control group on day 12 indicates that self-cure must have started slightly earlier and that the result of the administration of reserpine could have been to inhibit, to arrest or to delay the expulsive reaction. The final worm counts, by comparison with the detailed figures for the kinetics of expulsion given by Jarrett *et al.*[3], suggest that worm loss had already started before reserpine was given and that arrest or delay took place. This seems most likely to have been caused by prevention of full participation of mast cells in the reaction, and lends strong support to the hypothesis that the discharge of biogenic amines by mast cells, and the local permeability changes mediated by them, are concerned in the mechanism whereby antibodies are translocated from the lamina propria of mucous membranes to their site of action in the lumen.

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Induction of Breast Cancer in Altered Thyroid States

The development of mammary tumours in rats by orally feeding the chemical carcinogen 7,12-dimethylbenz(*a*)-anthracene (DMBA) has been shown to be influenced by the hormonal state of the animal[1]. We previously observed that breast dysplasia could be induced in iodine deficient and propylthiouracil (PTU)-treated rats given oestrogen or testosterone[2]. Furthermore, the incidence of breast cancer is higher among women with hypothyroidism and in those residing in regions where goitre is endemic[3]. The present study considers the rate of development of DMBA-induced breast cancer in rats made iodine deficient or hypothyroid.

Sprague–Dawley (Charles River) female rats obtained at 40 days old were randomly divided into six groups as noted in Table 1. Ten mg of DMBA, dissolved in 0·5 ml. of sesame oil, was given once by gastric tube at 50 days of age to all the animals. None of the animals showed any ill effects from the DMBA. Hypothyroidism was produced by giving 4 mg of PTU/100 ml. of drinking water *ad libitum*. Remington diet (less than 0·5 p.p.m. iodine) was given with double de-ionized drinking water. Two groups of animals (II and III) were started on Remington diet or PTU 4 days before the gavage feeding of the DMBA, while groups IV–VI were started on their PTU, iodine-deficient diet or combination 3 days after DMBA was given.

All animals were killed 60 days after being given DMBA. The nodules palpated were carefully diagrammed, and removed at autopsy for histological study to determine the type and extent of the lesions. Each of the palpable breast nodules was confirmed to be an epithelial neoplasm. Iodine deficient animals or animals treated with propylthiouracil maintained a growth rate comparable with that of the intact controls, while the animals receiving both Remington diet and propylthiouracil had a growth rate below that of the controls.

Rats maintained on the iodine deficient diet, PTU alone, or iodine deficiency diet plus PTU beginning 3 days after the instillation of DMBA develop palpable masses at a mean of 36·5, 37·3 and 37·1 days, respectively, compared with the control values of 42·5 days, always determined from the day of DMBA gavage (Table 1). When, however, the iodine deficient diet or PTU treatment was started 4 days before the feeding of DMBA, the mean time before tumour onset was 26·6 and 29·6 days, respectively, as compared with the control value of 42·5 days. While there are many factors yet to be considered, these results indicate that previous iodine deficiency or hypothyroidism significantly accelerate the experimental induction of breast neoplasms with DMBA in rats (P value less than 0·001).

Table 1. INCIDENCE OF MAMMARY GLAND TUMOUR IN RATS GIVEN DMBA WITH IODINE DEFICIENCY AND/OR PTU

	No. of rats	Rats with tumours	Appearance of first palpable tumours (days after DMBA) Range	Median	Mean ± S.E.	Average No. of tumours per rat in groups 60 days after DMBA
I Intact controls	10	10	31–49	42	42·5 ± 1·6	7·4
II Iodine deficient	6	6	24–33	27	26·6 ± 1·5	7·8
III PTU	6	6	24–35	31	29·6 ± 1·5	7·2
IV Iodine deficient	9	9	31–46	38	36·5 ± 1·6	7·9
V PTU	10	10	31–47	35	37·3 ± 1·4	8·1
VI Combination	9	9	33–46	38	37·1 ± 1·4	5·4

II and III, Started on therapy 4 days before DMBA.
IV–VI, Started on therapy 3 days after DMBA.

It is, however, interesting to note that the average numbers of tumours/animal in the groups 60 days after treatment with DMBA are all approximately the same except for the combined iodine deficient diet PTU group.

Jull and Huggins[4] showed that after treatment with DMBA fewer rats developed mammary tumours in thyroidectomized animals than in intact controls. They felt that the decrease in the incidence of breast cancer in their thyroidectomized rats could be attributed to the influence of the consequent smaller calorie intake which has been shown to have marked effects on the genesis of spontaneous and induced tumours. Helfenstein, Young and Currie[5] published results which indicated that hypothyroidism chemically induced by PTU is capable of producing the same effect.

Our studies indicate that both iodine deficiency and hypothyroidism do have an influence on the rate of onset of palpable tumours in DMBA-induced breast carcinoma of rats only when it is given before treatment with DMBA. It would seem, then, that after the initial onset of palpable tumours, the average number of tumours seen in all groups rapidly equalizes, additional tumours appearing at a relatively regular rate except in those animals (VI) given both iodine deficiency and propylthiouracil. This latter group shows a decrease in growth probably accounting for the reduction in the number of tumours.

These results emphasize the importance of factors relating to the thyroid in modifying the responsiveness of the breast to carcinogenic influence.

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