1959

Normal range of thyroid activity in newborn infants : determined by the uptake of I-131 by the thyroid gland in 24 hours

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NORMAL RANGE OF THYROID ACTIVITY IN NEWBORN INFANTS: DETERMINED BY THE UPTAKE OF I-131 BY THE THYROID GLAND IN 24 HOURS

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Submitted in Partial Fulfillment for the Degree of
Doctor of Medicine

College of Medicine, University of Nebraska

March 27, 1959

Omaha, Nebraska

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INTRODUCTION

Since Galen briefly described the thyroid gland in the second century A.D. and Vesalius's more detailed description in 1543, many men have done excellent work on the anatomy and physiology of this endocrine gland. However, it remained a somewhat confused state in regards to its influence on various body functions until a great advance was made when it was studied by the use of radioactive iodine.

As early as 1827 men experimentally studied the relationship between the thyroid and various body functions by thyroidectomy. King in 1836 formulated the concept of an internal secretion. In 1883 the Reverdins and Kiocher became aware of the similarity between myxedema and the clinical picture which develops after successful removal of the thyroid gland. However, it was not till 1896 that Vassale and Generali separated the entity of myxedema following thyroidectomy from that of tetany. The injection of a glycerine extract of thyroid to relieve myxedema and, finally, the feeding of lightly cooked sheep thyroid with successful relief of the disease completed the background for the modern development of knowledge about thyroid function.

The first association of iodine with the working of the thyroid gland was made in 1896 by Baumann, who discovered a particular concentration of this element within the gland. In 1900 Gley and Bourcet made known the fact that organic iodine was connected with the serum proteins. In 1915 Kendall crystallized l-thyroxine from alkaline hydrolysates of thyroid tissue. Harington and Barger in 1926 and 1927 discovered the chemical structure of thyroxine. And more recently Gross and Pitt-Rivers found tri-iodothyronine in the gland and in the plasma.[1]

Since 1934 when Fermi and his co-workers in Italy prepared radioactive isotopes, the study of the function of the thyroid gland has progressed rapidly. The use of radioactive iodine in the study of thyroid physiology was undertaken and reported first in 1938 by Hertz, Roberts and Evans. Since that time the literature on this topic has become voluminous.[2] Then in 1941 the firstpatients were treated independently and virtually simultaneously by Hertz and Roberts at the Massachusetts General Hospital and by Hamilton and Lawrence in San Francisco.[3]

An extensive review of the literature has revealed only two papers on studies that have been done to study the thyroid function on infants via the use of radioactive

iodine. The first I-131 study reported on newborn infants was by L. Van Middlesworth in 1954. He studied seven normal newborn boys, two and three days old. His results revealed that six of the seven infants accumulated 60 per cent or more of the I-131 dosage in the thyroid area. Two of these accumulated over 90 per cent of the I-131 test dose. The lowest uptake was 45.5 per cent which would be borderline high for an adult.[4] The second study was carried out by Martmer and his co-workers in 1956. They studied the uptake of I-131 by the thyroid gland in premature infants. They studied 65 premature infants ranging from 991 grams to 2,481 grams and 5 full term infants ranging from 2,522 grams to 2,694 grams which were delivered by cesarean section. The age range at the time of testing was from one to 63 days old. Their results showed an I-131 uptake in the thyroid gland after 24 hours which ranged from 7 to 60 per cent. They felt that technicalities and the possible surreptitious use of thyroid by the mother could account for the two cases which had an uptake below 10 per cent and the three cases bordering 60 per cent uptake. Their interpretation of these results is that they are within the limits of normal as recorded in studies of children and adults using the Geiger-Mueller counter; therefore, they assumed on the basis of this evidence

that the thyroid gland in premature and full term infants functions in a manner similar to that found in children and adults.[5]

The following discussion is based on a review of the literature mainly on diagnostic tests of thyroid dysfunction; but almost all of the results are based on studies of adult patients. A review of blood iodine concentrations by Rapport and Curtis give the following normal values of blood inorganic iodine: Curtis and Cole--12.0 gamma with a range of 8.9 to 13.8 gamma per cent while others report values ranging from 4.0 to 32.0 gamma (gamma equals 0.001 milligram). Man and others report a series of 72 children with age ranging from six weeks to 16 years where all had blood iodines within the normal range for adults. These authors feel that with decreased or absent thyroid function the whole blood inorganic iodine is in the range of 36 to 70 per cent of normal, and that organic blood iodine is also consistently low.[6] As noted above Man, et. al. reported the series on serum Protein-Bound iodine as determined by the permanganate acid ashing method - normal range is 4.0 to 8.0 micrograms per cent. She then studied 9 cases of cretins whose age range was from 3 months to 12 years and all values were

below two micrograms per cent. However, because this test requires 25 cc. of blood, normals have not been determined in infants.[7]

For many years it has been known that myxedema tends to raise the values for cholesterol in the blood, but rarely, if ever, disturbs the ester total ratio. But as shown by many studies, very little reliability can be associated with the blood cholesterol level. Federman and Robbins in a study of 12 cretins showed the mean was 348 mgs. per cent, but that the range was from 128 to 498 mgs. per cent.[8] Palmer and Leffler studied 164 cases of abnormal thyroid states and concluded that the cholesterol level was of no value.[9] Hutchison and McGirr studied 13 cases of goitrous hypothyroidism and here the blood cholesterol ranged from 184 to 500 mgs. per cent.[10] Simon, et.al., studied 17 patients with undifferentiated mental deficiency and 57 mongoloid children. He concluded that normal children showed lower values than the mongoloids; but while 62 per cent of the controls had values below 150 mg. per cent, 10 per cent of the mongoloids were also below this figure.[11]

A part of the same study that was carried out by Simon was to study the lipoproteins in the serum of

mongoloids, "sonoma controls" (which were the undifferentiated mental deficient children), and normal children. The mongoloids had consistently higher levels of lipoproteins between S_f 12 and S_f 20 than the other two groups; and this was to such an extent that when tested by the Chi square criterion it was significant at the 0.1 per cent level.[12]

Federman and Robbins also studied the alkaline phosphatase in 12 cretins and found that before treatment it ranged from 1.6 to 3.9 B.L. units with a mean of 2.5 but following treatment it increased to a mean of 5.4 B.L. units.[13]

There are many other tests of thyroid activity, but only three more of them will be discussed at this time. One of the earliest and most widely used is the basal metabolic rate (B.M.R.). As shown by Fraser this is probably the best index of the severity of the disorder, but as a measure of thyroid function, it has some defects, especially when the results can be varied so easily just by the conditions of the test.[14]

One of the very important and frequently used tests of thyroid function is the protein-bound iodine (PBI) level in the blood. Dailey and Skahen studied 1,125

determinations of the PBI by the method of Salter and McKay and used consecutive patients, excluding the following cases: 1. patients who had taken organic iodine compounds at any time; 2. patients who had taken inorganic iodine within the past two months; 3. pregnant patients. Their results were: 1. In 63 hypothyroid patients the mean was 3.58 gamma per cent with one standard deviation of 1.10 gamma; 2. In 804 euthyroid patients the mean was 6.16 gamma per cent with one standard deviation of 1.49 gamma; 3. In 258 hyperthyroid cases the mean was 10.21 gamma per cent with one standard deviation of 3.14 gamma. However, there is considerable over-lapping between these three groups. The top 25 per cent of the hypothyroid range is within the lower 25 per cent of the euthyroid range; the top 55 per cent of the euthyroid range is within the lower 25 per cent of the hyperthyroid level. Statistically it was found that the "t" value upon comparison of the mean levels of PBI for the hyperthyroid and hypothyroid groups was 2.8 which is significant at the 1.0 per cent level. The "t" value for the mean of the hyperthyroid and euthyroid groups was 1.98 which is significant at the 5.0 per cent level. The "t" value for the hypothyroid and euthyroid groups was 1.11

indicating no statistical difference. Therefore, they concluded that despite the overlapping the PBI is of diagnostic value, especially when it is elevated above 10.0 micrograms per cent. But for the diagnosis of hypothyroidism it is of little significance until it is below 4 micrograms per cent and then it just confirms what is usually clinically quite evident.[15]

Lamberg et.al., also did a study on the serum PBI. He had 450 cases on which 500 determinations of the PBI was done by the alkaline-incineration method of Barker. His results are quite favorable with the previous results. His normal range is from 3.5 gamma per cent to 8.0 gamma per cent. He noted quite marked variation when several determinations are made on the same person at intervals of 2-4 weeks and the cause of this variation was unknown; however, it was not a laboratory error because in 40 duplicate determinations the standard error of the mean in a single duplicate was plus or minus 0.56 gamma. His explanation was that butanol extractable iodine in the serum is bound to the serum albumin and is easily diffusible while the globulin fraction is more stable and in thyrotoxicosis mainly the albumin fraction is increased.[16]

Kessel and Politzer studied the PBI levels in mothers

and their infants at birth. Thirty-three cases were included in this study. In six cases the PBI level was higher in the infants cord blood than in the mother's blood; these cases were all males. The PBI levels in the mother's blood ranged from 3.0 to 11.6 micrograms per cent. In 21 of the mothers and also in 21 of the infants, the PBI level range was between the accepted normal range of 3.5 to 8.0 micrograms per cent. In only one mother and 4 infants the level was below 3.5 micrograms per cent. In 11 mothers and 8 infants the level was over 8.0 micrograms per cent. The determinations on the infants were performed on samples of cord blood.[17]

Danowski, et.al., did a study where they analyzed in duplicate the PBI concentrations by the method of Barker of 110 infants ranging up to one year of age. All of these infants had been born at term following an uncomplicated pregnancy. All examinations indicated that they were in good health and developing normally. Their results showed that at birth the PBI was the same as the mothers and then it rapidly increased to its peak from 1 to 4 days - mean 12.9 gamma per cent - and then slowly decreased the remainder of the first year.[18]

Federman, et.al., found the PBI in creatins to have a mean of 1.4 micrograms per cent with a range of 0.7 to

2.0 micrograms per cent.[19] Simon, et.al, found the mean serum protein bound iodine in 25 mongoloid children between 5-15 years of age to be 6.20 micrograms per cent and in 23 mongoloids between 16-25 years of age to be 5.25 micrograms per cent.[20] Blom and Terpstra[21] and Palmer and Leffler[22] have reported similar results - below 2.0 gamma per cent in severe hypothyroidism.

It is well known that there is radiologic evidence of bone age retardation in hypothyroid states of infants and children. The radiologic signs were grouped and very adequately explained in a report by Astley. He concluded that the use of bone age as an x-ray diagnosis of retardation is a useful link in the chain of diagnostic evidence but is not by itself of any great significance, because there are many other causes such as constitutionally small children, pituitary dwarf and chronic diseases such as steatorrhea that produce similar roentgenologic findings. However, a negative finding is more significant, if hypothyroidism is suspected after the first few weeks of life, normal or advanced bone age virtually excludes it. Astley feels that the main differential roentgenographic diagnosis is: 1. Irregular normal epiphyseal ossification; 2. Osteochondrosis; 3. Dysplasia epiphysialis multiplex.[23]

Wilkins has noted what he calls epiphysial dysgenesis associated with hypothyroidism. This presents a definite roentgenographic picture which is most often present in the head of the humerus and the head of the femur, but is not present for some time following the onset of hypothyroidism.[24] Cristie has done extensive work on the prevalence and distribution of ossification centers in newborn infants. He has shown conclusive evidence that race and sex are of utmost importance in an appraisal of the osseous pattern of newborn infants. This is based on the presence or absence of the center of ossification of the cuboid bone. In his most recent study he presents tables for the centers of ossification of the calcaneus, talus, cuboid, 3rd cuneiform, distal epiphysis of the femur, proximal epiphysis of the tibia, capitatum (magnum), hamate (unciform), head of the humerus and head of the femur.[25]

Bellini and Nevis present several interesting aspects of childhood myxedema. First is the characteristic faces of cretins; the face is small and the transverse diameters are predominantly increased; the forehead is flat with a short nose that is turned upward because of a depressed root. The eyes are widely separated and are small. The palate is flat. Often there is a pronounced prognathism along with a skull that appears to have an enlarged

volume and also has a brachycephalic configuration. They then list the main osseous changes that are due to deficit or absence of the thyroid function in childhood. These are: 1. Delayed appearance of ossification centers; 2. The centers, which appear tardily, present variations in structure and size; 3. In children in whom the hypothyroidisms is of long duration and epiphyseal dysplasia has developed, the changes may be permanent; 4. In children with hypothyroidism left to its spontaneous evolution, or treated tardily or irregularily, there is delayed epiphyseal synosteosis; 5. Changes are also observed in development of the vertebral arches, the pelvis and the cranial bones. These authors then list the roentgenographic findings seen on films of the skull of patients with childhood myxedema. These include the following: 1. Dense diploe, little differentiated, with diastasis of sutures; 2. Coarse greater wings of the sphenoid bones; 3. Diminished angle between the nasal bones and the frontal bone; 4. Circular sella turcica without posterior clinoids and sella is enlarged with sharp contours; 5. Small lower jaw with an open angle; 6. Absence of cranial sinuses with scarce pneumatization of the mastoid bone; 7. There is delayed dentition.[26]

Another roentgenologic finding that may be seen is an enlarged heart. Of 13 cases of hypothyroidism studied by Hutchison and McGirr six of them had a cardiac-thoracic ratio greater than 50 per cent.[27]

Federman, et.al., has stressed that retardation of bone age after six months is more likely to be due to some other cause than hypothyroidism; that that absence of humeral and distal femoral epiphysis at birth is probably due to hypothyroidism.[28]

And finally the group of tests that seem more accurate than any of the rest in determination of disturbed thyroid function are the various tests with the use of radio-active iodine (I-131). These tests are capable of measuring the rate of utilization of iodine by the thyroid gland. The main disadvantages to this test are invalid results occurring after the ingestion of certain drugs and when the body's stores of iodine are at one extreme or the other. The major advantages of these tests are: 1. Minimal inconvenience to the patient and 2. They are independent of the nervous state of the patient.[29]

Outside of the previously mentioned two studies that have been done on newborn infants, there are numerous variations of the basic tests that have been carried out

by many people in most age groups other than the newborn period. Reilly and Bayer studied the I-131 uptake by the thyroid gland and the urinary excretion of I-131 in normal and hypothyroid children. They studied 16 euthyroid children between the ages of 4 and 14 years. The dose of carrier-free I-131 used was 5 microcuries for those below 6 years and 10 microcuries for those above this age. In this group the thyroid gland accumulated between 8.7 and 29.8 per cent of the oral dose with the maximum between 24 and 96 hours. The urinary excretion varied between 29.3 and 70.6 per cent of the oral dose with the maximum between 24 and 48 hours. The same test doses were given to 5 hypothyroid patients. In these the uptake was approximately one per cent and the excretion was 70 to 90 per cent with the maximum between 24 and 48 hours. The authors feel that urinary excretion, presuming otherwise normal kidneys, may be a better test of thyroid influence on iodine metabolism than the thyroid uptake of I-131; they feel that the excretion is more constant and easier to measure.[30]

Lowrey, et.al., studied the I-131 uptake over the thyroids of children by giving 20-50 microcuries of I-131 orally and then measuring the counts over the thyroid at intervals of 5 to 20 minutes for at least two hours and

then calculating the per cent increase. His results showed a rapid uptake in normals during the first 60-80 minutes and then there was some tapering off, but all had greater than a 100 per cent increase at the end of one hour. None of the hypothyroid children exceeded a 40 per cent increase at the end of this time. The normal range at the end of two hours was 125 to 400 per cent increase. All cretins and myxedematous patients were less than 40 per cent at the end of two hours. To be sure that these low counts were not due to lack of absorption from the gastrointestinal tract, the initial high count that was present over the stomach fell rapidly in all subjects during the first hour.[31]

Quimby and McCune established the following normal percentages of I-131 in the thyroid gland after 48 hours following an oral dose of 20-40 microcuries of I-131. For children less than one year of age the average uptake is 12.3 per cent with the range of 7-20 per cent; between 1-4 years the average is 9.3 per cent with a range of 4-15 per cent; and between 5-14 years, the average is 13.5 per cent with a range of 9 to 20 per cent. All cretins and myxedematous patients that they checked had less than 1 per cent uptake at 48 hours.[32]

In Friedman's study of the I-131 uptake by 61 patients with mongolism and 68 euthyroid controls, both groups were in the accepted normal range. The range for the control group was 9 to 38 per cent uptake by the thyroid gland while in the experimental group it was 8 to 40 per cent of the orally administered dose. This may partially be explained by the fact that he had discontinued thyroid medication only 10 to 14 days prior to the testing. The normals he used and also accepted by most authors are: 1) 0-5 per cent uptake - hypothyroid; 2) 6-15 per cent uptake - borderline; 3) 16-30 per cent uptake - euthyroid; 4) 31-40 per cent uptake - borderline; 5) greater than 40 per cent - hyperthyroid.[33]

Fraser, et.al., devised the following method for determining thyroid function. Following a dose of I-131 he would collect and measure the amount of radioactivity present in the various urine samples which would be collected at the following time intervals - 0-8 hours; 8-24 hours and 24-48 hours. His calculations were based on the following formula:

$$T = \frac{(\%\ \text{I-131 in 0-8 hours}) \times 100}{(\%\ \text{I-131 in 8-24 hours})\ (\%\ \text{I-131 in 0-48 hours})}$$

The normal range of T is 2.8 to 12.8 with a mean of 5.15. In myxedema it is less than 2.1 and in hyperfunctioning

states of the thyroid gland it is above 17.4.[34]

Hamilton, et.al., showed in their study of 10 cases of severe hypothyroidism whose age range was up to 19 years that the uptake by the gland was so minute that there was no measureable quantity present until the fifth day following administration of the test dose.[35]

Many authors have shown that urinary excretion of I-131 is very valuable in the diagnosis of thyroid dysfunction. Mason collected complete urine samples at 2, 4, 6, 9, 12 and 24 hours. He showed if the entire sample was measured it was hard to differentiate any abnormality, but if the 6-24 hour sample was measured, there was then 4.5 per cent of the dose present in the urine from patients with hyperthyroidism; 10-25 per cent was present in the urine of euthyroid patients and 26-39 per cent in the urine of hypothyroid patients.[36] Arnott and Emery collected complete urine samples from 0-8 hours, 8-12 hours, 12-24 hours and 24-48 hours and showed definite differences in the three groups. They concluded that for hyperthyroidism the ideal sample was between 8-12 hours during which time the mean per cent of I-131 that was excreted was one-tenth that of normal. The ideal collection period in hypothyroidism was between 24-48 hours during which time

the percentage of I-131 excreted was five times that of normal. During this study they concluded that there was no evidence of correlation between urinary excretion of I-131 and the patient's age, sex, weight, exercise or urinary output.[37]

Rollman, Petit and Starr obtained serial determinations of I-131 in the plasma of 11 hyperthyroid, 12 euthyroid and 13 hypothyroid patients. This was done at frequent intervals for as long as 16 days. They found that the hyperthyroid patient shows a more rapid rise in the serum radioactivity, but that the peak was not as high as in euthyroid patients because more radioactivity was retained in the thyroid gland. In myxedema the slow absorption and excretion produced a delayed peak with a prolonged fall in plasma radioactivity. They concluded that this was a good test for hypothyroid states, but that euthyroid and hyperthyroid patients were not clearly differentiated.[38]

Reilly and Bayer studied 25 normal and 5 congenital hypothyroid children whose age range was from 9 months to 15 years by measuring the uptake of I-131 by the thyroid gland and the amount excreted in the urine. The I-131 uptake of the normal children was from 8.7 to 29.8 per cent;

however, the uptake of the cretins was only 1-2 per cent and was not influenced by the administration of thyroid. The urinary excretion of I-131 by the control group was 29.3 to 70.6 per cent and the excretion after 48 hours was negligible, while in the cretins, there was 29 per cent excreted the first 6 hours, 30 per cent more in the next 18 hours and a total of 79.5 per cent for 96 hours. However, if the cretins were on thyroid medication, the excretion of I-131 for the first 6 hours was 18.6 per cent, with an additional 23.7 per cent in the next 18 hours and a total of 55 per cent in 96 hours. The cretins were tested when taking 65 mg. of thyroid substance daily and again 4-6 weeks after this was discontinued.[39]

Oliner, et.al., studied 83 children whose ages ranged from 2-1/2 months to 18 years trying to derive normal values for thyroidal I-131 uptake and PBI-131 levels up to the age of 18 years. The I-131 uptake by the thyroid gland at 24 hours for 60 children ranged from 17 to 50 per cent with a mean of 31.1 per cent plus or minus 7.63(S.D.); and this did not differ from the I-131 uptake by the thyroid gland of 64 euthyroid adults. PBI-131 determinations at 24 and 48 hours were significantly elevated up to the age of 4 years as compared with adult levels. Although the values

in the 5-9 year old age group were within the normal adult range, the mean value was significantly elevated. As a result of this the author feels that the thyroid gland in children up to the age of 4 years is normally in a state of hyperfunction when compared with that of an euthyroid adult.[40]

OBJECTIVE

The objective of this proposed research problem is to attempt to establish the range of 24 hour uptake of iodine by the thyroid gland in newborn infants, using an I-131 tracer technic. If a normal range of I-131 24 hour uptake by the thyroid gland can be established, it is proposed to use this method as an aid in differentiating the causes of mental retardation. Because of the conflicting data in the literature on tests of normal thyroid function in newborn infants, the present study was carried out. In the two previous studies reported, one suggested that the newborn may experience a period of hyperthyroidism and the second study suggested that both premature infants and full term infants have thyroid function within the accepted normal range for older children and adults. Although more studies have been done in the estimation of protein-bound iodine and butanol-extractable iodine, these tests present some

difficulties because of the amount of blood required for analysis. Many authors agree that usually thyroid function must be greatly altered to arrive at a correct diagnosis with PBI determinations alone.

PROCEDURE AND METHOD

The newborn infant is given a known amount of I-131, approximately 5 microcuries by injection through an intubation tube at 8:00 a.m., three hours after the last feeding. Immediately following this there are two injections of two cc. of sterile normal saline from the same syringe washed through the tube. The tube is then removed and saved for counting residual activity. Sterilized equipment is used throughout, and the administration is done by the same person everytime. Twenty-four hours later the concentration of I-131 in the thyroid gland was determined. This was done by counting the disintegrations with scintillation counter recorded by a count-rate meter. The standard test dose was prepared by putting 1 cc. of the previously calculated I-131 solution into a polyethylene phantom representing the baby's neck.

A small cart is covered with a solid sheet of plasti-glass. On it in an eccentric position is a small saddle formed of plasti-glass. This is exactly centered over the

1-1/4 X 1 inch crystal of the scintillation counter which is set in a vertical position 13 cm. below the point the baby's thyroid will occupy, assuming normal anatomical position with the child's neck on the saddle. The crystal is covered with a 2 mm. lead filter.

The phantom representing the baby's neck is made of polyethylene, 51 mm. in diameter and 75 mm. in length. The cavity representing the thyroid is at the mid-point on one side, the center of the cavity is 8 mm. below the surface and is 5 mm. in diameter and 6 mm. long. It is closed with a threaded piece of polyethylene so that scattering mass is uniform throughout. The phantom is designed similar to the one used by Martmer in his study of newborns, and is a representation of the neck of a normal baby, both anatomically and in terms of density and scattering mass.

This phantom represents the amount of radioactive substance in 1 cc. of testing solution at any time as the I-131 undergoes physical decay.

Prior to making a determination of the uptake by an infant, the percentage rate meter is standardized for zero, 100 per cent and for high voltage. Then to take a reading, it is necessary only to lay the infant face down with the neck over the saddle and read counts per minute directly

from the rate meter. To assure a correct reading the infant is maintained in position for 60 seconds which with our instrument provides less than 2 per cent probable error. In this position the infant is comfortable, can breathe without difficulty and can be held as long as necessary with no possibility of injury. Following this one of the infant's thighs are held over the saddle for one minute also, and the counts per minute here are also recorded. At the same time the infant's readings are taken, a room background and standard (phantom placed on the saddle) is determined in counts per minute. Before another infant is placed on the table, the entire top, as well as the saddle, is cleaned with 70 per cent alcohol.

To determine the percentage uptake of I-131 by the thyroid gland in this series of newborn infants, the following formula was used: Percentage uptake equals

$$\frac{(\text{CPM Thyroid} - \text{CPM Bkgd}) - (\text{CPM Thigh} - \text{CPM Bkgd}) \times 100\%}{(\text{CPM Stand.} - \text{CPM Bkgd}) - (\text{CPM Tube and Syringe} - \text{CPM Bkgd}) \times \text{Amount Injected}}$$

For each infant studied an accurate prenatal history was obtained in regards to weeks of gestation, parity of the mother, abnormalities of the pregnancy, and medications the mother received prior to delivery. The period of delivery was investigated in regards to duration of labor, type of delivery and condition of the infant at birth.

The past history of the mother was also investigated in regards to previous illnesses, operations and medications - patent medicines or as prescribed by a physician. The family history was also obtained in regards to familial diseases and health of the immediate family. The height, weight, sex, race, age of the infant at the time of the determination of the thyroid uptake and physical condition of the infant were also recorded.

CALCULATION OF DOSE

In this period of cancer phobia, especially since some people propose a cause-and-effectrelationship between irradiation and the development of thyroid cancer, it will be shown that the amount of radiation in the five microcuries given as a test dose to the newborn infant is insignificant.

Using an average mass of 1 gram and a thickness of 0.5 mm. for the thyroid gland of an infant with Glasser's calculations for a 5 microcurie dose, the gamma exposure is negligible. The beta exposure, assuming a total absorption 880 beta roentgen would be serious. The range of the particular beta particle in question is 1.3 mm. and using a half thickness of the gland of 0.5 mm. maximum, an actual maximum absorption of 60 per cent and a half life of 7 days,

the total beta dosage would be 4.7 roentgen delivered at the exponential rate of 10 per cent per day. This figure is considered insignificant, being less than the equivalent of 3 exposures for x-ray films over a 30-day period. The iodine content of 5 microcuries is 4×10^{-11} gram.

Clark reviewed his 13 cases of thyroid cancer in patients 15 years of age or younger that he had seen in the previous six years. All of these had had previous irradiation: a. Three to the upper chest for thymic enlargement; b. Three to the neck for cervical adenitis; c. Five to the head and neck because of enlarged tonsils and adenoids; d. One to the anterior chest and face for sinusitis and peribronchitis; e. One to the chest for pertussis. In this group of 13 there were 12 females. The total dose of irradiation in air ranged from 200 to 725 roentgens in 11 of the cases. The size of the ports varied from 3 X 3 cm. to 10 X 15 cm. These were all in the range of therapeutic radiation. The age at the time of irradiation was from two months of age to 6 years. The age at time of histologic diagnosis was from 4 to 15 years of age. The interval from the time of therapy to the date of diagnosis was from 3 to 10 years with an average of 6.9 years. The children all had been well without evidence of thyroid disease prior to the diagnosis. At present, following

therapy, all are living and well and clinically free of cancer except one case which has x-ray evidence of pulmonary metastases. Clark concluded that in all of his cases the thyroid gland could have been in the field of irradiation.

Clark feels that because of the rapid increase in the diagnosis of cancer of the thyroid - only 8 cases reported between 1900-1930; 30 from 1930-1940; 121 cases from 1940-1950 (with 91 of these being reported from 1945-1950) and because this increase is so large; that in absence of any great improvement in methods available for the diagnosis or in the avilability of diagnostic method to the population during this time, that it must represent a true increase in cancer of the thyroid gland and that there is a definite relationship with irradiation to this area.[41]

However, most authors do not agree with the hypothesis of Dr. Clark. Duffy and Fitzgerald reported 28 cases of cancer of the thyroid in patients 18 years of age or younger. Ten of these patients had been subjected to irradiation of the thymus gland sometime between the fourth and sixteenth month of life. Although they suggested that irradiation might be an etiologic factor in cancer of the thyroid gland, they stated:

> "To propose a cause-and-effect relationship between thymic irradiation and the development of cancer would be quite unjustifiable on basis of the data on hand when one considers the large numbers of children who had received irradiation for an enlarged thymus."[42]

Simpson, Hempelmann and Fuller studied the frequency of neoplasms in 1,400 of 1,722 children who had received X-ray therapy to the thymic area between 1926 and 1951. The dosage ranged from 50 to 1500 roentgens in air to the anterior chest. Of these, 604 or 35 per cent of the 1,722 cases had received less than 200 roentgens; and none of these developed carcinoma. In the total series 17 children developed malignancies of which 6 were cancer of the thyroid. They concluded that the number of cases of thyroid cancer was increased in this group as compared with either untreated siblings or the general population. However, a considerable number of the siblings were excluded from the series because they were alleged to have had X-ray therapy. It must also be noted that the incidence of cancer among the untreated siblings is high compared with the general population.[43]

Daily and Lindsay reported 23 cases of thyroid cancer in patients under 20 years of age without mentioning previous irradiation.[44] Horn and Ravdin reported 22 cases of cancer of the thyroid in patients under 20 years of age and only one had a history of previous irradiation therapy.[45]

Warren, Alvizouri and Colcock reported 23 cases of cancer of the thyroid with only one having a history of previous irradiation.[46] Conti and Patton reviewed the history on 1,477 patients who had received irradiation to the thymus and there was no cancer of the thyroid in any of these patients.[47]

Uhlmann reported on 25 patients less than 21 years of age who had been referred to him for therapy of cancer of the thyroid during the previous 18 years. Of these only 4 had had previous irradiation and the time interval following irradiation before diagnosis ranged from 8 to 15 years. On the other hand during the same 18 years, 2,500 children had received radiation therapy for hypertrophied lymphoid tissue in the pharynx and for enlarged tonsils. During a seven year follow-up on 480 of these cases not a single instance of cancer of the thyroid was found.

This author also calculated the amount of radiation to the thyroid gland during x-ray treatments for benign hyperplasia of the nasopharynx. With the customary three treatments of 375 roentgens to each of two lateral 8 X 10 cm. fields over a two week period a maximum of 18 roentgens reaches the skin above the thyroid gland during this time. This is much less than the amount of radiation that reaches the thyroid gland during the usual fluoroscopic exam

of the chest; during which time the skin over the thyroid received 1 roentgen per 5 minutes but the posterior portion of the neck receives 18 roentgens per one minute.

In conclusion Uhlmann feels that the incidence of carcinoma of the thyroid as stated by Clerk does not substantiate the cause-and-effect relationship of irradiation to cancer of the thyroid gland. This author then shows that the x-ray was widely used between 1920-1925, and therefore, there should be an increase in the following 5 to 10 years, but only 10 cases from 1925 to 1930 were reported and only 12 cases of cancer of the thyroid gland were reported from 1930 to 1935. Also since cancer of the thyroid gland in adults prevails in females - 7:1 over males is a figure that is generally accepted - and since this also is known that there is preferential affliction for girls to have more cancer of the thyroid than boys; therefore, while x-ray therapy for benign conditions shows no sex preference, one would expect that cancer of the thyroid in children would be equal between the sexes. No such evidence has yet been reported. It is also a published fact that some of the supposedly benign lesions of the neck for which previous irradiation was given have been proven to be cancer of the thyroid. Because of these previous reasons as well as the lack of knowledge of previous radiation therapy in most

children with cancer of the thyroid, this author feels that there is no relationship between the two conditions.[48]

RESULTS

Twenty-eight newborn infants were given a tracer dose of I-131 of approximately 5 microcuries, by gastric intubation using a polyethylene tube. Twenty-four hours later the uptake of I-131 by the thyroid gland was measured by the scintillation counter as previously described.

Table I presents the sex, age, birth weight, amount of I-131 administered and the percentage uptake as recorded by the count rate meter. All of the infants were considered to be normal newborn infants as far as could be determined by physical examination. Cases numbered 1 and 3 are not included in the analysis of this series because the mother had received medications which are known to alter the function of the thyroid gland. Sixteen males and 12 females were studied whose age range was from 72 to 180 hours old, and whose weight ranged from 2,600 to 4,663 grams. The mean of the age range is approximately 90 hours.

TABLE I

UPTAKE OF I-131 BY THE THYROID OF NEWBORN INFANTS

SEX	CASE	AGE (HOURS)	BIRTH WEIGHT (GRAMS)	NUMBER OF cc.	MICROCURIES	UPTAKE I-131 (%)
M	1	129	2,625	1.0	5.16	7.0
M	2	128	3,568	1.0	5.16	19.5
F	3	122	3,111	1.0	5.16	2.3
F	4	110	2,655	1.0	5.16	18.0
F	5	180	4,105	1.0	5.16	17.2
F	6	90	4,663	1.2	5.69	30.9
F	7	88	2,677	1.2	5.69	14.3
M	8	97	4,220	1.2	5.22	12.6
M	9	94	3,133	1.2	5.22	29.0
F	10	84	3,388	1.4	5.59	26.1
M	11	100	3,211	1.4	5.59	36.4
F	12	90	2,963	1.4	5.59	6.3
M	13	85	3,325	1.4	5.13	8.9
F	14	100	4,225	1.6	5.38	30.2
F	15	100	2,655	1.6	5.38	13.7
M	16	96	3,899	1.6	4.94	20.0
F	17	95	3,147	1.6	4.94	23.9
F	18	96	2,600	1.0	4.85	11.3
M	19	98	3,628	1.0	4.85	26.4
F	20	86	3,490	1.0	4.85	22.2
M	21	84	3,059	1.0	4.85	35.4
M	22	100	3,610	1.2	5.34	19.4
M	23	94	3,752	1.2	4.91	9.3
M	24	98	3,289	1.4	5.26	29.7
M	25	82	3,515	1.4	4.83	28.2
M	26	88	3,514	1.6	5.07	16.5
M	27	101	3,591	1.8	4.80	11.1
M	28	72	3,159	1.8	4.80	11.1

Table II presents the distribution of cases by percentage of uptake of I-131 at 24 hours following administration of the radioisotope by intubation.

TABLE II

CASES GROUPED BY PERCENTAGE UPTAKE OF I-131, 24 HOURS FOLLOWING ADMINISTRATION

% UPTAKE	3.3-11.8	11.8-20.3	20.3-28.8	28.8-37.3	TOTAL
	6	9	5	6	26

Table III outlines the distribution of cases by sex and weight with the range of I-131 uptake at 24 hours by the thyroid gland.

TABLE III

DISTRIBUTION OF CASES BY SEX AND WEIGHT WITH RANGE OF I-131 UPTAKE

WEIGHT-gms	2600-3000	3001-3500	3501-4000	4001-4663
MALE	0	6 (8.9-36.4)	8 (9.3-28.2)	1 (12.6)
FEMALE	5(6.3-18.0)	3(22.7-26.1)	0	3(17.2-30.9)

The experimental extremes of I-131 uptake by the thyroid gland are from 6.3 to 36.4 per cent. The mean uptake of these 26 cases is 20.3 per cent. The standard deviation is 8.5. Fourteen of the cases, or 54 per cent, are within one standard deviation of the mean; all of the cases are within two standard deviations of the mean.

SUMMARY

A brief history of the development of knowledge about the thyroid gland is presented. A review of the literature about the various tests of thyroid function is presented. Current thinking about the association of the development of thyroid cancer with previous radiation is reviewed.

In a review of the literature only two studies were reported on thyroid function in normal newborn and premature infants using an I-131 uptake technic. The first of these two studies was carried out by L. Van Middlesworth in 1954. He studied seven male infants who were 48 to 72 hours old by determining the amount of uptake of I-131 by the thyroid gland 24 hours after intramuscular injection of one microcurie of I-131. His results ranged from 46 to 97 per cent uptake of this tracer dose by the thyroid gland at 24 hours. From this he concluded that:

> "These studies show that the thyroid uptake of iodide is stimulated in the newborn infant. Such data, together with the reports of high protein-bound iodine levels in the infants of the same age, suggest that the newborn infant may experience a period of physiologic hyperthyroidism. This could result from several possible mechanisms, i.e., (a) increased sensitivity of the thyroid to thyrotropic hormone; (b) increased production of thyrotropic hormone, or (c) complex alterations of endocrine balance."[49]

The second of these studies was carried out by E. E.

Martmer and his group in 1955. They studied the uptake of I-131 by the thyroid gland, 24 hours following the administration of 5 microcuries of I-131 either orally or by gastric intubation of 65 premature infants and 5 full term infants who were from 1 to 63 days old. They measured the uptake of I-131 by the thyroid by both a Geiger-Mueller counter and a scintillation counter. Their results ranged from 10 to 60 per cent. In an additional two cases with an uptake of less than 10 per cent and 3 cases bordering 60 per cent, they felt technicalities and the possible surreptitious use of thyroid by the mothers may have accounted for the variation.

They felt that their study suggested that the function of the thyroid gland of these 65 prematures and 5 full term infants was within the normal limits as determined by a 24 hour I-131 uptake measurement. They concluded that the activity of the thyroid gland of prematures and full term infants, as revealed by the 24 hour I-131 uptake technic following oral administration, is similar to that found in children and adults, and functions in the same manner as it does in an adult. Furthermore, they feel that any individual infant who shows evidence of possible hypofunction or hyperfunction of the thyroid gland as measured by the uptake of

I-131 should be investigated further to determine, if possible, the underlying cause of the variation from the normal uptake.[50]

Because of the lack of data on the exact status of the thyroid gland in newborn infants, along with the very great divergence of results in the two reported studies, the present study was carried out in an attempt to determine a normal range of thyroid activity. It is hoped that the results could be used as a diagnostic aid in differentiating causes for mental retardation at an early age.

In this series of 28 infants from the Nursery at the University of Nebraska Hospital were studied. Sixteen males and 12 females whose age range was from 72 to 180 hours old - mean 90 hours - and whose weight ranged from 2,600 to 4,663 grams were given approximately 5 microcuries of I-131 on an empty stomach by intubation and 24 hours later, the uptake was recorded by means of a count rate meter. The past history of the mother, family history, prenatal history and the physical condition of the infant was also investigated. Two of the infants in this series were not included in the statistical analysis because the mothers had received medications which are known to cause deviation of thyroid function. The per cent uptake of I-131 by the thyroid gland was determined by the formula:

$$\% \text{ Uptake} = \frac{(\text{CPM Thyroid-CPM Bgd}) - (\text{CPM Thigh-CPM Bgd})}{[\text{CPM STD-CPM Bgd}] - [\text{CPM Tube-CPM Bgd}]} \times \frac{100}{\text{Amt. (cc) given}}$$

Using this formulat the uptake of I-131 by the thyroid gland at 24 hours ranged from 6.3 to 36.4 per cent with a mean of 20.3 per cent and a standard deviation of 8.5. Fourteen cases, or 54 per cent are within one standard deviation; all of the results are included in two standard deviations of the mean.

CONCLUSIONS

1. The thyroid function of 28 newborn infants was studied by the uptake of I-131 by the thyroid gland.
2. Two infants were excluded from the series because of premedications their mother had received which might have altered the results.
3. The range of I-131 uptake was from 6.3 to 36.4 per cent. The mean was 20.3 per cent. The standard deviation is 8.5. Fourteen of the cases are within one standard deviation of the mean and all cases are within two standard deviations.
4. In this study sex and weight were not found related to thyroid function.

ACKNOWLEDGMENT

I am extremely grateful to Dr. R. E. Ogborn who advised and assisted me with this study, also to Dr. R. E. Waggener who assisted me with the clinical study of these cases. I also wish to thank the Radiology and Pediatric Departments of the University of Nebraska for without their help I would not have been able to carry out this study.

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