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The Influence of Disease of the Thyroid on Menstruation.

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THE existence of a functional inter-relationship between the thyroid gland and the ovaries has long been recognized and a good example of it is the thyroid enlargement which so often occurs in girls at puberty with the onset of menstruation. Menstrual irregularities also have frequently been described in thyroid disease, but they are not uncommon in other diseases in which metabolism is disturbed, as, for instance, in tuberculosis and diabetes. In the latter conditions, however, menstruation is usually suppressed while in thyroid disease both suppression and excess of menstrual activity may be found. To some extent this would seem to depend on the degree of thyroid activity, but a study of the literature shows that there is no very general agreement on this question. Amenorrhœa and menorrhagia are reported as occurring both in exophthalmic goitre and myxœdema, the two extremes of abnormal thyroid function.

The observations reported in this communication were, therefore, made to show the type of menstruation occurring in a large series of cases of thyroid disease of different grades. More than 300 patients have been examined, including nine cretins, 100 cases of adolescent goitre with varying degrees of disturbed thyroid function, 96 cases of exophthalmic goitre and hyperthyroidism, 41 cases of myxœdema, 24 cases of parenchymatous goitre and 22 cases of simple adenoma of the thyroid. Estimations of the basal metabolism have been carried out to provide confirmatory evidence of the degree of thyroid activity.

CRETINISM.

All authorities are agreed that in female cretins the onset of menstruation is generally delayed and in some cases may never occur. McCarrison¹ also states that the ovaries and uterus may remain infantile, in which case menstruation is never established,

or these organs may develop late, amenorrhœa being present during adolescence. Janney² and Falta³ express similar views. In our own series the number of female cretins who had reached the age of puberty and not been previously treated is insufficient to allow of any definite conclusions as to the effects of thyroid deficiency in childhood on the age of onset and type of menstruation, but it can be seen from the following table that our experience is well in accord with that of other observers. Table I gives the details in nine patients who had reached or passed the age of puberty. Seven of these had received thyroid treatment for varying lengths of time, two had been entirely untreated.

TABLE I. CRETINISM.

Case.	Age	Age of Onset	Type of Menstruation.	Years treated
1. V.B.	22	16	Regular 3/28.	2½
2. F.W.	15	15	Amenorrhœa since first period.	10
3. J.B.	15	13½	Regular.	4
4. E.S.	17	—	Not started.	Not treated
5. F.H.	31	21	Regular 4/28.	2 years at age 14.
6. M.K.	18	17	Regular 7/28.	7 but not continuous.
7. D.C.	17½	—	Not started.	Not treated.
8. D.E.	15½	—	Not started.	13
9. E.W.	15	—	Not started.	5 but not continuous.

First, as to the question of the age of onset of menstruation in this series: it can be seen that in the five cases in which menstruation had occurred, the average age of onset was sixteen in spite of the fact that all had received thyroid treatment for some years. This must be considered definitely later than the average in adolescent females in this country. In case 5 the patient (aged 31) had commenced taking thyroid at the age of fourteen and treatment had been continued for two years only. Menstruation started at twenty-one and since that time had always been regular. In the four remaining patients menstruation had not started. Two of them were only fifteen years old and so cannot be considered abnormal, but the other two were 17 and 17½ respectively, an age at which menstruation should normally have appeared.

Secondly, as to the type of menstruation which occurs in these cases: it can be seen that in four out of the five patients in which it was established, the rhythm and losses were normal and regular. In only one of these patients was menstruation subsequently suppressed. On theoretical grounds it would seem possible to conclude that if cretinism is diagnosed early and treated efficiently

the age of onset and type of menstruation does not depart far from the normal, but when diagnosis is delayed and treatment not instituted until after the age of normal puberty, the onset is late, though when established the menstrual periods tend to be normal and regular.

ADOLESCENT GOITRE.

We have already reported in conjunction with P. C. Brett⁴ a series of observations on the type of menstruation occurring in adolescent goitre. We found that the character of menstruation tended to vary inversely with the degree of thyroid activity. In 100 cases of adolescent goitre 79 per cent. appeared to be of the colloid variety with varying degrees of thyroid activity, as judged by clinical signs and estimations of the basal metabolic rate, while 16 per cent. were typical cases of exophthalmic goitre and differed in no way from the disease as found in adult life. The actual results of basal metabolic estimations in these patients are given in Table II.

TABLE II. ADOLESCENT GOITRES.

B.M.R.	Normal function.	Hyper-function.	Hypo-function.	Exoph-goitre.
	per cent.	per cent.	per cent.	per cent.
Above +10%	0	66	0	100
Within normal +10% -10%	100	34	63	0
Below -10%	0	0	37	0

The figures agree very closely with the clinical grouping and when thyroid function appears to be normal, 100 per cent. of the cases have basal metabolic rates within the normal limits. On the other hand, in exophthalmic goitre, 100 per cent. have basal metabolic rates above the normal limits. In the colloid goitres, in which varying degrees of thyroid activity are suspected, the basal metabolic rate estimations provide confirmatory evidence of this in the majority of cases. It must be noted, however, that in the colloid goitres, when hypofunction is suggested clinically, the basal metabolic rate is within the normal limits in 63 per cent. This, however, is not surprising, if the view is accepted that many of these goitres are compensatory enlargements and evidence of compensated thyroid deficiency. (Marine.)⁵

The results of a study of the type of menstruation in these cases are given in Table III,

TABLE III. ADOLESCENT GOITRES.

	Normal function.	Hyper- function.	Hypo function.	Exoph. Goitres.
	per cent.	per cent.	per cent.	per cent.
Menstruation not started	49	14	0	0
Menstruation normal.	42	45	48	28
Menorrhagia.	3	0	48	0
Delayed irregular scanty menstruation.	3	27	4	0
Periods of amenorrhœa.	3	14	0	72

From this table it can be seen that menstruation is regular and normal in approximately half the cases of colloid goitre, whatever the degree of thyroid activity, while in the majority of the remainder it varies inversely with it. When hyperthyroidism is present, the periods tend to be delayed, irregular and scanty, or absent for varying intervals; while in the cases which suggest some degree of hypothyroidism there is a tendency to menorrhagia. On the other hand, in the group of cases of exophthalmic goitre, menstruation is normal and regular in only one quarter of the cases, while in 72 per cent. there is a tendency to some degree of amenorrhœa.

Since publishing our paper on adolescent goitre, we have been able to observe further cases and confirm our conclusions. Menstruation tends to be normal in girls with no signs of thyroid disorder other than the presence of a goitre. On the other hand, it is often diminished or absent when hyperthyroidism is present, and excessive when thyroid activity is below normal.

EXOPHTHALMIC GOITRE AND HYPERTHYROIDISM.

The type of menstruation occurring in exophthalmic goitre and hyperthyroidism can be seen in Table IV. We have adopted this classification as, at the time these cases were seen, the modern grouping, suggested by Plummer,⁶ into exophthalmic goitre and toxic adenoma of thyroid had not been advanced, nor had Williamson and Pearce⁷ described their grouping on a histological basis into primary and secondary Graves' Disease, the clinical aspect of which conditions Fraser⁸ has since dealt with. The primary group is held to include those cases with diffusely

enlarged and vascular goitres and the classical picture of Graves' Disease—eye signs, tremor, tachycardia and nervousness. The secondary group includes those cases in which symptoms of intoxication appear, perhaps after some years during which a simple goitre has been present. The general intoxication is usually less than in the primary group, the eye signs slight and the cardiac disturbance relatively more marked. As Fraser points out there are other cases with a similar clinical picture, but no previous history of goitre, which are also included in this group. In these the gland is usually less enlarged, less vascular, more irregular and harder than in the typical form.

The first group (A) of our cases described as exophthalmic goitre contains typical cases of primary Graves' Disease with diffusely enlarged and vascular goitres and well-marked eye signs. The second group (B), described as hyperthyroidism, probably correspond more closely to the secondary group in which the gland is usually less enlarged and the eye signs absent or slight.

Estimations of the basal metabolic rate have been made on the majority of the patients in these two groups. The results obtained were on the average considerably higher in the first series, a high proportion of the patients having basal metabolic rates more than +50 per cent. above the normal. In the second series, the degree of thyroid intoxication was lower and the readings obtained were generally in the neighbourhood of +35 per cent. to +40 per cent.

TABLE IV.

Type of Disease.	No. of Cases.	Menstr. Normal.	Delayed, Irreg. or Amenorrhœa.	Menorrhagia.
		per cent.	per cent.	per cent.
A. Exophthalmic Goitre	67	42	57	1
B. Hyperthyroidism	29	65	27	8

It can be seen from the tables that amenorrhœa is present in considerably more than half the patients of the first series. In the remainder it is normal. Few instances of menorrhagia are found. In the second series, on the other hand, menstruation in 65 per cent. of the patients is normal and regular, while in 27 per cent. only is there this same tendency to amenorrhœa. The probable explanation of the different percentages in the two groups is that the degree of thyroid intoxication in the latter is not so great. On the whole, however, it appears that if menstruation is disturbed in conditions of hyperthyroidism it is most likely to be suppressed. These observations are in keeping with the results already reported in cases of adolescent goitre.

MYXEDEMA.

The type of menstruation occurring in myxœdema can be judged from an analysis of the menstrual histories of the 41 cases represented in Tables V, VI and VII. Amenorrhœa and menorrhagia have both been described in this disease, but an analysis of our cases points to there being another explanation for this apparent anomaly.

There seems little doubt that when myxœdema develops before the menopause, it is frequently accompanied by menorrhagia and seldom by amenorrhœa. In a considerable number of our cases, however, the disease developed after what would appear to have been a natural menopause, and we think that other instances of this sort probably account for the impression that myxœdema sometimes causes amenorrhœa. The problem would seem to depend on the age at which the menopause occurred and the relationship of the onset of myxœdema to it. We have divided our cases into three groups : —

- (a) Myxœdema occurring before the natural menopause.
- (b) Myxœdema occurring after the natural menopause.
- (c) Myxœdema occurring after premature menopause.

TABLE V.
MYXEDEMA DEVELOPING BEFORE NATURAL MENOPAUSE.

Case.	Age.	B.M. Rate.	Menstruation since Myxœdema.	Natural Menopause at
		per cent.		
1. Mrs. S.	48	- 35	Menorrhagia	Not reached
2. Mrs. H.	39	- 27.7	Menorrhagia	Not reached
3. Mrs. L.N.	44	- 30	Menorrhagia	Not reached
4. Mrs. A.	49	- 16.7	Normal	Not reached
5. Mrs. S.T.	48	- 16	Menorrhagia	47
6. Mrs. F.R.	40	- 37.5	Menorrhagia	Not reached
7. Mrs. R.	40	- 21.1	Normal	Not reached
8. Mrs. B.	49	- 30	Menorrhagia	47
9. Mrs. L.D.	53	- 22.8	Menorrhagia	45
10. Mrs. F.B.	53	- 16	Menorrhagia	48
11. Mrs. R.	34	- 40.8	Normal	Not reached
12. Miss A.	53	- 21	Menorrhagia	51
13. Mrs. T.	58	- 16	Menorrhagia	51
14. Mrs. E.L.	59	—	Menorrhagia	50
15. Miss W.	50	- 3.3*	Menorrhagia	45
16. Mrs. A.B.	43	—	Menorrhagia	Not reached
17. Mrs. T.	40	- 5	Normal	Not reached
18. Mrs. E.	56	- 40	Menorrhagia	48
19. Mrs. L.	59	—	Menorrhagia	45
20. Mrs. T.	60	—	Menorrhagia	55
21. Mrs. H.C.	48	—	Menorrhagia	Not reached
22. Mrs. H.	48	- 26.6	Menorrhagia	Not reached
23. Mrs. M.	36	- 29.3	Delayed, irregular and scanty.	Not reached

* On thyroid.

Table V shows a series of 23 cases in which myxœdema developed before the natural menopause. In half the cases of this group the patients had not reached the menopause when seen by us for the first time. In the remainder the history showed that the menopause had occurred at the average age, (the average for the 11 cases was $48\frac{1}{2}$) and had been preceded by menorrhagia generally of two or three years' duration. The basal metabolic rate was estimated in the majority of these patients, and in all those so examined it was considerably below the normal, and characteristic of myxœdema. In Case 15, in which the basal metabolic rate was only -3 per cent. it is to be noted that the patient was actually receiving thyroid extract when the estimation was carried out. A study of the table shows that no less than 18 of these cases suffered from menorrhagia as a symptom after the onset of myxœdema. In four menstruation was regular and normal, while in one instance only a tendency to amenorrhœa was found. In this series, therefore, 78 per cent. of the patients in whom myxœdema developed before the natural menopause suffered from menorrhagia.

TABLE VI.
MYXŒDEMA DEVELOPING AFTER NATURAL MENOPAUSE.

Case.	Age.	B.M. Rate.	Menstruation before menopause	Menopause	
				years ago.	At.
		per cent.			
1. Mrs. S.	51	—	Regular and normal	4	47
2. Mrs. E.	56	-53.7	Regular and normal	3	53
3. Mrs. N.	59	—	Regular and normal	7	52
4. Mrs. A.	75	-21.8	Regular and normal	25	50
5. Mrs. J.	56	-22.9	Regular and normal	6	50
6. Mrs. D.	49	-26.7	Regular and normal	2	47
7. Mrs. D.	51	-26.3	Regular and normal	4	47
8. Mrs. R.	50	—	Regular and normal	3	47
9. Mrs. S.	67	—	Regular and normal	15	52
10. Mrs. B.	50	-15	Regular and normal	3	47
11. Mrs. J.	50	-14.3	Regular and normal	8	52
12. Mrs. E.	56	-11	Regular and normal	6	50
13. Mrs. P.	70	-42	Regular and normal	20	50
14. Mrs. P.H.	55	—	Regular and normal	9	46
15. Mrs. R.	60	-35	Regular and normal	10	50

Table VI shows a series of 15 cases of myxœdema developing after the natural menopause. The average age of the menopause in this group was $49\frac{1}{2}$ and menstruation in all cases had previously been normal. The average period of time between the cessation of menstruation and the date at which these patients reported for treatment for myxœdema was eight and a half years, an interval which seems to justify the assertion that the onset of myxœdema

was not the cause of amenorrhœa; rather does it confirm the opinion which has been frequently expressed that myxœdema is a disease which tends to develop after the menopause when normal ovarian activity has ceased.

TABLE VII.

MYXŒDEMA DEVELOPING AFTER PREMATURE MENOPAUSE.

Case.	Age.	B.M. Rate.	Menstr. before menopause	Menopause		Myxœ- dema for
		per cent		At.	Years ago.	
1. Mrs. H.	45	-35	Regular	34	11 years (following stroke.)	3 years
2. Mrs. E.G.	52	-20.3	Regular	38	14 years (following pregnancy, one period after and then stopped.)	15 months
3. Mrs. A.B.	60	-28	Regular	40	20 years.	18 months*

*Following thyroidectomy performed for retrosternal goitre which she had had for four years.

Table VII shows a series of three cases which cannot be grouped either in Table V or Table VI owing to the fact that the menopause occurred prematurely. The cases were all quite typical of myxœdema and the basal metabolic rate was subnormal in all three, -35 per cent., -20.3 per cent. and -28 per cent. respectively. The onset of the disease, however, did not occur for many years after the menopause. In Case 1 the interval between the cessation of menstruation and the onset of symptoms of myxœdema was eight years; in Case 2, 12½ years, and in Case 3, 18½ years, so that it is extremely unlikely that the cessation of menstruation was in any way due to the thyroid disturbance which developed subsequently.

Taking into consideration, therefore, the whole series of 41 cases of myxœdema quoted in Tables V, VI, and VII, it appears that this disease develops before the natural menopause in rather less than two-thirds, and in the majority of these patients (78 per cent.) it is accompanied by menorrhagia. In the remainder, rather more than one-third, myxœdema develops after the menopause, and in this group menstruation previous to the menopause was quite normal.

PARENCHYMATOUS GOITRE.

For purposes of comparison with the groups above in which thyroid function was abnormal we will now give the details of the type of menstruation in a series of cases of parenchymatous

goitre and simple adenoma of the thyroid in which the function of the gland was little disturbed

Table VIII gives an analysis of the menstrual histories in 24 cases of parenchymatous goitre.

TABLE VIII.
PARENCHYMATOUS GOITRE.

Case.	Age.	Goitre Years.	Menstruation.	B.M. Rate.
				per cent.
1. M.G.C.	35	10	Regular 4/28	—
2. M.S.	40	1	Regular 4/28	+3.3
3. M.G.	32	8	Regular 7/28	—
4. K.B.	36	2	Regular	+16.7
5. A.C.	38	5	Regular 3/28	+0.3
6. I.S.	22	2	Menorrhagia 3/12	+5.4
7. K.A.	41	1/2	Menorrhagia	+7.2
8. L.W.	48	5	Irregular 4 years	-11.7
9. H.H.	26	9	Regular 5/28	+8.7
10. M.B.	28	4	Regular 3/28	-9.2
11. A.L.	28	4	Regular 3/25	-10.8
12. E.B.	35	2	Regular 4/28	—
13. L.F.	31	1	Regular 4/25	-8
14. M.F.	38	22	Regular 3/28	—
15. H.W.	31	1/2	Regular 5/30	-9.6
16. M.H.	24	?	Regular 3/28	+7
17. N.R.	57	10	Regular 7/28	+2.8
18. M.S.	39	24	Regular 5/28	—
19. M.C.M.	32	1/4	Regular 6/28	—
20. N.B.	18	1	Menorrhagia 7/12	-27.1
21. E.W.	50	6	Menorrhagia	—
22. J.C.	38	15	Menorrhagia 12/12	—
23. M.D.	50	24	Regular 10/28	—
24. M.P.	25	10	Regular	—

In this group menstruation is normal and regular in the majority of patients, namely 79 per cent. while in the remaining 21 per cent. there is a tendency to menorrhagia. There is no instance of amenorrhœa. Basal metabolic rate estimations were made in most of these patients and in every instance except one (No. 20) the results were within the normal limits. In Case 20 the basal metabolic rate was -27.1 per cent. below the normal limits and menorrhagia had been present for seven months. This patient was undoubtedly suffering from hypothyroidism. Sub-normal thyroid function was also suggested clinically in Cases 8, 21, and 22, in all of which patients the menstrual losses tended to be excessive. In the large majority, however, of these cases of parenchymatous goitre there was no gross disturbance of thyroid function, and it is to be noted that, in these circumstances, there is seldom any alteration of menstruation.

ADENOMA OF THYROID.

The menstrual histories in a series of cases of simple adenomata of the thyroid are given in Table IX.

TABLE IX.

ADENOMATA OF THYROID.

Case.	Age.	Adenoma yrs	Menstruation.	B.M. Rate.
				per cent.
1. L.B.	42	6/12	Regular 4/28	+ - 0
2. M.E.	26	14	Regular	+ 13.5
3. E.F.	29	6/12	Regular	+ 5.4
4. M.B.	53	2	Regular	- 10.9
5. A.T.	29	?	Regular	+ 5.4
6. D.C.	23	3	Regular	+ 11.9
7. D.B.	41	?	Menorrhagia	- 25
8. M.W.	25	9	Regular	- 18.9
9. A.H.	49	?	Regular 7/28	- 13.3
10. C.W.	38	?	Regular 5/28	- 4.7
11. R.M.	30	15	Regular 3/28	—
12. P.K.	32	6/12	Regular 4/28	+ 8.5
13. R.F.	37	3	Regular 3/28	—
14. M.F.	41	29	Regular 5/28	- 5
15. A.B.	53	4	Irregular	+ 6.3
16. D.B.	21	1	Amenorrhœa	+ 5.4
17. M.B.	41	?	Regular 4/28	+ 9.6
18. M.S.	42	?	Regular	—
19. M.T.	43	?	Regular 7/28	—
20. F.P.	40	?	Regular	- 6.3
21. C.H.	33	?	Regular 2/28	—
22. M.R.	24	?	Menorrhagia	- 14

Here again menstruation is regular and normal in the majority, namely 83 per cent., while in the remainder, half have a tendency to amenorrhœa and half a tendency to menorrhagia. Basal metabolic rate estimations carried out in these patients were mostly within the normal limits, though in cases 7, 8 and 22 the results were subnormal. Two of these patients had a low basal metabolic rate and also suffered from menorrhagia.

SUMMARY.

Taking into consideration the whole series of 300 cases of thyroid disease, it can be seen that menstruation may or may not be affected in these conditions, but when it is the alteration tends to be in a uniform direction. The type of menstruation varies inversely with the degree of thyroid activity, i.e., in hypothyroidism there is often a tendency to excessive hæmorrhage and in hyperthyroidism to amenorrhœa. The observations reported in this paper may be summarized as follows:—

1. In *cretinism* menstruation is usually delayed in onset and

if the condition is not adequately treated may never appear. If treated, menstruation tends to be regular and normal.

2. In those cases of *adolescent goitre* which show no signs of thyroid disturbance apart from the goitre, menstruation is generally normal. If hyperthyroidism is present, however, menstrual periods are often delayed, scanty and irregular, while in hypothyroidism there is a tendency to excessive losses.

3. In *exophthalmic goitre* normal menstruation is by no means uncommon, but in the more severe cases menstruation is likely to be disturbed. In such patients the periods tend to become scanty and irregular, and in the most severe cases amenorrhœa is generally present.

4. In *myxœdema* when the disease develops before the menopause menorrhagia is commonly present. This disease, however, very frequently develops after the menopause which may account for the impression that it is sometimes accompanied by amenorrhœa.

5. In *parenchymatous goitre* and in simple *adenoma of the thyroid* there is usually no disturbance of menstruation, but in a small proportion of these patients when there is evidence of hypothyroidism, menorrhagia has been noted.

In conclusion, we wish to thank Professor MacLean for his help in carrying out this investigation, those members of the staff of St. Thomas's Hospital who have kindly allowed us to examine their cases, and the Medical Research Council for defraying the expenses of this research.

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