

5-1-1964

Relationship of taster-nontaster" groups with thyroid disease"

Gerald L. Morris

University of Nebraska Medical Center

This manuscript is historical in nature and may not reflect current medical research and practice. Search [PubMed](#) for current research.

Follow this and additional works at: <https://digitalcommons.unmc.edu/mdtheses>



Part of the [Medical Education Commons](#)

Recommended Citation

Morris, Gerald L., "Relationship of taster-nontaster" groups with thyroid disease"" (1964). *MD Theses*. 37.
<https://digitalcommons.unmc.edu/mdtheses/37>

This Thesis is brought to you for free and open access by the Special Collections at DigitalCommons@UNMC. It has been accepted for inclusion in MD Theses by an authorized administrator of DigitalCommons@UNMC. For more information, please contact digitalcommons@unmc.edu.

RELATIONSHIP OF "TASTER-NONTASTER" GROUPS WITH
THYROID DISEASE

Gerald Morris

Submitted in Partial Fulfillment for the Degree of
Doctor of Medicine

College of Medicine, University of Nebraska

February 1, 1964

Omaha, Nebraska

TABLE OF CONTENTS

	Page
I. History and Introduction of P.T.C.	1
II. Chemical Composition	3
III. Genetic Information.	5
IV. Thyroid Disorders associated with "Tasters" and "Nontaster" Groups.	16
V. Methods of Studying Taster-Nontaster.	21
(a) G-N-Prop	
(b) Saliva Enzyme	
VI. Case Studies.	26
VII. Data Obtained	36
VIII. Summary.	39
IX. Bibliography	41

HISTORY AND INTRODUCTION OF PTC

The discovery that some people do taste P.T.C. and some do not was quite by accident. Dr. A. L. Fox was preparing some phenylthiourea in his laboratory in Wilmington, Delaware, when one of his assistants complained that there was a bitter taste in his mouth due to the dust of the P.T.C. Dr. Fox himself was not able to taste this substance. Dr. Fox decided to test this material on several subjects. From this testing he discovered two groups, one that could taste it and one that could not. The majority of the people fell into the group that could taste phenylthiourea and were called "tasters", the others being called "nontasters". Dr. Fox also conducted tests on the ability to taste other chemically related substances and reported his work in 1932. Soon after this two geneticists (Snyder, 1932; and Blakeslee, 1932) repeated this experiment and showed that the ability to taste phenylthiourea was inherited. Many methods such as placing crystals of P.T.C. on the tongue and testing filter paper soaked with P.T.C. were used. These methods were criticised because of the inherent inaccuracies of them. In 1949 Harris and Kalmus developed a procedure which has been adopted by most investigators. This procedure will be described later in the paper. This procedure proved to be a useful tool not only in genetic but also in anthropologic work. 18

In 1949 Harris and Kalmus reported a relationship between taste sensitivity and goitre. According to their previous work it had been established that various material with a = $\frac{N-C}{S}$ - grouping show differential taste grouping. Many of these substances are goitrogenic and some probably occur in common foods. Because of this they felt it would be valuable to examine the reactions to phenylthiourea of patients suffering from thyroid disease. They studied 352 patients with thyroid disease and 541 normal subjects. The patients with thyroid disorder were classified into two main groups, toxic diffuse goiter and nodular goiter. The following table shows the results:

The Results

Group	Total No.	No. and % of Nontasters
Normal Subjects	541	169 31.2%
Toxic Diffuse Goiters	218	67 30.7%
Nodular Goiter	134	55 41.0%

The proportion of nontasters in the group of patients with toxic diffuse goiter agrees well with the number found in the normal controls. There is, a somewhat higher incidence of nontasters among patients with nodular goiter. This is significantly different at the 5% probability level from the proportion found in the controls ($X^2 = 4.65$ for one degree of freedom). There was a similar proportion of nontasters among the cases of toxic and

nontoxic nodular goiter. 16

In 1960 Shepard and Gartler discovered a relationship between "nontasters" of phenylthiocarbamide among congenital athyreotic cretins. Much of the work discussed and to be presented in this paper are about this relationship. The patients studied in Shepards work were all documented examples of sporadic athyreotic cretinism. The parents and adult controls were tested with the 14 concentrations of phenylthiocarbamide according to the method of Harris and Kalmus. Thirty families containing 31 cretins were tested by the same observer, and all cretins but four could be tested accurately. It was found that 18 were nontasters and 9 were tasters. In the control group there were 29 out of 104. This is a significant difference $\chi^2 = 22$, D. F. = 1, P = .001 of the 30 mothers tested 15 were "non-tasters", of the 27 fathers tested 12 were "non-tasters". 21

CHEMICAL COMPOSITION

The taste differential of P.T.C. into two groups of tasters-non-tasters was first noted by Dr. A. L. Fox in 1931. Dr. Fox then conducted tests on the ability to taste numerous chemically related substances and reported his observations in 1932. 18

The materials which Fox found to have a taste differential are listed as follows: 1. para-ethoxyphenylthiocarbamide, 2. ortho-tolythiocarbamide, 3. meta-tolythiocarbamide, 4. Para-tolythiocarbamide, 5. para-nitrophenylthiocarbamide, 6. 2-5-

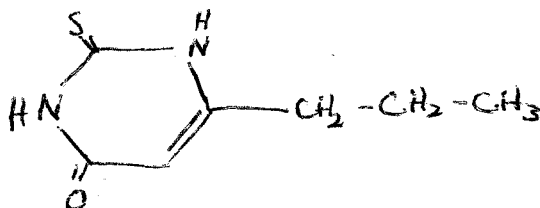
dichlorophenylthiocarbamide, 7. para-methoxyphenylthiocarbamide, 8a. para-fluorophenylthiocarbamide, 8b. para-chlorophenylthiocarbamide, 8c. para-bromophenylthiocarbamide, 9. B-naphthylthiocarbamide, 10. a-naphthylthiocarbamide, 11. para-B-hydroxyethoxyphenylthiocarbamide, 12. thiocarbamide, 13. sym di-ortho-tolylthiocarbamide, 14. sym di-meta-tolylthiocarbamide, 15. sym di-para-tolylthiocarbamide, 16. sym di (2 methoxy 5 methy 1 phenyl) thiocarbamide, 17. -N-meta-tolyl. N¹-phenylthiocarbamide, 18. N-para-ethoxyphenyl N¹-phenylthiocarbamide, 19. sym dibenzylthiocarbamide, and 20. dicrotylthiocarbamide. Riddle and Wybar, 1944 using the powder method of testing found that the individuals who could not taste P.T.C. were not able to taste thiouracil, and tasters for P.T.C. found thiouracil bitter.

It is easily seen that the chemical group responsible for taste bimodality is = N-C-₄.

Harris and Kalmus studied a similar group of compounds and found essentially the same results.

Fischer and Griffin, 1960, allude to a 7:3 ratio of tasters-nontasters to 6-n-propylthiouracil. 7 This same material 6-n-propylthiouracil, has been used in other studies of tasting. 9, 10. The 6-n-propylthiouracil has been used in some of the testing because the P.T.C. has an offensive odor. 10. P.T.C. has also been found to be useful in killing of certain species of rats by causing respiratory edema and temperature depression.

Propylthiouracil



$C_7H_{10} N_2 O S$

Mol. wt. 170.24

Description - White powdery crystalline substance, starch like in appearance with a bitter taste.

Solubility - slight sol in water, sparingly in alcohol, slight sol in chlorform and ether.

Propylthiouracil contains not less than 98% of $C_7H_{10} N_2 O S$ calculated on the dried basis. 20

GENETIC INFORMATION

Shortly after A. L. Fox (1931) found that the compound P.T.C. could divide people into two classes "tasters" and "nontasters" geneticists began to work to find the genetic relationship. Blackeslee and Salmon, 1931, studied a few families with P.T.C. crystals and decided that the inability to taste P.T.C. was due to a autosomal recessive gene in the homozygous form, Snyder, (1932) also came to this conclusion on testing 800 families with crystals of paraethoxy-phenylthiocarbamide. 22 In 1932 Blakeslee used a threshold method on 103 families. His base was "artesian-well water". The stock solution was 1:5000. Each of the following solutions were prepared by 4 times diluting the next higher one

with the weakest being 1:1,280,000. The date obtained by this method also supported the genetic hypothesis originated by Blakeslee and Snyder. 2 Harris and Kalmus again tested families in 1951 to confirm this original hypothesis. In their work they used 384 sib pars. In their work they failed to confirm the currently accepted hypothesis that nontasting is a simple recessive character. Their reasoning is as follow: "If we accept the hypothesis of single-gene difference causing a large part of the variation in the taste-threshold distribution, we are faced with the question as to why we find a comparatively sharp antimode in taste-threshold distribtuion, which does not correspond very closely to the distribution of the genotypes. The answer might well be in the field of developmental physiology; a certain medium level of threshold might, for inherent reasons, be less likely to develop than higher or lower thresholds. Such unstable situations undoubtedly do exist, but in this case we have no proof of such a mechanism". 12.

Most of the rest of this work's proof of the genetic relationship of P.T.C. taster and nontaster groups is based on the work of S. R. Das (1956). His work tends to confirm the earlier work of Blakeslee and Snyder. Because his work represents the largest sampling and also the most recent work done (1956), his statistics and methods are given as proof of the genetic hypothesis of a homozygous recessive autosome.

Das used 845 sib pairs in his studies. There was a total of 128 sibships all belonging to the R'arhi Bra'hmin community of West Bengal.

Table (1) Sibship composition, sib pairs etc., included in this study

No. members in each sibship	2	3	4	5	6	7	8	9	10	11	Total
No. of sibships	27	33	34	17	10	4	2			1	128
No. of sibs	54	99	136	85	60	28	16			11	489
No. of sib pairs	27	99	204	170	150	84	56			55	845

Because of prohibition of inbreeding this community is ideal for genetic studies. No subject below the age of 6 years was included. Only those sibships which comprised at least two members suitable for testing were used.

The method of Harris and Kalmus (1949) was used in this study. This method is described in another portion of this paper. Instead of boiled tap water, distilled water was used in the tests as well as in the preparation of solutions 1-14.

The distributions of the taste thresholds of 212 female and 277 male members belonging to 128 sibships are shown separately in Table 2. The distributions are bimodal with their antimode, at the No. 6. The line between "taster" and "nontaster" can be drawn between 5 and 6 or 6 and 7. Both these alternatives are used in the analyses presented.

Table (2) P. T. C. threshold distributions of 277 males and 212 females of 128 sibship pairs

Threshold No.	0	1	2	3	4	5	6	7	8	9	10	11 & 12	13 & 14	Total
Male	13	19	20	20	8	10	8	15	24	68	64	8	0	277
Female	10	16	11	16	4	7	3	12	21	48	56	8	0	212
Total	23	35	31	36	12	17	11	27	45	116	120	16	0	489

Homogeneity test by 2 x 12 Table (Fischer 1946) shows that the male and female threshold distributions are indistinguishable ($\chi^2 = 6.296$, 11 dif., P 0.8) Apparent frequency differences between the two sexes and the two alternative antimodes are not significant. The two most widely divergent groups that of females for antimode between 5 and 6 and males between 6 and 7 yield a χ^2 of 1.460 (1 dif., P .20).

Table (3) Taster and nontaster frequencies among 277 males, 212 female and 489 total members

Sex	Antimode between 5 and 6		Antimode between 6 and 7		Total
	Taster	Non	Taster	Non	
Males absolute	187	90	179	98	277
%	(67.51)	(32.49)	(64.62)	(35.38)	(100)
Females absolute	148	64	145	67	212
%	(69.81)	(30.19)	(68.40)	(31.60)	(100)
Combined absolute	335	154	324	165	489
%	(68.51)	(31.49)	(66.26)	(33.74)	(100)

Table 4 gives the frequency combinations of the P.T.C. thresholds in the 845 sib pairs. The data of table 4 has been grouped in

table 5 in 16 squares. The four corner squares include only the extreme tasters (thresholds 9-12) or the extreme nontasters (thresholds 0-4). In the remaining squares there appear those pairs, either one or both, the members of which are borderline cases. (thresholds, 5-8).

Table (4) Frequency distribution of the various P.T.C. threshold combinations in 845 sib pairs

	0	1	2	3	4	5	6	7	8	9	10	11	12	Total
0	9	5	1	1	1	1	-	1	8	9	14	-	-	44
1	8	8	3	5	3	1	-	4	5	10	6	-	-	53
2	5	5	5	7	1	4	1	1	5	4	14	-	-	52
3	1	11	7	15	2	2	1	2	2	9	6	-	2	60
4	1	2	2	7	1	2	2	2	2	8	3	-	2	34
5	2	2	2	9	6	2	3	-	3	7	5	-	3	44
6	-	2	1	4	1	1	-	1	1	5	4	1	2	23
7	-	2	3	1	-	-	-	5	10	3	6	4	-	34
8	5	7	2	4	-	-	2	4	4	22	16	2	1	69
9	3	14	16	17	2	2	5	9	7	58	55	5	3	196
10	2	10	5	10	2	2	5	6	12	58	85	16	3	215
11	-	-	1	-	-	-	-	-	1	6	9	3	-	20
12	-	-	-	1	-	-	-	-	-	-	-	-	-	-

Table 5 Grouping the sib pairs of Table 4, so as to separate out extreme and intermediate tasters and nontasters

Elder sib P.T.C. No.	PTC No.				Total
	0-4	5-6	7-8	9-12	
0 - 4	116	14	26	87	243
5 - 6	29	6	5	27	67
7 - 8	24	2	23	54	103
9 - 12	83	14	35	300	432
Total	252	36	89	468	845

The sib pairs data in Tables 4 and 5 give us frequencies of the four under mentioned types of sib pairs.

1. The pairs in which both sibs are tasters.
2. The pairs in which elder sib is a taster and younger a nontaster.
3. The pairs in which the elder sib is a nontaster and younger one a taster.
4. The pairs in which the sibs are nontasters.

The expected frequencies of these four types of sib pairs in a total number of 845 have been estimated on two alternative hypothesis.

- A. The first hypothesis is that dual P.T.C. taste character in man is determined by two autosomal allelomorphic genes and that the taster gene is completely dominant over the recessive nontaster allele.
- B. The second hypothesis assumes the above combinations are just

by chance.

Hypothesis A

Let t represent the proportion of nontasters in the population, the nontasting recessive gene frequency q , would be given by

$$q = t$$

For the present material therefore, we have, for the antimode between (Table 3) 5 and 6 $q = .3149 = .5612$, and for the antimode between 6 and 7 (table 3) $q = .3374 = .5808$.

On the assumption of complete mixing and complete genetic equilibrium of the population, relation frequencies of the four above mentioned types of sib pairs can be expressed in terms of q as explained in the following paragraphs.

In Table 6 the probabilities of the mating genotypes are shown in the second column and the probabilities that a member in a sibship is a taster or nontaster is given in the last two columns for each of the six mating genotypes.

Table (6) Probabilities of the 6 mating genotypes and a taster or nontaster member in sibships, corresponding to them

	Matings		Probability of a sib being	
	Genotype	Probability	Taster	Nontaster
1	TT x TT	$(1-q)^4$	1	0
2	TT x Tt	$4q(1-q)^3$	1	0
3	Tt x Tt	$4q^2(1-q)^2$	3/4	1/4
4	TT x tt	$2q^2(1-q)^2$	1	0

Table (6) Con't

5	Tt x tt	$4q^3(1-q)$	1/2	1/2
6	tt x tt	q^4	0	1

T, the dominant gene; t, its recessive nontaster allele.

The probability of getting a pair with both sibs taster corresponding to a particular mating genotype is given by the product of the probability of the mating type and the square of the probability of a taster sib corresponding to the same mating type. Adding up such probabilities for all 6 mating types, the required total probability of the pairs in which both sibs are tasters is given by - Prob. of a taster-taster pair = $\frac{1}{4} (1-q) (4+4q - 3q^2-q^3)$. In a similar manner, that probability of a pair with the elder sib a taster and the younger sib a nontaster is obtained by adding up the continued products of the probability of a particular mating type and the corresponding probability of a taster sib and a nontaster sib. Thus we get - Prob. of a taster - nontaster pair = $\frac{1}{4} q^2 (1q) (3+q)$. The same expression will do for 3 and in 4 the probability of a nontaster, nontaster pair = $\frac{1}{4} q^2 (1+q)^2$.

Multiplying the probability of a particular type of sib pair by 845, the total number of sib pairs studied, the corresponding expected frequencies as presented in column 4 of Table 7 are found, the value of q having been obtained from $q = \sqrt{f}$.

Hypothesis B

If the four above mentioned types of sib pairs result from

a chance combination - as would be expected in the total population without any reference to sibship and independent of the influence of any hereditary factor we will assume Hypothesis B. If t represents the proportion of nontaster in the population, as an estimate of the probability of an individual in the population being a nontaster. The probability of being a taster in that case would be $1-t$.

1. Prob. of both sib being tasters in a pair = $(1-t)^2$.
2. Prob. of elder taster and younger nontaster pair = $(1-t)t$.
3. Prob. of elder nontaster and younger taster pair = $t(1-t)$.
4. Prob. of both sibs being nontasters = t^2 .

As before multiplying each of these probabilities by 845 the corresponding frequencies have been evaluated and put in column 5 of Table 7.

Analysis of the results

The figures in the observed column of Table 7 come from Table 4 and the two expected come from equations previously discussed. All the X^2 values show that neither hypothesis A or B are in conformity with observed frequencies. The one between 5 and 6 and 6 and 7 yield only slightly different results. The X^2 on the recessive hypothesis A, however, are 4-5 times less than the corresponding values on the chance recombination hypothesis B.

Table (7) Frequencies of the four types of sib pairs expected on the hypothesis A and B compared with those deserved

	Types of sib pairs	Observed	Expected Hypothesis A	Expected Hypothesis B
Antimode between 5 and 6 t=0.3149 q=0.5612	1) Both tasters	438	474.9	396.6
	2) Elder taster and younger nontaster	138	104	182.3
	3) Elder nontaster and Younger taster	120	104	182.3
	4) Both nontasters	149	162.1	83.3
X ² (2 dif.)			17.5	87.11

Antimode between 6 and 7 T=.3374 q=.5808	1) Both tasters	412	453	317
	2) Elder taster and younger nontaster	145	107	188.9
	3) Elder nontaster and younger taster	123	107	188.9
	4) Both nontasters	165	178.0	96.2
X ² (2 dif.)			20.55	86.93

This leads to the following conclusions:

- 1) That the chance combination hypothesis is too widely in disagreement with the observation.
- 2) That the present data fail to confirm the hypothesis of recessive inheritance of P.T.C., but
- 3) That genetic hypothesis of recessivity comes definitely much nearer to the observed facts than the postulate of chance association.

It is also likely that inaccurate diagnosis of the borderline "tasters"

and "nontasters" due to overlapping inaccurate testing, age group differences, or some unsuspected genetic or environmental factors, might be responsible for the observed difference between the recessive inheritance theory of P.T.C. and the experimental results. In Table 8 the extreme phenotypes were used and show much better correlation.

Table (8) Frequencies of the four types of sib pairs separating the extreme "tasters" and "nontasters" from the border line cases and their closeness of fit with the heredity and chance distribution hypothesis

	Types of pairs	Observed	Expected Hypothesis A	Expected Hypothesis B
Antimode between 6 and 7 t=0.3374 q=0.5808 (Extreme phenotypes corner squares of Table 5) X ² (3 dif.)	1) Both tasters	300	314.1	257.3
	2) Elder taster and younger nontaster	87	74.2	131.0
	3) Elder nontaster and younger taster	83	74.2	131.0
	4) Both nontasters	116	123.5	66.7
			4.340	75.892
Antimode between 6 and 7 t=0.3374 q=0.5808 (Borderline cases of Table 5)	1) Both tasters	112	138.8	113.7
	2) Elder tasters and younger nontasters	58	32.8	57.9
	3) Elder nontaster and younger taster	40	32.8	57.9
	4) Both nontasters	49	54.6	29.5
			26.69	18.449

THYROID DISORDERS ASSOCIATED WITH "TASTERS" AND
"NONTASTERS" GROUPS

Harris and Kalmus reporting work of Chesny, Clawson and Webster (1928) noted the development of goiter and decrease in BMR of rabbits fed exclusively on cabbage. From this came experiments with iso-thiocyanates and eventually thiourea and thiouracil have been found to disrupt the function of the thyroid gland and reduce formation of thyroxine. Other associated drugs such as propylthiouracil have similar effects also and are used in the treatment of thyrotoxicosis.

Differences in taste sensitivity may indicate metabolic differences between individuals with respect to these materials.¹⁴

From results of the above studies Harris and Kalmus decided to study the reactions of P.T.C. on patients suffering from different forms of thyroid disease. Their thyroid disease patients were divided into two groups. Toxic diffuse goiter and nodular goiter. In their work, referred to also in the introduction, 30.7% of the toxic diffuse group were nontasters and 41.9% of the nodular goiter were nontasters. This compares with 31.2% as nontasters with normal subjects. ¹⁶

Kitchen et.al. proposes a causal relationship between taster-nontaster groups and the type of thyroid disorder which they will have. They also feel in the multiple adenoma group the genotype is about twice as important in males as females.

They state that it is improbable, in view of the marked differences in P.T.C. taste response found in toxic diffuse and multiple adenomatous goiter, that the effect in thyroid disease depends solely on the ability or inability to detect the specific bitter and unpleasant taste of the thiocarbamides and so act as a means of avoiding the toxic hazard of natural compounds of this sort. They feel that it is more likely that this easily measured action of the gene is only part of a wider fundamental biochemical action.

From a biochemical stand point taste response is continued to materials which possess a n-g-S linkage. They are active reducing agents and have been shown to inhibit tyrosinase. Their biological action is in the inhibition of the synthesis of thyroxine. The effect occurs only in the thyroid, is uninfluenced by iodine medication and results in thyroid hyperplasia under the stimulus of pituitary thyrotrophin.

The results of their survey in adenomatous goiter suggest the hypothesis that the inability to taste P.T.C. is associated with a greater susceptibility to the action of goitrogens. If this were so, cycles of seasonal involution and hyperplasia would occur in thyroid particularity in nontasters of P.T.C. and it is just this pathological sequence which is known to give rise to adenomatous goiter in later life.

They state that if their work is correct that the taster status

determines the nature of the goiter - that is, whether it will be nodular or diffuse. If the hypothesis that non-tasters are more susceptible to thiocarbamides is correct, it seems possible that the homozygous tasters (TT) are even more susceptible than the heterozygotes (Tt). Such insusceptibility would then have to be assumed to render the gland more prone to toxic diffuse goiter, and thus one of the natural restraining mechanisms in thyroid homostasis is removed. In their work with 125 toxic diffuse goiters 104 were tasters, 21 nontasters (15.8% with 216 multiple adenomas, nontoxic, 131 tasters and 85 nontasters (39.35%). 19

The first positive results showing relationship between nontasters of P.T.C. and congenital athyreotic cretins were found by Shepard and Gartler (1960). The families studied were all thoroughly documented examples of sporadic athyreotic cretinism. In 24 of the 31 cases studied, either a serum protein bound iodine or an I¹³¹ accumulation or both supported the diagnosis. The parents were tested with 14 concentrations of P.T.C. according to the method of Harris and Kalmus. Their threshold was the weakest concentration of which they were able to differentiate four beakers of water from four beakers of test concentration. The testing of the children and infants was carried out by serially increasing the concentration until the bitterness was detected. This was repeated in most cases until the threshold was established by three responses of the same concentration. 31 cretins were tested and all but four

could be tested accurately.

It was found that 18 were nontasters and 9 were tasters, as compared to the control group of 29 nontasters and 104 tasters. This is a significant difference ($X^2 = 22$, D.F = 1, P = .001) Thirty of the mothers were tested and 15 were nontasters, and of the 27 fathers tested 12 were nontasters. Of the 29 unaffected siblings who were available for study, 18 were nontasters. The incidence of nontasters among parents and siblings of cretins as compared to normal is significantly increased ($X^2 = 21.6$, D.F = 1, P = .001). They offer the hypothesis that the nontaster fetuses may be susceptible to embryonic thyroidectomy by the goitrogen thiocarbamide substances found in food. 21

In Frasers series even a greater % of nontasters were found. His series with presumptive diagnosis of athyreotic cretinism consisted of 28 children (21 girls, 7 boys). 17 could be tested with reasonable accuracy, the remainder being too young to give a reliable response. Of the 17, 15 were nontasters and only 2 tasters. On studying the parents, 33 were available for study, 18 were nontasters and 15 tasters. Athyreotic cretins are hard to distinguish clinically from the minority (perhaps as many as 25%) in whom thyroid failure is due to gross biochemical defects in thyroxine synthesis. Because these defects are determined by recessive inheritance, familial incidence or consanguinity of the parents may provide a clue. The only reliable guide however in this differential diagnosis is a radioiodine study.

Ten metabolic cretins were also tested of these 5 were tasters, 4 nontasters and one could not be tested.

The researches speculated that the tasting-nontasting differential may reflect some more deep seated variation which controls the metabolism and disposal of antithyroid substances. This mechanism maybe defective in nontasters. Under certain circumstances this may lead to euthyroid goiter, under others to destruction of the thyroid gland and athyreotic cretinism.

Reference is also made in this paper to a 3 : 1 ratio of tasters nontasters in juvenile myxedema. 5

Fraser, Morgans and Trotter tested a group of patients with the syndrome of sporadic goiter and congenital deafness with P.T.C. According to the method of Harris and Kalmus, and found out of 18, 3 nontasters and 15 tasters. 6

Table (9) Distribution of tasters and nontasters among normal subjects, athyreotic cretins, and parents of athyreotic cretins

Group	Reference	Tasters	Non Tasters	Not Tested
Normal controls	Kitchen et.al. (1959)	0.6%	29.4%	
Athyreotin cretins	Present series	2	16	11
	Shepard & Gartler	5 25%	18 75%	4
Parents of Athyreotic cretins	Present series	15	18	25
	Shepard & Gartler(1960)	30 50%	27 50%	3
Metabolic cretins	Present series	5	4	1
Syndrome of deafness with goiter	Present series	17 68%	7 32%	
Juvenile myxedema	Present series	3	1	

(5)

METHODS OF STUDYING NONTASTER-TASTER

When A. L. Fox in 1931 discovered the difference between groups of peoples, "tasters" and "nontasters", his only method of tasting was that of placing crystals of P.T.C. on the tongues of subjects and letting them determine if they could or could not taste these crystals. 18 Another method used for determining between tasters and nontasters was by testing with filter paper impregnated with phenylthiourea (Parr, 1934). 13 A third method of studying is by the use of serial dilutions of solutions in water. Blakeslee and Salmon first used this method in 1932. 4 A proper method of studying taste had to be devised which brought about a high degree of accuracy and which could be quickly given. The following is the method of Harris and Kalmus (1951) in which taste testing is done.

A stock solution containing 13% of phenylthiourea is made up in boiling tap water and serial dilution are made up as given in Table 1. The test proper consists of two stages:

Table (10)

Solution No.	PTC Mgm per liter
1.	1300.00
2	650.00
3	325.00
4	162.00
5	81.25
6	40.63
7	20.31
8	10.16
9	5.08
10	2.54
11	1.27
12	.63
13	.32
14	.16

- 1) Starting from the higher dilutions and working down the subject is given a few cc. in a tumbler until he is able to determine taste. This gives an approximate value for the threshold.
- 2) The subject is then presented with 8 tumblers, four of these contain a few cc. of water and four contain a few cc. of the solution determined in (1). The glasses are arranged at random and the subject is told that four contain the substance and four contain water. He is then told to taste them and separate into the two groups of four. The amount of fluid is not limited and the tumblers may be refilled during the test if desired. If the two groups of four can be correctly separated, the test is done again at the next lower concentrations, until the subject is unable to separate the two groups accurately. The test is also repeated with increasing concentrations until a concentration is reached which gives a completely correct answer.

In this study boiled tap water was used both for making up the solutions and the controls. It was stored in bottles and kept at the same temperature.

It was found at the concentration below the one considered to be their threshold concentration some subjects stated that they could detect a slight taste in some of the tumblers containing P.T.C. but not all. It is possible that the true physiological threshold is lower than the one that they determined. 13 From the testing of Das using the method of Harris and Kalmus the drawing of a line between tasters and nontasters could be made between 5 and 6 or between 6 and 7. Using

5 and 6 they got taster 68.51% and nontaster 31.49%. Using 6 and 7 they got taster 66.26% and nontaster 33.74%. 4

Fischer and Griffin, 1961, used a slight variation of the Harris and Kalmus method as described below. Instead of using P.T.C. they used G-n-propylthiouracil. The main reason being that the material provides no smell as does P.T.C.

The prop was dissolved in double distilled free water. Serial dilutions were made so that a solution number represented the molar concentrations as given in Table 11 below. The taste thresholds were determined according to the method of Harris and Kalmus. Three ounce paper cups (No. 44 of the Lily Tulip cup Corporation) were used for the prop and for the placebo. 7.

Table (11)

Solution Number	Molarity
20	3.84×10^{-1}
19	1.92×10^{-1}
18	9.6×10^{-2}
17	4.8×10^{-2}
16	2.4×10^{-2}
15	1.2×10^{-2}
14	6×10^{-3}
13	3×10^{-3}
12	1.5×10^{-3}
11	7.5×10^{-4}
10	3.75×10^{-4}
9	1.88×10^{-4}
8	9.38×10^{-5}
7	4.69×10^{-5}
6	2.34×10^{-5}
5	1.17×10^{-5}
4	5.86×10^{-6}
3	2.93×10^{-6}
2	1.46×10^{-6}
1	7.32×10^{-7}
1	3.66×10^{-7}

(7)

In my study I also followed the method of Harris and Kalmus with the slight variation of using distilled water in place of the boiled tap water. I also used 6-n-propylthiouracil as my testing material. There were two reasons for using this: (1) with prop there is no revealing smell as found with P.T.C. and (2) the easy availability of propylthiouracil.

The chemical advisability of using 6-n-propylthiouracil is given in another part of this paper. This 6-n-propylthiouracil used was from the Lilly Company. Testing was done with the lily cups as described previously. Table 12 gives the concentrations used and the number of the solution. It will be seen that this numbering and concentration compares with that of Harris and Kalmus using P.T.C.

Table (12)

Solution No.	Concentration Molarity
1	6×10^{-3}
2	3×10^{-3}
3	1.5×10^{-3}
4	7.5×10^{-4}
5	3.75×10^{-4}
6	1.88×10^{-4}
7	9.38×10^{-5}
8	4.69×10^{-5}
9	2.34×10^{-5}
10	1.17×10^{-5}
11	5.86×10^{-6}
12	2.96×10^{-6}
13	1.46×10^{-6}
14	7.32×10^{-7}

Another method for determining tasters and nontasters has been found by doing salivary enzyme studies.

Fischer and Griffin reported in 1959 that variations in taste sensitivity are associated with genetic variations controlling the amount and composition of the soluble enzyme system, tyrosine iodinase (saliva factor). P.T.C. and related compounds containing the H-N-C=S grouping are apparently specific inhibitors of the soluble enzyme system. Their bitter taste can be modified by the fact that the system will accept a number of other substrates other than, but structurally related to tyrosine. 8

6-N-propylthiouracil placed with saliva indicates a faster rate of reaction for extreme nontasters than for tasters.

The testing is done as described in the following, "A 20 minute sample of mixed morning saliva stimulated by rubber band was centrifuged at 14° for 30 minutes at 3,000 rpm. The supernatant was re-centrifuged and 1 ml portions of it were diluted 1:5 with this buffer to p t 7.36 at 23° C. and supplemented with 6-n-propylthiouracil, final concentration of this and 6-N-Propylthiouracil are .05 M and 3.75×10^{-5} M. Later, the rate of reaction in a sample was followed in a Perkin-Elmer 'Spectracord 4000-A' spectrophotometer at 17° , 27° , and 37° in the ultra-violet range. The decrease in optical density was read at the (maximum) between 276 and 284 mu in 8 minutes. This decrease, which is not photosensitive, indicates a significantly faster rate of reaction for extreme 'nontasters' than for 'tasters' ". 9

Prop is used in these studies because it does not contain

impurities in the commercially available form, has no odor and is the least toxic among the thioureas. 10

CASE STUDIES

Three types of thyroid disease were used in this study. They were congenital athyreotic cretins, sporadic non-edemic cretins (metabolic cretins), and juvenile myxedema.

The following is a classification of Hypothyroidism by Edwin B. Astwood.

- A. Congenital hypothyroidism (cretinism)
 - 1. Athyreotic cretinism (failure of development of thyroid gland)
 - a. Complete
 - b. Partial
 - 2. Defective synthesis of hormone, due to
 - a. Iodine deficiency (edemic cretinism)
 - b. Enzymatic defect (familial goitrous cretinism)
 - c. Inhibition of synthesis - by antithyroid drug during pregnancy
- B. Acquired Hypothyroidism (Juvenile myxedema)
 - 1. Destruction of thyroid gland by
 - a. Surgical excision
 - b. Thyroiditis or Hashimoto's struma (Antibody reaction?).
 - c. Unknown cause
 - 2. Secondary to TSH deficiency
 - a. Panhypopituitarism

b. Specific TSH defect

3. Due to antithyroid drug

(1)

The first type of thyroid disease to be discussed is that of congenital athyreotic cretinism. In the typical athyreotic cretin the weight at birth is usually 8 pounds or more. The entire abdomen is usually protuberant as the result of laxity of the abdominal musculature. There is usually also an umbilical hernia. The base of the skull is short, and there is a persistence of the cartilaginous junction between the pre and post spheroid bones which normally ossifies in the 8th month of fetal life. Besides, the incomplete growth found in cretinism there are also actual deformities of the vertebral bodies as a consequence of retardation of bone age. There is almost a complete lack of epiphyseal growth and a great delay in the development of centers of ossification. Also because of delay in ossification of membraneous bones, the frontal suture is unusually wide, and the anterior fontanel is exceptionally large. As the picture develops, the facies is one of the most characteristic features. The face is round, stupid with a yellowish color. The eyelids are puffy, and the palpebral fissures are narrowed but horizontal in contrast to the slant observed in Mongoloids. The nose is flat and thick with an open mouth. The cretin usually has an open mouth from which protrudes a large thick tongue. The voice is flat and harsh. The neck is short and thick, the skin is dry and cool and presents a picture

of a nonpitting edema. The hair is dry, sparse, fine and lifeless. As the disease progresses without treatment, the above symptoms progress, and the feeble-mindedness of the child becomes even more apparent. Dentition is late and growth is retarded. In untreated cretins who have reached the age of 8 or 10 years, the measurement from umbilicus to soles of the feet is often less than that from umbilicus to crown.

The main tool in diagnosis is that of serum protein-bound iodine. Tracer studies with radioactive iodine show no pick-up. The demonstration of delayed ossification in membranous or long bones together with an elevated blood cholesterol may be sufficient to confirm a diagnosis of cretinism. 11

The next type studied is that of congenital goitrous cretinism. The physical appearance is the same as that of the athyreotic cretin with the possible exception of presence of a goiter. This type of cretinism represents an inborn error of metabolism with many possibilities for a defect in the synthesis of thyroid hormone may exist. The thyroid may fail to concentrate iodine, or once having accumulated iodide, may be unable to oxidize it and iodinate tyrosine residues. It might be that the organic binding by the gland is enhanced but the enzymatically controlled hormone synthesis from iodinated tyrosine is impaired. An organic iodine compound may be synthesized and released to the circulation which is not thyroxine or triiodothyronine. 11

The presence of goiters associated with cretinism and/or hypothyroidism in the absence of iodide deficiency was noted by Osler in 1897. He also showed familial incidence indicating a genetic factor.

The radioactive iodine uptake is usually high in congenital goitrous cretins. Butanol extractable iodine does not measure either iodinated tyrosines or complex iodinated proteins like thyroglobulin, but measures thyroxin. If there is a discrepancy between P.B.I. and B.E.I. determinations. There is an indication of a circulating iodoprotein other than thyroxin such as in thyroiditis, thyroid Ca, and secondary to irradiation of the thyroid. 3

The last type of thyroid disease studied is that of Juvenile Myxedema. Many of the characteristics of juvenile myxedema are intermediate between those of cretinism and adult myxedema. The physiognomy is not entirely like that of cretins.

The patients early growth and development are normal, later they are markedly retarded. The extremity-trunk ratio is infantile. The genitalia tend to be normal but puberty is delayed. Diagnostic studies for juvenile myxedema consists of determinations of the basal metabolic rate, plasma protein-bound iodine, and serum cholesterol, radioiodine studies, therapeutic trial with desiccated thyroid, and roentgenograms of the skeleton. The results are similar to those found in cretinism and for adult myxedema. 23

In this study a review of the charts of the University of

Nebraska Hospital and Childrens Memorial Hospital of Omaha were used. An initial letter and questionnaire form were sent to the patients asking for permission to study and basic physical and genetic information. The questionnaire was made up from symptoms of the three above thyroid diseases from textbooks of endocrinology, 17, 1, 11, 23 The letter and form follows.

GE

THE UNIVERSITY OF NEBRASKA
COLLEGE OF MEDICINE
42ND AND DEWEY AVENUE
OMAHA 5, NEBRASKA

November 12, 1963

Dear _____

I am sending you a series of questions and forms to be filled out concerning your thyroid disease. We would like to study you and your family in regard to genetic significance of your disease, that is if the disease tends to "run" in your family. We would like to do physical examinations and run a few tests. We are doing this in attempts to find a new diagnostic test which shows a tendency for thyroid disease to occur in a family.

Sincerely yours,

QUESTIONNAIRE

DATE _____

Your Name _____

Your Address _____

Date of birth _____ Place of birth _____

Parents' Name _____ Mother's Maiden Name _____

In answering the following questions, if you need more space for answering completely, please use the back of this sheet.

Cross out the term which does not apply.

1. I (Have) (Have not) had thyroid trouble. If you have now or have had, then state tests, treatment given and drugs used.
2. My height is _____.
3. My weight is _____.
4. I (do) (do not) have a round face.
5. I (have) (have not) had puffy eyelids.
6. I (do) (do not) have a thick, flat nose.
7. I (do) (do not) have a large thick tongue.
8. I (do) (do not) have a short thick neck.
9. I (do) (do not) have a goiter.
10. My deciduous (baby) teeth started coming in at what age _____ and were completed at what age _____.
11. I completed my permanent teeth at what age _____.
12. I (do) (do not) have a pot belly.
13. I (do) (do not) have a hernia around my navel.
14. I (do) (do not) have short stubby fingers.
15. I (do) (do not) have a yellowish colour to my skin.
16. My skin (is) (is not) cool.
17. My skin (is) (is not) dry.
18. My hair (is) (is not) fine and dry.

19. How many children have you and your wife (husband) had? _____
 Were any of them born early? _____
 Have you (has your wife) had any miscarriages? _____
 Were any of your children born dead? _____

20. Do you have, or have you had any other major or minor healing problem? If so,
 list: _____

21. What has been your schooling?
 Grade school _____
 High school _____
 College _____

22. Special talents _____

23. What work do you do? _____

24. Date of last medical examination? _____

25. Name of doctor who examined you _____
 His address _____

26. Names and addresses of doctors who have treated you:

(Name)	(Address)
_____	_____
_____	_____
_____	_____
_____	_____

27. Name and address of hospitals where I have received care:

<u>Name - Address</u>	<u>Date</u>	<u>Reason for Hospitalization</u>
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

28. Do you know of ANY relatives who have any thyroid disease or conditions?
 if so, name them with their relationship to you, and the condition or disease they have:

<u>Name</u>	<u>Relation</u>	<u>Disease</u>

29. YOUR CHILDREN:

	<u>Name</u>	<u>Married Name</u>	<u>Birth Date</u>	<u>Address</u>	<u>Date of Death</u>	<u>Cause of Death</u>
1.						
2.						
3.						
4.						
5.						
6.						
7.						

30. YOUR BROTHERS AND SISTERS:

	<u>Name</u>	<u>Married Name</u>	<u>Birth Date</u>	<u>Address</u>	<u>Date of Death</u>	<u>Cause of Death</u>
1.						
2.						
3.						
4.						
5.						
6.						
7.						

31. YOUR GRANDCHILDREN:

	<u>Name</u>	<u>Married Name</u>	<u>Birth Date</u>	<u>Address</u>	<u>Date of Death</u>	<u>Cause of Death</u>
1.	_____	_____	_____	_____	_____	_____
2.	_____	_____	_____	_____	_____	_____
3.	_____	_____	_____	_____	_____	_____
4.	_____	_____	_____	_____	_____	_____
5.	_____	_____	_____	_____	_____	_____
6.	_____	_____	_____	_____	_____	_____
7.	_____	_____	_____	_____	_____	_____

I hereby give my permission to the medical genetics team of the University of Nebraska College of Medicine to obtain medical information from _____ where I or my _____ (relationship) _____ (name) received treatment.

Witness: _____ Signed _____

Witness: _____

DATE _____

I hereby give my permission to the medical genetics team of the University of Nebraska College of Medicine to obtain medical information from my family physician (s) concerning _____

Dr. _____ (Address) _____

Dr. _____

Dr. _____

Dr. _____

Dr. _____

Witness: _____ Signed: _____

Witness: _____

DATE FROM STUDIES

From hospital records 11 cases of athyreotic cretin, metabolic cretin and juvenile myxedema were found. Only 3 of these patients could be located and two of these were willing to be tested with the propylthiouracil. A short summary of these patients and the results of their "taste testing" has been provided.

The propylthiouracil taste testing was done on 10 medical students as a control with 2 of these being in the "nontaster" range and 8 in the "taster" range. The dilutions at which they could differentiate distilled water from propylthiouracil are represented by the same numbering as given in the previous text.

A # 6	F # 7
B # 6	G # 3
C # 8	H # 9
D # 2	I # 6
E # 7	J # 8

Patient M.A.M.

This is a eight year old white female. She was first seen in the University clinics, for failure to thrive when she was at the age of 13 months. Physical examination at this time showed smooth pale and dry skin. Her head showed flatness in the occipital region with minimal prom in frontal region. She had an umbilical hernia. Skin creases did not go clear across her hands. Neurological examination showed reflexes which were bilaterally active. PBI on 9-27-57 was 3.6 and on 10-4-57 was 3.2 Radioiodine study at age of

one year was 4 hour pickup 6.8% and 24 hour 8.5%. A repeat RI pickup was 10.49% at 5 hours and 15.5% at 24 hours. A PBI was repeated on 3-16-60 showing 7.2. The original diagnosis of this patient was that of athyreotic cretin but in view of the PBI's it would seem that a diagnosis of juvenile myxedema would be more accurate. She had been on 1 grain thyroid since the age of one year.

At the present time the child is in the 1st grade having repeated Kindergarten twice. She has been described by her mother as the slowest member in her class. Only positive physical findings at this time are those of a smooth, dry, scaling skin.

Family history shows that her father and grandfather were the same person. Her mother had an 8th grade education quitting school at the age of 16. Her I.Q. was listed as 47. This is all that could be obtained on family history as the patient has been adopted and is living with her foster parents.

Taste testing as described in the previous text places her in the "nontaster" group as she is able to differentiate water from propylthiouracil 100% correctly at a dilution of 1.5×10^{-3} .

Patient L.B.

This 48 year old white male was first diagnosed as a cretin in 1930. He has been on & off thyroid since then. He has been diagnosed as a metabolic cretin, the deficient is being studied now but at the time of this writing his exact deficit is not known.

Physical examination shows him to be a short male about 5'1" tall with short legs, his height above umbilicus being longer than below his umbilicus. His speech is "thick" and he is hard of hearing. His face is wrinkled and has sort of a "monkey"like appearance. His thyroid is soft and enlarged about 2X normal. His tongue is enlarged in relation to his mouth. His feet are cold with a paucity of hair on the lower legs and feet.

A PBI on 5-22-63 was 2.9 and the cholesterol was 260.

Family history shows that his 71 year old mother is hypothyroid and takes thyroid medication. One brother takes thyroid medication for hypothyroidism and another has had a goiter removed. The patient has three children, the oldest daughter of which is hypothyroid and takes thyroid medication.

Taste testing as described in the previous text places him in the "nontaster" group as he is able to differentiate water from prophythiouracil 100% correctly at a dilution 7.5×10^{-4} .

SUMMARY

Dr. A. L. Fox discovered accidentally in 1930 that some people have the ability to taste P.T.C. and others do not. It was not long before, it was discovered that other substances would divide the general population into two groups that of "taster" and of "nontaster". It was found that the chemical radical responsible was that of $= N - \overset{\cdot}{C} = S$. It had been proposed and tested that the ability to "taste" or not to "taste" was on a recessive autosomal genetic basis and this has been substantiated. Many of these substances containing $= N - \overset{\cdot}{C} = S$ are goitrogenic and it was felt that there might be some relationship to thyroid disease. Taste testing was first done with goitrous patients and it was found that patients with nodular goiter were more prone to be in the nontaster groups. Taste testing was then tried on cretins and found that a significantly higher rate of nontasters were found in this group. Some further work in this area seemed to show a high incidence of "nontasters" in the athyreotic cretin group but near normal distribution in the metabolic cretin and juvenile myxedema group. All of these studies have been done with a limited number of patients however.

By going through old records of patients at the University and Childrens Hospital I found 11 cases which seemed to be documented good enough to have the diagnosis of juvenile myxedema, athyreotic cretin, and metabolic cretin. I started correspondence with all these patients and was able to locate and

obtain permission to test only two of these patients. One is a metabolic cretin and the other although originally diagnosed as an athyreotic cretin probably represents juvenile myxedema. Both of these patients fall into the "nontaster" groups. This neither substantiates nor refutes the hypothesis that "nontasters" occur more often in hypothyroid states. Many more patients must be tested. Ten medical students tested with the same material show 20% "nontasters" and 80% "tasters" which compares with the previous ratios of 30% "nontasters" and 70% "tasters" in the general population.

Because of patient L.B.'s family history with a great number of hypothyroids, taste testing of the entire family will be done to see if any correlation between "nontasting" and metabolic cretinism may exist.

BIBLIOGRAPHY

1. Astwood, Edwin B., Clinical Endocrinology I, Grune and Stratton, 1960, New York.
2. Blakeslee, A. F., Genetics of Sensory Thresholds, Taste for Phenylthiocarbamide, Proc. Nat. Acad. Sc., 18: 120, 1932.
3. Blizzard, Robert M., Inherited Defects of Thyroid Hormone Synthesis and Metabolism, Metabolism, 9:1 232, 1960.
4. Das, S. R., A Contribution to the Heredity of P.T.C. taste Character Based on a Study of 845 Sibpairs, Ann. Eugen. Lond., 20-21: 334, 1956.
5. Frazer, G. R., Cretinism and Taste Sensitivity to Phenylthio-Carbamide, Lancet., May, 1961, pp. 964.
6. Frazer, G. R.; Morgan, M.E., and Trotter, W. R., The Syndrome of Sporadic Goiter and Congenital Deafness, Quart. J. Med., 29, 279 (1960).
7. Griffin, F. and Fischer R., On factors Involved in the mechanism of Taste Blindness, Exp. 15, 447, 1959.
8. ----- and -----, "Taste Blindness" and Variations in Taste-Threshold in Relation to Thyroid Metabolism, J. of Neuro-psychiatry, Vol. 3, No.2, Dec., 1961.
9. ----- and -----; Differential Reactivity of Saliva from 'Tasters' and 'Nontasters' of 6-n-propylthiouracil, Nature, 187: 417, 1960.
10. -----, -----, England, S., and Pasamanick B., Bio-chemical Genetic Factors of Taste - Polymorphism and their Relation to Salivary Thyroid Metabolism in Health and Mental Retardation, Med. Exp. 356-366, 1961.
11. Garfield, Duncan, G., Diseases of Metabolism, Saunders 9th Edition, (1959).
12. Harris, H. and Kalmus H., The Distribution of Taste Thresholds for Phenylthiourea of 384 Sibpairs, Ann. Eugen. Lond., 15: 226, 1961.
13. ----- and -----, The measurement of Taste Sensitivity to Phenylthiourea, Ann. Eugen. Lond., 15-16, 1951.

14. ----- and -----; Genetical Differences in Taste Sensitivity to Phenylthiourea and to Antithyroid Substances, Nature, 163, 875, 1949.
15. ----- and -----, Chemical Specificity in Genetical Differences of Taste Sensitivity, Ann. Eugen., 15:32, 1949.
16. ----- and ----- and Trotter, W. R., Taste Sensitivity to Phenylthiourea and Goiter and Diabetetics, Lancet., 2: 1038, 1949.
17. Hurxthal, and Musulin, Clinical Endocrinology, J.B. Lippincott Co., pp. 381-391, 1953.
18. Kalow, Werner, Pharmacogenetics, Heredity and the Response of Drugs, W. B. Saunders, Co., Philadelphia, 1963.
19. Kitchen, F. D., Howel-Evans, W., Clark, C. A. , McConnell, R. B., and Shepared, P. M., P.T.C. Taste Response and Thyroid Disease, British Med. J.,1; 1069-74, 1959.
20. Pharmocopeia of the U.S.A., 16th Revision, Mack Publishing Co., 1960.
21. Shepard, T. H., and Gartler, S. M., Increased Incidence of Nontasters of Phenylthiocarbamide among Congenital Athyretic Cretins, Science, 131: 929, 1960.
22. Snyder, L. H., Studies in Human Inheritance IX, The Inheritance of Taste Deficiency in Man, Ohio J. Sc., 32: 436, 1932.
23. Williams, Robert H., Text Book of Endocrinology, W. b. Saunders Co., Philadelphia, Third Edition, 1962.