

Iodine Replacement in Fibrocystic Disease of the Breast

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Objective: To determine the response of patients with fibrocystic breast disease to iodine replacement therapy.

Design: Review of three clinical studies beginning in 1975: an uncontrolled study with sodium iodide and protein-bound iodide; a prospective, control, crossover study from iodide to molecular iodine; and a prospective, control, double-blind study with molecular iodine.

Setting: University affiliated breast-treatment clinics.

Patients: Study 1: 233 volunteers received sodium iodide for 2 years and 588 received protein-bound iodide for 5 years. Study 2: the treatment of 145 patients from study 1 treated with protein-bound iodide for several months who still had symptoms was switched to molecular iodine 0.08 mg/kg; 108 volunteers were treated initially with molecular iodine. Study 3: 23 patients received molecular iodine, 0.07 to 0.09 mg/kg body weight; 33 received an aqueous mixture of brown vegetable dye and quinine. The numbers in study 2 increased over the review period so that 1365 volunteers were being treated with molecular iodine by 1989.

Interventions: All patients in study 3 had pre- and post-treatment mammography and measurement of serum triiodothyronine, thyroxine and thyroid-stimulating hormone levels.

Main Outcome Measures: Subjective evaluation — freedom from pain — and objective evaluation — resolution of fibrosis.

Results: Study 1: 70% of subjects treated with sodium iodide had clinical improvement in their breast disease, but the rate of side effects was high; 40% of patients treated with protein-bound iodide had clinical improvement. Study 2: 74% of patients in the crossover series had clinical improvement, and objective improvement was noted in 72% of those who received molecular iodine initially. Study 3: in the treatment group 65% had subjective and objective improvement; in the control group there was a subjective placebo effect in 33% and an objective deterioration of 3%.

Conclusions: The fibrocystic breast reacts differently to sodium iodide, protein-bound iodide and molecular iodine. Molecular iodine is nonthyrotropic and was the most beneficial.

Objectif: Mesurer la réponse des patientes souffrant de mastose sclérokystique à un traitement de suppléance à l'iode.

Conception: Une revue de trois études cliniques amorcées en 1975 : une étude ouverte de l'iodure de sodium et de l'iode lié aux protéines; une étude prospective, contrôlée, en chassé-croisé de l'iodure et de l'iode moléculaire; et une étude prospective, contrôlée, à double insu avec de l'iode moléculaire.

Contexte: Des cliniques de traitement des maladies du sein affiliées à une université.

Patientes: Première étude : 233 volontaires qui ont reçu de l'iodure de sodium pendant 2 ans et 588 qui ont reçu de l'iode lié aux protéines pendant 5 ans. Deuxième étude : le traitement de 145 patientes

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qui avaient participé à la première étude et qui avaient reçu de l'iode lié aux protéines pendant plusieurs mois et qui montraient des signes résiduels de mastose, fut modifié pour de l'iode moléculaire à 0,08 mg/kg; 108 volontaires reçurent initialement de l'iode moléculaire. Troisième étude : 23 patientes reçurent de l'iode moléculaire, à raison de 0,07 à 0,09 mg/kg; 33 reçurent une solution aqueuse de colorant brun végétal et de quinine. Les nombres dans la deuxième étude augmentèrent pendant son déroulement de sorte qu'ils atteignirent 1365 volontaires traités à l'iode moléculaire, en 1989.

Interventions : Toutes les patientes ayant participé à la troisième étude subirent mammographie pré et post-traitement ainsi que des déterminations des taux sériques de triiodothyronine, de thyroxine et d'hormone thyroïdienne.

Principaux effets mesurés : Subjectif — l'absence de douleur — et objectif — la disparition de la fibrose.

Résultats : Première étude : 70 % des sujets traités à l'iodure de sodium eurent une amélioration clinique mais montrèrent un taux élevé d'effets secondaires; 40 % des patientes recevant de l'iode lié aux protéines bénéficièrent d'une amélioration clinique. Deuxième étude : 74 % des patientes dans la série en chassé-croisé eurent une amélioration clinique et une amélioration objective fut notée chez 72 % de celles qui avaient reçu de l'iode moléculaire initialement. Troisième étude : dans le groupe traité, 65 % montrèrent une amélioration subjective et objective; dans le groupe témoin, on enregistra une amélioration subjective placebo dans 33 % des cas et une détérioration objective de 3 %.

Conclusions : La mastose sclérokystique réagit différemment à l'iodure de sodium, à l'iode lié aux protéines et à l'iode moléculaire. L'iode moléculaire n'est pas thyroïdienne et a donné les meilleurs résultats.

Fibrocystic breast disease (FBD) is characterized by lumpy, painful breasts, generally in reproductive-aged women. Initially the syndrome occurs in the premenstrual phase but can progress to involve the whole cycle. Symptoms can also occur in menopause, particularly if estrogens are being used.

Histologically, FBD shows microcysts, epithelial hyperplasia, apocrine metaplasia and fibrosis. The fibrosis is the basic hallmark of the disease. Macrocysts greater than 1 cm in diameter occur in 10% of patients with the syndrome. Biochemical and cytologic analysis of macrocyst fluid shows that 55% contain high levels of potassium (more than 120 mmol/L) and low levels of sodium (less than 20 mmol/L) and are associated with apocrine changes; the other 45% contain high levels of sodium (more than 120 mmol/L) and low levels of potassium (less than 5 mmol/L) and are associated with flat epithelial cells.^{1,2} Observations indicate that the cyst fluid in the microcysts has a high potassium content with apocrine cells present.³

The diagnosis of FBD is increas-

ing in frequency. In 1928 an autopsy series reported a 3% incidence,⁴ whereas in 1973 an autopsy report quoted an 89% incidence.⁵ The latest review by the American Academy of Pathology gives a minimum incidence of 50% but suggests that 80% of North American women are afflicted with the syndrome during their reproductive lifetime.⁶

The suggested etiology of the syndrome has included a prolonged luteal phase,⁷ an upset in the estrone-estriol ratio,⁸ increased estrogen levels⁹ and other hormonal dysfunctions.^{9,10} A dietary theory implicating coffee and tea has been popular,¹¹ but this has been disproved by several studies.^{12,13} Some authors¹⁴⁻¹⁷ have stated that FBD is a normal but exaggerated physiologic cycle and that it may be a "nondisease."

The term "iodine" has been misused for many years to describe any iodine compound. Chemically the elemental form of iodine (I_2), with an atomic weight of 125.9015, is the only substance that should be called iodine. However, there are some 130 compounds containing the element iodine. These have, by

common usage, been called generic iodine. Each compound is different and consists of simple bindings such as sodium or potassium to produce iodides (I^-). Potassium iodide has been added to our salt in Canada since 1929 and has reduced the incidence of cretinism and goitre. The fact that sodium or potassium iodide, when mixed with water, forms a solution that is 95% iodide (I^-) and 5% free iodine (I_2) is of relevance to our findings in this study. More complex bindings of the iodine molecule to organic compounds produce substances that are chemically different but again are called "iodine," such as iodine caseinate. In this presentation, the term iodine (I_2) will refer to aqueous molecular iodine whereas all other iodine-containing compounds will be indicated as iodide (I^-) or generic iodine.

In this paper we report on three clinical trials of iodide (I^-) and iodine (I_2) replacement therapy to ascertain the response of the fibrocystic breast: iodide (I^-) replacement therapy with (a) sodium iodide (Lugol's iodine) and (b) iodine caseinate; a crossover study from iodide

to iodine; and a double-blind prospective study with iodine.

Patients and Methods

Study 1

Initially, 233 volunteers were treated with Lugol's iodine (sodium iodide [I⁻]) for 2 years. Compliance was difficult owing to the vile taste of this compound. Lugol's iodine is 95% iodide and 5% iodine. The dosage was 5 to 10 drops daily, on a body-weight basis. This study was an open-ended trial without controls because we found it was impossible to create a placebo that was realistic.

In the second arm of this study 588 patients were treated with iodine caseinate (iodized casein [I⁻]). The study period was 5 years and the dosage of iodine caseinate was 10 mg daily. This study was also conducted without controls.

Study 2

When it became evident in the rat model that there was a differential reaction in the breast tissue to iodides and to molecular iodine,¹⁸ it was decided that molecular iodine should be tried on human volunteers with FBD. Study 1 included 145 subjects who had been treated with iodine caseinate for a number of months but still had residual symptoms and signs of FBD. Therapy in these patients was switched to aqueous molecular iodine at a dosage of 0.08 mg I₂/kg, and the patients were assessed at 9.9 months after crossover.

One hundred and eight more subjects (de novo group) were treated initially with aqueous molecular iodine and were evaluated at 8.9 months.

The original series of 233 volunteers was enlarged to 1365, ob-

served through 4813 women-years of treatment (Table 1). These women were assessed at 4 to 6 months (group 1), 7 to 18 months (group 2) and more than 18 months (group 3). The mean age of these women was 41.6 years (range from 11 to 87 years) and the mean duration of symptoms was 44.6 months (range from 1 to 360 months).

Scoring system for study 2 subjects. A precise method of recording our data was developed with a numerical scoring system. This simple method numbers the quadrants of the breast from 1 to 4 (Fig. 1). The following five pathological changes that can occur in the fibrocystic syndrome were noted: micronodularity, tenderness, fibrous tissue plaques, macrocysts and turgidity (hyperactivity). The presence or absence of these changes was recorded. For example, if the micronodularity of microcystic disease was present in the upper half of the breast, the numerical score would be 1 (micronodularity) + 2 (two breast quadrants) = 3. If all five changes occurred in all quadrants in one breast the score would be 1 + 2 + 3 + 4 (all four breast quadrants) × 5 (all five changes) = 50, and for both breasts 100.

Subjective evaluation. The patient's evaluation of her own symptomatology was expressed numeri-

cally: 0 — symptoms worse, 1 — symptoms unchanged, 2 — less pain, only premenstrual discomfort, 3 — no pain, unable to predict menstruation.

Objective evaluation. The subjective scoring system was employed and graded as follows: 0 — no palpable abnormalities (normal), 1 — a score of less than 7, 2 — a score greater than 7 but less than the pre-treatment score and 3 — a score greater than the pre-treatment score.

Study 3

Fifty-six volunteers were enrolled in a prospective double-blind study at the Virginia Mason Clinic in Seattle, Wash. This study was supervised by D.A.L. and L.D.H. The patients were enrolled over 2 months and were treated for 6 months. All had mammography before and after treatment. In addition, serum triiodothyronine, thyroxine and thyroid-stimulating hormone levels were measured for all patients before and after treatment. The patients were randomly assigned by the pharmacist to the treatment or the placebo arm.

The patients were assessed at 2-month intervals, with a final assessment at a mean of 191 days. Subjective evaluation in this study

Table 1. Demographic Data on Volunteers With Fibrocystic Disease in Study 2 — A Clinical Trial of Replacement Therapy With Molecular Iodine (N = 1365)

Demographic characteristic	No. (%) of women
Premenopausal	871 (63.8)
Postmenopausal	494 (36.2)
Taking birth control pills	915 (67.0)
Taking estrogen	252 (18.5)
Parous	1081 (79.2)
Previous breast surgery	
Biopsy	304 (22.3)
Mastectomy	25 (1.8)
Family history of fibrocystic breast disease	333 (24.4)

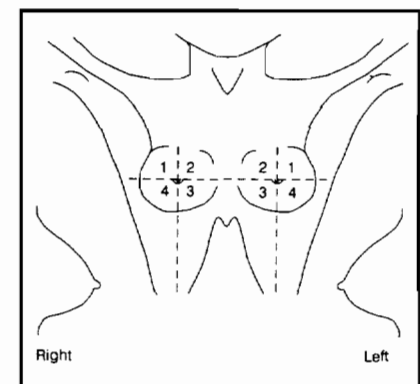


FIG. 1. Numerical designation of breast quadrants for fibrocystic breast disease.

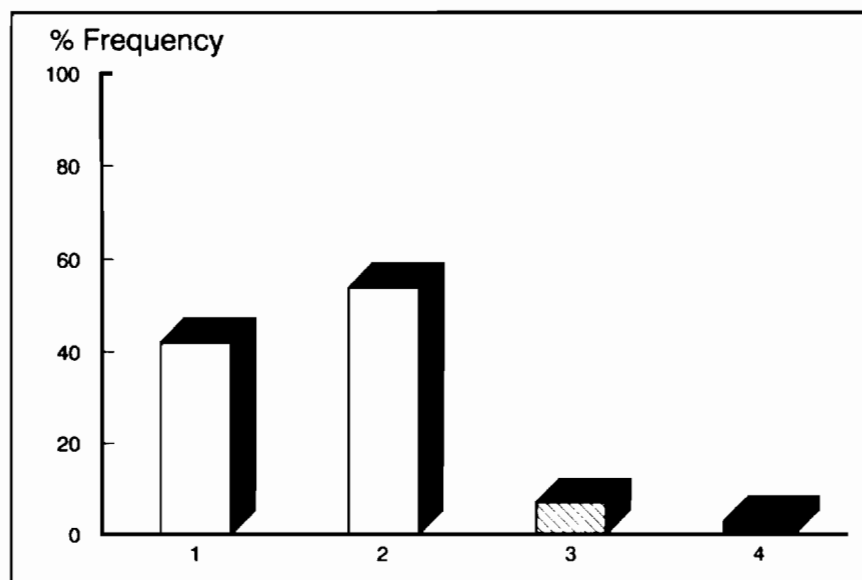


FIG. 2. Results of replacement therapy with iodized casein. 1 = return to normal without pain, 2 = residual premenstrual pain and fibrosis, 3 = slight reduction in pain and cysts and 4 = no change.

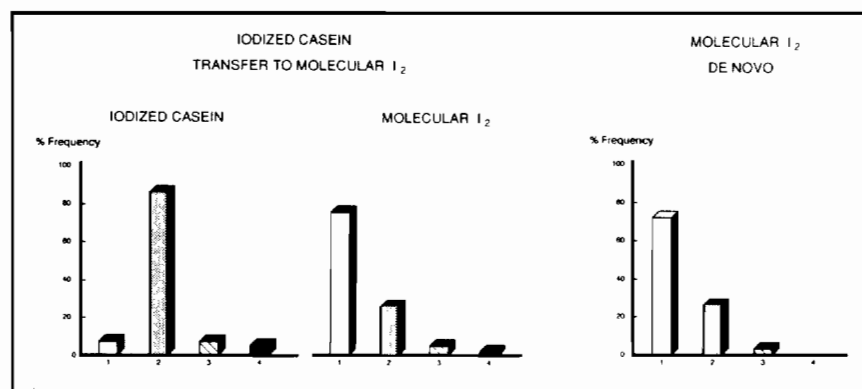


FIG. 3. Comparison of results of replacement therapy in patients treated first with iodized casein and then with molecular iodine and in patients treated with molecular iodine alone. 1 = return to normal without pain, 2 = residual premenstrual pain and fibrosis, 3 = slight reduction in pain and cysts and 4 = no change.

Table II. Objective Numerical Score for Patients in Study 2, Before and After Treatment*

Time of scoring	Group 1 (n = 292)	Group 2 (n = 639)	Group 3 (n = 434)	Total (n = 1365)
Before treatment				
Mean	30.12	31.29	31.16	30.99
Range	1 - 80	3 - 80	4 - 100	1 - 100
After treatment				
Mean	3.15	1.18	1.51	1.97
Range	0 - 46	0 - 62	0 - 40	0 - 62
p value†	0.0001	0.0001	0.0001	

*Duration of treatment: group 1, 4 to 6 mo, group 2, 7 to 18 mo, group 3, more than 18 mo
† χ^2 analysis

was in three categories: 0 — worse, 1 — no change and 2 — less pain or pain free. Objective evaluation was carried out by two examiners, who used a numerical grading system slightly modified from the one described earlier. They were unaware of the treatment status of the patients under study.

Twenty-three patients (mean age 43.6 years) received aqueous molecular iodine, 0.07 to 0.09 mg of I₂/kg body weight daily. The placebo group (mean age 39.2 years), received an aqueous mixture of a brown vegetable dye with quinine added for flavour.

Results

Study 1

Iodide replacement therapy. Clinically the improvement rate was 70%. Side effects included changes in the thyroid indices in 4% of patients, the development of iodism in 3% and the occurrence of acne, which was unacceptable to the patients.

Iodine caseinate replacement therapy. A good response was noted in 40% of the patients (Fig. 2). Side effects involved 9.5% of the patients and have been described in detail elsewhere.^{18,19}

Study 2

Of the 145 patients in the cross-over series, 108 (74.5%) showed an improvement, having pain-free breasts; the remainder still had some premenstrual pain and residual fibrosis.

In the de novo group, the 108 patients responded more swiftly, with complete disappearance of their microcysts within 5 months; 98% were pain free at evaluation, and objective improvement was noted in 71.8% (Fig. 3).

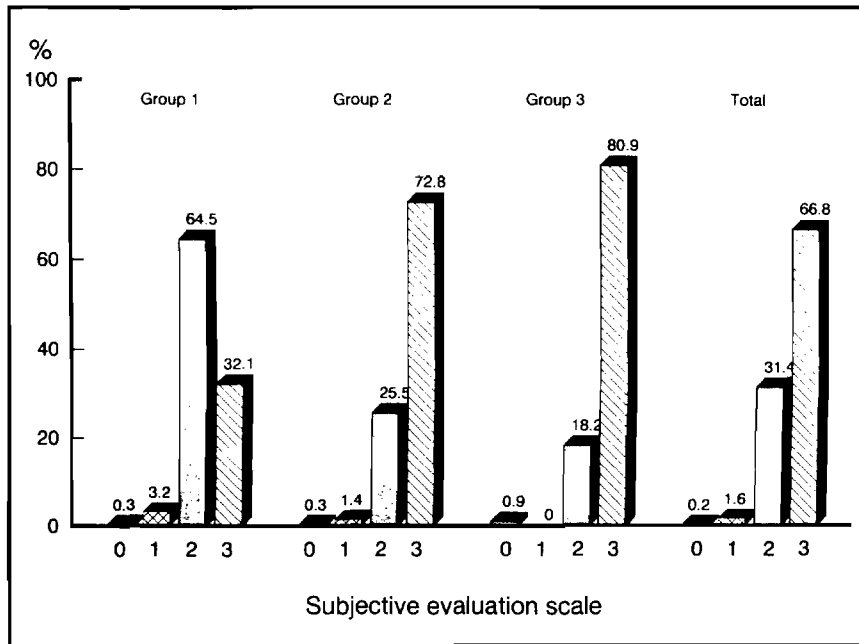


FIG. 4. Effect of duration of treatment with molecular iodine evaluated subjectively. 0 = worse, 1 = unchanged, 2 = improved (less pain with only premenstrual discomfort) and 3 = freedom from pain and lumps. Group 1 = 4 to 6 months, group 2 = 7 to 18 months and group 3 = more than 18 months.

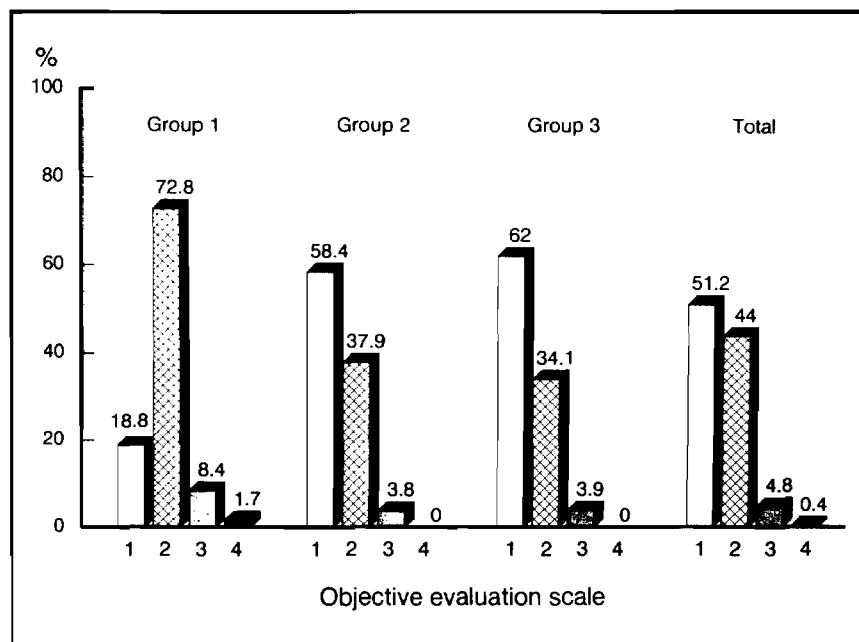


FIG. 5. Effect of duration of treatment with molecular iodine assessed objectively by numerical scoring. 1 represents numerical score of 0, 2 represents numerical score less than 7, 3 represents numerical score less than pretreatment score, 4 represents numerical score greater than pretreatment score. Group 1 = 4 to 6 months, group 2 = 7 to 18 months and group 3 = more than 18 months.

These results indicate the superiority of molecular iodine over iodides when treating fibrocystic breast disease.

Both subjective and objective improvements, according to the evaluation scale, were time dependent (Table II, Figs. 4 and 5). Sixty-five percent of women experienced a reduction in breast size as the fibrocystic condition was corrected (Fig. 6).

The side effects of treatment with molecular iodine were minor and involved 149 (10.9%) of the patients, including 78 (5.7%) who had a short-lived period of increased pain (Table III). This period of pain seemed to correspond to a softening of the breast and disappearance of fibrous tissue plaques on clinical examination.

During this period of observation six women failed to respond to any type of therapy, including aqueous molecular iodine (I₂), tamoxifen, danazol, bromocriptine or progesterone. These women subsequently underwent subcutaneous mastectomy. Histologic examination indicated a total disruption of the normal breast architecture (Fig. 7). The pathological review of the mammary tissue from these patients was remarkably similar, with dense fibrosis that isolated breast acini from the duct system. We conclude, therefore, that there is a "point of no return" in fibrocystic disease. Once this point is crossed, surgical excision of the diseased tissue is the only method of treatment. This state can be suspected when a total white-out is observed on the mammogram.

Study 3

There was a placebo effect in 11 (33%) women of the control group, which is in keeping with previous reports on the treatment of benign breast disease.²⁰

On objective evaluation, the control group's numerical assessment deteriorated by 3% during the study compared with a 65% improvement in the treated group ($p < 0.001$, χ^2 analysis) (Table IV).

On subjective evaluation, 15

(65%) women in the treated group showed improvement, compared with 11 (33%) in the control group (Table IV). The laboratory results were unchanged, and no side effects were reported.

Repeat mammography failed to

show any significant change (2 to 5 years are required for any mammographic change to be manifest and the final evaluation in this study was at 6 months).

Despite the small size of the two participating groups, the results clearly indicate that the placebo effect in the control group was at the rate expected for studies of the treatment of benign breast disease. The objective findings worsened in this group in the 6 months under study. In contrast, the treated group demonstrated unequivocal objective results by χ^2 analysis (Table IV).

Discussion

Eskin worked for many years in the animal laboratory on the hypothesis that a low iodine or an iodine-deficient state rendered the rat breast more susceptible to dysplasia and carcinoma.²¹ His model consisted of Sprague-Dawley rats raised from birth on a Remington diet, which is iodine free with perchlorate blockade and causes an iodine-deficient state. His rat model approximated the microscopic findings seen clinically with the triad of cystic spaces, epithelial and apocrine hyperplasia and interacinar fibrosis. Previous rat models produced by hormonal manipulation

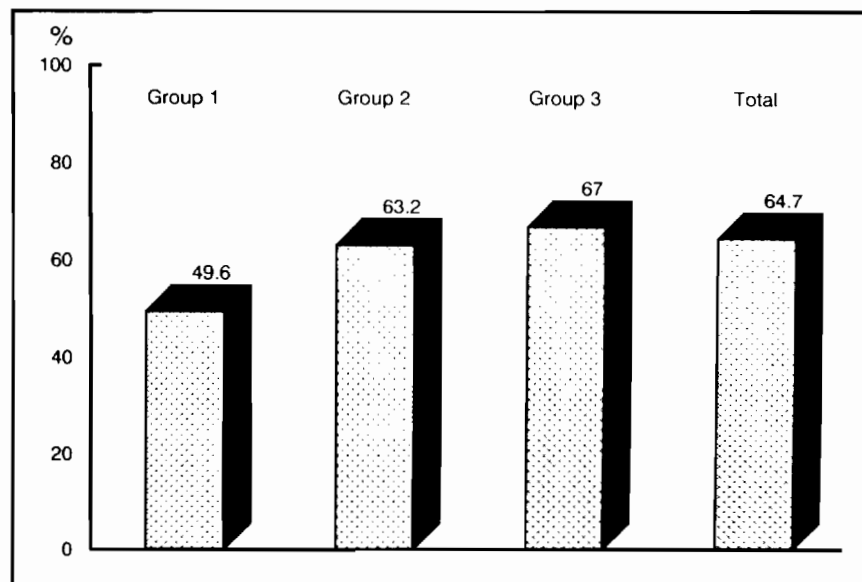


FIG. 6. Effect of duration of treatment on breast size: percentage of women who reported decrease in breast size measured by brassiere size. This varied from one-half cup size to five cup sizes and was time dependent. Group 1 = 4 to 6 months, group 2 = 7 to 18 months and group 3 = more than 18 months.



FIG. 7. Histologic appearance of breast tissue refractory to treatment with molecular iodine. Note complete absence of normal acinar intraductal structure (hematoxylin-eosin stain).

Table III. Side Effects of Aqueous Molecular Iodine Therapy in Study 2 - Women

Side effect	No. (%) of women
Acne	15 (1.1)
Nausea	8 (0.6)
Diarrhea	2 (0.1)
Hair thinning	13 (1.0)
Hyperthyroidism	2 (0.1)
Hypothyroidism	4 (0.3)
Skin rash	3 (0.2)
Iodism	2 (0.1)
Headaches	3 (0.2)
Increased pain	78 (5.7)
Other	22 (1.6)
Total	149 (10.9)

resulted in excess fluid and hyperplasia but lacked the fibrotic element.^{22,23}

Eskin showed that there is a hierarchical response in the rat mammary gland to the type of iodine compound administered to correct the changes induced by iodine deprivation. Lugol's iodine (I⁻) corrects the cystic spaces and partially corrects the epithelial hyperplasia and the fibrosis. The 5% free iodine (I₂) in Lugol's iodine could explain the partial resolution of the syndrome. Iodine caseinate (I⁻) partially corrects the cysts and the hyperplasia but does not ameliorate the fibrosis. Iodine in its elemental form, I₂, corrects the entire disease process. Thus, it seems that I₂ is the preferential form of iodine for breast metabolism. This activity is localized in the terminal and intralobular duct cells.²⁴⁻²⁶

The human response to sodium iodide (I⁻), protein-bound iodide (I⁻) or iodine (I₂) paralleled Eskin's findings in the experimental model. Our previous findings with sodium iodide and protein-bound iodide (I⁻) have been reported; they showed a lesser response than we have obtained with molecular iodine (I₂).^{18,19} In addition, all iodides are thyrotropic, as Eskin has demonstrated, whereas I₂ seems to be involved primarily in extrathyroidal activities. Our complication rate of abnormal thyroid indices was not above the expected incidence in the Great Lakes goitre region in untreated controls.

The exact mechanism of action of

I₂ on breast tissue is not understood. We do know that there is a differential absorption of iodides (I⁻) and iodine (I₂) from the gut of the Sprague-Dawley rat.²⁷ It has been established that the only areas of the breast in which iodine can be found are in the terminal and intralobular duct cells, a minuscule proportion of the total breast volume.²⁴⁻²⁶ It is this area that is primarily involved in cystic and malignant changes. We theorize that the trace element, molecular iodine, is necessary for breast normality. Its absence renders the epithelium of the terminal and intralobular ducts more sensitive to estrogen stimulation. This hypersensitivity can produce excess secretions over the limit of absorption, thus distending the acini to produce microcysts. The fluid in microcysts is extremely high in potassium,³ and this could act as an irritant, producing fibrosis and eventually cyst isolation.

Iodides are necessary for thyroidal normality and are trapped by the thyroid. Thyroid tissues are rich in peroxidase, which oxidizes iodide (I⁻) to iodine (I₂) on the way to the formation of monoiodotyrosine, diiodotyrosine and finally triiodothyronine and thyroxine. Breast tissue is peroxidase poor, and as such it cannot extract iodine (I₂) from the circulating iodides. This has been demonstrated by Eskin and others.²⁴⁻²⁸

It appears that the trace element I₂ is essential for breast normality. The effect of the molecule on the terminal and intralobular duct cells

may be to render them less sensitive to circulating estrogens. As such it could be classed as a natural "anti-estrogen." If this premise is borne out by further animal testing and larger clinical trials, it will be of importance for breast health, normality and longevity.

We thank the volunteers in the Kingston and Seattle areas who participated in these studies. We thank the referring physicians for their continuing support. We thank Mrs. Jane Derrick for completion and analysis of the data and Dr. Arlene Crowe for her invaluable assistance in the preparation of this paper. We also express our sincere appreciation to Mrs. Marie Gallagher for the countless revisions she has endured.

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Table IV. Results of Subjective Evaluation After 6 Months of Treatment in Women in Study 3 — A Prospective Double-Blind Trial of Aqueous Iodine Therapy

Evaluation	Control group (n = 33)	Treated group (n = 23)
	No. (%)	No. (%)
Subjective		
Worse	0 (0)	0 (0)
No change	22 (67)	8 (35)
Improved	11 (33)	15 (65)

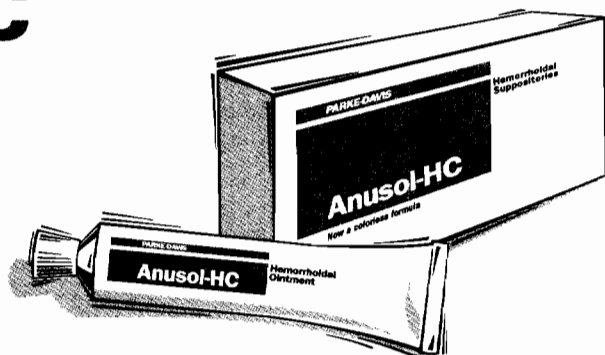
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