effect on platelet function, plasma coagulation and fibrinolysis, and did not affect gastrointestinal function or chronic arthritis in rats. High doses produced a progressively more pronounced depressant behavioural effect, but acute toxicity was low. The large safety margin of oxatomide was confirmed in the elaborate chronic toxicity studies in rats and dogs.

The pharmacological profile of oxatomide clearly warranted studies in man. It soon appeared that, upon oral administration, the new compound was very effective in reducing wheal and flare responses to allergens in atopic patients. Allergic rhinitis and conjunctivitis disappeared within 3 days in 60% of the large group of patients who were taking 20 mg of oxatomide 3 times a day in a double-blind study[16]. In asthmatic children, oxatomide and cromolyn sodium proved to be effective inhibitors of exercise-induced asthma. Oxatomide was superior to cromolyn sodium, as the airway obstruction was significantly inhibited at all post-exercise time intervals, and as the peak decrease of the 1st sec forced expiratory volume was significantly smaller[17].

As is expected from a potent H_1-antagonist, oxatomide prevents the effects of histamine on the isolated guinea-pig ileum, in pulmonary tissue and in the skin of various species. At the same time, oxatomide differs from classical antihistamine agents in several respects. In vitro the new compound exhibits a slowly developing but sustained activity which is partly non competitive. Oxatomide's high activity in rats, guinea-pigs and dogs is obtained after oral administration and suppression of anaphylactic or allergic reactions in the 3 species is pronounced after a dosage at least as low as that required for the suppression of histamine-induced reactions. This pronounced anti-allergic activity appears to be linked to the inhibition of histamine release. However, by contrast to cromolyn sodium and to other similarly acting compounds, oxatomide is highly active for a long time after oral administration. Furthermore the new compound is active against immediate hypersensitivity reactions, irrespective of sensitization by IgG or IgE homocytotropic antibodies. In conclusion, 2 important mechanisms for the inhibition of hypersensitivity reactions appear combined at effective doses of oxatomide, inhibition of mediator release, as well as potent antagonism of their spasmogenic activity. In animals, virtually total abolition of anaphylactic and allergic reactions is thus obtained at doses free of behavioural effects and far below toxic levels. The 1st clinical observations in man indicate that this pharmacological profile may result in a novel type of effective antiasthmatic drug.

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Radioimmunoassay of some hormones simultaneously measured in serum and breast cyst fluid

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Summary. Blood and breast cyst fluid were drawn simultaneously for hormonal determination. There was no difference between serum and cyst fluid values of PRL and TSH. A significant difference was noted for LH ($p < 0.01$) and FSH ($p < 0.05$), serum concentrations being higher than cyst fluid concentrations.

There is a high incidence of breast cyst, but little has been published regarding the hormonal composition of this easily obtainable cyst fluid[3]. Benign cystic disease of the human breast is not generally considered in itself to be a precancerous lesion, but earlier studies have suggested that women who develop benign breast disease are at increased risk of later acquiring breast cancer[4–7]. The frequency of benign disease in breast tissue removed at mastectomy is reported to be 39%, and mammary carcinoma developed in the affected cases 1.73 times as often as it did in the general population[8]. Women with cystic disease have about 4 times the breast cancer rate of comparable women without cystic disease[9]. Another study reported also shows the prevalence of malignant transformation in the total series of 876 cases to be 3.1%[10]. The presence of intracystic carcinoma is very rare[11–13].

These observations have led to 2 hypotheses on the mechanism of possible association between cystic mastitis and cancer[14]. According to the first, cystic disease could be a premalignant condition that either predisposes to neoplatic change or is an early manifestation of malignant change. According to the second, benign and malignant breast diseases could have factors in common, such as hormonal pattern. In line with the latter hypothesis, we

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Table 1. Simultaneous measurement of hormonal concentrations in serum and cyst fluid

Patient	PRL-concentration S (ng/ml)	CF	LH-concentration S** (mIU/ml)	CF	FSH-concentration S* (mIU/ml)	CF	TSH-concentration S (μU/ml)	CF
MN 1	4.1	4.3	80.0	4.5	80.00	3.70	1.00	1.00
DB 2	31.0	12.5	27.0	12.5	2.55	1.00	1.05	4.50
PZ 3	20.0	11.3	25.5	14.0	7.00	1.00	1.00	4.15
MC 4	4.4	6.8	23.0	4.5	10.20	3.00	2.70	1.90
ML 5	59.0	16.5	22.5	8.4	5.00	1.00	1.00	1.55
RB 6	6.4	80.0	15.5	5.2	5.20	1.00	2.70	1.00
LP 7	21.0	9.8	62.0	7.2	15.30	1.00	2.50	6.85
EF 8	76.0	70.0	16.5	10.0	5.30	1.00	2.70	1.70
DR 9	7.5	23.5	13.0	18.5	14.00	1.00	3.50	1.00
KB 10	11.9	13.5	56.0	13.5	38.00	4.40	6.35	10.15
RG 11	9.1	9.3	13.0	4.1	–	–	–	–
BG 12	15.9	13.5	80.0	40.5	37.00	3.95	3.10	6.50
JA 13	12.5	24.5	17.0	37.0	–	–	1.00	12.25
LM 14	–	–	41.5	40.5	4.50	1.00	1.00	1.00

*$p < 0.05$; **$p < 0.01$.

decided to measure hormonal concentrations in serum and cyst fluid samples obtained at the same time. The study was undertaken with the view that the women who have cystic diseases are more likely to develop cancer elsewhere in the breast than women without cystic disease. We hope that we might be able to pick up an abnormal concentration of certain hormones in the etiology of the cystic disease of the breast. Accordingly, we plan to follow these patients for 10 years or more for development of possible carcinoma.

Methods. A. Patients: 14 patients coming to surgeons for aspiration of the breast cystic fluid were studied. Blood samples were obtained at the time of cyst aspiration. B. Radioimmunoassay of Hormones: 1. Human Prolactin (PRL): The reagents (V-L S No. 1) used in this study were supplied by the National Pituitary Agency, National Institutes of Arthritis, Metabolism and Digestive Diseases (NIAMDD). The iodination and setting of the assay was carried out as described by Sinha et al.[15]. 2. Human Thyroid Stimulating Hormone (TSH): The double antibody system of Utiger[16] was used with antigen and first antibody supplied by NIAMDD. Reference was supplied by Dr Bangham on behalf of the World Health Organization, International Laboratory of Biological Standards (WHO-ILBS). 3. Human Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH): Immunoassay reagents were supplied by NIAMDD and assay was carried out with Odell's methodology for LH[17] and Midgely's for FSH[18]. Valies were expressed in terms of second IRP-HMG, which was supplied by WHO-ILBS.

Results. The values in serum and breast cyst fluid are shown in table 1. The Wilcoxon Rank test was used to determine if there were differences between the serum and cyst levels[19]. PRL: Serum and breast cyst fluid were analyzed for PRL concentration in 13 patients. 3 had higher cyst fluid concentration, 4 higher serum concentration, and 6 had equivalent values. There was no significant difference between serum and cyst values. LH: In 11 patients, the serum level of LH was higher than the cystic level, in 2 patients, the cyst fluid level was higher than that of serum, and in 1 patient, the serum and cyst values were equivalent. The serum levels were significantly higher than those of the cysts ($p < 0.01$). FSH: 12 patients had serum concentrations higher than those in the respective cyst fluids. The difference was statistically significant at $p < 0.05$. TSH: Serum levels were higher than those in cyst fluid in 4 patients, lower in 6 patients, and no difference in 3 patients. The differences were not significant.

4 patients had multiple cysts which were separately aspirated and analyzed individually for different hormones. The data are summarized in table 2. In regard to TSH, there was no difference between cyst fluid levels in the same patient. The FSH data were too limited to evaluate. LH and PRL levels of different cysts in the same patient appeared to vary. None of the differences were as great as some of those between serum and cyst fluid.

Discussion. This study was undertaken because of the postulation that cystic disease is related to hormonal abnormalities[20], and the women with cystic breast disease are more at risk to develop malignant breast tumor than the normal population[8]. In support of this view, there are several observations. 1. It has been reported that the occurrence of breast cancer in near relatives is a risk factor for breast cancer[21]. 2. It has been shown that serum PRL levels in breast cancer patients and matched control are not different, but it was different in the high risk group[22]. 3. In another study, patients with breast cancer and their sisters have been reported to have abnormal androgen excretion[23]. Follow-up of the patients may help in identifying a hormonal marker for future clinical course of the patients.

Table 2. Concentration of hormones in multiple cysts

Patient	PRL ng/ml	LH mIU/ml	FSH mIU/ml	TSH μU/ml
DB cyst 1	12.5	12.5	< 2.00	4.50
cyst 2	9.9	9.4	< 2.00	3.90
RG cyst 1	9.3	4.1	–	–
cyst 2	14.0	9.6	–	–
BG cyst 1	13.5	40.5	3.95	6.50
cyst 2	7.6	20.5	3.85	4.20
cyst 3	16.0	7.8	< 2.00	4.70
JA cyst 1	24.5	37.0	–	12.25
cyst 2	35.0	8.1	–	12.50

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