radiation dose is given rather than the total dose. In this case it could be important that radiation for medical purposes is given at high dose rates in the approximate range of 40 to 100 r a minute, while the average dose rate from natural background radiation is 2×10^{-6} r a minute.

Summary and Conclusions

The deaths from leukaemia in England and Wales for the period 1945 to 1957 have been classified under three headings—acute leukaemias of all types, chronic myeloid leukaemia, and chronic lymphatic leukaemia. The age-specific mortality rates have been calculated for each type of leukaemia, for each sex, and for three periods of time—1945 to 1949, 1950 to 1954, and 1955 to 1957.

A study of these data suggests that the principal feature in the real increase in leukaemia is a change in the incidence of acute leukaemia. This is compatible with the concept that an increased exposure to ionizing radiations plays some part in the changed incidence of the disease.

We are indebted to the Registrar-General of England and Wales for the extraction of the data and for permission to publish the results, and to Miss F. Callaby, Mrs. A. Frackiewicz, Mrs. E. A. O. Gray, and Mrs. V. Peetz for their assistance in the analysis.

REFERENCES

Armitage, P., and Doll, R. (1954). *Brit. J. Cancer*, **8**, 1.
—— —— (1957). Ibid., **11**, 161.
Burnet, M. (1958). *New Engl. J. Med.*, **259**, 423.
Clemmesen, J., and Sørensen, J. (1958). *Dan. med. Bull.*, **5**, 73.
Court Brown, W. M., and Doll, R. (1957). *Spec. Rep. Ser. med. Res. Coun. (Lond.)*, No. 295.
Hewitt, D. (1955). *Brit. J. prev. soc. Med.*, **9**, 81.
Loutit, J. F. (1958). *Practitioner*, **181**, 553.
MacMahon, B., and Clark, D. (1956). *Blood*, **11**, 871.
Registrar-General of England and Wales (1958). *Statistical Review of England and Wales for the Year 1956*. Part III. Commentary. H.M.S.O., London.
Stewart, A., Webb, J., Giles, D., and Hewitt, D. (1956). *Lancet*, **2**, 447.
Wald, N. (1957). *Acta haemat. jap.*, **20**, 152.
World Health Organization (1955). *Epidem. vital Statist. Rep.*, **8**, 81.

On April 27 England and Wales will have new standards for ice-cream. The main changes made by the new regulations are that standards are to be fixed for dairy ice-cream and for milk ice which are required to contain milk fat and must not contain any other fat ; that saccharin and other artificial sweeteners are not to be used in any ice-cream or in milk ice, and no mimimum sugar content is laid down ; that ice-cream made with non-milk fat is not to be labelled or advertised in a way which is suggestive of butter, cream, or milk ; but such ice-cream may continue to be sold as " ice-cream " and it may bear a statement that it contains skimmed milk solids ; that, after November 30 of this year, all pre-packed ice-cream which is made with non-milk fat must be labelled as containing vegetable or non-milk fat if it is sold as " ice-cream." The present requirements that ice-cream must contain not less than 5% fat and not less than $7\frac{1}{2}$% milk-solids-not-fat are included in the new regulations and so continue in force. The new regulations will revoke and replace the existing Food Standards (Ice-Cream) Order, 1953. The Secretary of State for Scotland proposes to make corresponding regulations which will apply in Scotland.

P.T.C. TASTE RESPONSE AND THYROID DISEASE

BY

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For over a hundred years a familial disposition in thyroid disease has been known. Since Romberg (1851) recorded Graves's disease in twins there have been many genetic studies using the classical method of pedigree analysis, but the results have been conflicting. Bartels (1953), on the basis of his own work (Bartels, 1941) and a review of the literature, concluded " that sporadic thyroid affections such as simple goitre, hypothyroid, and hyperthyroid states are probably genetically determined."

Fox (1932) discovered that some people taste phenylthiocarbamide (P.T.C.) and others do not. Further investigation established that this bimodal taste response was an example of human genetic polymorphism ; about 30% of Europeans and white Americans were non-tasters and 70% were tasters (Barnicot, 1950 ; Harris and Kalmus, 1950a).

In 1942 Richter and Clisby noticed marked thyroid hyperplasia in rats which had been fed with P.T.C., and subsequent work has established that the thiocarbamides in general are active goitrogenic substances. Among them are to be found the thiouracils as well as some naturally occurring goitrogens which have been isolated from turnips, brussels sprouts, rape, and kale, and found to belong to the same chemical family—all having the $-N-C-$ grouping.

$$\begin{array}{c} \| \\ S \end{array}$$

This relationship between P.T.C. and thyroid gland activity led Harris, Kalmus, and Trotter (1949) to test the taste response to P.T.C. of groups of patients with thyroid disease. Their data suggested that non-tasters of P.T.C. were slightly more susceptible to the development of adenomatous goitre than controls, but they found a normal taste distribution in patients with toxic diffuse goitre (" primary thyrotoxicosis "). As no subsequent study of this kind has been reported we have carried out a survey at the Thyroid Clinic, David Lewis Northern Hospital, Liverpool, and describe here the results of testing the P.T.C. taste response of 447 patients with thyroid disease and compare the results with those in 265 control individuals.

Material

The 447 patients who had undergone thyroidectomy were taken at random from attendances at the thyroid clinic between May, 1956, and May, 1958, and were taste-tested with P.T.C. by the method described below. In addition, we selected eight patients with toxic

diffuse goitre who had not been operated on (see below). The majority of the patients lived on Merseyside, which is not an area of endemic goitre.

The control group of 265 subjects was constructed by taste-testing hospital nurses and university students. The mean age of the control group (21.2 years) was some 10-20 years younger than the patient group, but, as age does not influence the distinction between tasters and non-tasters, this was not regarded as disadvantageous. However, with increasing age there is a slight loss of taste sensitivity to P.T.C. (Harris and Kalmus, 1950a), and this is commented on later.

Methods
Taste-testing

The P.T.C. taste response was determined by the method of Harris and Kalmus (1950a), and is based on the ability of individuals to discriminate various dilutions of the test substance from water.

Starting from a high dilution and working down, the subject tastes a few millilitres of the solutions until a definite taste is perceived. At high dilutions this substance in a " taster " is appreciated on the posterior surface of the tongue and pharynx, and thus patients are asked to swallow the solution intact instead of retaining it in their mouths and so diluting the solution with saliva. Having found an approximate threshold, the subject is then given eight glasses—four containing the P.T.C. solution at the concentration shown in the preliminary test, and four containing water. The eight glasses are arranged at random and the subject is asked to separate the two groups. If this is done correctly a further eight-glass trial is made at the next weaker dilution, but if the subject is unable to separate the two groups accurately the test is repeated with increasing concentrations of P.T.C. until a threshold is obtained.

At the time the taste-testing was performed (by either F.D.K. or W.H.E.) the nature of the goitre was unknown to us. Further data concerning the family history and the domicile were obtained and a specimen of saliva was also taken for determination of the secretor character (see Clarke et al., 1956).

In addition, 15 patients were taste-tested before and after thyroidectomy to determine whether any change in the threshold occurred and also to check the accuracy of the tasting method in our hands. In 11 of the 15 patients retested the taste threshold was unaltered, in two patients there was a change of threshold of one dilution (6 to 7 and 7 to 8), and in two patients a change of two dilutions (6 to 8 and 11 to 9). Thus in no instance did this slight alteration affect the distinction between tasters and non-tasters.

Classification

The classification of thyroid disease adopted was as follows: Group 1: single adenoma (a) toxic (" hot nodule "), (b) non-toxic. Group 2: multiple adenoma (a) toxic (" secondary thyrotoxicosis "), (b) non-toxic. Group 3: diffuse goitre (a) toxic (" primary thyrotoxicosis "), (b) non-toxic. This was similar to that used by Harris et al. (1949) except for the separation of single adenomata into group 1, as a result of a discussion with Dr. Trotter (personal communication, 1956). Further comments on this group are made later. The term " adenoma " is retained although these nodules, usually multiple, are known to be the result of recurring cycles of hyperplasia and involution.

Diagnosis

At a later date, when the P.T.C. testing had been done, the diagnosis in each patient was made after considering the following evidence: (a) clinical features and the course of the disease; (b) the operative findings; (c) the macroscopic and microscopic findings in the thyroid of the operative specimen; and (d) [131]I studies in many instances.

It should be emphasized that the data outlined above were available for each person in this series, since the patients were attending an established special clinic.

Patients who had undergone thyroidectomy were chosen, as examination of the excised gland provides more precise information than clinical examination alone. This was done in view of the fact that many thyroid adenomata are impalpable and that either exaggerated lobulation of a diffusely hyperplastic gland or the gland in thyroiditis may simulate multiple adenomata. In addition, because group 3a was small, we added eight typical cases of toxic diffuse goitre in young people who had not been operated upon. This could be done because the diagnostic error is much smaller here than with multiple adenomatous goitre.

To keep personal error and bias to the minimum each case was assessed by two of us (W. H. E. and F. D. K.), and the final diagnosis was made only after joint discussion but without knowledge of the taste threshold.

We appreciate that accuracy of diagnosis is crucial in an investigation of this sort. By analysing each case by the methods shown above, we consider that error has been reduced to a minimum, although clearly not eliminated. As expected with such criteria it was found impossible to establish a diagnosis in 16 patients in this series, and these are excluded from the analysis. They have, however, been included in the tables to show the taste threshold distribution.

Comment on Group 1b

This group of cases in which a single nodule was found is especially liable to errors in diagnosis. Great care was taken to check the histological pattern, since we felt that many pathological states could mimic a single nodule. On gross and microscopical examination the group was found to consist of the following morphological types: (a) colloid adenoma, mainly macro-acinar (29 cases); (b) cystic adenoma, due to degeneration (5 cases); (c) fleshy adenoma, mainly micro-acinar (8 cases); (d) papillary adenoma, border-line malignant (1 case). Types a and b may be the result of a localized hyperplastic/involution process which may eventually become widespread throughout the gland.

In the thyroid, although hyperplastic areas are difficult to distinguish from neoplastic proliferation, types c and d, in our view, exhibit the features of neoplasia rather than of hyperplasia. However, in view of the small numbers involved this group has not been subdivided.

Results

Table I shows the basic data of the thyroid patients and the control group. It will be seen that the former are divided into their appropriate diagnostic categories.

Table II gives the P.T.C. threshold distributions of all the individuals in Table I, together with those of the 16 unclassifiable patients mentioned above. The histograms (Figs. 1 to 4) show diagrammatically the taste distributions of the main groups.

TABLE I.—*General Data on Goitre and Control Distribution*

	Group 1		Group 2		Group 3		Con-trols
	a	b	a	b	a	b	
Total No. in groups ..	2	43	30	216	133*	7	265
Female	1	38	27	191	112	6	210
Male	1	5	3	25	21	1	55
Mean ages in years ..	46·2		46·0		39·4	31·4	21·2
Age range ,, ,, ..	18–70		15–80		14–60	20–45	19–50
Domiciled in Liverpool and Wirral areas ..	75%		65%	66%	65%	70%	46%
Parents or sibs with goitre	20%		33%	33%	16%	42%	6%

* Includes 8 non-operation cases.

Statistical Analysis

The dividing line between tasters and non-tasters has been taken as being between serial dilutions 4 and 5, since all the data are consistent with there being an antimode in the region of dilution 4. There is no significant difference in the frequency of non-tasters between males and females of the control group, and the frequency is consistent with other investigations in England (Barnicot, 1950; Harris and Kalmus, 1950a). A slight excess of non-tasters is usually found in males and is of the order . observed here. However, a significant difference would not be expected from a sample of the present size.

There is also no evidence of heterogeneity between males and females with respect to the frequency of non-tasters in the toxic diffuse goitre and single adenoma categories. However, in the multiple adenoma class there are about twice as many non-tasters among the males, and this sex difference is highly significant (see Table III). Consequently, in the subsequent analysis the sexes have been treated separately in this disease
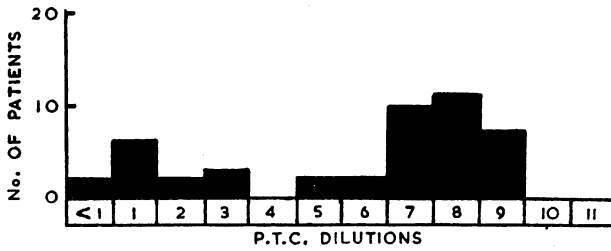

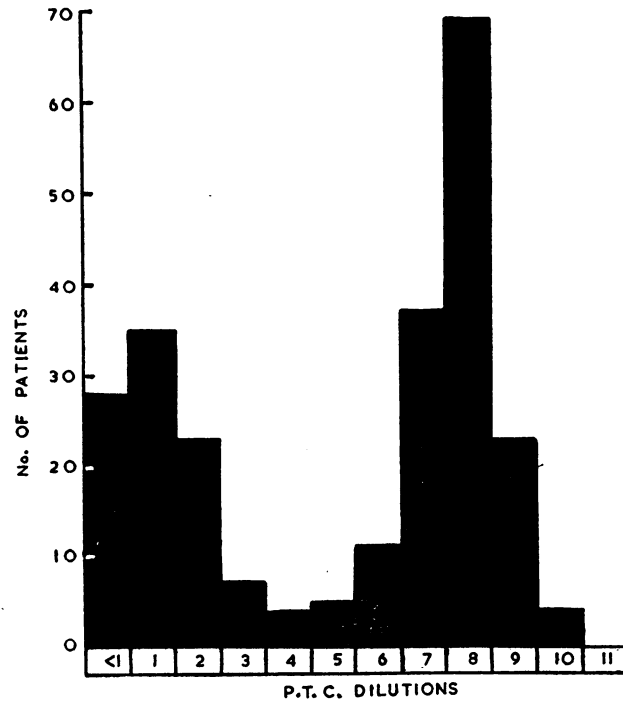FIG. 1.—Groups 1a and 1b: Single adenoma. 45 patients.

FIG. 2.—Groups 2a and 2b: multiple adenoma. 246 patients.

group. A comparison between the toxic and non-toxic conditions within this category shows that there is no significant difference between males and females.

Compared with the control population there is a highly significant deficiency of non-tasters among people with toxic diffuse goitre and an excess among those with multiple adenomata, the excess being significantly more marked in the males. As would be expected, therefore, the males and females with toxic diffuse goitre and those with multiple adenomata are very different from one another with respect to the frequency of non-tasters. The single adenoma category is not different from the controls and toxic diffuse goitre categories, nor is there heterogeneity between the females of this group and those with

TABLE II.—*Data on Taste Threshold in Goitres and Controls*

Group	Total	Tasters	Non-tasters	P.T.C. Dilutions												
				<1	1	2	3	4	5	6	7	8	9	10	11	12
1a	2	1	1	1 F	—	—	—	—	—	—	—	—	1 M	—	—	—
1b Male	5	5	—	—	—	—	—	—	2	—	—	2	1	—	—	—
Female	38	26	12	1	6	2	3	—	—	2	10	10	5	—	—	—
Total ..	43	31	12 (27·8%)	1	6	2	3	—	2	2	10	11	6	—	—	—
1a+b .. Total ..	45	32	13	2	6	2	3	—	2	2	10	11	7	—	—	—
2a Male	3	—	3	2	1	—	—	—	—	—	—	—	—	—	—	—
Female	27	18	9	4	3	2	—	—	—	1	5	7	3	2	—	—
Total ..	30	18	12 (33·3%)	6	4	2	—	—	—	1	5	7	3	2	—	—
2b Male	25	10	15 (60%)	5	7	3	—	—	1	—	3	6	—	—	—	—
Female	191	121	70 (36·6%)	17	24	18	7	4	4	10	29	56	20	2	—	—
Total ..	216	131	85 (39·35%)	22	31	21	7	4	5	10	32	62	20	2	—	—
2a+b .. Total ..	246	149	97 (39·3%)	28	35	23	7	4	5	11	37	69	23	4	—	—
3a Male	18	15	3	—	2	—	1	—	—	2	5	7	1	—	—	—
Female	107	89	18	3	4	8	1	2	3	3	31	45	7	—	—	—
Total ..	125	104	21 (15·8%)	3	6	8	2	2	3	5	36	52	8	—	—	—
3a clinical only ..	8	7	1	—	1	—	—	—	—	—	2	2	3	—	—	—
3a operative+clinical ..	133	111	22 (16·6%)	3	7	8	2	2	3	7	38	55	8	—	—	—
3b	7	5	2	—	1 M	—	1	—	1	—	—	2	2	—	—	—
Rejected group, diagnosis impossible	16	11	5 (31·2%)	1	2	1	1	—	—	2	5	1	2	1	—	—
Controls Male	55	36	19	6	10	—	1	2	3	2	2	16	9	4	—	—
Female ..	210	151	59	8	33	14	3	1	7	3	15	50	57	15	1	3
Total ..	265	187	78 (29·4%)	14	43	14	4	3	10	5	17	66	66	19	1	3

C

TABLE III.—*Statistical Analysis*

Comparison	χ^2	D. of F.	P
Control ♂-♀	0·69	1	>0·3
Single adenoma (group 1b) non-toxic ♂-♀.. ..	—	—	>0·1
Multiple adenomata			>0·05
(Group 2a) toxic ♂-♀	—	—	>0·05
(Group 2b) non-toxic ♂-♀	4·12	1	<0·05
,, ♂ toxic—non-toxic	—	—	>0·2
,, ♀ ,, ,, ...	0·11	1	>0·7
,, toxic+non-toxic ♂-♀	7·04	1	<0·01
Toxic diffuse goitre (group 3a)			
Operative series: ♂-♀	—	—	>0·5
Clinical series: ♂-♀	—	—	>0·5
Operative—clinical series	—	—	>0·5
Single adenoma (group 1b):			
Non-toxic—control	0·04	1	>0·8
Multiple adenomata (group 2)			
♂ toxic+non-toxic—control ♂	5·80	1	<0·02
♀ ,, ,, ,, ♀	2·77	1	>0·05
	8·57	2	<0·02
Toxic diffuse goitre (all cases) (Group 3a):			
Toxic—control	7·15	1	<0·01
Toxic diffuse goitre (all cases):			
♂ toxic—multiple adenomata ♂ toxic+non-toxic	—	—	<0·001
♀ ,, ,, ♀ ,, ,,	12·26	1	<0·001
Single adenoma:			
♂ non-toxic—multiple adenomata ♂ toxic+non-toxic	—	—	<0·013
♀ non-toxic—multiple adenomata ♀ toxic +non-toxic	0·14	1	>0·7
Single adenoma:			
Non-toxic—toxic diffuse goitre	2·01	1	>0·1

multiple adenomata. However, the males are significantly different from the multiple adenomata males, having a lower frequency of non-tasters.

When considering the nature of the association revealed by the statistical analysis it is necessary to take into account the mean age in the various categories since it is known that sensitivity to P.T.C. decreases with age. Consequently, by taking the dividing line between tasters and non-tasters of all groups as falling between dilutions 4 and 5, one might obtain a difference in the frequency in non-tasters which results merely from a difference in the mean age of individuals in the categories and does not reflect a genetic diversity. A χ^2 analysis of the numbers of individuals in each dilution group within the taster class (combining dilutions 5 with 6 and 9 with 10 because of small numbers) reveals that there is no significant
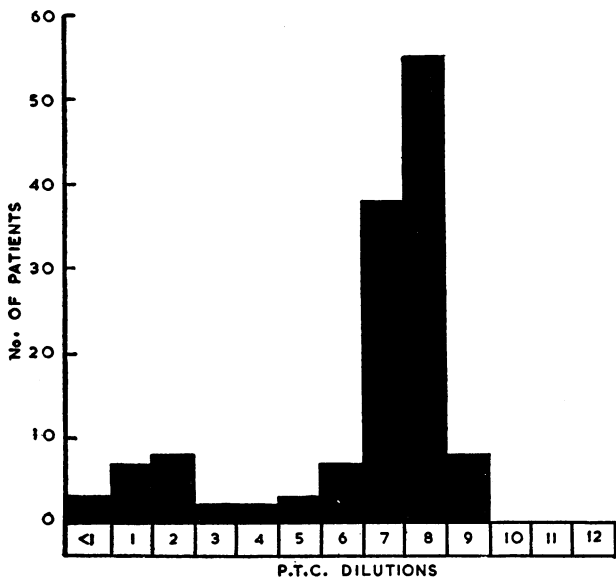

FIG. 3.—Group 3a: 133 patients.

heterogeneity between the diffuse goitre, single, adenoma and multiple adenomata categories ($\chi^2_6 = 10.3$, P>0.1). We are therefore safe in concluding that the highly significant differences between the toxic diffuse and multiple adenomata categories reflect a real genetic difference and are not caused by a general decrease in sensitivity to P.T.C. with age.

The control group has a lower mean age than the total goitre group and therefore might be expected to be more sensitive to P.T.C. Any discrepancy resulting from this would mean that the control group would have to be adjusted to contain more non-tasters; consequently the significant difference between the controls and diffuse goitre categories would be enhanced and not reduced. In fact, a χ^2 analysis reveals that within the taster class there is a very significant
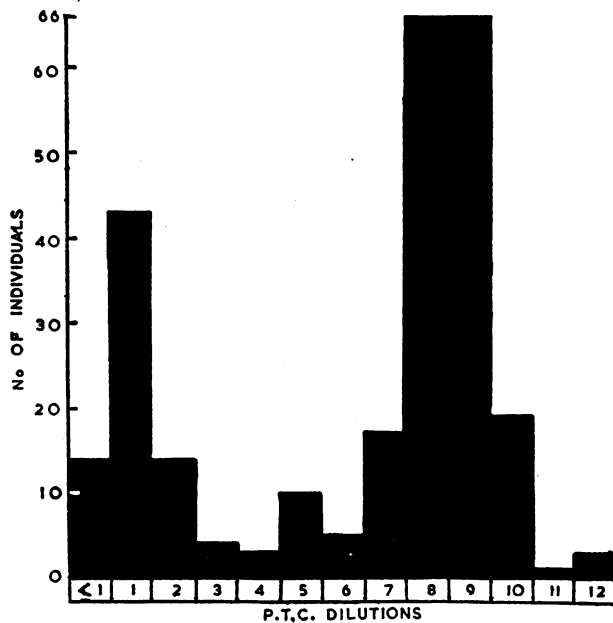

FIG. 4.—Control group: 265 individuals.

difference between the combined goitre and control group ($\chi^2 = 79.7$, P<0.001), the mean threshold dilution being 8.3 for the control but only 7.6 for the goitre groups, as would be expected from the greater mean age of the latter. However, a more detailed analysis reveals that the shift in sensitivity with age is not the same at all dilutions, being far greater in the higher dilutions and smaller in the region of thresholds 4 and 5. This is revealed in part by the heterogeneity χ^2 in which dilutions 9 and 10 together supply nearly two-thirds of the value of the χ^2. Almost the same proportion is contributed to the heterogeneity χ^2 within the combined goitre group by the highest dilution—namely, 9 and 10 combined.

The greater change at higher dilutions can be partly adjusted for if one assumes that 0.1 times the dilution is the compensation factor which should be applied to the control group at each dilution. For example, all the individuals at dilution 10 will be placed in dilution 9. but only 0.5 of those in dilution 5 will be transferred to 4, the non-taster category. Such an adjustment removes the heterogeneity between the goitre and control groups, and the change of five individuals from the taster controls to the non-tasters does not invalidate the statistical conclusions on goitre. In fact, it is evident from the data that such a large adjustment as five

individuals between the taster and non-taster categories is unwarranted, since it is quite clear that the figure 0.1 should itself be reduced at lower dilutions.

Further evidence of the absence of misclassification due to an age effect between tasters and non-tasters comes from the multiple adenomata category. There is no increase in the incidence of non-tasters with age (range 15–80 years), demonstrating that there can be no significant tasting error.

We can conclude that, despite the circumstance that our control group was younger than the goitre group, the differences confirmed by statistical analysis reflect real differences in genotype frequencies and are not just a consequence of age.

Blood Group and Secretor Data (Table IV)

Analysis shows that there is no significant heterogeneity between the blood-group distributions, the frequencies of non-secretors in the three main groups of thyroid disease combined, and the controls (P>0.1 ; P>0.2 respectively). We can say, therefore, that the data show no evidence that there is an association between these characters and the varieties of thyroid disease examined. Further, the figures support the view that the goitre subjects and controls were drawn from comparable populations.

TABLE IV.—*Blood Groups and Secretor Status*

Phenotype	Group 1 a+b	Group 2 a	Group 2 b	Group 3 a	Controls
O $\{$ S	9	10	68	35	81
O $\{$ ss	3	2	28	12	28
A $\{$ S	13	9	49	22	54
A $\{$ ss	8	1	12	17	24
B $\{$ S	—	2	14	9	12
B $\{$ ss	—	—	4	4	3
AB $\{$ S	1	—	4	4	4
AB $\{$ ss	—	—	—	1	2
Total ..	34 % ss = 32·5	24 % ss = 23·1	179	104 % ss = 32·7	208 % ss = 27·7

Discussion

An abnormal taste distribution has been found in two main groups of patients with thyroid disease—those with multi-adenomatous goitre, both toxic and non-toxic, and those with toxic diffuse goitre. Before ascribing a causal relationship to the associations, four considerations must be borne in mind.

1. *Biased Diagnosis.*—Although care was taken to avoid bias, occasionally the nature of the goitre might have been remembered when taste-testing was carried out. Consequently, it is possible that there was a subconscious bias in assigning a score to people in thresholds lying in the region of 5. However, the score assigned depended on the reactions of the patient to various solutions and not on the observer. Moreover, retesting has shown little error in the technique, and owing to the small numbers of people in thresholds 3, 4, and 5, the bias would have to be enormous. We therefore believe that such an effect cannot account for the associations. The other possibility, which is more difficult to assess, is that there was bias in the diagnosis of the type of goitre if the taste threshold was remembered. In fact, although it might be fairly easy to remember the diagnosis of the goitre in patients who had attended the clinic regularly, the chances of remembering the taste threshold, which was usually

ascertained only once, would be much smaller. Moreover, there seems no reason for remembering the thresholds of males rather than those of females, so the sex difference cannot be accounted for in this way. It seems fairly certain, therefore, that neither of these biases materially affects the result.

2. *Incorrect Diagnosis.*—In such a difficult field as goitre diagnosis there are bound to be some errors, and it is impossible to assess the magnitude of these. However, mistakes in diagnosis, provided they are not biased as a result of the knowledge of the taste threshold, could not, on their own, manufacture a statistical association with this genetic marker. In fact, they would obscure the association, and consequently the relationship between tasting and goitre cannot solely be due to errors in diagnosis.

3. *Difficulties in Diagnosis.*—We were unable to establish a diagnosis in 16 out of this series of 447 patients, 6 of these patients exhibiting in the thyroid gland macroscopic and microscopic features of diffuse hyperplasia with localized adenomatous change. However, this proportion is small and constitutes only 3.5% of the whole series. Merely excluding difficult cases without reference to their taste threshold could not give rise to an association between tasting and nodular or diffuse goitre if none really existed.

4. *Racial Stratification.*—It is conceivable that within the population there are strata which are high or low in the frequency of tasting and which also differ in the type of goitre they develop without the two being related. The association between the nature of the goitre and the frequency of the taster/non-taster classes can hardly result from an undetected stratification of this type within the English population. Not only are the differences too large, but the sex difference within the multiple adenomata group, and the difference between multiple and toxic diffuse goitres, are quite inconsistent with such a hypothesis when the domicile and origins of the individuals in the survey are investigated.

A Causal Relationship

If a causal hypothesis is accepted the results of this analysis indicate that the taster/non-taster genotypes are important in determining the type of thyroid disease which an individual may develop, and that in the multiple adenoma group the genotype is about twice as important in males as in females.

It is improbable, in view of the marked differences in P.T.C. taste response found in toxic diffuse and multi-adenomatous goitre, 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. It is more likely that this easily measured action of the gene is only a part of a wider fundamental biochemical action.

From a biochemical standpoint the differential taste response is confined to a group of substances possessing a $-N-C-$ linkage (Harris and Kalmus, 1950b). They

$$-\overset{\parallel}{\underset{S}{N-C}}-$$

are all active reducing agents, and P.T.C. itself has been shown to inhibit tyrosinase. Their biological action is to inhibit the synthesis of thyroxine. This effect occurs within the thyroid, is uninfluenced by iodine medication, and results in thyroid hyperplasia under the stimulus of pituitary thyrotrophin. One such compound, L.5.vinyl-

2-thio-oxazolidone (" goitrin "), has been isolated from turnips and its presence demonstrated in the seeds of cabbage, rape, kale, and brussels sprouts (Astwood, Greer, and Ettlinger, 1949). Greer (1957) showed that kale seed, of all the members of the mustard family (Cruciferae), contains the largest quantities of this substance.

The finding of this compound in nature stimulated interest in its role in the pathogenesis of goitre, but its clinical importance, in comparison with that of iodine deficiency, is generally thought to be slight. This view was reinforced when it was shown that cooking these vegetables (*Brassica*) destroyed the enzyme system responsible for the formation of the goitrogen from its precursor (" progoitrogen "). It was then noted that brassicae are a source of winter food for cattle and that milk may be the vehicle for the transmission of the goitrogen to man. Clements and Wishart (1956) described an outbreak of goitre among children in Tasmania in an area where iodine prophylaxis had been practised carefully. They demonstrated a goitrogen, which they were unable to identify, in the milk from cows which had been fed on kale (choumoellier) but not in milk from cows fed on fodders which did not contain either brassicae or kale.

In this country Greene, Farran, and Glascock (1958) confirmed these findings experimentally in rabbits fed on kale milk, but they were unable to demonstrate significant depression of serial ^{132}I uptake curves in seven healthy men after one month of taking milk from kale-fed cows. In our opinion the ^{132}I method is not comprehensive enough to exonerate the role of kale milk as a goitrogen in man, particularly in view of the previous finding of Clements and Wishart (1956).

The results of this survey in adenomatous goitre naturally suggest the hypothesis that the inability to taste P.T.C. is associated with a greater susceptibility to the action of goitrogens of a similar chemical type, and cows' milk could be an important source of such compounds in the winter months. If this were so, cycles of seasonal involution and hyperplasia would occur in the thyroid, particularly in non-tasters of P.T.C., and it is just this pathological sequence which is known to give rise to adenomatous goitre in later life.

A notable finding in the series of adenomatous goitres is the considerably higher incidence of non-tasters of P.T.C. in the male as compared with the female patients. The male:female ratio in sporadic goitre lies between 1:8 and 1:15, except in areas of endemic goitre, where the sex ratio approaches unity. In view of the fact that, in the female, cyclical changes of involution and hyperplasia are known to occur in the thyroid in relation to the menstrual cycle and child-bearing, it might be anticipated that genetic influences (other than those affecting sex) would be less important in women than in the male. Our findings show this clearly, the incidence of non-tasting in the males with adenomatous goitre being 60%, in contrast to the female rate of 36.6%.

It remains to consider the association between tasting and diffuse goitre, a finding which was not reported by Harris et al. (1949). If the association we have found is real it seems likely that the taster status determines the nature of the goitre—that is, whether it be nodular or diffuse. If the hypothesis that non-tasters are more susceptible to thiocarbamides is correct, it seems possible that the homozygote tasters (TT) are even less susceptible than the heterozygotes (Tt). Such

insusceptibility would then have to be assumed to render the gland more prone to toxic diffuse goitre, and thus one of the natural restraining mechanisms in thyroid homoeostasis is removed. This could result in a highly sensitive gland which might react more vigorously to psychic stimuli via the medium of the pituitary and hypothalamus. The data are not of a sort to test this hypothesis, but it is capable of experimental verification. Whether these hypotheses are correct or not, the associations described make it possible to attack the pathogenesis of all types of non-endemic goitre from a new angle.

Summary

The P.T.C. taste threshold was determined in 447 patients with thyroid disease and in a control group of 265 individuals by the eight-glass technique of Harris and Kalmus.

In 246 cases of adenomatous goitre, a significantly high incidence of non-tasters (genotype tt) was found, and this was proportionately greater in men (60%) than in women (36.6%).

In 133 patients with toxic diffuse goitre a significant excess of tasters was found (genotypes TT, Tt), but without sex difference.

The findings suggest that the taster/non-taster genotypes are of importance in determining the type of thyroid disease, and the possible mechanisms are discussed.

The distribution of the ABO blood groups and secretor status in multi-adenomatous and toxic diffuse goitre was not found to differ significantly from that of the control group.

REFERENCES

Astwood, E. B., Greer, M. A., and Ettlinger, M. G. (1949). *Science*, **109**, 631.
Barnicot, N. A. (1950). *Ann. Eugen. (Lond.)*, **15**, 248.
Bartels, E. D. (1941). *Heredity in Graves' Disease*. Munksgaard, Copenhagen.
—— (1953). In *Clinical Genetics*, edited by A. Sorsby, p. 529. Butterworth, London.
Clarke, C. A., Edwards, J. W., Haddock, D. R. W., Howel-Evans, A. W., McConnell, R. B., and Sheppard, P. M. (1956). *Brit. med. J.*, **2**, 725.
Clements, F. W., and Wishart, J. W. (1956). *Metabolism*, **5**, 623.
Fox, A. L. (1932). *Proc. nat. Acad. Sci. (Wash.)*, **18**, 115.
Greene, R., Farran, H., and Glascock, R. F. (1958). *J. Endocr.*, **17**, 272.
Greer, M. A. (1957). *Amer. J. clin. Nutr.*, **5**, 440.
Harris, H., and Kalmus, H. (1950a). *Ann. Eugen. (Lond.)*, **15**, 24.
—— —— (1950b). *Ibid.*, **15**, 32.
—— —— and Trotter, W. R. (1949). *Lancet*, **2**, 1038.
Richter, C. P., and Clisby, K. H. (1942). *Arch. path. (Chicago)*, **33**, 46.
Romberg, M. H. (1851). *Klinische Wahrnehmungen und Beo-bachtungen*. Hertz, Berlin. Quoted by Bartels (1941).