mained high for some months, till the patient fell down stairs, when she felt something give away. On examination, the vaginal vault was prolapsed with recurrence of the cystocele and rectocele. It was not so lax, however, as to permit of being pushed up to the anterior abdominal wall for suturing to the rectus fascia—Brady's operation. About this time, Wharton's *Gynæcology* carried a description of Grant Ward's operation—reinforcement of the round ligaments with ox fascia. We had no ox fascia, but decided to use fascia lata. Instead of running the strips under the bladder peritoneum, we decided on a simple technique adapted from Simpson-Montgomery's suspension. It seemed logical that since the fascia was to reinforce the round ligaments, it should follow along the course of these ligaments. The result was excellent, and the vaginal vault has held up for over five years.

After several cases, we tried to avoid the thigh incision by employing fascia from the abdominal wall, obtained through the hysterectomy incision. Fascia from the midline proved unsuitable, as its decussating fibres ran transversely, and the strip tended to pull apart. We then decided on strips of external oblique fascia ripped out in the direction of its fibres. This was employed in several cases. At that time, we were as yet unaware that Aldridge had previously employed a somewhat similar technique for obtaining short broad fascial strips to underlie an incontinent urethra, the technique of which is reproduced in Te Linde's *Operative Gynæcology*.

Recently, Dr. Paul R. Fletcher of St. Louis, has described an over-the-bladder technique, similar to that of Ward, employing fascial strips obtained from the *outer* part of the rectus abdominis fascia. The remarks of Dr. Norman F. Miller of Ann Arbor, in discussing Dr. Fletcher's paper, interest us considerably:

> "In his present technique, Dr. Fletcher uses fascial strips from the rectus sheaths approximately 3 cm. apart. Fascial strips taken much further apart, as from the external oblique, or more easily, as a transplanted strip of fascia lata, would, it seems to me, make a vastly better support. Thus a strip of fascia lata extending from one inguinal ring to the other, paralleling the subperitoneal course of the round ligaments, would provide good support and offer an added advantage of permitting an entirely normal direction of the supported vagina, without the possibility of interfering with bladder function."

The technique envisioned by the University of Michigan's great teacher is identical with that with which we have been "experimenting" over the past five years with satisfactory results in twelve cases. Possibly it is past the experimental stage.

SUMMARY

Fascial suspension of the vagina was introduced by Grant Ward of Johns Hopkins Hospital. It is an advance in gynæcological surgery. Fascia lata may be employed and is unexcelled, or fascia may be obtained from the abdominal wall, if it is unmarred by old incisions.

The operation is indicated in: (1) Cases of prolapse complicated by intrapelvic pathology requiring abdominal hysterectomy, the commonest example being the woman with uterine tumours and the cervix at the outlet. (2) Cases of prolapse of the vagina after total hysterectomy, where the vaginal vault cannot be pushed up to the level of the abdominal wall and sutured to the fascia.

A modification of Ward's technique is presented.

BIBLIOGRAPHY

1. WARD, G. E.: *Arch. Surg.*, **36**: 163, 1938.
2. ALDRIDGE, A. H.: *Am. J. Obst. & Gyn.*, **44**: 398, 1942.
3. FLETCHER, P. F.: *Am. J. Obst. & Gyn.*, **56**: 41, 1948.

380 Driveway.

PROTEIN-BOUND PLASMA IODINE AS AN AID IN THE DIAGNOSIS OF THYROID DISEASE*

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THE development of reliable micromethods[1, 2] for the determination of iodine in blood has provided an additional aid in the diagnosis and treatment of thyroid disorders. The iodine has been determined both in whole blood[3, 4] and in serum or plasma,[1, 5] but the work of Salter[6] indicates that the circulating thyroid hormone resides entirely in the plasma, the red cells containing little or none.[5, 6, 7, 8] The hormonal iodine is either a part of or is bound in some manner to the plasma proteins.[9] There is also in the plasma a small variable amount of inorganic iodide which has no hormonal activity, although

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a recent report by Wolff and Chaikoff[10] indicates that its level may govern the rate of hormone synthesis by the thyroid. Therefore the concentration of protein-bound plasma iodine is used as an index of the amount of circulating thyroid hormone.

The normal range of protein-bound iodine has been reported to be 6 to 8.4 μgm. %,[11] 4.8 to 7.7 μgm. %,[12] and 4 to 8 μgm. %.[7, 13] Values above the normal have been found to be associated with hyperthyroidism and values below the normal with hypothyroidism[7, 11, 12, 14] and there is general agreement that the test is highly specific for the diagnosis of dysthyroid states.

The purpose of this report is to supply further data substantiating these claims and to report rare instances in which abnormal values have been found in conditions not ordinarily associated with thyroid dysfunction.

METHOD

Duplicate 6 ml. aliquots of plasma, prepared from heparinized venous blood collected in the morning under fasting conditions were used for analysis. The proteins were precipitated with zinc hydroxide[13] and separated from any inorganic iodide by discarding the supernatant fluid resulting from centrifugation before and also after each of two washings with 50 ml. of water. The precipitated plasma proteins were subjected to the chromic acid oxidation and distillation procedure of Taurog and Chaikoff,[1] the quantities of reagents being altered to accommodate the 6 ml. amount of plasma.

The alkaline distillate of iodine was drained into a 50 ml. beaker and evaporated on a hot plate, without boiling, to a volume of about 2 ml. This was transferred with two 0.5 ml. washings to a small test tube; one drop of a dilute solution of methyl orange was added and the solution neutralized with 3N H_2SO_4, one drop in excess being added. Four drops of freshly prepared bromine water were added to oxidize the iodine to iodate. The excess bromine was removed by boiling, and the boiling continued until the volume in the test tube was reduced to 1.5 ml. Following cooling the tube was chilled in ice water and kept cold during the ensuing titration. One drop of a freshly prepared 0.4% KI solution was added and the resulting free iodine titrated with 0.001N thiosulfate with the aid of a microburette of the Rehberg type; one drop of 0.1% starch being used as an indicator.

With this procedure duplicate estimations agreed within 0.8 μgm. % or less. Recovery of iodine added in amounts in the range encountered, (0.3 to 0.5 μgm.) was from 87 to 105%. In many cases aliquots of the same plasma were taken for cholesterol and plasma protein determinations.

Salter[15] has pointed out that if organic iodine compounds such as priodex, lipiodol, etc., have been administered, they will act as contaminants, for they are precipitated with the protein precipitating reagents and give rise to enormously high values. They may remain in the body for long periods of time, acting as contaminants. This has been our experience also.

Basal metabolic rate determinations were measured by means of the Benedict-Roth machine. All patients were in the fasting state and the estimation was made in the morning either before rising or after 1 to 2 hours' rest. In most cases the determinations were made on the same or within a few days of the iodine analyses. Two 6 minute tests were made on each patient. If the discrepancy in oxygen consumption was greater than 5% a repeat test was carried out. In each case the lowest oxygen consumption was taken as the basal reading. The validity of this value was checked by repeat determinations on two successive days on 13 patients. The calculated rates for these days showed an average difference of 4 while the greatest difference was 11.

SUBJECTS

The subjects of this investigation were ward or out-patients of the Winnipeg General Hospital, members of the staff and medical students. They have been divided into 5 groups on the basis of the usual clinical and laboratory criteria. Doubtful diagnoses were reviewed after 6 months when the response to specific therapy was also taken into consideration. All diagnoses were made without reference to the protein-bound iodine estimations. Any subject who had been given organic iodine compounds was rejected. The 5 groups were constituted as follows:

1. *Normal.*—A group of 34 individuals who had no evidence of thyroid disease and 28 of whom were completely normal. The other 6 were patients awaiting elective orthopædic procedures such as removal of knee cartilages. The age range was from 16 to 64 years with a sex distribution of 30 males and 4 females.

2. *Hypothyroid.*—A group of 16 individuals in whom thyroid hypofunction was diagnosed. Two doubtful cases with normal iodine values in which no final clinical assessment of thyroid status was made have been omitted. The group consisted of 12 females and 4 males, the age range being from 18 to 72 years with the exception of one cretin aged 22 months.

3. *Hyperthyroid.*—A group of 18 individuals in whom hyperthyroidism was diagnosed. It consisted of 14 females and 4 males, the age range being 17 to 70. In this group were 3 cases of recurrent hyperthyroidism following thyroidectomy, while the others had received no previous treatment.

4. *Non-toxic goitre.*—A group of 13 individuals who had enlarged palpable thyroids in whom there was no evidence of toxicity or malfunction. The age range was 21 to 73 years with a sex distribution of 12 females and 1 male. Some of the patients complained primarily of thyroid enlargement but the majority also had indefinite complaints such as asthenia for which no organic reason was found.

5. *Miscellaneous.*—A group of 32 individuals selected to represent various conditions which are detailed in Table I.

TABLE I.
DETAILS OF MISCELLANEOUS GROUP

Subject	Age	Sex	Protein bound iodine μgm. %	B.M.R.	Cholesterol mgm. %	Plasma protein gm. %	Diagnosis
63953	38	F.	5.7	+ 6	235	7.9	Psychoneurosis
59200	64	F.	5.2	- 8	—	7.2	Psychoneurosis
64204	47	F.	8.0	- 9	210	6.7	Psychoneurosis
9604	65	M.	3.9	+23	—	7.3	Involutional depression
58092	33	F.	6.1	- 4	205	7.0	Anxiety neurosis
16307	27	F.	11.2	+18	233	7.1	Anxiety neurosis
49470	60	F.	8.1	- 0	250	6.5	Anxiety neurosis
10818	66	F.	6.0	—	—	—	Congestive heart failure
A1073	50	M.	6.1	- 3	233	5.9	Congestive heart failure
A648	46	F.	4.7	+11	—	—	Hypertension
47631	49	F.	4.4	- 5	—	6.9	Hypertension
15152	60	F.	14.0	- 0	—	6.8	Hypertension
43656	68	F.	11.3	- 9	260	6.8	Hypertension
64030	32	F.	4.6	- 0	166	7.5	Hypertension
A1723	68	F.	4.3	+19	—	7.4	Diabetes, Hypertension
A1094	56	F.	5.1	-15	220	7.1	Diabetes, Hypertension
58880	30	F.	4.6	-15	165	—	Obesity
A7766	27	M.	8.1	+18	—	—	Cushing's disease
A4782	41	M.	6.0	+13	166	7.5	Addison's disease
A1737	22	F.	7.3	+ 4	—	7.4	Hypogonadism
63685	28	F.	10.2	—	—	—	Pregnancy
A3951	18	F.	3.1	- 8	510	3.4	Nephrosis
M	6	F.	2.2	—	—	2.8	Nephrosis
A3687	20	F.	2.0	+ 0	336	3.5	Nephrosis
A5799	48	M.	2.9	-24	—	—	Nephrosis
16204	24	M.	7.4	- 1	164	7.1	Jaundice, infectious hepatitis
A582	54	F.	7.0	-10	306	7.1	Jaundice, carcinoma pancreas
13792	71	M.	8.0	- 0	—	6.6	Paget's disease
15158	21	F.	3.8	+ 9	—	—	Hodgkin's disease
4964	50	F.	7.5	+20	—	—	Bronchogenic carcinoma
26424	65	M.	8.2	+21	—	—	Syphilis of liver
A135	75	F.	4.0	+56	—	5.8	Myelogenous leukæmia

RESULTS

The results relating to normal subjects and those having clinically diagnosed thyroid disorders are clear-cut. The 34 normal subjects had a mean value of 5.9 μgm. % ± 1.3 (S.D.) with a range of 4.0 to 9.3 μgm. %. The subjects at each extreme had none of the clinical stigmata of thyroid dysfunction. The 4 females in the group had an average value of 5.7 μgm. %. Age likewise did not appear to have an effect. The average value of 24 subjects between 20 and 30 years of age was 5.9 μgm. % and for 7 subjects between 37 and 64, excluding one person with the exceptional value of 9.3 μgm. % was 6.1 μgm. %.

The group of 16 hypothyroid subjects showed an average value of 1.5 μgm. % ± 1.1 (S.D.), with a range of 0.0 to 3.3 μgm. %. Within this group 3 patients with very severe hypothyroidism had no detectable protein-bound iodine. On the other hand, 7 patients with clinically less severe hypothyroidism had low values of 1.5 μgm. % or less. Six other patients clinically much like these 7 had values between 1.8 and 3.3 μgm. %. Thus the values

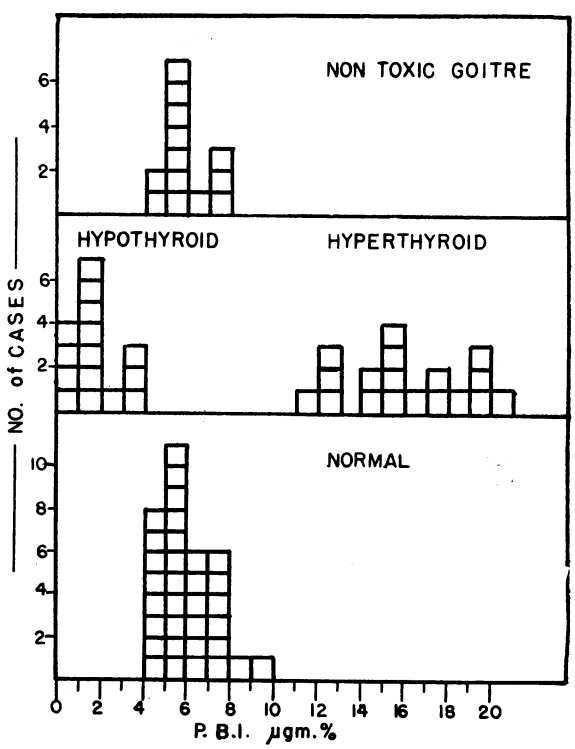

Fig. 1.—The distribution of protein-bound plasma iodine values in normal and dysthyroid states.

do not appear to show any clear-cut relationship to the severity of clinical manifestations. The duration of the symptoms did not have any apparent relationship to the protein bound iodine.

The group of 18 hyperthyroid subjects had an average of 15.9 μgm. % ± 2.7 (S.D.), with a range of 11.8 to 20.0 μgm. %. The 4 most toxic patients in this group had the highest values, between 19 and 20 μgm. %, and in general there was a relationship between the severity of the clinical manifestations and the

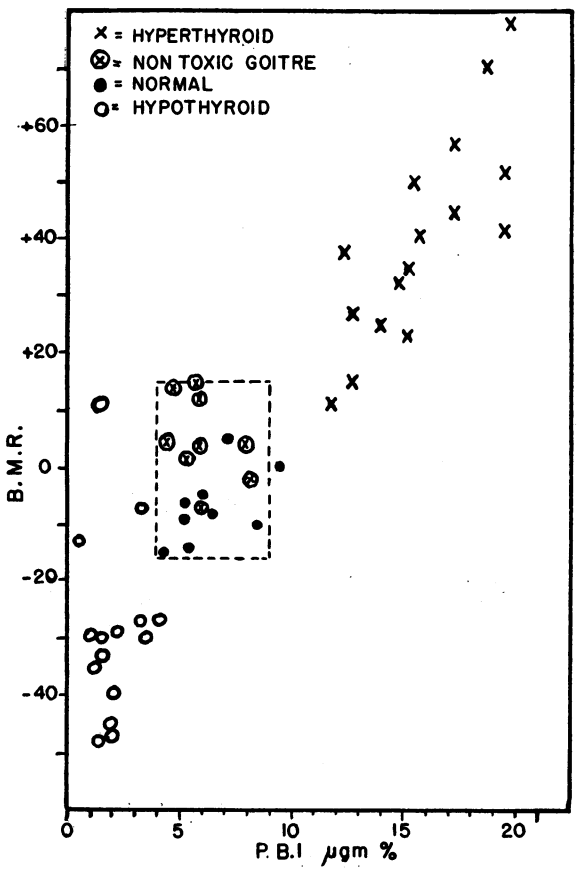

Fig. 2.—The relationship between protein-bound plasma iodine and basal metabolic rate.

protein-bound iodine levels. Exophthalmos was present in 7 cases and was not related to the severity of the other manifestations nor to the protein-bound iodine levels.

The group of 13 subjects with enlarged thyroid glands, but who had no evidence of thyroid dysfunction, had an average value of protein-bound iodine of 5.8 μgm. % ± 1.0 (S.D.) with a range of 4.5 to 7.8 μgm. %.

To facilitate comparison of these 4 groups the frequency distribution of the protein-bound iodine values is shown in Fig. 1. It will be seen that the peaks of incidence for the hypothyroid, normal, and hyperthyroid groups are well separated and there is no overlapping. The incidence of values in the group with non-toxic goitre is essentially similar to that found in the normal group. The asymmetrical distribution apparent in some of the groups indicates that the mean and standard deviation for the groups must be interpreted with caution.

Because protein-bound iodine determinations seemed to provide an index of thyroid function in close agreement with the clinical assessment of the cases, it was of interest to compare them with basal metabolic rates. This has been done in Fig. 2 in which the normal limits for protein-bound iodine have been set at 4 and 9 μgm. %, and for basal metabolic rate at + 15 and – 15. All normals on whom the basal metabolic rate was measured were within these assigned normal limits as were the corresponding iodine values with one exception. All 18 cases of hyperthyroidism had elevated iodine values but 2 had a basal metabolic rate of + 15 or less. The cases of hypothyroidism showed less correlation. All of these had depressed values for protein-bound iodine but 3 out of 16 had a basal metabolic rate greater than – 15.

In order to ascertain if abnormal protein-bound iodine values were present in conditions other than hypo- and hyper-thyroidism a miscellaneous group of subjects was examined. These are detailed in Table I which shows that this group displayed a wider range than the normal. Slightly elevated values were found in 2 cases of hypertension which had normal basal metabolic rates and no other indication of thyroid disease. One case of anxiety neurosis also had a slightly raised value but here the basal metabolic rate was also elevated and it is possible that mild hyperfunction of the thyroid gland may have co-existed. The value in the only pregnant individual examined was above the normal range. This has been shown by Heinemann *et al.*[16] to be typical of the condition. Low values were found in nephrosis and were associated with low plasma proteins. The single cases of Hodgkin's disease and involutional depression had values just below the lower limit of the normal range. In this group the basal metabolic rate and protein-bound iodine were often at variance.

DISCUSSION

The estimation of protein-bound plasma iodine appears to be a very reliable aid in the diagnosis of thyroid disease; the results reported above indicate that groups of hypo- and hyper-thyroid individuals have values for protein-bound iodine clearly demarcated from normal. It is noteworthy that none of the patients with clinical evidence of thyroid disorder had a normal protein-bound iodine value. This sharp division is of obvious advantage in diagnosis and because of this the test is superior to basal metabolic rate determinations. However, it should be stressed that the subjects of this and other series have been selected and segregated into groups because they exhibited certain clinical signs. It may be that the incipient and milder forms of thyroid dysfunction are as yet not recognized and so have inadvertently been omitted. An endeavour is now being made to collect cases with borderline values and of uncertain clinical status as regards thyroid disease and to evaluate the test with such subjects.

The observation that cases of non-toxic goitre have a distribution of protein-bound iodine similar to that of normal subjects, confirms the clinical view that the functional state of the thyroid in this condition is adequate. Abnormal values rarely occur except in diseases of thyroid origin. Notable among these exceptions is nephrosis which is associated with depressed values, and presumably other conditions associated with low amounts of plasma albumen would likewise have low values for protein bound iodine. Peters and Man[17] recently have also shown low plasma albumen levels to be associated with depressed values for protein bound iodine. In addition nephrotics often have a low basal metabolic rate and elevated value for blood cholesterol.[14] However, on clinical grounds, the differentiation of such cases from hypothyroidism is usually simple. Slightly elevated values were found in 2 cases of hypertension; this parallels the findings of Curtis and Feltman[3] and Turner[4] that whole blood iodine was sometimes elevated in hypertension.

Protein-bound iodine estimations were found to agree more closely with clinical assessment than did the basal metabolic rate, and this superiority is particularly shown in the miscellaneous group. This is not surprising considering the numerous factors which influence the latter estimation. In comparison with other measurements such as serum cholesterol, pulse rate, basal temperature, plasma proteins, the iodine values were much more reliable.

SUMMARY

Protein-bound iodine determinations were performed on 113 subjects: 18 hyperthyroids, 16 hypothyroids, 13 cases of non-toxic goitre, 32 miscellaneous conditions and 34 normal subjects.

Values for normal subjects ranged from 4.0 to 9.3 μgm. % with a mean value of 5.9 ± 1.3 μgm. %. Cases of hyperthyroidism had values above the normal range while those of hypothyroidism were below normal range. Cases of non-toxic goitre had values within the normal range as with a few notable exceptions did cases of non-thyroid disease.

The protein-bound iodine correlated fairly well with the basal metabolic rate except in diseases of non-thyroid origin.

Because protein-bound iodine levels are always abnormal in the presence of significant thyroid dysfunction and with rare exceptions normal in other conditions, it is concluded that their determination is a reliable diagnostic procedure in thyroid disease.

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REFERENCES

1. TAUROG, A. AND CHAIKOFF, I. L.: *J. Biol. Chem.*, **163**: 313, 1946.
2. RIGGS, D. S. AND MAN, E. B.: *J. Biol. Chem.*, **134**: 193, 1940.
3. CURTIS, J. M. AND FELTMAN, M. B.: *Arch. Surg.*, **50**: 207, 1945.
4. TURNER, K. B., DELAMATER, A. AND PROVINCE, W. D.: *J. Clin. Invest.*, **19**: 515, 1940.
5. RIGGS, D. S., LAVIETES, P. H. AND MAN, E. B.: *J. Biol. Chem.*, **143**: 363, 1942.
6. SALTER, W. T. AND BASSETT, A. M.: *Trans. Ass. Am. Physicians*, **56**: 77, 1941.
7. SALTER, W. T., BASSETT, A. M. AND SAPPINGTON, T. S.: *Am. J. M. Sc.*, **202**: 527, 1941.
8. SILVER, S.: *J. Lab. & Clin. Med.*, **28**: 329, 1942.
9. SALTER, W. T., BASSETT, A. M. AND SAPPINGTON, T. S.: *Am. J. M. Sc.*, **202**: 516, 1941.
10. WOLFF, J. AND CHAIKOFF, I. L.: *J. Biol. Chem.*, **174**: 555, 1948.
11. TALBOT, N. B., BUTLER, A. M., SALTZMAN, A. H. AND RODRIGUEZ, P. M.: *J. Biol. Chem.*, **153**: 479, 1944.
12. LOWENSTEIN, B., BRUGER, M., HINTON, J. W. AND MEMBER, S.: *J. Clin. Endocrin.*, **4**: 268, 1944.
13. MAN, E. B., SMIRNOW, A. E., GILDEA, E. F. AND PETERS, J. P.: *J. Clin. Invest.*, **21**: 773, 1942.
14. DUNCAN, G. G.: Diseases of Metabolism, W. D. Saunders Co., Philadelphia, 2nd ed., 1947.
15. SALTER, W. T.: *West. J. Surg., Obst. & Gyn.*, **55**: 15, 1947.
16. HEINEMANN, M., JOHNSON, C. E. AND MAN, E. B.: *J. Clin. Invest.*, **27**: 91, 1948.
17. PETERS, J. P. AND MAN, E. B.: *J. Clin. Invest.*, **27**: 397, 1948.