The concept arose step by step directly from our initial observations on the non-carcinogenic tumour-inhibiting substances in coal-tar. It was developed as a basis for planned experimental work and as such has proved most useful. I am much indebted to Burnet's stimulating idea of "self-markers," which, extended into the cancer field, provided at a later stage an essential link in the hypothesis.

Summary

Non-carcinogenic polycyclic hydrocarbons which strongly inhibited the growth of some transplanted tumours were isolated from coal-tar oil.

These compounds, as compared with related *carcinogenic* hydrocarbons, were non-toxic and did not inhibit somatic growth. Nevertheless their tumour-inhibiting effect was shown to be of the same specific nature as that induced by the carcinogens. Neither had any direct cytotoxic effect on the tumour.

Both types failed to inhibit spontaneous or chemically induced tumours, or transplanted tumours lacking antigenicity to the host.

It was conclusively shown, partly with the aid of cortisone, that the tumour-inhibiting property was due to a stimulation of the immune reaction to homologous tumour tissue.

Evidence is presented which favours the view that these compounds have the specific property of altering certain protein complexes so that they behave as iso-antigens and excite the production (mainly locally) of homologous antibody. Their mode of action is discussed and the important role of the plasma cell in the immune response demonstrated.

Some evidence was obtained that chemical carcinogens when in intimate contact with red cells and epidermal cells induce the production of homologous antibodies to iso-antigens in similar cells.

Evidence is presented suggesting that tumour-inhibiting and carcinogenic capacity are biologically closely related. It is therefore postulated that the immune reaction induced by a carcinogen is the essential primary stage in chemical carcinogenesis.

It is suggested that all the tumour-inhibiting polycyclic hydrocarbons are able to induce the primary "initiation" stage, but that only the carcinogens are able to "promote" the cell to the stage of neoplasia by their additional non-specific hyperplastic action.

It is postulated that the "initiation" stage of chemical carcinogenesis is that at which an antigenic change in the "identity protein(s)" to an iso-antigen occurs. The antibody response thus elicited either destroys the precancerous cell at some stage, or continuous hyperplasia leads to an ever-increasing immune reaction which may finally induce an adaptation in the cell. The adaptation involves the loss of "identity-protein" complexes, and the neoplastic cell emerges.

Evidence was obtained that a tumour-inhibiting polycyclic hydrocarbon delayed the *outgrowth* of a mouse spontaneous tumour. For this and many other reasons it is suggested that the initial stage in the development of every malignant tumour may involve the loss, or antigenic change followed by loss, of "identity proteins."

Suggestions are made concerning how this loss could occur with such different cancer-inducing agents as viruses, ionizing radiations, and long-continued hyperplasia alone.

The basic concept is that all neoplastic cells lack one or more substances (probably protein complexes or their related enzyme systems) which confer tissue and individual identity on the cell. The cell thus becomes more antigenically "neutral" and does not attract in the same degree the normal immunologically regulated disposal mechanism. It is argued that this lack of "identity proteins" constitutes in itself the neoplastic state, and that the attributes, gradations, and progressions of this state are defined by the nature and extent of the loss.

Individual acknowledgments for all the willing help we had will be expressed in later detailed papers, for the work described is linked up with other investigations that did not concern us here.

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A NEW THERAPY FOR PREVENTION OF POST-OPERATIVE RECURRENCES IN GENITAL AND BREAST CANCER

A SIX-YEARS STUDY OF PROPHYLACTIC THYROID TREATMENT*

BY

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All who have treated operable cancer of the breast or female genitals have tried to eradicate the cancer by radical operation, by radium or deep *x*-ray treatment, or by a combination of these methods. But after this initial treatment we tend to sit back and wait. Wait—let me be frank—for a recurrence of the cancer. The mistake made in cancer therapy is that we begin the fight most vigorously, but halt the battle too early without having tried post-operative prophylactic treatment against the killer's recurrence.

In 1938 I mentioned for the first time the beneficial effect of male hormone in two cases of inoperable breast cancer, after having proved the effect of testosterone on the breast and female genitals (Loeser, 1938a, 1938b). I thought at that time I had found the solution in prophylactic treatment against cancer recurrence. This hormonal treatment—which was published long before Huggins's contrasexual therapy in cancer of the prostate

*After a paper read, by invitation, at the International Gynaecological Congress, Geneva, July 28, 1954.

—is now a well-established method of influencing inoperable growth and recurrence. But I, like many others, was not entirely satisfied. From 1950 onwards (Loeser, 1950, 1951, 1953, 1953–4) I got much better results by combining the male hormone with thyroid hormone, and described this method in cases of inoperable breast cancer at the International Cancer Congress in Paris (Loeser, 1950). I had observed that treatment with one sex hormone alone could, in the long run, kill the patient by more or less completely blocking the anterior pituitary. This may shrink to a third of its normal size, as proved by necropsy, and can eventually rob the body of the adrenotropic and thyrotropic hormones necessary for the maintenance of normal life.

I am here concerned with the prophylactic treatment of breast and genital cancer after radical operation or *x*-ray treatment with thyroid hormone alone, and will explain why this treatment is so encouraging, and seems to me to be the best weapon in our armamentarium against cancer recurrence, by upholding normal cell metabolism.

According to observations on 180,000 men and women made by the American life assurance companies, we know that more overweight persons acquire cancer than persons of normal weight, and the death rate from cancer in obese persons is higher than in those of normal weight. Among overweight patients we often find that hypothyroid subjects —as can be proved easily by their histamine skin content (see below)—are more prone to develop cancer than hyperthyroid subjects. Hyperthyroid patients seldom suffer from cancer. But what is generally less well known is the fact that after partial thyroidectomy (when usually seven-eighths of the thyroid gland is removed) a greater number of women between 40 and 60 years develop breast or genital cancer than the average population in the same age group.

Table I shows some statistics. I am not greatly influenced by statistics; nevertheless, one cannot ignore them completely.

TABLE I.—*Incidence of Cancer in Different Diseases*

Character of Affections	No. of Patients	Age Group	No. of Cancer Cases
1. Allergic conditions (Frankland, Pepys, compiled by Loeser)	300	40–60	1 (0·3%)
2. Hyperthyroidism (Lerman, 1947)	1,300		7 (0·5%)
3. Myxoedema (Lerman, 1947)	150		6 (4%)
4. After thyroidectomy (Buxton and Willcox, 1952)	68		4 (5·9%)
5. After thyroidectomy (Ellerker and Loeser*)	100	40–60	7 (7%)
6. Goitre and conditions after thyroidectomy (Repert, 1952)	360	Menopausal	12%

No. 1. St. Mary's Hospital and Royal National Throat, Nose and Ear Hospital, London (examinations made at my instigation). Nos. 2 and 3. Massachusetts General Hospital, U.S.A. No. 4. Middlesex Hospital, London. No. 5. Royal Free Hospital, London (examinations made at my instigation). No. 6. Butterworth Hospital, Durango, Colorado, U.S.A.
* A paper to be published shortly.

Among the gynaecological patients I have seen during the last seven years were 14 who had previously undergone a thyroidectomy (13 because of nodular goitres and 1 because of toxic goitre). In six of these patients benign tumours of the uterus and ovaries had developed, and in eight of them a carcinoma of the breast, two to five years after the thyroidectomy.

Two of the breast-cancer patients are of special interest. One of them had a partial thyroidectomy (nodular goitre), and at the time of the operation an early breast cancer was detected. Ten days after the thyroidectomy a radical mastectomy was performed and the patient died from rapidly developing metastases in the bones. The cancer had developed in a body deficient in thyroid hormone. The other patient had a radical mastectomy because of an early breast cancer, and three years later an adenomatous goitre was removed by partial thyroidectomy. The goitre had been present for a number of years. This patient died very rapidly from metastases in the bones and lung six months after the thyroidectomy. Here also cancer developed in a body deficient in thyroid hormone.

It was no coincidence that in these two unfortunate women new cancer metastases shot up like mushrooms after a partial thyroidectomy. The removal of so much thyroid tissue had robbed the body of its best defence mechanism against pathological cell formation; a hitherto dormant cancer awakened after the operation and killed its host. Similar observations have been made by Dargent and Lavigne (1953).

The question arises, How does the thyroid hormone act as an anticarcinogen? If patients receive small or moderate amounts of thyroid over a prolonged period, these patients' own thyroid glands can be put to rest, because of a decreased secretion of thyrotropic hormone by the anterior pituitary (Loeb, 1920; Johnston, 1951). The mechanism of this action on the pituitary gland is in all likelihood not of the same character as the action of sex hormones on the pituitary. Thyroid hormone has paramount control over the cell activity in the body. It has a caloric action, an action upon growth, maturation, and differentiation; an action on the proteins, lipids, and upon all other endocrines, not to speak of its influence on the nervous system. It acts antagonistically against the gonads and suprarenals. It has a metamorphotic property by contrast with the pituitary hormones, which increase growth rate. The action of oestrogens in producing vaginal cornification is diminished by thyroxine. But after thyroidectomy or thiouracil treatment the oestrogenic cornification is increased (Levitt, 1954).

If a carcinogen (dibenzanthracene) is injected into mice it produces tumours, but if this carcinogen is injected together with thyroxine, the rate of disappearance of the carcinogen from the tissues is increased and the tumour response is lowered. Thiouracil, on the other hand, greatly increases the incidence of dibenzanthracene-produced tumours. Thyroxine had little or no effect upon the growth of already established dibenzanthracene-produced tumours (Bather and Francks, 1952).

Thyroxine plays an important part in the normal cell defence by increasing the metabolic destruction of the carcinogen. It is essential for basic cell metabolism, controlling cell respiratory catalysts, and enzymatic action. Practically every chemical reaction which occurs in the body is an enzyme reaction. These enzymes, these catalytic proteins, are living matter dependent on the thyroid content in the blood. As far back as 1932 I could show, in the Warburg experiment, that the cell metabolism of placenta and benign and malignant tumours could be influenced by hormones.

I shall now deal with the work I have done in collaboration with many others in London hospitals.

Clinical Observations

One hundred patients who had previously undergone a partial thyroidectomy were followed up by Mr. Ellerker, of the Royal Free Hospital, London, and myself (Table I). Among these we found seven with cancer development (one of the cervix, six of the breast). All these cancer growths had been removed by radical operation some years after a preceding thyroidectomy for goitre, and the patients were alive at the time of re-examination. Among the remaining 93 thyroidectomized cases, 32 had developed a chronic mastitis (endocrine basis) or fibroids of the uterus. These 32 cases had never received thyroid hormone after thyroidectomy. But among the then remaining 61 patients were 14 who had received thyroid hormone after thyroidectomy, and in only four could a chronic mastitis be diagnosed.

This fact shows that a lack of thyroid hormone in the body favours tumour development. The defence mechanism against tumour formation cannot be maintained when there is insufficient thyroid hormone, whatever the cause for this deficiency may be.

Blood Lipids in Hypothyroid and Hyperthyroid Women

In the 40–60 years age group, 59 women were examined for lipid content of the blood. Plasma cholesterol, lipid phosphorus, total lipids, and neutral fats were determined in the department of clinical investigation of the London Clinic. Since women in this age group possess more fatty tissue than younger women, it was not surprising to find higher values of blood lipids. When oestrogens are given to these women the blood lipids rise still more, whereas androgens have no marked influence on the lipid level (Gertler and Oppenheimer, 1953).

Hypothyroid women, by contrast with hyperthyroid, show a very elevated lipid level, but after thyroid treatment the lipids decrease considerably. In three women with inoperable breast carcinoma and two with inoperable ovarian carcinoma, who received massive doses of thyroid hormone —up to 25 gr. (1.6 g.) daily for four to six weeks—which made them temporarily thyrotoxic, the lipids declined to a very low level and the inoperable cancer growth decreased in size. Two cases of previously inoperable breast cancer became operable; one of these patients is still alive, and after two years was clinically cured. Already, 53 years ago, Beatson tried to influence inoperable breast cancer by oophorectomy and massive thyroid doses; and before him, in 1887, Schinzinger was the first to remove the ovaries in breast cancer cases. Removal of the gonads or adrenals—as I see it—supports the production of more thyroid hormone and acts in this way. Gonadectomy and adrenalectomy can therefore be replaced by thyroid medication.

A low level of lipids in the blood in cancer cases is a prerequisite for the prophylactic treatment of cancer recurrence. Such a condition is found—as our investigations have shown—in hyperthyroid and often in allergic conditions, and, as is seen from Table I, the incidence of cancer is lowest in these two groups—lower, in fact, than among the average population.

Correlation between Thyroid Hormone and Histamine Cell Content

At my instigation, Dr. Feldberg, of the National Institute for Medical Research, Mill Hill, examined the histamine content of the skin of 49 patients, who were menstruating normally, pregnant, or menopausal; the results will be published shortly. Skin was removed from hypothyroid and hyperthyroid as well as from allergic patients, from women treated with thyroid hormone, and from cancer patients during the last three and a half years.

Histamine, it seems to me, is a local protein-bound cell hormone. Nobody really knows why the cells in the body anchor histamine, which is easily released into the blood stream after injury to the cell from outside or inside the body. All the cells in the body, but not those of the brain (with the exception of the hypothalamus and the pituitary gland), contain protein-bound histamine. Different organs contain different amounts of histamine—the liver and spleen having more than the skin.

After an intensive burn a scar has little histamine. Years after such a burn a local skin cancer may develop. In the skin round a precancerous hyperkeratosis practically no histamine was found by contrast with the skin further away from the scar, where much histamine was found. In the skin through which deep *x* rays had penetrated the histamine was very much diminished. Could smoking perhaps also reduce the cell histamine content in the lung?

For our purpose a piece of the skin was removed from patients, and within 60 minutes the extract of the fresh, living skin was assayed against histamine on the atropinized guinea-pig's ileum preparation. There is no doubt that hypothyroid persons show much less histamine than the hyperthyroid (Table II). Pregnant women have no more histamine than those menstruating normally. Women with cancer of the breast or genitals often show a low histamine content. Patients with fibroids of the uterus show higher histamine content than cancer patients.

TABLE II.—*Histamine Content of Skin from 22 Patients With Disorders of the Thyroid or After Thyroid Treatment*

Age	Site of Skin Removal	Histamine µg. g.	Thyroid Disorder
30	Abdomen	2·5	
32	,,	3·6	
29	,,	3·6	
41	,,	4·0	Hypothyroidism
34	,,	4·7	
53	Breast	5·2	
57	Abdomen	8·4	
40	,,	10·5	
40	Neck	11·5	
42	,,	12·7	
57	Breast	13·6	
32	Abdomen	13·9	Hyperthyroidism
40	Neck	15·0	
40	,,	15·0	
32	Abdomen	17·4	
40	Neck	17·6	
42	Abdomen	10·6	
56	Breast	11·0	Treated with massive doses of dry thyroid
50	,,	12·0	
48	Abdomen	13·8	

In patients who were fed with medium or high doses of thyroid the histamine content of the skin went up considerably (Table III). If a menopausal patient had oestradiol implanted the histamine in the skin went down and the lipids in the blood soared up. If testosterone was injected intramuscularly the cell histamine was much less influenced.

TABLE III.—*Effect of Oral Administration of Large Doses of Dried Thyroid on Histamine Content of Human Skin*

Histamine in µg./g.		
Before Thyroid Administration	During Thyroid Administration	Increase
1·8	4·2	133%
3·6	8·0	122%
4·7	5·0	6%
7·5	7·5	*
8·4	11·6	38%
10·0	15·8	58%

*In this patient suffering from a very advanced ovarian carcinoma, with multiple metastases in liver and spleen and ascites, the thyroid treatment had no effect other than a temporary relief, and the patient died after a few months.

There is a quantitative relationship between the amount of thyroid hormone produced in the human body or artificially incorporated by thyroid treatment and the intracellular deposition of histamine. The histamine content in the cells is controlled by the thyroid hormone. The more thyroid hormone, the more histamine, the lower the level of lipids in the blood. The less thyroid hormone, the less histamine, and the higher the blood lipid level.

These facts are significant, since cancer develops more often in hypothyroid, non-allergic, and obese women of the 40–60 age group than in allergic or hyperthyroid women of the safe age group. After our investigations one could say that increase of thyroid hormone in blood, high histamine content of tissues, and low blood lipids were associated with a decreased tendency to tumour formation; and that decrease of thyroid hormone in blood, low histamine content of tissues, and high blood lipids were associated with an increased tendency to tumour formation.

It was therefore a logical conclusion to treat women permanently with thyroid hormone after radical mastectomy or hysterectomy for cancer, or after deep *x*-ray treatment, in order to produce as much histamine as possible in their tissues, to depress the blood lipids, and thereby strengthen the resistance of the host against possible cancer recurrence.

It is, so to speak, a ploughing of the terrain (of the tissues of the body) in which cancer recurrence could gain

a foothold later on: a ploughing through at a very early time when cancer cells may be left behind after a radical operation adjacent to the field of the operation or farther away. A permanent thyroid hormone medication means, perhaps, also the continuous dysfunction of a carcinogen which otherwise would transform a normal cell into a cancerous one.

But carcinogens other than of hormonal origin which may produce a cancer *in situ* are legion. With advancing years and declining thyroid activity we all may have such a cancer *in situ* somewhere, which remains latent so long as the thyroid gland is fully effective.

Thyroid hormone cannot destroy the actual cancer cell, but, as a "terrain therapeuticum," can keep the actual cancer cell dormant for a long time, as we have seen in the treatment of inoperable breast, uterine, and ovarian cancer.

Radioactive thyroxine tried in four of my cancer cases in University College Hospital, London, was not deposited in the cancer growth and did not seem to act locally. In these cases local histamine iontophoresis on the tumour itself was administered in order to increase temporarily the blood flow to the growth and surrounding tissues and to render them more accessible to thyroid hormone.

Prophylactic Post-operative Treatment with Thyroid Hormone

Since October, 1948, thyroid hormone (dry thyroid gland extract), in daily doses ranging from 1 to 5 gr. (65–320 mg.) was given to patients who had undergone radical mastectomy or hysterectomy because of cancer. No untoward symptoms were observed in the majority, and the weight of the patients was not significantly influenced. (The gain in weight, so often observed after these operations when the cancer growth is removed, is not desirable, as such weight gain can lower the cell metabolism.) Lipid examinations of the blood were made from time to time. If the lipids declined too much (cholesterol under 100 mg./ml.), the thyroid dosage was decreased; if the lipids were normal or too high the thyroid dosage was increased. The following lipid level was regarded as desirable: total cholesterol, 150–175 mg./ml.; lipid phosphorus, 9–10 mg./ml.; total lipids, 500–600 mg./ml.; neutral fats, 200–300 mg./ml.

Unfortunately the number treated in this way was very small. Four patients so treated have been under observation for more than five years: (*a*) one bilateral ovarian carcinoma which already showed peritoneal spread; (*b*) one endometrial cancer on the borderline of operability; and (*c*) two breast-cancer cases with axillary gland involvement. Both of them had post-operative deep *x*-ray treatment. Three of the four patients were overweight; all of them had plasma cholesterol over 280 mg./ml. The four patients are now in good health and clinically cured. In the ovarian-cancer case a mediastinal tumour appearing in the sixth year after the beginning of the thyroid treatment proved to be a thymoma which disappeared completely after deep *x*-ray treatment.

Of a further 14 women who were observed for more than four years after radical mastectomy, nine were overweight. An axillary gland involvement existed at the time of the operation in 10 of them; four had no axillary involvement. All were scirrhous carcinomata, and in all but three the plasma cholesterol was over 260 mg./ml. Only one of these 14 women had a recurrence—this was in the brain, and it caused her death.

Thus there were 18 cases in all, with only one certain recurrence.

Far be it from me to draw any conclusion from the examination of these two small groups, and I will not even report on my other series of cases which have been observed over a period of only one to three years since the beginning of thyroid treatment. Such a small series may lead to erroneous deduction, and observation for less than five years is too short for a real evaluation of whether or not thyroid treatment has inhibited new cancer formation.

I think, however, that the results warrant the use of prophylactic thyroid hormone treatment, and I hope that many will try it against cancer recurrence. Only examinations on a large scale will show the real value of this method.

Summary

The incidence of female breast and genital cancer is far lower in allergic and hyperthyroid conditions (Group A) than in hypothyroid women or women after a partial thyroidectomy because of goitre (Group B).

Women belonging to Group A have on average a much higher histamine content in their cells than women in Group B, and the lipid content of the blood is much lower in Group A than in Group B.

The more thyroid hormone circulating in the blood the higher the histamine content in the cells, the lower the level of the lipids the less tendency to cancer formation.

The less thyroid hormone circulating in the blood the lower the histamine content in the cells, the higher the level of the lipids the more tendency to cancer formation.

Intracellular protein-bound histamine is regarded as a defence hormone against cancer formation under the control of the thyroid hormone.

Thyroid hormone, given in massive dosage in cases of inoperable cancer of the breast and genitals, slowed down cancer growth.

Thyroid hormone in daily dosage ranging between 1 and 5 gr. (65 and 320 mg.) was given over six years as a prophylactic against cancer recurrence after radical operations because of breast or genital cancer, and after deep *x*-ray treatment. The good results which were obtained should encourage further trial of this method on a large scale.

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