TREATMENT OF GOITER IN CHILDREN

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1. *THE changing picture of endemic goiter.* With the increased transportation of frozen foods from one portion of the country to another, and with the widespread use of iodized salt, there are few if any areas in the United States where most people do not receive an adequate amount of iodine. For this reason, the naturally iodine-deficient areas, in which goiter formerly was endemic, no longer produce a high incidence of goiter. In the areas in which goiter once was endemic, the goiters that are seen today are sporadic and familial rather than endemic in character. Because these goiters rarely are the result of iodine deficiency, treatment with iodine is not apt to be helpful.

2. *Nontoxic diffuse goiter.* Two types of nontoxic diffuse goiter occur today in children. One may be called "hypofunctional hyperplasia" of the thyroid, and the other is struma lymphomatosa.

(a) *Hypofunctional hyperplasia.* This condition may be seen in newborn infants; it may occur in early infancy; or it may develop during childhood. It is characterized by a high uptake of radioiodine (I^{131}) usually without an increase in the amount of protein-bound iodine. The basic defect is the failure of the thyroid gland to synthesize properly functioning thyroid hormone. The thyroid may maintain its ability to concentrate iodine, but it cannot incorporate the iodine into a properly functioning hormone.[1] For this reason, hypothyroidism develops; the pituitary is stimulated to increase its output of thyrotropic hormone; the thyroid responds by hypertrophy and hyperplasia; and a diffuse goiter develops. Biopsy specimens of such goiters show diffuse hyperplasia histologically indistinguishable from that seen in Graves' disease, but clinically no evidence of hyperthyroidism is present.

The administration of iodine to a patient with hypofunctional hyperplasia increases rather than diminishes the hypothyroidism, and results in an even greater thyroid deficiency and in even more rapid hypertrophy and hyperplasia of the gland. The problem here is not a deficiency of iodine but a deficiency in the mechanism that incorporates iodine into thyroid hormone. The administration of iodine in large doses to patients with this type of gland appears to suppress further the ability of the gland to make thyroid hormone, just as it does to a much more striking degree in patients with Graves' disease. Consequently the growth of the gland is not suppressed by feeding iodine but is stimulated.

The proper treatment for hypofunctional hyperplasia is administration of desiccated thyroid. An adequate exogenous supply of hormone relieves the gland of the necessity of making thyroid hormone, suppresses the output of thyrotropic hormone, and results in rapid involution of the enlarged gland. Oftentimes a gland that was enlarged five or six times may return to normal size after a month or two of treatment with full doses of desiccated thyroid. If treatment is stopped, the goiter usually recurs.

The requirements of thyroid hormone by an infant or a child are much larger than have generally been supposed, and should not be calculated accord-

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ing to the ordinary criteria of weight or age by which dosages of drugs usually are calculated. A newborn infant frequently requires at least 1½ gr. of desiccated thyroid* daily to effect proper involution of a large diffuse goiter showing hypofunctional hyperplasia. Small children tolerate 2 gr. of desiccated thyroid* readily, and children more than three or four years of age usually tolerate full dosages: in effect, 3 gr., and usually require such dosages to obtain desired involution of the gland.

The type of desiccated thyroid tablet given is important because there is considerable variation in the strength of different products. A U.S.P.† standardized brand should be used, and it is important that the desiccated thyroid tablets are *uncoated*, because a coating often interferes with their being absorbed.

(b) *Struma lymphomatosa.* A second form of diffuse goiter that occurs in children is struma lymphomatosa (Hashimoto's thyroiditis). Although in children it is rarely seen in its typical form (with oxyphilia, fibrosis, lymphocytosis, and germinal centers), minor degrees of the same changes, including infiltration of the thyroid with lymphocytes are fairly common. These changes are often described as "lymphadenoid goiter."

The etiology of struma lymphomatosa is not clear. It has recently been suggested by Roitt, Campbell, and Doniach[2] that the basic cause is autoimmunity, with sensitization of the body to its own thyroglobulin. This sensitization is thought to result in the destruction of thyroglobulin by an antibody, and this in turn results in hypothyroidism, in stimulation of the pituitary to increase its output of thyrotropic hormone, and in compensatory hypertrophy and hyperplasia of the thyroid cells. Whether or not this explanation is correct, varying degrees of failure of thyroid function are the rule in struma lymphomatosa, and treatment with full doses (2 to 3 gr.) of desiccated thyroid daily results in suppression of the output of thyrotropic hormone and in shrinkage of the goiter. Usually, after two months of treatment, children's diffuse goiters due to struma lymphomatosa have returned to normal size but, unless a maintenance dose of 1 or 2 gr. of desiccated thyroid is given daily, the goiter is certain to recur.

3. *Nontoxic nodular goiter.* Nodular goiter in children is rare, but sometimes in children who have an extensive family history of goiter or who have congenital goiter or cretinism, large multinodular goiters may develop early. These may be extreme examples of the same diathesis that causes sporadic nontoxic nodular goiter seen in patients in mid-life. The childhood type of goiter appears to be the result of enzymatic defects in the thyroid causing impairment of thyroid function.[1] Most of these multinodular goiters are associated with subclinical hypothyroidism; the hypertrophy of the thyroid, with formation of nodules may take place because the pituitary stimulates the growth of the thyroid or because of a hypersensitive response of certain groups of cells to thyrotropin.[3]

The development of multinodular goiters in children can be prevented and in some cases corrected by administration of full doses of desiccated thyroid. All nodules do not involute in response to such therapy, and sometimes, when the goiters are large enough to be conspicuous, thyroidectomy is indicated.

**Thyroid U.S.P., The Armour Laboratories.*

†United States Pharmacopeia.

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Whenever a subtotal thyroidectomy is performed for a nodular goiter in a child or a young adult, the patient should be warned that unless he takes desiccated thyroid in doses of at least 1 or 2 gr. daily, *indefinitely*, the same factors that caused the goiter to develop in the beginning will still cause a new goiter to develop in the remnants of the thyroid. All children operated upon for nodular goiter should, therefore, take desiccated thyroid throughout life to compensate for this permanent inability to synthesize sufficient thyroid hormone.

Since nodular goiters of the type commonly occurring in adults are rare in children, the significance of a thyroid nodule in a child is much greater, from the standpoint of possibility of malignancy, than is a similar nodule in an adult. Most of the nodules of benign multinodular goiters are soft, whereas most carcinomas of the thyroid are extremely hard and appear as solitary tumors or diffuse infiltrations of a part or all of the gland. In children any hard nodularity or infiltration of the thyroid should be viewed with grave suspicion, and in the majority of cases such nodules or areas of infiltration should be removed completely.

4. *Toxic diffuse goiter (Graves' disease)*. Toxic nodular goiter is almost unknown in children, but toxic diffuse goiter (Graves' disease) occurs fairly frequently. When it does occur it is apt to be typical in every respect and associated with exophthalmos, an easily palpable diffuse enlargement of the thyroid, tachycardia, and muscular weakness. Except in the young child, in whom weakness may be the predominant symptom and the child may be suspected of suffering from muscular dystrophy, the diagnosis usually is clear.

Hyperthyroidism in children responds well to treatment with antithyroid drugs, but usually control is maintained only while the antithyroid drug is being given. In my experience prompt recurrences after treatment is stopped are the rule, and the more severe and typical the hyperthyroidism the less apt antithyroid drugs are to effect permanent control of the disease. The choice of definitive treatment lies between administration of radioiodine and preparation with an antithyroid drug followed by subtotal thyroidectomy.

In young children, subtotal thyroidectomy is a satisfactory means of controlling hyperthyroidism, but, because of the small size of the larynx, operation entails a slightly increased surgical risk. In the event of postoperative edema of the larynx, or paralysis of even a single vocal cord, tracheotomy may be necessary. In the hands of experienced thyroid surgeons, this complication should be rare, but in children under ten years of age it is a distinct hazard. Recurrences are fairly common if radical subtotal thyroidectomies are not performed, and if they are, the incidence of hypothyroidism is high. In a series of 21 patients treated by partial thyroidectomy at the Cleveland Clinic Hospital there was recurrent hyperthyroidism in five, and four were rendered hypothyroid.

Another disadvantage of thyroidectomy in children is that regardless of how the incision is made keloids usually develop. For the first year or two these keloids may be disfiguring, but eventually they flatten out into broad and oftentimes conspicuous scars, so that cosmetically, thyroidectomy is not so satisfactory in children as it is in adults.

Administration of radioiodine is a much simpler and probably safer way of treating hyperthyroidism in children. In the past ten years, we have treated

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22 children in this way, and in the majority of cases, doses as small as 4 or 5 mc. controlled the hyperthyroidism. In this series, in one patient recurrent hyperthyroidism developed and three patients became hypothyroid.

Since from 80 to 90 per cent of the radioiodine is concentrated in the thyroid, relatively little radiation is received by the rest of the body. For example, after a dose of 4 mc. given to a girl with Graves' disease with a high uptake of I^{131} in the thyroid, the amount of radiation received by the ovaries is on the order of that received in an ordinary gastrointestinal series of roentgenograms. In order to have any effect on menstruation, doses of several hundred millicuries are required as compared to the four or five employed in Graves' disease.

To date there have been no reported cases in which thyroid carcinoma has developed. Experimental work on animals suggests that radiation per se is not carcinogenic in the thyroid unless thyroid function is depressed and the output of thyrotropic hormone is increased. Under these circumstances, radiation can be carcinogenic in animals, but complete protection against the development of benign or malignant tumors of the thyroid of animals can be obtained by feeding the animal desiccated thyroid, and suppressing the abnormal stimulation that otherwise comes from the pituitary.[4] If hypothyroidism develops after treatment with radioiodine it is therefore important that desiccated thyroid be given to maintain normal thyroid balance.

On the basis of all clinical and laboratory evidence now available it would seem that the risk of inducing a fatal carcinoma of the thyroid in a child by giving small doses of I^{131} is considerably less than the intrinsic risk of thyroidectomy.

5. *Cancer of the thyroid.* Although cancer of the thyroid is not common in children, I have, during the past 20 years, treated 18 children who had thyroid carcinoma. Seventeen of the neoplasms were papillary carcinomas or follicular variants of the papillary which behave in exactly the same way as the papillary carcinomas. These tumors are not encapsulated, but involve the surrounding thyroid tissue and metastasize predominantly to regional lymph nodes. In children, papillary carcinoma may also metastasize to the lungs. The only nonpapillary carcinoma of the thyroid which I have seen in a child was in an 11-year-old girl, and it was an encapsulated angioinvasive carcinoma that grossly was indistinguishable from a benign solitary adenoma of the thyroid. The youngest child was three years old at the time of operation for carcinoma of the thyroid; the oldest was 15 years. The age distribution was uniform in the children between these ages. Eleven of the 14 children whose early histories were adequate had roentgen radiation around the head, neck, or thorax when they were infants; three had no irradiation. Six were given irradiation for thymic enlargement, two for eczema, two for enlarged adenoids or tonsils, and one for enlarged lymph nodes.

In only four of the 18 patients with cancer of the thyroid was a nodule in the thyroid the leading sign of the disease. In 14 cases, cervical nodes appeared before a change was detected in the thyroid, and in seven patients, even after the cervical nodes were palpable, the tumor in the thyroid was so small that it was not felt at the first examination. Thus, in nearly half of the patients the

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primary tumor was occult. In four patients, pulmonary metastasis occurred before the presence of the thyroid nodule was noticed. Delay in treatment after observation of the first sign of the disease varied from 1 week to six years, but did not seem to have as much influence upon the prognosis as one might expect. Five patients were operated upon less than six months after the first sign of the disease was noted; four of them are well, and one at present has residual disease. Five were operated on more than three years after the first sign of the disease; three of them are well, and two have residual disease. The period of follow-up in the two groups averages four and one-half and five years, respectively. Each of four patients who had pulmonary metastasis before operation had metastasis before the nodule in the thyroid was noticed.

In two patients it is possible that delay in treatment adversely influenced the course of the disease. In the first of these, a five-year-old boy, operation was delayed for a year after the lymph nodes were first noticed, and at the time of operation the primary tumor had invaded the trachea. This was the only locally inoperable cancer in the series. In the second case, the patient waited two years after the appearance of cervical lymph nodes, and roentgenograms of the chest then showed extensive pulmonary metastasis. It is impossible to determine whether earlier treatment would have avoided this complication.

Involvement of lymph nodes was more extensive than in adults. Eleven of the 18 patients had 20 or more nodes involved, four had from 10 to 20, two had from 5 to 10, and it was only in the case of the angioinvasive carcinoma that no cervical nodes were involved. Thus, in contrast to the findings in adults, in whom only 65 per cent of the papillary carcinomas metastasize to regional lymph nodes, all of the papillary carcinomas in this series of children had so metastasized at the time of operation.

The type of papillary carcinoma of the thyroid which occurs in children appears to be susceptible to control by feeding desiccated thyroid, as evidenced by the results of treatment of five patients in this series. The pituitary's output of thyrotropic hormone is suppressed by thyroid and, in the majority of cases this results either in failure of the tumor to grow, or in actual involution of the existing tumor. In view of the endocrine sensitivity of these tumors, it seems unwise to subject children with papillary carcinomas to any form of therapy, such as treatment with I^{131}, that may induce hypothyroidism, and thereby stimulate the tumor to grow.

The 18 children in this group have been followed up to 20 years since operation, an average follow-up period of more than five years. Only four patients have had recurrences in the regional lymph nodes and none has had recurrence in the thyroid area. Three of the four recurrences took place within a year of the first operation and after simple removal of the involved nodes there has been no further recurrence. The operations that have been performed have resulted in no severe dysfunction or deformity. In the 16 operable cases there has been only one case of permanent tetany, and no permanent tracheotomies have been necessary. Most of the operations were done through wide transverse thyroidectomy incisions, and in no case was the sternocleidomastoid muscles resected or the contour of the neck altered.

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Sufficient time has now elapsed to make it clear that the combination of an adequate, nonmutilating operation that removes all of the grossly involved thyroid and all of the grossly involved groups of nodes, together with continuance of treatment with desiccated thyroid suffices to prevent local recurrence of the disease. Moreover, distant metastasis has not taken place after operation for any of the operable papillary tumors in this series. Seventeen of the 18 patients are living and none have evidence of recurrence in the neck. The one patient who died had been treated elsewhere by total thyroidectomy, bilateral radical neck dissection, and I^{131}. He came to us with advanced pulmonary metastasis and so much cyanosis and dyspnea that he could not take full doses of thyroid. The four children who had pulmonary metastasis before operation have done well and in each case the metastasis has regressed or has been held in check by feeding of desiccated thyroid. The one child with a nonpapillary, angioinvasive carcinoma is living seven years after operation with no local recurrence but with metastasis to bone. From the results of this form of treatment it appears that it is not necessary to perform mutilating radical neck dissections on children in order to insure protection against local recurrence and systemic spread of papillary carcinoma.

Summary

1. Diffuse nontoxic goiter in children usually is the result either of hypofunctioning hyperplasia of the thyroid or variations of struma lymphomatosa. In either case the patients should be treated by feeding of desiccated thyroid rather than by iodine.

2. Nontoxic nodular goiter is rare in children. Its growth is best prevented by feeding of desiccated thyroid, and can sometimes be corrected by such feeding.

3. Solitary nodules should be removed because of the high incidence of carcinoma in such nodules in children.

4. Graves' disease in children can be treated by subtotal thyroidectomy following preparation with antithyroid drugs or, better, by administration of small doses of radioiodine.

5. Most carcinomas of the thyroid in children are papillary and metastasize to cervical nodes. In three fourths of the cases the enlarged nodes were observed before the thyroid tumor was noticed.

6. Most children with papillary carcinoma of the thyroid can be adequately treated by operations performed through a transverse thyroidectomy incision, which neither deforms the neck nor interferes with the function of its muscles.

7. Eleven consecutive patients having operable papillary carcinoma of the thyroid with no evidence of pulmonary metastasis have been treated in this way and are free of disease up to 20 years following operation.

8. The feeding of desiccated thyroid inhibits the growth of most of the carcinomas of the thyroid that occur in children, and should be given *routinely and indefinitely* after thyroidectomy to all patients operated upon for cancer.

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9. For most of the types of goiter that occur in children today, feeding of desiccated thyroid is a much more effective remedy than is iodine.

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