

vital organs as adrenals, thyroid, liver, kidneys, spleen, and heart. Moreover, as the data in Tables II and III demonstrate, by such treatment it is possible to bring back involuted adrenals, liver, kidneys, and heart towards or to their relative weight present at the earlier age. It is necessary, however, to mention that these results were obtained in ovariectomized animals. The results of similar experiments on intact normal animals are under examination, and probably will reveal some important differences.

As shown in the present experiments, when examining the useful action of any factor on the process of ageing it is dangerous not to take into consideration the harmful effects which are present simultaneously with the useful ones. The harmful effects might become especially dangerous in prolonged treatment or with larger doses, although the favourable effect might be much more striking with larger doses (Tables I and II) than with weaker ones (Table III).

Summary

Experiments were performed in order to study the effects of ovariectomy and of oestradiol benzoate-butyrate, progesterone, androsterone, and thyroid hormone, administered separately or in various combinations, on the process of ageing in ovariectomized rats. Involution of some organs, as shown by changes in their relative weights, was taken as an indication of ageing.

Ovariectomy—i.e., artificial "climacteric"—as judged by relative involution of organs, accelerates the process of ageing in rats.

All the hormones investigated possess two more or less pronounced properties: a stimulating, in most cases hypertrophic, action, and simultaneously in some cases a pathological or depressing effect, on uterus, vagina, preputial glands, thymus, spleen, and such vital organs as adrenals, thyroid, hypophysis, liver, kidneys, and heart, also on fat deposition and body growth. These effects were exerted on all of these organs and functions, or on some of them only.

The stimulation and hypertrophy of the organs and tissues bringing their structure nearest to normal was obtained when all four hormones were administered simultaneously in suitable, not excessive, doses. In this way a co-operation of useful properties and more or less complete neutralization of pathological effects occurred.

Thus simultaneous administration of the hormones may prevent some damaging effects due to hyperhormonization produced by a single hormone. Such hypersecretion of a single hormone is unnatural in the normal organism, in which all hormones are secreted simultaneously in a certain balanced ratio.

The plurihormonal treatment used stopped the ageing involution of some organs in ovariectomized rats, and, moreover, brought the relative weights of these organs towards or up to the level observed at a younger age.

The above-mentioned results, however, do not warrant any definite conclusion whether the hypertrophy developed in some organs by the hormonal treatment should be considered as a kind of artificially produced deformity or else, as it appears to be, as some favourable check to the process of ageing. These results prove only that some processes of ageing can be influenced arbitrarily.

It is necessary to emphasize strongly that before we can define any agent as an anti-ageing factor, especially for therapeutic purposes, more manifold investigation than that of the changes in weight and histological structure of some organs (as in the present experiments) must be made. For this purpose, both experimental and clinical, many-sided and prolonged morphological, biochemical, and physiological experiments are necessary.

It is obvious that a complete picture of the effect of plurihormonal treatment on the process of ageing will be obtained only with the use of a combination of all the main hormones, especially those of the adrenal cortex and hypophysis.

I am indebted to Messrs. Ciba Ltd., in particular to Dr. K. Miescher, for a generous supply of sex hormones, and to Messrs. Burroughs Wellcome and Co. for desiccated thyroid.

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SERUM IRON IN NORMAL WOMEN

BY

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It was Fontes and Thivolle who first demonstrated that minute amounts of iron circulate in the serum. Since then much work has been done on serum-iron analyses, but not until recent years have the methods in use been sufficiently reliable.

The normal values for serum iron have not yet been fully established. Some authors have reported sex differences in the serum-iron concentration, while others deny their existence. So far, the normal amounts observed vary between 0.035 and 0.22 mg. per 100 ml. Most authors estimate the serum iron to be about 20 γ per 100 ml. lower in women than in men. Altogether about 1,000 determinations have been carried out on 21 "normal" subjects. These cannot be said, however, to be sufficient to elucidate this problem, particularly as the technique employed by the various authors has varied. It is possible, too, that the serum-iron concentration may have changed somewhat (i.e., given slightly pathological values) in individuals who have been looked upon as healthy. For determination of serum-iron values it is essential to be careful in the choice of the "normal" individual, because serum iron is a very labile plasma element, the concentration of which is dependent on many factors—e.g., absorption and excretion of iron, size of the depots, haemoglobin production, breakdown of haemoglobin, etc. In order to be quite sure that "normal" individuals are used it is necessary to ascertain whether the diet of the person concerned has contained a sufficiency of vitamins and minerals with a suitable amount of vegetables and meat. Then all the states of deficiency that influence iron metabolism will have been excluded. In addition, it is necessary to make sure that he has not recently been suffering from an infection or, if so, that recovery is complete; for infections interfere with iron metabolism, as is evident occasionally from the occurrence of infection anaemia.

It seems probable that the greatest variations in serum-iron concentration will be found in women, for the blood lost during menstruation may reasonably be expected to reduce the amount of serum iron. Besides, most women go

through one or more pregnancies, which may be assumed to influence iron metabolism and therefore the serum-iron concentration. Finally, the life of a woman may be divided into three periods, the menarche and the menopause forming the borderlines. All these conditions suggest that the iron metabolism must be far more active in women than in men, as in the latter only pathological conditions may conceivably affect it.

While the normal values for serum iron obtained by individual authors vary to some extent, collectively they give a fairly good idea of where the limits are to be set. Heilmeyer and Plötner (1937), Skouge (1939), Albers (1941), and Dahl (1945) give somewhat lower values than do other authors.

Present Investigation

Among the subjects in the present series in whom the above-mentioned requirements have been met, three showed a serum-iron concentration of only 68 γ per 100 ml. and one of 69 γ . The highest values measured were 194, 166, 154, 146, and 143 γ per 100 ml., while all the others were under 140 γ .

According to these findings it seems not improbable that in women the normal serum iron varies between 70 and 140 γ per 100 ml. If in a woman we meet with a value under 70 γ we are probably dealing with a case of sideropenia; and if the value exceeds 140 γ it is not unreasonable to assume that the case is one of sideraemia (perhaps physiological sideraemia). It is difficult to decide when increased values are pathological, but values over 200 γ per 100 ml. must be regarded as decidedly so.

Technique.—First Poul Wehmeyer and I tried the technique of Bröckner-Mortensen and Carsten Olsten (1940); but later I employed the method of Balle (1942) and Höyer (1943), which has proved to be rapid and very accurate. Briefly, the method is as follows:

Sufficient blood is withdrawn to give 3 ml. of serum. One can manage with 1.5 ml., but then the duplicate analyses can be carried out only on diluted serum, and this makes the error 2 to 4% greater. To 3 ml. of serum, 1.5 ml. of 6/N HCl is added, and the whole shaken; this liberates the serum iron. When the mixture has been standing for 15 minutes, 3 ml. of 20 vol. % trichloroacetic acid is added, again shaking; this precipitates the proteins. After standing for a few minutes the mixture is centrifuged at 5,000 revolutions a minute for 30 minutes. To 3 ml. of the clear supernatant fluid 80 c.mm. of concentrated nitric acid is added, and also 0.8 ml. of 5/N potassium thiocyanate solution. The result is read within 10 minutes in a Pulfrich photometer with a 50-mm. microcuvette and filter S53. The control solution consists of iron-free water with the addition of the above-mentioned reagents.

The haemoglobin determination and the red blood count were performed on venous blood immediately after its withdrawal; the blood was obtained from a median vein.

Results

Altogether 112 analyses were performed on blood from healthy women, and the results are recorded in Tables I, II, III, and IV.

TABLE I.—Serum-iron Determination on 9 Girls before the Menarche. The Average Value is 111 γ per 100 ml.

Age	Height (cm.)	Weight (kg.)	Hb%	Erythrocytes in Millions	Serum Iron in γ /100 ml.
9	121	22	90	4.72	100
11	146	39	102	5.02	136
12	130	28	99	4.69	102
12	143	36	102	5.11	116
13	145	36	91	4.89	126
14	158	49	86	4.94	97
14	164	51	98	4.33	100
14	151	48	97	4.98	83
15	160	52	88	4.18	136

In nine girls in whom menstruation had not yet started the serum-iron values were between 83 and 136 γ per 100 ml. (Table I). One girl whose first menstruation appeared 19 days before the examination (the first subject in Table II) showed a serum-iron value of 84 γ . In 63 women with normal menstruation the serum-iron concentration varied between 68 and 154 γ per 100 ml. In 16 women in whom the menopause had appeared it varied between 76 and 194 γ

TABLE II.—Serum-iron Concentration in 63 Normal Women between the Menarche and the Climacteric

Age	Height (cm.)	Weight (kg.)	No. of Days After Last Menses	Hb%	Erythrocytes in Millions	Serum Iron in γ /100 ml.
14	168	70	19	100	4.72	84
15	167	68	6	92	4.61	126
15	158	61	3	91	4.32	86
16	163	57	During	92	4.28	113
16	158	54	14	94	4.76	121
17	170	62	26	88	4.43	146
17	166	70	2	88	4.87	94
17	174	70	18	88	4.43	136
17	164	60	10	86	4.39	84
18	164	60	24	92	4.88	98
18	169	65	24	86	4.18	93
19	166	65	8	89	4.48	106
19	180	72	19	92	4.60	106
20	166	56	9	84	4.00	137
20	166	72	8	88	4.70	130
20	178	72	23	86	4.14	126
20	161	60	12	108	4.90	139
21	166	62	31	106	5.06	139
21	152	32	4	101	4.63	72
21	162	50	15	92	3.98	68
21	160	61	9	98	4.71	94
21	168	68	11	92	4.58	113
21	162	54	23	100	4.68	115
22	177	73	20	100	4.99	80
22	169	63	2	92	4.80	124
22	166	60	2	91	4.61	75
22	165	53	During	90	4.59	75
22	171	65	13	95	4.58	95
22	161	58	1	106	5.03	93
22	164	50	1	88	4.24	94
23	176	76	8	99	4.77	83
23	169	66	3	92	4.10	95
23	168	65	3	94	4.87	82
24	174	68	28	97	4.75	139
24	158	64	14	91	4.75	82
25	175	65	19	94	4.17	120
25	175	63	During	84	4.81	98
26	160	61	30	98	4.66	106
26	173	81	22	89	4.46	143
26	171	69	13	88	4.82	134
28	162	69	23	102	5.00	114
28	169	72	3	101	5.04	93
29	173	69	3	85	4.62	88
29	178	72	25	90	5.04	115
30	170	59	14	88	4.56	118
31	173	81	6	90	4.50	102
31	171	88	9	88	4.66	114
32	165	69	12	92	4.55	120
32	153	54	18	88	4.20	83
32	162	82	18	89	4.56	118
33	170	80	14	98	4.58	83
35	167	68	12	92	4.52	68
35	164	59	2	86	4.33	69
35	166	67	6	86	4.01	68
36	159	64	8	101	4.69	134
36	163	69	10	98	5.40	140
37	159	61	9	90	4.30	136
38	183	89	11	97	4.86	96
39	174	72	20	99	4.60	124
41	169	76	11	89	4.29	113
43	172	78	9	87	4.46	78
44	168	59	16	87	4.28	78
45	168	78	20	103	5.06	97

TABLE III.—Serum Iron in 16 Normal Women after the Menopause (Average 113 per 100 ml.)

Age	Height (cm.)	Weight (kg.)	No. of Years After Climacteric	Hb%	Erythrocytes in Millions	Serum Iron in γ /100 ml.
48	158	58	11	99	4.46	126
48	167	60	2	83	4.09	108
48	166	67	3	94	4.63	194
49	170	78	3	96	4.62	132
50	169	81	1	100	4.82	93
51	157	68	3	92	4.78	107
53	162	68	5	98	4.26	76
57	164	74	10	97	4.70	92
58	166	70	3	102	5.04	81
58	162	69	10	102	5.16	103
59	154	59	7	90	4.29	116
60	162	73	8	100	4.98	86
62	167	89	19	100	4.76	138
63	161	59	18	92	4.01	80
64	162	91	20	104	4.86	107
77	156	62	28	87	4.28	166

TABLE IV.—Parallel Changes in the Haemoglobin Percentage, Erythrocyte Count, and Serum Iron During the Menstrual Cycle of Four Hundred Women

No. of Days After Last Menses	No. 1			No. 2			No. 3			No. 4		
	Hb%	Erythrocytes in Millions	Serum Iron in $\gamma/100$ ml.	Hb%	Erythrocytes in Millions	Serum Iron in $\gamma/100$ ml.	Hb%	Erythrocytes in Millions	Serum Iron in $\gamma/100$ ml.	Hb%	Erythrocytes in Millions	Serum Iron in $\gamma/100$ ml.
During	84	4.61	98	88	4.41	88	82	4.02	80	79	4.00	78
6	85	4.45	78	90	4.50	102	84	4.16	83	82	4.04	86
13	89	4.34	93	87	5.32	93	86	4.46	88	89	4.20	80
20	94	4.28	126	92	4.45	105	94	4.74	102	90	4.38	87
27	89	4.04	155	95	4.51	112	100	4.96	106	90	4.41	94
During	80	3.89	69	92	4.39	96	90	4.29	87	85	4.13	83

TABLE V.—Serum-iron Values in Relation to the Menstrual Cycle

Days of Cycle	Serum Iron in $\gamma/100$ ml.	Days of Cycle	Serum Iron in $\gamma/100$ ml.
During	95.3	16-18	112.3
1-3	88.3	19-21	100.6
4-6	98.6	22-24	114.8
7-9	112.3	25-27	130.5
10-12	108.7	28-30	122.5
13-15	99.2	31-33	139.0

(Table III). The average values for girls and elderly women were 111 and 113 γ per 100 ml. respectively, while the average for menstruating women was 105 γ . This indicates that the serum-iron concentration is somewhat lower in menstruating women than in the non-menstruating.

It has been asserted that this lower value in menstruating women is due to the loss of iron month after month. The

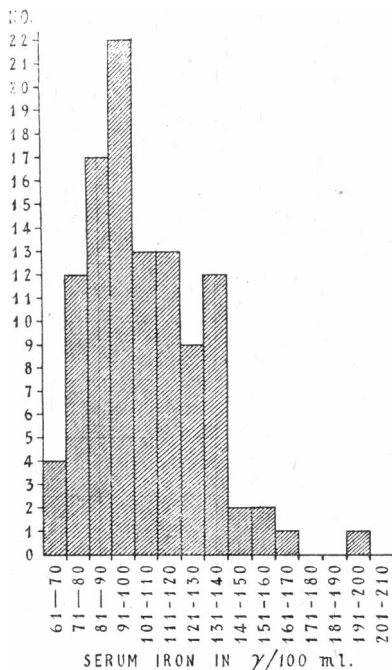


Chart showing amount of serum iron in normal non-pregnant women.

work here reported indicates that this theory is correct. In order to obtain further corroboration four perfectly normal women were examined throughout a menstrual cycle (Table IV). The examination showed that the serum iron reached its highest value immediately before the menstruation, while the lowest values were found during and immediately after.

In Table V the 63 serum-iron values obtained in menstruating women (from Table II) are grouped after the menstrual cycle. Here, too, we find higher values shortly before the expected menstruation.

The Chart illustrates the distribution of the serum-iron values obtained in the present series. It shows how the normal limits—70 and 140 γ per 100 ml.—are arrived at.

Summary

Determination of the serum iron has been carried out on 92 healthy females receiving an adequate diet. The five highest values were 194, 166, 154, 146, and 143 γ per 100 ml.; while the three lowest values were 68 γ .

The serum-iron concentration was found to be lower in menstruating women than in those not menstruating.

The theory that the lower serum-iron value in menstruating women was due to loss of iron month after month is considered to be proved by the results obtained.

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REFRACTORY IRON-DEFICIENCY ANAEMIA TREATED WITH INTRAVENOUS SACCHARATED OXIDE OF IRON

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In a recent article by Nissim (1947) the use of saccharated oxide of iron for intravenous injection is described. The following case is reported because the patient responded dramatically to parenteral iron therapy subsequent to the failure of the oral administration of iron in large amounts for long periods, supplemented at various times with ascorbic acid, thyroid extract, molybdenized ferrous sulphate, parenteral liver extract, and folic acid.

Case History

The patient, a woman aged 29, was first admitted to hospital on June 13, 1945, with a three-months history of breathlessness and fatigue. Her appetite and diet had always been satisfactory, she had never suffered from dyspepsia or diarrhoea, her periods were not excessive, and there was no evidence of any other source of blood loss. On examination there was no oedema. The nails, although brittle, were not flattened. Some atrophy of the papillae of the tongue was present. The liver, spleen, and lymphatic glands were not enlarged. Physical examination of the cardiovascular, respiratory, renal, alimentary, and central nervous systems revealed no pathological features. The patient's intelligence was below average.

A test meal showed that free hydrochloric acid was present in the gastric juice. There was no excess of urobilinogen in the urine, and the stool benzidine test was negative. Radiological examination of the alimentary tract revealed no abnormality. The haemoglobin was 30%; erythrocytes, 2,850,000 per c.mm.; colour index, 0.53; white cells, 2,800 per c.mm.; reticulocytes <1%. The sternal marrow contained numerous late normoblasts of the type seen in iron-deficiency anaemia.

There was no response to ferrous sulphate, 3 gr. (0.2 g.) thrice daily for 24 days, followed by 6 gr. (0.4 g.) thrice daily for 20 days. Supplements of ascorbic acid, thyroid extract, and liver extract were given in turn, with no beneficial results. Accord-