Sporadic goitrous cretinism

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SPORADIC GOITROUS CRETINISM

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Submitted in Partial Fulfillment for the Degree of Doctor of Medicine

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INTRODUCTION

This paper has been written in an attempt to review some of the literature on sporadic goitrous cretinism and to present a case study of a patient with suspected sporadic goitrous cretinism. The physiology of normal and abnormal thyroid hormone synthesis has been discussed and possible location of enzymatic defects has been delineated.

Although many cases of sporadic or non-endemic goitrous cretinism have been discovered in the past, it has only been possible in the last several decades to more closely analyze the exact etiology of these cases. The great advances in the use of radioactive isotopes and the steps taken in biochemical research and application have facilitated the study of these problems.

Much work remains to be done. There is not as fine a dividing line between the various etiologies as is desirable, but before we can devise better diagnostic methods we must come to better understand the thyroid gland and the synthesis of thyroid hormone.

-1-
The history of sporadic cretinism actually dates back to 1897 when Osler\textsuperscript{30} reported sixty cases throughout the United States, but introduction of the concept of inborn errors of metabolism was introduced in 1908 by Garrod.\textsuperscript{10} He introduced the term 'inborn errors of metabolism' to describe biochemical abnormalities which were genetically determined, present throughout life and relatively non-lethal. He also suggested that it would be ultimately possible to attribute the biochemical aberrations found in these conditions to specific enzyme defects. He originally considered four types - albinism, alcaptonuria, cystinuria and pentosuria. More recent investigation has confirmed Garrod's work and has extended his ideas to a remarkable extent. One of the most fruitful extensions has been to delineate certain types of thyroid disease because they are hereditary, congenital, persist through life and are relatively non-lethal.

Pendred\textsuperscript{31} in 1896 described a condition in which the afflicted person is usually euthyroid, but may be hypothyroid in association with goiter and deafness. The goiter usually appears in childhood and histol-
ogically shows marked hyperplasia and has a marked tendency to recur after partial thyroidectomy. The associated deafness is present from birth, is usually symmetrical and may be severe enough to cause deaf mutism. In this condition, it is probable that a genetic defect at the same locus is responsible for both deafness and thyroid enzyme defect.

In Osler's sixty cases, seven had goiters, and in one family, three of five children had a goiter associated with cretinism. Subsequently, numerous instances of hypothyroidism and goiter have been reported. Hamilton et. al.\(^1\) in 1943 reported the occurrence of goiter in two patients with hypothyroidism in which the uptake of \(^{131}\)I was elevated. In 1946, Lerman, Jones and Calkins\(^2\) studied two hypothyroid brothers who lived in a non-goitrous region and who had developed goiters at five and twelve years. When removed, the thyroid glands showed marked hyperplasia. In 1950, Stanbury and Hedge\(^3\) published a report of their now famous family of goitrous cretins. They described three siblings with goiter, all of whom were hypothyroid. These patients' thyroid glands rapidly accumulated large amounts of radiiodine which was promptly discharged following administration of oral potassium
thiocyanate. It was concluded that the siblings' thyroid glands could trap iodine normally but could not convert it to thyroxin. Hubble in 1953 described four siblings with hypothyroidism and goiter in one family. In the particular patient studied, the uptake of $^{131}$I was elevated and thyroxin was isolated from the thyroid gland after its removal. The thyroid gland showed marked hyperplasia. In 1953, McGirr and Hutchinson reported studies on twelve non-endemic goitrous cretins. Seven were closely related, two were members of another family and three were unrelated to either family or to each other. The thyroidal $^{131}$I studies in most of the patients were elevated. These investigators concluded that the thyroid glands of their patients were capable of incorporating iodine into an organic form and releasing it from the gland, but that the released compound was not normal thyroxin.

Although different in some respects, the thirty-two cases reported through 1954 had a number of features in common. In nineteen there were multiple familial incidences suggesting genetic transmission. Uptake studies revealed that the thyroid glands in those studied were capable of trapping normal or increased amounts of radiiodine. In no instance did any of the...
patients live in iodine deficient areas. Intense hyperplasia was revealed in all the thyroid glands removed.

Since 1954 many additional case reports have been presented revealing a multiplicity of possible defects in the thyroidal synthesis of thyroxin.
NORMAL THYROID PHYSIOLOGY

Iodine is absorbed by the gastrointestinal tract and enters the iodine pool. This pool is composed largely of the extracellular fluid compartment or approximately thirty-five percent of the body weight. The salivary glands and gastric glands as well as the thyroid gland concentrate iodine. The initial step in the synthesis of thyroid hormone is selective accumulation of iodine in the thyroid gland. This process is called the "iodine pump." It requires energy and fails in thyroid tissue under anaerobic conditions. The normal thyroid maintains a concentration of inorganic iodide which is twenty to thirty times that of serum.

Similarly the concentration of iodide in the salivary gland is many times that of the serum. The iodide concentration is higher for serous (parotid) than for mixed saliva and is lower when the salivary secretion rate is raised. The gastric mucosa concentrates iodide to approximately the same degree as the thyroid and salivary glands and is quite independent of the acidity of gastric secretion. Removal of iodide from the iodine pool occurs primarily by urinary excretion and by iodination of proteins in the thyroid.
gland to form thyroid hormones.

The thyroid trapping mechanism is obscure but is probably enzymatically controlled and oxygen dependent. The presence of sulfahydryl groups is apparently extremely important as sulfahydryl inhibitors inhibit iodine trapping. Perchlorate, KSCN and thiourea derivatives, to a lesser extent, are prominent in this group. KSCN in addition causes discharge of iodide from the gland if elemental iodide fails to be converted to elemental iodine. Conversely, thyrotropic hormone from the pituitary gland enhances the trapping of iodide. Immediately after entrance of iodide into the gland it is converted to iodine by an enzymatic oxidation process. Cytochrome oxidase and peroxidase have been suggested to promote this oxidation. However, certain antithyroidal agents prevent the oxidation of iodide. Thiouracil will prevent this process and it is known that it is a peroxidase inhibitor but doesn't inhibit cytochrome, so for this reason peroxidase is thought to be the involved enzyme.

Following formation of elemental iodine, iodination of tyrosine molecules, first at the three and then at the five position occurs very rapidly to form monoiodo-tyrosine. Next, coupling of the various iodinated
tyrosines results in release of aminopropionic acid and formation of iodinated thyronines. The coupling may be enzymatically controlled or it may occur spontaneously, in which case it would be dependent upon spatial arrangement of the tyrosines in the globulin molecule. It is thought that the coupling of two molecules of diiodo-tyrosine must be an oxidative process because it has been demonstrated to occur chemically in association with a hydrogen peroxide solution. Coupling of two molecules of diiodotyrosine forms thyroxin, a potent thyroid hormone recognized since 1915 by Kendall. Coupling of a molecule of mono-and diiodotyroxine forms the more active 3:5:3' triiodothyronine, but this compound is synthesized in only small amounts. These substances are then stored in the follicle as thyroglobulin. Thyroglobulin does not normally escape from the follicle, but is acted upon by protease and peptidase enzymes with release of the iodinated tyrosines and thyronines. Following digestion of thyroglobulin in the follicle by proteolytic enzymes, thyroxin and 3:5:3' triiodothyronine diffuse into the blood. In contrast, iodinated tyrosines are not normally found in the peripheral blood, not even in thyroid vein blood.

Roche et al. have demonstrated a dehalogenase which dehalogenates "free" mono- and diiodotyrosine but
not thyroxin or 3:5:3' triiodothyronine. The liberated iodine may then be utilized by the thyroid for the iodination of thyronine. The enzyme responsible is found in the thyroid, liver and kidney.

Protein binding occurs following the release of the active principles from the thyroid gland into the bloodstream. Three separate normally occurring proteins are responsible. In 1952, Gordon first described binding of thyroxin by a moiety traveling on electrophoresis between alpha-1 and alpha-2 globulin. Subsequent workers have named it the "thyroid binding protein" or "T.B.P." T.B.P. is elevated by estrogen therapy, in pregnancy, in hypothyroidism, the newborn period and in liver disease. It is decreased by androgen therapy. Albumin is the second protein known to bind iodinated thyronines, principally triiodothyronine. In 1958, a third previously unrecognized serum protein was found but has not been completely described. It had a high affinity for thyroxin but no affinity for triiodothyronine.

The mean biologic half life in serum for thyroxin and triiodothyronine is 5.9 and 3.2 days respectively. These rates are accelerated in hypermetabolism and are decreased in hypothyroidism. Thyroxin and triiodothyronine are metabolized by the kidneys and liver. Only ten to fifteen percent of the circulating organ-
ically bound iodine is excreted in the feces. Both thyroxin and triiodothyronine are metabolized in the cells by deshalogenation, deamination, decarboxylation and conjugation primarily as the glucuronide. An enzyme capable of conversion of thyroxin to triiodothyronine has been shown in rat kidney by Larson and so it has been suggested that triiodothyronine is the "active" principle of the thyroid hormone.

IODINE AND THYROID METABOLISM

CLINICAL FEATURES

Infants with familial goitrous cretinism have thyroid glands incapable of converting iodine to thyroid hormone because of an inborn defect at one step or another in the pathway of synthesis. These infants show varying degrees of hypothyroidism from an early age, but the thyroid gland may not become enlarged until they are older. 49

The common symptoms and signs of hypothyroidism such as weakness, lethargy, dry skin and hair, puffy eyes, paresthesias, hoarseness, constipation and cold intolerance are well known. Children with hypothyroidism often have different presenting findings depending upon the severity of their disease. Severely affected infants are inactive, feed poorly and are constipated. The skin is pale, cool and has a dusky appearance. Sweating is absent. The tissues may feel loose and flabby. Unless treated, the infant usually fails to grow and develop normally. The body is short and infantile in proportions. The head seems large for the body. The facies is characteristic. The forehead is low and the base of the nose is broad and flat, so that the eyes are wide apart. The eyelids are a little puffy and wrinkled. The lips are thick, the
mouth half open and a thick tongue usually protrudes slightly. The voice is often deep and hoarse. The teeth appear very late. The abdomen is large and pendulous, with poor muscle tone and an umbilical hernia is often present. The hair is sparse, coarse and dry.

These children are content to sit or lie quietly for long periods of time and are little interested in their surroundings. The ability to sit and walk is acquired late; speech is especially late and in some cases no more than a few words are ever learned.15

In the older patient, the characteristic facies is one which is puffy, expressionless at rest, pale, slightly yellow and at times shows a malar flush. The patient often has an untidy appearance which is probably due to a lack of interest in his personal appearance. Means24 and Lloyd23 have described changes in the voice and speech which are pathognomonic of myxedema. The voice is husky with a low pitch and an increased catarrhal or nasal quality. Deafness is a common symptom of hypothyroidism and this is usually perceptive in type.17 The blood pressure may be low or normal and the pulse rate is not necessarily slow. The cardiac output is low. It is thought that if the heart is enlarged it is due to pericardial effusion rather than cardiac dilatation.11 Alterations in the function of the central
nervous system are probably more widespread than usually recognized. Loss of memory, mental lethargy, and complacency are common. Headache, auditory hallucinations, psychosis, tinnitus and vertigo may be present. Paresthesia may occur in a high proportion of patients with hypothyroidism. Constipation may in some cases be due to actual enlargement of the colon as demonstrated by roentgen examination. Some female patients have amenorrhea but the majority have menorrhagia. A goiter is commonly present in familial cretinism because as the levels of circulating thyroid hormone falls, increased TSH is produced thus causing hypertrophy and hyperplasia of the gland in an attempt to compensate. In typical cases, the attempt to increase thyroid hormone levels clearly fails and the above manifestations appear.
ETIOLOGY

In a recent study by Childs and Gardner, an hereditary tendency in the common type of sporadic cretinism was sought. Although there seemed to be such a tendency, they found that a familial prevalence was distinctly uncommon. Consanguineous mating was barely more common among parents of sporadic cretins than among parents of normal children. In the more rare sporadic goitrous cretinism, there is a marked contrast. In this condition, familial prevalence and consanguinity of the parents are common. The familial tendency was first recognized by Osler who commented on the occurrence of consanguinity. Accordingly, it has been postulated that the conditions leading to sporadic goitrous cretinism may be due to an appropriate "inborn error of metabolism," that they must be genetically determined, and that biologically, they are anomalies of the type originally described by Garrod.

Particular support for the theory of hereditary transmission of one form of sporadic goitrous cretinism comes from the remarkable group of itinerant 'tinkers' located in Western Scotland by Hutchinson and McGirr.
Their family tree has been traced back for 160 years. (See Figure 2.) The original male member of the family, Y, came from Ireland and married a McX, his full cousin. A female Y in a later generation also married a McX, her full cousin, and the amount of consanguineous marriages in the group is remarkable. It is thought that the consanguinity was encouraged by the increased isolation of the 'tinker folk' from the other inhabitants of the country because of their unique and self-demarcated mode of life.

Ten goitrous cretins are known to have appeared among thirty-one persons in four sets of siblings. In addition, there have been four cases of Werdnig-Hoffmann paralysis.

The pedigree of this 'tinker' family satisfies three of the criteria of simple recessive inheritance. 32

(1) The parents of affected persons were normal to outward appearance. (2) There was a striking familial prevalence - in three of four sets of siblings there was more than one cretin. In recessive inheritance the ratio of affected to normal is 1:3. The ratio is exceeded in this family, but the total number of normal siblings was probably not accurately known. (3) All affected children were the offspring of consanguineous
Two additional criteria of autosomal recessive inheritance are not satisfied. (4) The offspring of marriages of affected persons with normal persons are usually normal. (5) The offspring of two affected persons are all affected.

The information provided by this family tree even at present strongly supports the opinion that the enzyme defect in these 'tinker' patients is genetically determined and that it is transmitted by a single autosomal recessive gene. It is a reasonable assumption that these cases of goitrous cretinism described in Scotland with frankly abnormal clinical features, namely, thyroid enlargement and hypothyroidism and biochemical evidence of a gross metabolic defect were homozygous.

In one of the Dutch cases of sporadic goitrous cretinism, the proband had several relatives who had a detectable but less obtrusive biochemical abnormality and little or nothing in the way of clinical features apart from goiter. They were, in all likelihood, heterozygous. If the disease is the result of a single enzyme defect and if the enzyme is dependent upon a single recessive gene, the gene must be incompletely recessive for defects to occur in the heterozygous.
state. Such a hypothesis is in keeping with the modern genetic conception that a defect transmitted by an autosomal gene as a recessive, in the heterozygous state, may produce minor but detectable metabolic abnormalities although the florid symptomatology of the homozygous state is naturally lacking.²⁹

There is no evidence that the gene involved in goitrous cretinism is ever sex-linked because in all family series studied there always seems to be a male to female ratio of cases approximating 1 to 1.²⁸ There does seem to be a greater percentage of Caucasian cases of sporadic goitrous cretinism than Negro cases even when differences of population are considered.⁴
FAMILY TREE OF SCOTTISH TINKERS

TYPES OF INBORN ENZYMATIC OR METABOLIC DEFECTS

The major cause of familial goitrous cretinism is a genetic abnormality leading to faulty metabolism in the thyroid gland of thyroid hormone synthesis. Defects in the thyroid gland seem to be present because of enzymatic abnormalities in the major pathways of iodine metabolism. There are other causes of sporadic non-endemic goitrous cretinism, however. Defective serum binding of thyroxin can lead to this form of cretinism. An inability of the body cells to metabolize thyroid hormone or hormones is listed as a factor in the etiology of this disease also.

Since the trapping of iodine is the first step in the production of thyroid hormone, this should be the first subject in a report of defects in iodine metabolism. Federman et. al.\(^9\) in 1958 reported an apparent congenital defect in the trapping mechanism for iodine. This occurred in a child of fifteen months of age who had both goiter and hypothyroidism. In this patient, the thyroidal \(^{131}\text{I}\) uptake remained zero even after the administration of forty units of T.S.H. in divided dosage over the previous four days. With such a defect the thyroid gland was unable to concentrate iodide.
The salivary glands and gastric mucosa, which, like the thyroid are derived from the primitive gut and which are normally able to concentrate iodide, share in this inability. The exact cause of this defect is not known. It is apparently quite rare.

The inability to oxidize iodide, the second step in iodine metabolism, has also been recognized as an inherited error of metabolism. Stanbury and Hedge\textsuperscript{38} in 1950 reported the first cases of sporadic cretinism in which such a specific defect was found. The investigators reported from Boston an investigation of four cretinous children in one family. The parents were first cousins and their first three children were not hypothyroid nor did they have goiters. The four succeeding children were all goitrous cretins. The defect in these individuals was identified because the \textsuperscript{131}I uptake was high and rapid, but after administration of KCNS the gland immediately discharged the \textsuperscript{131}I. The protein bound iodine remained low. They concluded that the thyroid gland couldn't convert iodide to an organic form because of failure in the conversion of iodide to iodine. It is believed that the defect present is related to the peroxidase enzyme which is probably responsible for the normal conversion of iodide to -20-
iodine. Almost no organic iodide can be demonstrated in the thyroid glands of these patients when analyzed by chromatography. Some investigators believe that the existing defect is not in the conversion of iodide to iodine but due to an enzymatic defect in the process of organic binding of iodine with the tyrosyl residues of thyroglobulin. Several studies have subsequently been reported on goitrous individuals with the same defect; some have associated hypothyroidism and some do not.\textsuperscript{9, 36, 35, 6}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{FIGURE 3}
KSCN administration produces immediate discharge of I\textsubscript{131} when a defect in I\textsubscript{1} \rightarrow I\textsubscript{2} is present. Normally KSCN produces only minor discharges.
\end{figure}

A specific inability to halogenate tyrosines in the presence of elemental iodine has not been definitely described. However, Haddad and Sidbury\textsuperscript{12} have studied a congenital goitrous cretin who may have had such a defect. This patient avidly accumulated iodide and discharged it secondary to KSCN administration. Although they utilized an \( \text{H}_2\text{O}_2 \) generating system while incubating thyroid homogenates of the patient's gland with \( \text{I}_\text{131} \), these workers were unable to demonstrate the formation of iodinated tyrosines. This was in contrast to the effect observed on homogenates of normal glands. In a patient unable to iodinate tyrosine in the presence of elemental iodine, KSCN would discharge iodide from glands as the equilibrium of \( 2\text{I}^- \leftrightarrow \text{I}_2 \) would shift to the left as KSCN removed the product on this side of the equation.

In patients with defective organification of iodine, as in patients with inability to convert iodide to iodine, there is a rapid and early uptake of \( \text{I}_\text{131} \) but with spontaneous release of \( \text{I}_\text{131} \) to low levels at twenty-four hours. Also in these patients administration of KSCN results in considerable discharge of \( \text{I}_\text{131} \) from the thyroid gland.

The next step in the synthesis of thyroxin where
an enzymatic defect may occur is the coupling of
diiodotyrosine in the normal formation of thyronines.
The inability to form iodinated thyronines from iodinated
tyrosines in individuals with congenital goitrous cretin-
ism was first reported by Stanbury et al. Mosier, 42
Blizzard and Wilkins subsequently reported two similar
patients. In 1957, Werner, Block, Mandel and Kassenaar 46
reported studies done on a five-year old Negro girl with
a congenital goiter and mild hypothyroidism. She had
marked elevation of PBI ranging from seventeen to twenty-
eight micrograms per 100m. Uptake of I_{131} was also mar-
kedly elevated on several occasions. Paper chromato-
graphic studies on the blood following I_{131} administra-
tion revealed the presence of monoiodotyrosine, diiodo-
tyrosine, thyroxine and triiodothyronine in equal amounts.
When the thyroid was removed nine months after the
chromatographic studies, only small amounts of thyroxine
and triiodothyronine were found. Normal deshalogenase
activity was present. They concluded that although
some thyroxine could be synthesized there was a block
in the oxidative coupling of diiodotyrosine and that
this block was due to the lack of a specific oxidation
enzyme.

In both reports, there was no triiodothyronine or...
thyroxin demonstrable in the digested thyroglobulin of the gland. Werner et. al.⁴⁶ have reported what may have been a similar defect. Their case, however, differed in having a high protein bound iodine and excessive amounts of circulating iodotyrosines. This occurred despite adequate dehalogenation of diiodotyrosine by thyroid tissue removed from this patient. These discrepancies remain unexplained.

Generally in cases of cretinism due to failure of iodotyrosyl coupling, it can be shown that uptake of I₁₃₁ is very rapid and reaches almost 100%. KSCN administration does not cause release of large amounts of administered I₁₃₁. Propylthiouracil, however, causes tremendous release of iodine not organically bound.⁴⁸

The next step in normal thyroid metabolism after formation of thyronine and the formation of thyroglobulin is storage and later release of the active hormone from the thyroglobulins by protease or peptidase enzymes. Absence of one of the protease or peptidase enzymes responsible for thyroglobulin digestion would be expected to produce goiter and/or hypothyroidism. Hamilton et. al.¹³ have reported two goitrous hypothyroid individuals whose thyroid glands contained normal or near normal amounts of thyroxin (11-16%) as
determined by chemical analysis. Their interpretation was that these individuals had a defective protease or peptidase system.

Other metabolic errors of syntheses may be associated with abnormal formation or release of thyroglobulin. The congenital goitrous cretins mentioned previously with inability to couple iodinated tyrosines conceivably may have steric aberrations of the thyroglobulin molecule rather than specific coupling enzyme defects.\(^7, 8, 47\)

Another enzyme found in normal thyroid glands but absent in certain goitrous cretins is the enzyme responsible for dehalogenation of excess iodotyrosine, thus conserving both the iodine and probably also the tyrosine for reutilization in the production of thyroid hormone. In 1955, Stanbury, Kassenaar, Meyar and Terpstra\(^39\) reported studies carried out on an adult treated with thyroid powder since he was nine months of age. A younger sibling also had a goiter at birth and required thyroid medication at about two years of age. The clinical signs of hypothyroidism were present and the protein bound iodine was 0.5 micrograms per 100 ml. The uptake of \(I_{131}\) was rapid reaching seventy-four percent in two and one-half hours and then at twenty-four hours only thirty-six percent of the administered
I_{131} remained. I_{131} in the blood disappeared rapidly for seventy minutes but then rose again and reached a maximum level at twenty-four hours. Subsequent paper chromatographic studies showed labeled monoiiodotyrosine and diiodotyrosine as well as triiodothyronine and thyroxine in the serum. A thiocyanate test done on the goitrous sibling revealed a rapid uptake of I_{131} but no discharge of radiiodine followed KSCN administration. Monoiodotyrosine and diiodotyrosine labeled with I_{131} administered intravenously were found to be excreted in the urine unchanged as compared to fifteen normal individuals who almost completely deiodinated the administered compounds. Then they studied the ability of thyroid slices from the younger sibling to deiodinate labeled diiodotyrosine and found no deshalogenase activity present in the gland. They thus concluded that in these patients there was an inability to deiodinate monoiiodotyrosine and diiodotyrosine completely, with these substances subsequently being excreted in the urine. Therefore, the continuous loss of thyroid hormone precursors, namely iodine and tyrosine, resulted in hypothyroidism and goiter.

In normal rats and humans, the deshalogenating enzyme responsible for removing iodine from tyrosine and probably thyroid hormone is also present in tissues.
other than the thyroid. Stanbury et al. found that when diiodotyrosine is introduced into the blood it is rapidly degraded. In the rat the blood concentration falls to ten percent of its initial value within half an hour. In myxedematous humans, Albert and Keating found the concentration to fall to one percent of its initial value in eight hours. The injected diiodotyrosine was excreted partly intact, partly as iodine and partly as degradation products. It is only partially precipitable with the serum proteins. Little is known about the peripheral metabolism of monoiodotyrosine. Thus it can be seen that in patients with a defect in the thyroid deshalogenase enzyme there is also a generalized deshalogenase enzyme defect in the body and not limited to the thyroid gland.

Several other patients with this defect have since been reported, and, as in the members of a family with goiter and hypothyroidism reported by McGirt and Hutchinson, had diiodotyrosine in their blood and urine. This etiology of sporadic goitrous cretinism is probably one of the most common.

Increased thyroxin binding protein has been considered as a possible cause of sporadic goitrous cretinism. Beierwaltes and Robbins presented a family in which it
was found that the PBI was elevated in two members. The father had a PBI which ranged between 11.8 and sixteen μg. percent but with no symptoms of thyrotoxicosis. The BBI also was high ranging about thirteen μg. percent. A subnormal $\text{I}^{131}_3$ triiodothyronine erythrocyte uptake was present, however, suggesting that the serum PBI elevation was related to increased affinity of the plasma proteins for thyroid hormone. This suspicion was confirmed by these investigators by the finding of an increase in thyroxin-binding capacity of thyroxin binding protein by reverse-flow serum electrophoresis. No abnormality was detected in thyroxin binding to albumin or prealbumin. Although the extra thyroidal organic iodine pool was expanded to roughly the same size as that found in patients with untreated thyrotoxicosis, the degradation rate in micrograms of thyroxin per day was within the normal range. The finding that one of this man's three children also had elevated serum PBI and BBI levels, a subnormal $\text{I}^{131}_3$ triiodothyronine erythrocyte uptake and an elevated TBP capacity constitutes evidence that the abnormality is familial and could conceivably be hereditary. Although the patients presented in this work were not cretins or even hypothyroid, such an etiology
could conceivably cause these diseases, and possibly cases with this problem will be discovered.

Another possible, although not proven, etiology for hypothyroidism and cretinism is complete lack of thyroxin binding protein. Tanaka and Starr have reported a patient in which there was an absence of thyroxin binding protein. The patient was a thirty-eight year old white male who had no symptoms of hypothyroidism and no thyroid enlargement was present. Laboratory work showed a protein bound iodine of three micrograms percent, a serum cholesterol of 308 mg. percent and a total serum protein of 7.3 grams percent with normal fractions by electrophoresis. Several determinations of the binding of radioactive thyroxine indicated an absence of thyroxin binding globulin. An attempt was made to determine binding of radioactive tetraiodothyropropionic acid also with results indicating an absence of thyroxin binding globulin. This man was evidently producing sufficient thyroxin and enough was reaching the tissues to maintain normal metabolism yet this too may someday prove to be responsible for certain cases of sporadic cretinism.

An inability to metabolize thyroid hormones has also been postulated as a possible cause of sporadic
goitrous cretinism. In a case presented by McGirr et al., it was found that their patient did not respond to dry thyroid medication but responded dramatically to L-triiodothyronine. This patient was a girl aged four years and three months. Her development had been slow and she was typically cretinous with thick ugly features, large tongue, protuberant abdomen, and she was obviously mentally defective. Bone age was less than one year. Her plasma bound iodine was 1.8 micrograms percent. Radioactive I\textsubscript{131} studies revealed a twenty-four hour uptake by the thyroid gland of only fourteen percent of the administered dose. Treatment was started with dry thyroid and the dose was rapidly increased to twenty grains daily and subsequently reduced to five grains daily. While on this medication, she changed from a sluggish somnolent state to one of irritability and aggressiveness. She lost 0.7 Kg. in weight and her height increased four cm. Her cretinous appearance did not improve. After about four months of treatment with dry thyroid, she was started on L-triiodothyronine in a daily dose of 100 micrograms. In eighty-two days of treatment with this drug she improved dramatically. She lost her cretinous features and expressionless facies. She began to speak in sentences, her
weight increased by 2.9 Kg. and her height increased by seven cm. The dose of triiodothyronine was finally lowered to forty micrograms daily and she improved so that she was normal for her height and weight and in keeping up with her own age group in school work.

From the findings above, McGirr and coworkers postulated that the peripheral deiodination of thyroxin to triiodothyronine is effected by enzymes; absence or deficiency of such enzymes might lead to a state of partial hypothyroidism which would not be cured by dry thyroid or L-thyroxin but only by triiodothyronine.

Still another cause of sporadic goitrous cretinism is defective thyroid hormone. DeGroot, Pastel, Litvak and Stanbury recently reported studies done on a patient with hypothyroidism and goiter with a protein bound iodine of two micrograms per 100 ml. and a twenty-four hour radiiodine uptake of fifty-seven percent. Intravenously administered radioactive iodine labelled thyroxin and diiodothyronine were metabolized normally. KSCN failed to cause a discharge of trapped $^{131}I$. Labelled $^{131}I$ which appeared in plasma was only partially extractable with acid butanol. The butanol extractable iodine proved to be thyroxin and triiodothyronine and the insoluble fraction was an abnormal

-31-
iodinated protein having the mobility of albumin. They concluded that this patient was either forming an abnormal thyroprotein in the gland or that abnormal fractionation of thyroglobulin with release of metabolically inactive iodinated protein into the serum was occurring.

Normally, butanol at low pH, extracts all of the iodine in the serum. The non-butanol extractable compound has not been completely identified. A similar substance has also been found in the blood of patients with long standing nodular goiter without hypothyroidism and in some patients with cancer of the thyroid.
DIAGNOSIS

Most standard laboratory procedures are unsatisfactory for establishing the type of sporadic goitrous cretinism present and most are unsatisfactory even for an early diagnosis of cretinism. The determination of the basal metabolic rate in infants is not practicable. Determination of the serum cholesterol has been used as a laboratory test for hypothyroidism; however it may even be normal in patients who have no measurable circulating thyroid hormone at all. Serum cholesterol levels are even more variable in infants and children than they are in adults. Determination of creatinine excretion is of relatively little value, since it is difficult to obtain complete urine collections, especially from female infants. Bone age also has a wide range of normal, so it does not necessarily supply a definitive diagnosis. Radioactive iodine uptake may be high or normal in severe cretinism. The butanol extractable iodine or BEI is probably the best standard test for the early detection of congenital hypothyroidism and the most valuable tool for the evaluation of the adequacy of therapy. It does have the disadvantage of being a difficult laboratory analysis. The new erythrocyte
uptake of $\text{I}_{131}$ labelled triiodothyronine is said to be highly effective in the diagnosis of hypothyroidism as well as in gauging the adequacy of therapy especially when $L$-triiodothyronine is used. It doesn't, however, seem to have much more to offer than some of the tests already in use except possibly in simplification of method and avoidance of administration of radioactive materials to the patient. It is altered in abnormal pregnancy, anticoagulation therapy, liver disease, metastatic malignancy and paroxysmal atrial arrhythmia. ¹⁴

Diagnosis of specific defects in thyroid hormone synthesis depends largely upon radioactive iodine studies and chromatography of serum as well as homogenates of involved glands. Radioactive iodine uptake is usually high in congenital goitrous cretinism. Thyroid stimulating hormone exogenously administered usually has no effect probably because endogenous TSH is being produced maximally and the gland is responding maximally.

Absence of $\text{I}_{131}$ uptake, although characteristic of the patient with athyreotic cretinism, is compatible with an enzymatic defect in which the gland is unable to trap iodine. ⁹ In patients with a defect in the oxidation of iodide to iodine, there is a rapid uptake of administered $\text{I}_{131}$ which usually reaches maximum con-
centration in about two hours. If two grams of KSCN is then administered, it will produce a rapid discharge of $^{131}$I not oxidized to organic iodine and bound to tyrosine. Carbamide drugs will produce a similar block in thyroid synthesis. Surgical procedures are of help when an oxidative defect is present largely because they supply thyroid tissue with which chromatography can be accomplished. Chromatography reveals that no iodinated compounds are present in these patients' glands. Some individuals with defective biosynthesis at later steps may have rapid turnover of iodine, thus releasing large amounts of iodine into the iodine pool. This "free" iodine can be discharged from the thyroid gland thus resembling the iodine discharge which occurs secondary to KSCN administration, a repeat uptake without KSCN is necessary to eliminate the possibility of actual rapid release and turnover with an artificial artifact of dumping. 26

In patients with defective coupling of diiodotyrosine there is a high $^{131}$I uptake and an elevated PBI but chromatographic studies on the blood after $^{131}$I administration reveals monoiodotyrosine and diiodotyrosine. These precursors of thyroxin are normally present only in thyroid gland tissue. KSCN administration -35-
does not cause release of large amounts of $^{131}$I in these patients, but some discharge will be present. Propylthiouracil will cause release of large amounts of iodine in these cases.

In congenital goitrous cretinism with hypothyroidism, the protein bound iodine is usually low. If the defect is one of those associated with release of thyroglobulin or "thyroglobulin-like protein," the protein bound iodine may be normal or high. Also, in the presence of excessive circulating iodinated tyrosines, the protein bound iodine may be high if done by the alkaline precipitation method. However, this was not found by Stanbury and co-workers in their patients with a dehalogenase enzyme defect.\textsuperscript{39, 40} Since butanol extractable iodine measures primarily the calorigenically active thyroid hormone thyroxin, a discrepancy between the PBI and the BEI assists in classification of the enzymatic defect present. Such a discrepancy would indicate a circulating iodoprotein other than thyroxin. This would be the case in defective iodothyrosyl coupling and in dehalogenase enzyme deficiency when monoiodotyrosine and diiodotyrosine in large amounts are present in the blood. Complex circulating iodoproteins may be found in some patients with thyroiditis, thyroid
carcinoma, and secondary to irradiation of the thyroid as well as in certain ill defined disorders of the thyroid gland in which abnormal hormones are produced.
TREATMENT

The treatment of sporadic goitrous cretinism is the same as the treatment of cretins from any etiology. The primary aim of treatment is improvement of mental development as well as physical development. At present most work done by investigators in the field indicates a relatively poor outcome as regards mental development of patients with congenital hypothyroidism even though they received treatment which is considered adequate by many authors regarding early onset of therapy and dosage. Bruch and McCune\(^3\) concluded that the hypothyroid child reaches a plateau in mental development and that even large doses of desiccated thyroid were not effective in producing adequate mental development. They used 0.1 to ten grains daily in children whose age at initiation of treatment ranged from three months to eight years.

Many theories have been forwarded as to why results have been poor as far as mental development is concerned after treatment of cretinous patients. In most of the cases there is considerable delay before the onset of adequate therapy. If diagnosis of cretinism depends upon clinical signs, the obvious stigmata
must be present before a definitive diagnosis can be made. These stigmata take time to develop after birth. Therefore it is essential that the clinician maintain a high index of suspicion for such signs as newborn constipation, thick skin, large tongue, yellow skin and bizarre facies, and that these suspicions be confirmed by laboratory procedures.

The treatment of choice in sporadic goitrous cretinism has not been decided. Desiccated thyroid can be used with good results in most cases. A major problem exists in development of methods for guiding therapy. A fixed dose, prescribed as so many milligrams per kilogram or so many milligrams per square meter, cannot be used since there is considerable individual variation in the daily dose required to maintain a normal butanol extractable iodine level. A commonly recommended method for carrying out therapy is to gradually increase the dose of thyroid until toxicity is observed. This procedure seems unsatisfactory in many instances, however since behavior such as irritability has been interpreted as indicating excessive thyroid medication and dosage has been decreased even though subsequently the BEI was demonstrated to be far below the normal level.

Stevenson and Danowski\textsuperscript{43} studied the effects of thyroid
or thyroxin on the development of premature infants. They reported that thyroid in doses of more than 120 mg. per day were necessary for pharmacological effects in premature infants. They postulated that the thyroid gland produces and releases thyroxin at the same rate as in normal older persons and that this amount approximates the quantity included in two grains of thyroid daily. They concluded that medication for the hypothyroid child should be adjusted in accordance with this observation. In view of these findings, the medications for infants under one year with amounts up to 90 mg daily and for older children with amounts up to 180 mg. of desiccated thyroid daily seems reasonable.

The use of L-thyroxin has been advocated also by some workers in the field. There have been reported some complication from its use, however. Some patients seem to have a tendency to develop osteoporosis when it is used. Still other patients develop hypertension although it is only transient.

The method of increasing the dose of desiccated thyroid by Cooke and Man seems to be a good one. Small doses of thyroid, such as 15 mg., are given for two to three days and then, at intervals of four to five days increments of fifteen to thirty mg. may
be added so that doses of forty-five to ninety mg. may be attained in two or three weeks. It is their belief that the BEI should be maintained between five and seven micrograms percent, but it must be recognized that a maximum BEI is not attained for approximately two weeks after maintenance of thyroid therapy at a given level. Thus the BEI should be measured after two weeks of therapy, then at monthly intervals until a normal level is attained. It should be checked at three month intervals under one year of age and at six month intervals thereafter.

The use of triiodothyronine is rarely indicated. It is necessary in the case of defective peripheral enzymes necessary to deiodinate thyroxin. This is rare indeed.

Other patients with specific types of enzyme deficiencies may benefit by the use of high doses of potassium iodine. This is useful in cases in which iodine is lost from the body as in patients with defective deiodination of iodothyrosyl. These patients however, also can be treated with thyroid hormone replacement. This is probably easier and would reduce the tendency of the gland to hypertrophy and produce goiter but is more expensive.
CASE PRESENTATION

The patient studied was a forty-seven year old man (L. B. # 4-66-64) who was first seen at University Hospital in June, 1962. However, he was first diagnosed as having hypothyroidism in 1930 at age fourteen. Since that time he has taken thyroid medication "off and on" until he was sent to UNH for evaluation. During his stay at UNH in 1962 he complained of cold intolerance, easy fatigability, shortness of breath and ankle edema. Physical examination revealed a blood pressure of 140/84 with a pulse of 80. He was 5 feet 3½ inches tall and his intelligence was estimated to be considerably below normal. His speech was slow, slurred and low pitched. He was slightly hard of hearing. His thyroid gland was palpable and was judged to be about twice the normal size. There was grade I ankle edema.

Laboratory studies at that time revealed a PBI of 3.7 micrograms percent, T₃ uptake of 1.09 (normal 0.86 to 1.20), cholesterol of 248 mg. percent and a radioactive iodine uptake of 49.9% at 3 hours and 85.1% at 24 hours after 25 microcuries were administered orally. (normal 15 to 40% in 24 hours) He was instructed at that time to gradually increase his thyroid medication.
to a peak of 90 mg. per day.

His next visit to University Hospital was in June of 1963. His complaints at that time were similar to those above. He had not taken thyroid medication regularly.

Laboratory studies at that time revealed a PBI of 2.9 micrograms percent, cholesterol 320 mg% and a radioactive iodine uptake of 51% at four hours and 58.2% at 24 hours. Chest X-rays and an EKG were considered to be within normal limits.

The patient's family history is interesting and probably quite essential in the condition which is probably present.

\[\text{Family Tree Image}\]

Mr. B. was readmitted for further evaluation of his thyroid condition in January of 1964. Studies thus far in his diagnostic workup will be presented below. Baseline radioactive iodine uptake with an oral dose
of 53 microcuries of $^{131}I$ was 26% at 4 hours, 31% at 6 hours (normal 6 to 24% at 6 hours) and 37.2% at 24 hours (normal 10 to 40% at 24 hours). Next radioactive iodine uptake with oral administration of two grams of potassium thiocyanate was carried out. Forty-eight microcuries of $^{131}I$ were given. At 4 hours the uptake was 26.7%. The patient was given the KSCN immediately after this reading. At one hour after administration of KSCN, 24.8% of the dose remained. At 2 hours 27.9% of the dose remained and at 20 hours after KSCN administration 23.1% of the original dose of $^{131}I$ remained in the thyroid gland. These values were considered to be within the normal range.

From the above results, it has been shown that trapping of iodide does occur and also that conversion of iodide to iodine occurs along with iodination of tyrosine. These results are shown first of all by the rapid uptake of $^{131}I$ (26% at 4 hours) and also by the lack of discharge of $^{131}I$ after administration of KSCN.

The next step in the diagnostic workup of this patient is to evaluate the mechanism for coupling of iodinated tyrosine to form iodothyronine. This will be done by the use of Tapazole after a proper baseline discharge of $^{131}I$ is recorded over a long period of
time. If a defect does exist in the coupling mechanism, $^{131}\text{I}$ will be discharged after Tapazole is administered.

Plans are also being made at this time to inject diiodotyrosine into the blood stream to ascertain the presence of systemic deshalogenase enzyme.

Therefore at this point in the diagnostic workup of this patient no conclusions can be made as to the site of possible enzymatic defects except trapping defects and defects in the oxidation of iodide can be ruled out.

Many diagnostic procedures are needed to classify a patient with sporadic goitrous cretinism into the category in which his defect falls. Classification of a specific patient's defect is probably not warranted unless it is done for research or educational purposes because of the cost to the patient and because the treatment is usually not altered by this information.
SUMMARY

The major types of defects of thyroid hormone metabolism are those which involve thyroid hormone synthesis, the binding of thyroxin by the serum and an inability of the body cells to metabolize thyroid hormone. The enzymatic defects which involve thyroid hormone synthesis are: (1.) Trapping defects (2.) Inability to oxidize iodide to iodine (3.) Inability to halogenate tyrosine in the presence of elemental iodine (4.) Inability to couple iodinated tyrosines (5.) Inability to hydrolyze thyroglobulins (6.) Abnormal formation or release of thyroglobulin or thyroglobulin like substance (7.) Inability to deshalogenate "free" iodotyrosine.

Diagnosis of the specific defect in hormone synthesis involves use of techniques involving radioactive iodine, KSCN, Tapazole of propylthiouracil, diiodotyrosine and chromatography. Other methods used in diagnosis of the presence of hypothyroidism and sometimes in the diagnosis of the specific defect in sporadic goitrous cretinism are PBI, BEI, erythrocyte uptake of I_{131} labelled triiodothyronine and rarely serum cholesterol levels.

Treatment for patients with sporadic goitrous
cretinism consists usually of giving therapeutic doses of desiccated thyroid although sometimes large doses of iodide will suffice if certain iodide losing defects are present. Rarely triiodothyronine must be used for treatment.

A case report of a patient with suspected sporadic goitrous cretinism has been presented. Diagnostic workup has been only partial at this time but trapping defects and inability to oxidize iodide to iodine have been ruled out. More work remains to be done.

The etiology of sporadic goitrous cretinism is a genetic defect which is inherited usually according to the laws of simple recessive inheritance. These criteria are: (1.) The parents of affected persons are normal to outward appearance (2.) There is a striking familial prevalence with a ratio of affected to normal persons being 1:3 (3.) All affected children are the offspring of consanguineous marriages (4.) The offspring of affected persons with normal persons are usually normal and (5.) The offspring of two affected persons are all affected. Not all cases follow these rules. Some family histories obey some of the rules of recessive inheritance but not all, while others seem to follow all the rules.


