2 3 4} That is, the reaction product(s) from the oxidation of iodide by peroxidase can vary depending upon the concentration of the reactants. It is not, therefore, unreasonable that at physiologic levels of iodide tyrosine is iodinated while at elevated levels other iodine species, like I_2 , are formed. Peroxidase mediated formation of iodinated lipids at elevated iodide concentrations is reasonable from the perspective of iodine chemist since molecular iodine (I_2) formation could be expected under these conditions. In fact, Sybollon has used this reaction as the basis of the first product developed by the company^{5 6}.

The requirements for the formation of iodinated lipids are (1) a peroxidase, (2) an elevated concentration of iodide and (3) hydrogen peroxide. These conditions can be met in the mammary gland, oviduct and uterus.⁷

Use of Iodine by Biological Organisms

The first living cells to produce oxygen over 3 billion years ago were Algae. Oxygen forms chemical species (e.g., hydrogen peroxide, superoxide) that can oxidize biological material therefore these Algae cells were the first forms of life to require an antioxidant. Iodide can reduce hydrogen peroxide and superoxide molecules and it was a logical choice as an antioxidant since iodide is present in sea-water. Venturi has suggested that the first essential function iodide played in living systems was as an antioxidant.⁸ Kupper has recently confirmed that these Algae cells use a peroxidase and iodide to reduce hydrogen peroxide.⁹

The first use of iodine in Algae cells did not require thyroid hormones since the role for iodine was presumably limited to reducing toxic oxygen species. Today, mammals require thyroid hormones for normal growth and the regulation of a number of essential homeostatic functions. These functions are very different from the antioxidant role suggested by Venturi in lower life forms. The human thyroid hormones are referred to as T_3 and T_4 . The chemical name for T_3 is triiodothyronine and the chemical name for T_4 is tetraiodothyronine; T_4 is usually referred to thyroxine. The only difference between T_3 and T_4 is one extra iodine atom as their name implies. Both T_3 and T_4 are formed in an identical pathway from the amino acid tyrosine. It is likely that T_3 or T_4 were formed long before they were used to regulate human metabolism since tyrosine can be iodinated by placing it in a test tube with oxidized species of iodine. There is evidence that this is exactly what happened since thyroxine (T_4) has been found in the remains of invertebrates that are about 700 million years old.¹⁰ At this time thyroxine was just one of many iodinated chemical species that were formed by the action of oxidized iodide species. Thyroxine could not act as it does in our bodies since the protein receptors (T_3 receptors) necessary for activity were not yet present, the first such receptors were observed in mammals about 300 million years ago.

A number of clinical observations support Dr. Venturi's idea that iodide can serve as an antioxidant in cells.^{11 12 13 14} In fact, only about 30% of the iodine in our bodies is in the thyroid gland or incorporated into thyroid hormones. Our bodies have evolved to use iodinated tyrosine (i.e. thyroid hormones) as one of its primary regulatory mechanisms; however, it is very likely that iodine plays other roles in non-thyroidal tissues.

Control of the Formation of Thyroid Hormones

The actions of thyroid hormones in different animal groups and species vary and this reflects evolutionary adaptations¹⁵. When primitive marine vertebrates emerged from the iodine-rich sea into fresh water, which is deficient in iodine, and then onto land they needed a new mechanism to store iodine. Migratory fish like trout and salmon still experience thyroid hypertrophy in captivity as do sharks.¹⁶ The use of iodine in the body has evolved from the initial need for an antioxidant. The thyroid gland itself had to evolve to meet environments that were iodine deficient like those found in sub-Saharan Africa or Eastern Europe. In these and other locations daily dietary iodine

intake is often less than 0.050 mg. The efficient mechanisms in the thyroid for uptake and storage of iodine are designed to optimize the use of dietary iodine in iodine deficient areas. A chronic lack of iodine causes developmental deficiencies and remains today the leading cause of mental retardation in the world.

At the other end of the dietary intake spectrum, there are populations that consume large quantities of iodine in their diet. For instance, the populations inhabiting the Hokkaido seacoast region of Japan daily consume foods estimated to contain 100 mg of iodine or more; daily urinary iodine excretion of between 8 and 30 mg of iodine has been measured in this population.^{17 18} Human dietary intake of iodine therefore varies by more than 200 fold and the thyroid needed to develop a mechanism to regulate itself when exposed to high levels of iodine or risk thyrotoxicosis. The thyroid's adaptation to chronic levels of elevated dietary iodine has been termed the *autoregulatory effect*.

Many researches attempted to unravel the basis for the autoregulatory effect up through the 1970s. The clinical effects of elevated iodine intake were agreed upon: iodine is transported into the thyroid but elevated levels of thyroid hormones are not synthesized. The data developed indicated that an organic form of iodine that was formed under high iodine load. This iodinated organic species inhibited the thyroid's response to stimulation by the hormone that normally controls its actions, i.e. thyrotropin stimulating hormones (TSH)¹⁹. Eventually research from a variety of different laboratories identified iodinated organic species^{20 21 22 23 24 25 26 27 28 29}. Lipid molecules were being iodinated instead of tyrosine; arachidonic acid is one of the primary lipid molecules to be iodinated (docosahexaenoic acid is another). The molecules formed by the iodination of these polyunsaturated fatty acids (iodolipids) have been demonstrated to exert a broad antiproliferative effect on the metabolism in the thyroid.

In resting cells, arachidonic acid is stored within the cell membrane, esterified to glycerol in phospholipids. The binding of certain chemical signals to receptors on cell membranes can initiate phospholipid hydrolysis and releases the fatty acid (arachidonate) into the cell. Once released, free arachidonate has three possible fates: reincorporation into phospholipids, diffusion outside the cell, and metabolism inside of the cell. The metabolism of arachidonate is carried out by three distinct enzyme pathways expressed in cells: cyclooxygenase, lipoxygenases, and cytochrome P₄₅₀. Several products of these pathways act (1) within cells to modulate the activities of ion channels, protein kinases, ion pumps, and other uptake systems or (2) outside of the original cell at a distance. Arachidonic acid metabolizing enzymes are emerging as significant mediators of growth stimulation for epithelial cells^{30 31 32 33 34}. Iodinated arachidonic acid could well be a natural inhibitor of some of these enzymes.

Thyroid hormones are formed by iodinating (placing iodine on) tyrosine. Peroxidase is the enzyme responsible for the formation of thyroid hormones. The first step in this process is the peroxidase mediated transfer of electrons from iodide to hydrogen peroxide; this is how iodide serves as an antioxidant. This transfer converts hydrogen peroxide into water and liberates an oxidized species of iodide. The aqueous chemistry

of oxidized species of iodide is complex as several different iodine species are formed in water. Hatch¹ first worked out these equations in 1984 and Gottardi^{4 35 3} has subsequently provided a complete solution and developed a computer program that calculates the concentration of these different iodine species under different conditions of pH and concentration. The distribution of different iodine species changes as a function of iodine concentration and increased levels of iodine favors a higher concentration of molecular iodine. It is not surprising that alternative iodinated species are formed at elevated concentrations of iodine in the thyroid since it has been known for many years that³⁶ that high concentrations of iodide “inhibit” thyroid peroxidase activity. This “inhibition” consists of the formation of I₂ (molecular iodine) rather than iodination of tyrosine; this is not really a classical inhibition of the enzyme but rather an alternative reaction pathway.

Molecular iodine (I₂), the iodinating species generated by both thyroperoxidase and lactoperoxidase, is a highly polarizable and hydrophobic molecule that is 50-100 times more soluble in organic solvents than water. Lactoperoxidase, like thyroid peroxidase, is a membrane bound protein and any molecular iodine that diffused from the active site could partition in the adjacent lipid layer; molecular iodine would iodinate unsaturated double bonds of these lipids leading to the formation of several different iodinated lipids. Boeynaems³⁷ has demonstrated the transformation of arachidonic acid into several different iodolactones by lactoperoxidase in a model system. Venturi³⁸ has demonstrated addition of molecular iodine across the double bonds of lipids.

The overall pattern of biological observations to date is consistent with the underlying properties of aqueous iodine chemistry. At physiologic levels of iodine the thyroid makes T₃ and T₄ under the control the TSH. At elevated dietary intake of iodine peroxidase catalyzes the formation of molecular iodine which then forms iodinated lipids that down-regulate the thyroids normal activity and have demonstrated a broad antiproliferative effect.

Clinical and Non-clinical Observations

Epidemiology

Areas of low iodine intake are associated with increased rates of breast cancer. Various authors have drawn an association between iodine intake^{39 40 41} and breast cancer rates while others have correlated thyroid status breast cancer rates^{42 43}. Even though these initial observations were made over 30 years ago these associations have continue to be examined by a diverse group of clinicians^{44 43 45 45}.

Japan has a high level of daily dietary iodine intake (>5 mg/day^{46 17}). Seaweed consumption is a widely popular staple that contains high levels of iodine. Japan has one of the lowest age-adjusted breast cancer mortality rates⁴⁷ in industrialized countries but the rise in breast cancer rates has been attributed to “westernization” of the diet⁴⁸. Japanese immigrants to the U.S. experience a rise in breast cancer rates as their diet approaches that of their U.S. counterparts⁴⁹. Epidemiological data cannot prove this

association but a correlation study in Spain⁵⁰ found a significant association between regions of low iodine intake and breast cancer rates.

Animal Studies

Iodine deficiency in estradiol-treated rats leads to pathological changes in breast tissue including cystic changes, periductal fibrosis and lobular hyperplasia^{51 52}. The observed histological changes can be reversed by reintroduction of iodine⁵³.

The DMBA rat model is used by researchers to explore the potential effect an agent can have on breast cancer^{54 55 56 57}. Experimental results in this model system support an antitumor effect for iodine. Kato⁵⁸ and Funahashi⁵⁹ used this animal model to demonstrate that iodine suppresses the formation of breast tumors. When iodine was combined with progesterone the effect was enhanced. The enhancement of iodine uptake by progesterone was previously reported in other hormone-responsive tissues including the uterus and oviduct⁶⁰. A more detailed summary of the experiments using iodine to suppress breast tumor formation in rats follows.

Sprague-Dawley rats with 7,12-dimethyl ben(a)anthracene (DMBA) induced breast tumors (15 rats/group) were daily administered progesterone alone or with iodine for 4 weeks, followed by a 4 week treatment-free observation period. Control rats received physiological saline. Five rats/group were sacrificed before start of treatment; at the end of the 4 week treatment period, and at the end of the 4 week post-treatment period. Tissue iodine content was determined in each tumor. In addition, thyroids, adrenals, and ovaries were collected and analyzed for iodine content after the 4 week post-treatment observation period. The combination of progesterone and iodine significantly suppressed tumor growth when compared with the saline control group. At the end of the 4 week administration period, the groups receiving iodine in combination with progesterone showed a higher tumor iodine content. In all treatment groups but the controls, amounts as high as ~30 : g of iodine per g of tissue were detected. Prior to treatment and at 4 weeks post-treatment, virtually no iodine was detected in tumors.

Six tumors that had regressed significantly in size and 6 tumors that had grown continuously were selected at random at the end of the 4 week treatment period and analyzed for iodine content. All 6 regressed tumors exhibited a high iodine content with a mean value of 106.3 ± 0.96 : g/g tissue. In the growing tumors, the mean iodine content was as low as 1.125 ± 0.96 : g/g tissue. There was no tumor suppression without iodine uptake and a large iodine uptake was associated with major tumor suppression. Perhaps these results are not surprising as Asian medicine has used iodine-rich seaweed to soften and reduce breast nodules. At least one well respect group⁴⁴ of breast cancer researchers planned to examine the effect of iodine with progestin in human patients with metastatic breast cancer.

Pregnancy

Breast tissue efficiently concentrates iodine in order to provide this essential element to

the newborn. Dysplastic and malignant breast tissue has been shown to have an enhanced ability to sequester and organify iodine⁶¹. It is interesting that this iodine absorption and organification occurs^{52 53} in the same ductal epithelium where the majority of breast cancers occur⁶². During pregnancy there is enhanced iodine uptake which is under hormonal control. This may explain the reduction in nodularity and tissue density that is often observed following pregnancy⁶³. There may be a correlation between uptake of iodine by the breast during lactation and the subsequent reduction in breast cancer risk since studies have shown that early parity and lactation reduces the rate of breast cancer⁶⁴.

Fibrocystic Breast Disease

In 1966 two Russian clinicians reported the results using iodine to treat patients with fibrocystic breast disease⁶⁵. Patients (n=176) were treated for 18 to 26 months and 75% were observed to improve. The late Dr. William Ghent began to experiment with iodine therapeutics for the treatment of fibrocystic breast disease in the late 1970s. By 1984 he had identified the fact that molecular iodine is less thyrotoxic than iodide and more effective in treating the symptoms of fibrocystic breast disease. At this point Dr. Ghent conducted study MX02-CLN-03⁶⁶. The details of this study and study MX-CLN-04 are provided below.

Study MX02-CLN-03 was a single-center, open-label, uncontrolled study of the effects of administering daily doses of aqueous I₂ to patients diagnosed with FBD. The majority of patients (1104 of 1388) were not receiving any form of iodine at the time they were enrolled in the study; however, a subset (284 of 1388 patients) was recruited from the patient population that had been previously receiving another form of iodine in a prior study. The patients ranged in age from 12 to 89 years, with the mean age of 42.7 years. The menopausal status at the time of entry into the trial was recorded for 1348 patients: 885 were premenopausal, 85 were perimenopausal, and 378 were postmenopausal. Patients were prescribed daily doses from 2 mg to 6 mg of aqueous I₂, on the basis of body weight. These doses were modified by the investigator according to tolerability and intended therapeutic benefit. The duration of exposure to aqueous I₂ was recorded for 1365 of the 1388 enrolled patients. The median duration of exposure was 13 months, with a maximum exposure of 64 months.

Efficacy MX02-CLN-03: The therapeutic effect of aqueous I₂ on FBD was assessed by: (1) a numerical standardized physician assessment of five clinical findings associated with FBD (micronodularity, tenderness, fibrosis, macrocysts, and turgidity); (2) a subjective patient global evaluation of disease severity made by the patient; and (3) an objective physician global evaluation of disease severity made by the Investigator. The change in the standardized physician assessment of FBD is available for 666 patients who had both pretreatment and treatment ratings. The mean change in the total rating during the course of treatment was a significant decrease of 29.7 (f=15.0) (p<0.001), which represents a decrease in disease severity. The objective physician global evaluation of disease severity assessed each patient's

response to treatment and included a macrocyst and tenderness rating. According to this assessment, a substantial proportion (51%) of the evaluable patients (1360) demonstrated complete resolution of their FCD symptoms. The subjective patient global evaluation was available for 1360 patients. Two-thirds of the patients perceived total resolution of their FCD symptoms, and an additional 31% reported an improvement in their level of pain.

Although the results from the first study with pure I₂ were impressive the trial was not designed in a rigorous manner since (1) there was no control group and (2) the investigator knew the treatment that each patient received. A new study was designed and conducted primarily by Dr. Lucius Hill at the Swedish Medical Center in Seattle, Washington. Study MX02-CLN-04 was a prospective, double-blind, randomized, placebo-controlled study designed to compare I₂ with placebo for the treatment of both pain and the fibrosis and cystic components of FBD.

Study MX02-CLN-04: Patients ingested a single daily oral dose of 10 to 25 mL of aqueous I₂ solution or a placebo solution for 7 months. The iodine doses contained 1.95 to 4.88 mg of iodine. There were 106 patients enrolled at three sites; however, there are only data for 92 patients in the final data base (46 iodine-treated, 46 placebo). The study population was all female and ranged in age from 25 to 64 years. Approximately 40% of the patients experienced an interruption in the daily dosing due to a shortage of clinical trial material. On average, the interruption of medication lasted approximately 1 month. Physicians rated tenderness at baseline; over 60% of the patients enrolled in this study were scored at the top percentile (20 out of 20) in breast pain.

Efficacy MX02-CLN-04: The efficacy assessment consisted of objective evaluations and subjective evaluation of changes in FBD symptoms. The primary efficacy parameter was an objective assessment of the patient's symptoms that included tenderness, nodularity, fibrosis, hyperactivity, and macrocysts. There was a highly significant active-placebo difference for the all-patient population ($p < 0.001$), for patients with no treatment interruption ($p < 0.001$), and for patients with one or more treatment interruptions ($p < 0.001$). When the symptoms of FBD were analyzed separately, significant improvements were seen in tenderness ($p < 0.001$), nodularity ($p < 0.001$), and fibrosis ($p = 0.006$), but not in hyperactivity or macrocysts. This study is the first double-blind, placebo-controlled study to demonstrate a statistically significant outcomes in a well-controlled trial.

The secondary efficacy parameter was Patient's Subjective Score, which was a subjective assessment by the patient of her FBD symptoms. In both the all-patient population and patients with no interruption in medication, there was a greater proportion of iodine-treated patients than placebo-treated patients who subjectively assessed their conditions to have improved or resolved ($p = 0.035$ and $p = 0.016$, respectively).

Symbollon developed a stable well-defined dosage form of molecular iodine and

designed a trial to challenge the earlier clinical observations with iodine. The study was conducted to determine if daily administration of supraphysiological (i.e., higher levels than that required to maintain thyroid function) levels of iodine have an effect on patients with clinical cyclic mastalgia as previously suggested in the literature. The primary hypotheses for this study was: (a) patients treated with iodine will exhibit a greater decrease in breast pain than women treated with placebo; (b) there will be a dose related effect for iodine, such that patients treated with lower doses will report less benefit than those treated with higher doses; and (c) any reductions in nodularity will be associated with pain relief and require at least 3 mg/d of iodine. Symbolon chose to run this trial for only 6 months because prior reports indicate a response from patients can be observed at this time even 18 months of treatment is required to achieve the optimum response.

Study SYM-CL-02: Study SYM-CL-002 multicenter, placebo-controlled, randomized, double-blind, dose-ranging study that compared the safety and efficacy of placebo, 1.5, 3.0 and 6.0 mg per day of I₂ in women with FBD⁶⁷. Otherwise healthy, euthyroid, premenopausal women with clinically significant, moderate or severe, symptomatic fibrocystic breast disease, with moderate or severe pain and tenderness occurring at least 6 days of each month for the previous 6 months were enrolled in this study. Diffuse nodularity or breast thickening involving 25% of the surface of both breasts was required. Of the 111 study participants included in this analysis, 17 were randomly assigned to receive placebo, 16 to receive IoGen 1.5 mg/d, and 38 to receive IoGen 3.0 mg/d and 40 to receive IoGen 6.0 mg/d. The imbalance in the number of subjects in the different dosing groups was intentional and based upon the previous studies of Ghent that suggest that a dose of 3.0 to 6.0 mg/d is required for efficacy.

Efficacy MX02-CLN-04: Cyclic mastalgia patients report that peak pain occurs from 18 days before menses to two days after menses⁶⁸. It is therefore not possible for physicians to make an accurate pain assessment for all patients during the luteal phase. Danazol was approved for the treatment of breast pain, tenderness and nodularity associated with FBD in 1976 entirely based upon physician assessments despite this confounding factor. In 1997 the Lewin Group, the leading quality-of-life experts in the United States, developed original pain assessment scales to distinguish the different types of breast pain that this patient population experiences⁶⁹. These pain symptoms were selected based upon input from patients, physicians and a literature search. The approach taken by the Lewin group divides breast pain and breast tenderness into four discrete pain symptoms; two symptoms for pain and two symptoms for tenderness. Specifically, patients rate breast pain by scoring the frequency and bothersomeness of (1) dull aching pain and (2) sharp shooting pain sensations; breast tenderness is assessed by scoring (1) pain due to movement and (2) pain due to pressure or touch. The eight responses are then scaled into an Overall breast pain score that ranges from 0 to 100. This breast pain instrument was revalidated in SYM-CL-02. The largest mean reduction in Overall breast pain was reported by the 6.0 mg group and the magnitude of pain reduction increased with dose in a statistically significant manner at both month 3 ($p < 0.01$) and month 6 ($p < 0.01$). The majority of change in the Overall pain scale occurred by month 3 for all treatment groups and all of the benefit in the 6.0 mg group was observed by month 3, i.e. 45.4% and 45.0% respectively. Vishnyakova and Mura'yeva also reported that after 2-3 months of treatment pain resolve^d **Error! Bookmark not defined.** and Ghent had previously calculated that the mean response time for therapy was about 50 days. The data from SYM-CL-02 is consistent with these observations. It

appears that (1) I₂ can effectively treat the symptoms of patients that are severely impacted by FBD and (2) the 6.0 mg dose is adequate to effectuate the maximal response for the majority of patients within three months. The results of this trial have been published if the reader wishes more information ⁶⁷.

Conclusions

An unbiased review of the literature indicates that iodine can exert multiple effects on mammary tissue and that these effects are not likely to be due to thyroid hormones. One very likely mechanism for the effect of supraphysiological levels of iodine in patients with FBD has been advanced by Cann and van Netten ⁴⁴. They believe that the same mechanism that down regulates metabolic activity in the thyroid occurs in mammary tissue. This idea is imminently reasonable since the only necessary elements necessary for the autoregulatory effect in thyroid tissue is (a) the presence of peroxidase (thyroperoxidase) and (b) an elevated concentration of iodide. The reaction properties of iodide with both the peroxidase in mammary tissue and the thyroid (thyroperoxidase) with are very similar ^{70 71 72 73}. In fact, the enzyme that was first used to demonstrate the iodination of arachidonic acid was lactoperoxidase not thyroperoxidase ⁷⁴.

The varied and sundry clinical observations concerning iodine have fostered suggestions in the medical community that iodine intake is related to breast cancer risk or that iodine be used as a chemopreventative. The first such serious suggestion was made as early as 1967 by Bruce V. Stadel, M.D., M.P.H. who is currently a medical officer in the Division of Metabolic and Endocrine Drug Products at the FDA ⁴⁰. The attention and thoughts of many different clinicians have led them to associate iodine intake with breast cancer ^{75 76 77 78 (reference not available) 79 80 81 82}.

One of Dr. Ghent's interests was to reduce the incidence of breast cancer. Dr. Ghent had more experience with iodine therapy than any other practicing physician since he treated women from all across North America for more than 20 years. He observed that the rate of breast cancer in his patients that were on iodine therapy were lower than that in the general populations. Ghent observed a 2-fold reduction in the incidence (0.00079 cancer/women year) of breast cancer in patients (n=3,165; 10,124 women years) treated with iodine as compared to the local population in Ontario (0.00164 cancer/women year).

Is it reasonable that iodolactones are responsible for the basis for the reported effects of iodine on breast cancer rates reasonable? One recently published study ⁸³ suggests Cann's hypothesis is sound. In fact, there are other proven relationships in women with cyclic mastalgia that also support this suggestion. The only uncontested hormonal imbalance observed in these patients is an exaggerated release of the hormone prolactin (PRL) in response to thyrotropin releasing hormone (TRH). In the normal mammary gland, prolactin and the steroid hormones, estrogen and progesterone, act synergistically to increase mammary gland growth, development and differentiation. ⁸⁴ ⁸⁵. Clinicians suspected that prolactin plays a role in breast cancer but drugs that inhibit the release of prolactin from the pituitary, like bromocriptine, do not benefit cancer patients ⁸⁶.

Approximately 50% of subjects who have cyclic mastalgia exhibit a subtle imbalance in the control of prolactin release^{87 88 89 90 91}. This diagnostic test of prolactin seems to measure a variable that seems to be related to cyclic mastalgia since: (1) the status of a patient's dynamic PRL release predicts their response to endocrine therapy^{92 93} and (2) normalization of this variable is correlated with pain relief^{94 95}.

Numerous studies measuring the level of prolactin in circulating blood were conducted during the 60s and 70s and contradictory findings were observed; it simply not possible to show that circulating levels of prolactin were related to FBD. One well respected breast cancer researcher realized that circulating hormone levels of prolactin may not reflect the concentration of prolactin at its target tissue, i.e. the breast. Dr. David Rose made measurements to compare the concentration of prolactin in blood to that found in breast duct fluid. Rose found that these two measurements did not agree⁹⁶. Rose has demonstrated that lactogenic activity in breast ducts is significantly higher in cystic breast disease patients than in normal controls in contrast to PRL measurements made on sera^{97 98}. The measurement by Rose strongly suggest increased proliferative activity in women that experience cyclic mastalgia. Consistent with this idea,⁹⁹ has observed that prolactin release in response to TRH is significantly higher in women whose breast secretions contain milk proteins for both normal and fibrocystic breast tissue which supports the idea that an increased lactogenic activity is associated with this imbalance.

No studies exist that contradict the observation that cyclic mastalgia patients experience an elevated level of mammary stimulation from prolactin. It turns out that this observation has a direct relationship to iodine metabolism. Active transport of iodide is under control of prolactin in breast tissue^(100 101 102). If breast tissue is exposed to atypically high levels of prolactin we would be expected to measure elevated levels of iodine in mammary tissue; this is exactly what Kilbane has observed¹⁰³. The proposed relationship is very interesting in that increased mammary stimulation by prolactin, which threatens to cause excess cellular proliferation, also causes increased accumulation of iodine, which can exert an antiproliferative effect via the formation of iodinated lipids.

PRL from the pituitary is not, however, the principal focus of breast cancer researchers. Research has recently demonstrated that mammary cells can synthesize and secrete prolactin^{104 105 106 107} independent of the pituitary. The roles of endocrine and non-endocrine prolactin appear to be different^{108 109}. This so-called non-endocrine prolactin is an area of active research in breast cancer. Both PRL and PRL receptor mRNA are expressed in the vast majority of breast cancer biopsies independent of the presence of estrogen and progesterone receptor. These observations suggest that a breast cancer drug aimed at PRL should target mammary PRL which is acting on mammary tissue (an autocrine/paracrine relationship) instead of suppressing the synthesis and secretion of pituitary PRL.

The drugs that have been demonstrated the ability to reduce nodularity and pain in patients with FBD are bromocriptine, tamoxifen, and danazol. None of these drugs

have any analgesic effect. The conclusion is obvious, drugs must effectuate a change in the underlying tissue structure in order to impact the symptoms associated with FBD. The clinical data developed to date demonstrates that elevated iodine does exert a physiological effect on breast tissue and this effect is almost certainly an antiproliferative one. We suspect that this effect is mediated by iodinated lipids that have already been demonstrated to inhibit cAMP formation and the phosphatidylinositol (PI) cascade.

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