ered from the point of view of the chemical raw materials available for development. The lucid account of nutritional and other problems that eggs and embryos have solved in adapting to the limitations of their environment is a most interesting and valuable contribution to the study of evolution and natural history. Part 3 is devoted to the morphogenetic mechanisms, including the special metabolisms of embryonic life with its sequence of energy sources, etc., and also such general questions as dissociability, growth, polarity, etc. In considering growth, attention is focused on the relative proportions of constituent materials at different stages in the development of the individual and in widely different species.

The treatment is broad and inclusive throughout. While the book is primarily concerned with recent facts and concepts, these are constantly projected in perspective against historical and philosophical background. A spirit of optimistic mechanism pervades the treatment, and an old subject is admirably treated in the light of current knowledge under the picturesquely modern heading, "The Liquidation of the Entelechy." The concept of levels of organization is stressed, and finally a parallel is drawn between organic and social development.

Cancer and teratomatous tumors are considered in relation to the organizer phenomena. Striking chemical similarities and overlapping functions are noted among certain substances acting as sex hormones, carcinogens and primary organizers (evocators). Cancer appears to involve the problem of anomalous differentiation or lack of differentiation, and thus to be related to phenomena studied in experimental and chemical embryology. Students of cancer will wish to familiarize themselves with Dr. Needham's account and point of view.

The book is abundantly and well illustrated, and a convenient system of numbering the sections or subjects is employed. The quality of the paper, as in most recent books, is not up to pre-war standards. An interesting side-light on the creation of books in England under conditions of war was shown this winter at the Yale University Library when copies of the various steps in the preparation of this book, the manuscript, galley, page proof, microfilm of the corrected page proof, etc., were put on display. These copies had all been sent as they came into being to Dr. Ross G. Harrison as insurance against destruction of the originals.

Throughout, attention is called to probable future trends in research and to needed experiments yet undone. The bibliography is the most complete and extensive in existence since "Chemical Embryology" and includes references to recent reviews. This book represents a great accumulation of facts and a masterly synthesis of knowledge. It will be indispensable to the investigator and teacher alike.

DOUGLAS WHITAKER

SPECIAL ARTICLES

THIOURACIL IN THE TREATMENT OF THYROTOXICOSIS[1]

RECENT interest in the possible medical treatment of patients with thyrotoxicosis has been stimulated by the observations that certain sulfonamides, as well as thiourea[2, 3, 4] and its derivatives, induce a hypometabolic state when fed to rats for several weeks. The evidence that has been accumulated suggests that the lowering of the metabolic rate results from a decrease in the production of the thyroid hormone, which is presumably due to the action of these drugs on the thyroid gland. The latter becomes enlarged and hyperplastic, but its content of colloid is greatly depleted. The changes in the thyroid do not occur if the animal is fed desiccated thyroid or if a hypophysectomy is first performed. The above drugs do not interfere with the elevation of the metabolic rate induced by thyroxin or desiccated thyroid. The pituitary gland responds with the same type of hyperplasia as follows thyroidectomy.

Astwood[5] found that of a large group of sulfonamides and thiourea derivatives which he tested, thiouracil was the most effective in inhibiting the production of thyroid hormone. He used thiouracil in the treatment of three patients with thyrotoxicosis and in each case the metabolic rate returned to normal and the symptoms were relieved. However, when the drug was discontinued after one or two months, the manifestations of the disease reappeared. The course of one patient was complicated by the development of agranulocytosis.

During the last few months, we have used thiouracil[6] in the treatment of nine patients with thyrotoxicosis. This substance is a thiourea derivative with the following formula:

[1] From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston.

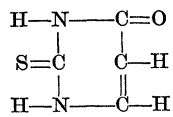
[2] Julia B. Mackenzie, C. G. Mackenzie and E. V. McCollum, SCIENCE, 94: 518, 1941.

[3] C. G. Mackenzie and J. B. Mackenzie, *Endocrinology*, 32: 185, 1943.

[4] E. B. Astwood, J. Sullivan, Adele Bissell and R. Tyslowitz, *Endocrinology*, 32: 210, 1943.

[5] E. B. Astwood, *Jour. Am. Med. Asn.*, 122: 78, 1943.

[6] Thiouracil was supplied through the courtesy of the Lederle Laboratories, Inc., Pearl River, N. Y.



It is a white crystalline powder which is readily soluble in sodium hydroxide, slightly soluble in water (1: 2000) and insoluble in ether, ethyl alcohol and acids. It is a relatively stable compound, either as a solution or as a powder. It has no odor, but has a bitter taste.

Seven of the subjects were kept in the hospital for a few weeks and the other two were seen as out-patients at seven-day intervals. In most cases basal metabolic rates were determined about every seven days. A careful watch was maintained for any complications, the blood and urine being examined frequently. The unit dosage of thiouracil was 0.2 gram. During the first three weeks of treatment the total daily dosage was 1.0 or 1.2 grams spread out during the twenty-four hours; but during the second three-week period this was gradually reduced to about 0.2 or 0.4 gram daily. The daily excretion of thiouracil in the urine was followed in most cases and its concentration in the blood was determined.

All the patients had typical clinical manifestations of thyrotoxicosis. The duration of the illness ranged from six months to two years, except for one patient in whom it probably had existed for twenty-two years. In most cases, the thyroid gland was 2 or 3 times normal size. The early changes of malignant exophthalmos were observed in one patient. The initial basal metabolic rates ranged from plus 88 to plus 36 with an average of plus 63 (Fig. 1). In each case the

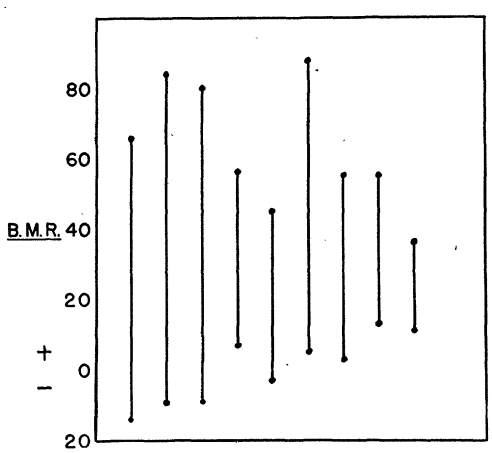


FIG. 1. Note the initial basal metabolic rates in each of nine patients and its response to treatment with thiouracil in each subject.

clinical evidence of thyrotoxicity had disappeared and the basal metabolic rates had reached normal levels (average metabolic rate was plus 1) within from three to seven weeks following the initiation of treatment with thiouracil. The severe cases improved as rapidly, or even more rapidly, than the milder cases.

In the four patients in which studies of the protein-bound iodine of the plasma were conducted there was found a decrease to a normal or subnormal level within about four weeks after beginning treatment.

In three patients the thyroid gland became slightly larger during the first two weeks of treatment but subsequently decreased to about the pre-treatment size. In the other six patients the gland progressively decreased in size and returned to normal in two cases. The patient with the early changes of malignant exophthalmos experienced an increase in the oculopathy during the course of treatment with thiouracil. However, when desiccated thyroid was administered with the thiouracil the eyes showed definite improvement and the thyroid gland became smaller.

No serious complications were encountered in any case. Two patients developed slight transient swelling of the legs associated with a slight increase in the serum chloride and a decrease in the carbon dioxide combining power of the blood. No abnormalities in the serum proteins, non-protein nitrogen of the blood, phenolsulphonephthalein in the urine, nor in the routine urine examinations were found.

In 2 patients with untreated myxedema, we found that thiouracil did not inhibit the usual rise in the metabolic rate induced by the administration of 1.5 grains, daily, of desiccated thyroid. The foregoing observations indicate that thiouracil does not interfere with the effects of thyroxin when it is administered in a preformed state, but rather inhibits the formation of the thyroid hormone.

The optimum dosage of thiouracil has not yet been determined. In an effort to throw light on this point we have studied the rate of absorption of the drug from the gastro-intestinal tract, its distribution throughout the body and its rate of excretion. The method employed for the estimation of thiouracil is that of Williams, Kay and Jandorf.[7] The absorption of the drug from the gastro-intestinal tract was found to be very rapid. For example, following the ingestion of 0.2 gram of thiouracil the maximal blood level of the drug was obtained fifteen minutes later. When it is given in doses of 0.2 gram at four-hour intervals, about twenty-four hours are required to reach a constant blood level and a constant rate of excretion of the drug in the urine. When this dosage is maintained for several days, the blood level is maintained at about 3 mgms per 100 cc and about 300 mgms per day are excreted in the urine. Most of the drug in the blood is in the cells, the white cells containing a

[7] R. H. Williams, G. A. Kay and B. J. Jandorf. To be published.

greater concentration, but a smaller total amount than the red cells. Studies are now being conducted to determine the optimum concentration of thiouracil in the thyroid and the time required to attain this level.

The present report is a preliminary one dealing with the early response of thyrotoxic patients to treatment with thiouracil. The assessment of the full value of this drug must await prolonged and extensive studies, including careful observations for signs of toxicity.

ROBERT H. WILLIAMS
GROSVENOR W. BISSELL

EFFECT OF VARIOUS CHEMICAL AGENTS AFFECTING PERMEABILITY OF THE MUCOSA ON THE FORMATION OF ULCERS

SCHIFFRIN[1] produced ulcers in the cat by running a 3 per cent. solution of pepsin in 0.1 N hydrochloric acid through a segment of the jejunum, but was unable to bring about ulceration when the acid alone was used. He emphasized the important role of pepsin in the formation of ulcers and was able to prevent the lesions by protecting the mucosa with colloidal aluminim hydroxide and aluminim phosphate.

The purpose of the investigation reported here was to study the influence of certain substances known to have marked effects in lowering surface tension or in otherwise increasing permeability of the mucosa to insulin, on the incidence and extent of the ulcerations initiated by pepsin and HCl. Chemically pure pepsin and insulin have similar molecular weights (unit weights by the ultra-centrifuge).

The method used in these studies was as follows. An incision was made in a dog under dial-urethane anesthesia, and the jejunum was brought to the surface of the abdomen. Three or 4 segments about 3 inches long, chosen in such a manner as to insure a good blood supply to each loop, were cannulated and reinserted into the abdomen, which was then closed. Solutions, preheated to 37° C., were allowed to flow by gravity through the loops at the rate of 3 cc per minute for 12 hours, or until a perforation occurred in one of the loops. The loops were then removed, split along the mesenteric line and examined grossly and microscopically. Thirty-two dogs were used. The particular loops used were not examined for spontaneous ulcers before perfusion, because to do so would require sacrifice of them before the experiment. However, in a large number of normal dogs used in this and other investigations[2] the spontaneous occurrence of a discrete ulcer has never been seen.

The concentrations of the substances used were: 0.1 N hydrochloric acid, 2 per cent. powdered U.S.P. Merck pepsin, 0.03 per cent. calgon (sodium hexametaphosphate), 0.1 per cent. hexylresorcinol, 0.05 per cent. pinacol (tetramethyl glycol), and 1 cc of methyl salicylate per liter of solution.

RESULTS

Table 1 gives the number of times a given solution was tried, the number of times ulcers were formed, and the percentage of this occurrence with the various solutions. Also included are the pH's of the solutions.

TABLE 1

OCCURRENCE OF ULCERS IN PERFUSED LOOPS

Solution	pH	Number of loops used	Number of times loops used appeared with ulcers	Percentage occurrence of ulcers
2 per cent. pepsin in distilled water	3.80	3	0	0
0.1N HCl	0.90	4	0	0
0.1N HCl and 0.1 per cent. hexylresorcinol.	1.05	3	0	0
0.1N HCl and 0.1 per cent. methyl salicylate	1.00	3	0	0
0.1N HCl and 0.03 per cent. calgon	1.15	6	1	16.6
0.1N HCl and 0.05 per cent. pinacol	1.00	3	1	33.3
0.1N HCl and 2 per cent. pepsin	1.10	22	6	27.3
0.1N HCl and 2 per cent. pepsin and 0.1 per cent. methyl salicylate	1.00	8	4	50.0
0.1N HCl and 2 per cent. pepsin and 0.1 per cent. hexylresorcinol.	1.10	13	7	53.0
0.1N HCl and 2 per cent. pepsin and 0.03 per cent. calgon	1.10	13	9	69.2
0.1N HCl and 2 per cent. pepsin and 0.05 per cent pinacol	1.10	7	5	71.4

In the loops through which pepsin alone was run the tissue appeared to be perfectly normal. When hydrochloric acid was run alone, the villi were sometimes partly destroyed. Hydrochloric acid with pepsin usually caused the villi to be destroyed with the frequent appearance of small ulcers. Hydrochloric acid with hexylresorcinol, calgon, pinacol or methyl salicylate usually produced some destruction of the villi. When calgon, pinacol, hexylresorcinol or methyl salicylate were introduced with both hydrochloric acid and pepsin, the submucosa was completely destroyed, usually showing black areas, as well as a high percentage of ulcers. On numerous occasions as many as 10 to 15 ulcers would appear in one loop when either of these compounds was used with HCl and pepsin. This was never the case when they were not used.

[1] M. J. Schiffrin, *Proc. Soc. Exp. Biol. and Med.*, 45: 592, 1940.

[2] R. L. Driver and J. R. Murlin, *Am. Jour. Phys.*, 132: 281, 1941.