to be much more dramatic than the more steady fall in the number of cases affecting the toes only. This is explained on the theory, already outlined, that the earliest lesions are almost always between the toes, and that during the experiment the spread from toes to body was largely prevented by early treatment and the use of foot-towels.

Month	Average Time Taken for Cure	Distribution of Lesions in New Cases			
		Feet and Body	Feet Only	Body Only	Total
May	—	41	48	2	91
June	14·75 days	2	21	0	23
July	8·5 ,,	2	18	0	20
August ..	7·75 ,,	3	10	0	13

Relapse Rate.—There were no relapses in June, but five occurred in July and five in August—eight of these were cases of tinea interdigitalis only. However, in order to give a fair picture of the total ringworm state of the unit these have been included under new cases.

Discussion

It is emphasized that this experiment was carried out without alteration in the normal working routine of a very active unit, and in fact, because of the essential operative work on which the men were employed, it was very often necessary for a man with ringworm to miss one of his daily treatments. Therefore it is practicable not only for an active unit but also for immediate application in the wider field of civil life. Outbreaks of ringworm, particularly tinea interdigitalis and tinea cruris, are liable to occur in any civil community where communal washing facilities are provided, and especially in schools, factories, and mines.

Summary

A description is given of a successful experiment designed to reduce the high incidence of ringworm among troops in the Tropics. The importance of the spread of the disease via floors, from lesions between the toes (tinea interdigitalis), is emphasized, and this is made the basis of the preventive measures adopted. The application of these findings to civil life is noted.

The success of the experiment was largely due to Captain John Middleton, R.A.M.C., regimental medical officer to the unit concerned, to whom I am most indebted. I would like to thank the Director-General, Army Medical Services, for permission to publish, and Lieutenant-Colonel C. F. Michell, R.A.M.C., adviser in dermatology to the War Office, for his encouragement and assistance.

REFERENCES

Brain, R. T. (1941). *Med. Pr.*, **206**, 278.
Fraser, P. K. (1940). *J. R. Army med. Cps*, **74**, 145.
Gray, A. M. H. (1934). *British Medical Journal*, **2**, 541.
Legge, R. T., Bonar, L., and Templeton, H. J. (1929). *J. Amer. med. Ass.*, **93**, 170.
Linn, L. W., and Magarey, F. R. (1941). *Med. J. Aust.*, **2**, 452.

" The School Dental Service has substantially recovered from the wartime relapse due to the calling up of dental officers, but we still have a long way to go to make it truly comprehensive and efficient," said Mr. George Tomlinson, Minister of Education, speaking in London on April 3 at the annual dinner of the Dental Officers Group of the Society of Medical Officers of Health. Stating that the average interval between periodic inspections was still a good deal more than twelve months and needed to be reduced, Mr. Tomlinson said that nearly 70% of the children in schools had dental inspections in 1946 and that 72% of those found to need treatment were willing to accept it. Almost every local education authority had now appointed a senior dental officer, and it was expected that the few stragglers would soon come into line, but the expansion of the service was hindered, as with other parts of the educational system, by shortage of labour and materials. Much could be done by improvisation, however, and local education authorities were encouraged to provide additional clinics by taking over existing buildings and adapting them cheaply. Emphasis on preventive rather than curative aspects of dentistry was becoming more common. Nutrition was a vital element in this, and the school dental service together with the school milk and meals service and the school medical service formed a great co-operative enterprise designed to foster the physical welfare of the children.

EFFECTS OF SEX AND THYROID HORMONES ON THE PROCESS OF AGEING IN FEMALE RATS

BY

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This paper is a summary of the results of experiments published in detail in four previous papers (Jones and Korenchevsky, 1946 ; Korenchevsky and Jones, 1946, 1947, 1948), and contains the general conclusions to be drawn from them. The effects of ovariectomy and of androsterone, oestradiol benzoate-butyrate, progesterone, and thyroid hormone, given alone or in various combinations, were investigated on the process of ageing in ovariectomized rats. All these hormones, including the androgenic hormone androsterone, are naturally present in the female organism. The literature relating to some parts of this subject is extensive, and it was reviewed in detail in the previous articles. Therefore, for economy of space, the papers of only a few workers are here referred to. For the same reason our previously published detailed tables are summarized in three abbreviated tables and the illustrations are omitted.

Main Lines and Methods of Gerontological Research

The best definition of old age was given by Prof. Warthin (1930): essentially old age is a major involution of the organism, of all its vital organs and tissues and of all their functions. Surprisingly, this ageing involution starts in most organs very early, at childhood. Therefore gerontological research can be carried out on individuals of any age. Hence there are two chief approaches to gerontology: *research on ageing* in young or adult individuals (as in the present experiments) and *research on actual old age or senility* in old animals or old human beings. It is obvious that both these ways are equally important. For therapeutic purposes of geriatrics the investigation of ageing in the earlier years of life is of great importance, since it might contribute to the problem of prevention of the present premature and abnormal senility.

The ageing involution of at least some organs should first show itself in the decrease in their relative weight—i.e., in the relative hypoplasia of organs (Korenchevsky, 1942). On the other hand, if any factor has some anti-ageing effect on a certain organ, it should increase the weight and produce hypertrophy of that organ. Obviously the changes in weight of organs alone cannot be sufficient for conclusions on hypertrophic, atrophic, or especially on any degenerative changes. For this purpose at least histological examination is necessary in order to eliminate errors in cases of enlargement of the organs due to oedema or hyperaemia, and to discover degenerative changes, etc. However, a complete understanding and an accurate definition of the processes of ageing and of the anti-ageing properties of any factor examined could be obtained only after the performance of several morphological, physiological, and biochemical investigations, both experimental and clinical.

Technique of the Present Experiments

Five experiments were performed on 197 female rats, of which 11 were normal controls, 29 ovariectomized controls, and 157 ovariectomized rats treated with hormones. The

*I should like to express my gratitude to Lord Nuffield for the grants which have made possible the establishment and work of the Gerontological Research Unit, and to Prof. A. C. Hardy and Prof. E. G. T. Liddell for the kind hospitality extended to the Unit in the Departments of Zoology and Physiology of Oxford University.

duration of Experiments I and II was 56 to 76 days, and of Experiments III–V, 43 to 52 days.

Besides these five experiments a re-examination and a recalculation were made from some other earlier experiments in which a total of 54 normal and 325 ovariectomized rats were used in order to study the effects of ovariectomy and oestradiol administration. In different experiments the weights of organs might vary, and those in the experimental groups have to be compared with the weights of the respective control groups of each experiment. All sex hormones in experiments I–IV, and oestradiol benzoate-butyrate in Experiment V, were injected in oily solution. Progesterone and androsterone in Experiment V were injected as a crystalline emulsion suspended in 5% gum acacia. Desiccated thyroid was administered by mouth with a pipette in the form of a sweetened emulsion. Thyroxine was injected subcutaneously.

Each of the hormones investigated, except progesterone, was administered separately or in various combinations with other hormones. Progesterone was always injected with oestradiol B.-B. The following weekly doses were used.

Experiment I.—Desiccated thyroid, 105 mg. ("small dose"); oestradiol B.-B., 0.015 mg. ("small dose"), injected for three weeks only, or 0.09 mg. ("large dose"), injected every week; androsterone 4.5 mg.

Experiment II.—Desiccated thyroid, 250 mg., + thyroxine, 0.8 mg. ("large dose"); oestradiol B.-B., 0.015 mg., injected for the first three weeks and two last weeks ("medium dose"). The doses of oestradiol B.-B. ("large dose") and androsterone were the same as in Experiment I.

Experiments III and IV.—Desiccated thyroid, 65 mg., three times a week; oestradiol B.-B., 0.028 mg., during first week only; progesterone, 2 mg., daily during last 19 days.

Experiment V.—Desiccated thyroid, 60 mg., three times a week; oestradiol B.-B., 0.015 mg., injected three times during first week only; crystalline suspensions of androsterone, 10 mg., and progesterone, 10 mg., injected every 8th or 10th day.

The following methods of investigation were used: weighing of the organs and body fat (as indicated by weight of the abdominal fat); examination of the size of the cells by outlining them on paper and weighing the paper replicas obtained; measurement of the nuclei; count of mitoses; usual histological examination of the sections stained with haematoxylin and eosin, and, for lipoids, with sudan black. All organs were weighed after fixation in Bouin's solution, except brain and hypophysis, which were fixed in 4% formol-saline. The relative weights have been calculated per unit of "fat-free" body weights for reasons explained below.

All details of the methods used were given in the previous papers (Jones and Korenchevsky, 1946; Korenchevsky and Jones, 1946, 1947, 1948). All results obtained were statistically analysed by means of Fisher's t-test for small samples. For the greater part of the statistical analyses I am indebted to Mr. B. Benjamin, the head of the L.C.C. Statistical Bureau, and for the other part to my co-worker, Miss V. E. Jones.

Ageing Hypoplasia of Organs

When the relative weights of organs in our normal intact female rats were calculated in the usual way—i.e., without subtraction of body fat—a progressive decrease of these weights was shown with ageing. A confirmation of these results was found in Donaldson's (1924) data and, after their recalculation, in those of Prof. Freudenberger and his co-workers (1935–1939). Neither Donaldson nor Freudenberger *et al.* investigated the amounts of body fat. Such an omission might lead to serious mistakes for two reasons: (1) The size and weight of an organ are determined to a greater or lesser extent by the amount of work which that organ has to perform independently of, or for the maintenance and functioning of, correlated organs and tissues; from this point of view the inert fat tissues cannot be compared with any active tissue—e.g., muscular, glandular, nervous, etc. (2) When compared with a thin animal, the large fat deposition in the body of a fat animal will, when the organs are calculated per unit of body weight, give a fictitious decrease in the organs.

Since we always weighed abdominal fat, using this value, we could roughly calculate the total body fat in our experiments. From the age of about 30 to 50 days to that of about 800 days these "fat-free" weights show a decrease (relative hypoplasia of organs) in thyroid, thymus, liver, kidneys, spleen, and brain. This decrease, however, was less pronounced than in the Donaldson–Freudenberger data, and in some organs (ovaries, adrenals, hypophysis) was developing from the age of sexual maturity only, or sometimes (heart) even later.

Effects of Ovariectomy (Artificial Climacteric).—Ovarian hypoplasia and hypofunction are the foremost factors in producing the climacteric in the senescent female organism. Therefore from an experimental point of view the condition produced in the young or adult female organism by ovariectomy might be considered as an artificial, premature, and extreme "climacteric" of purely gonadal origin. Thus the investigations of the changes produced by ovariectomy might explain several features in the climacterical symptom-complex. Comparing the age at which it appears and the rate of its development, the relative decrease of organs in our experiments was more pronounced in ovariectomized rats than in the normal controls. So far this has been confirmed histologically in the case of sex organs, liver, kidneys, and thyroid. The interpretation of the changes in adrenals is more difficult. Thus, as judged by the rate of involution of organs, ovariectomy accelerates the process of ageing.

Effects of Hormones on Ovariectomized ("Climacterical") Rats.—Tabulated detailed data and photomicrographs were given in the previous papers. The chief aim here is to demonstrate those non-sex organs in which the changes obtained were definite and statistically significant. Some new unpublished data are included in the tables. In order to show that the effects of hormones are evident both in actual and in relative weights, Table I contains the actual weight of organs, while Tables II and III contain the relative weights per 200 g. of "fat-free" body weight. So far histological examination has been made of uterus, vagina, adrenals, thyroid, liver, and kidneys.

TABLE I.—*Effect of Androgenic, Oestrogenic, and Thyroid Hormones, Administered Separately or Simultaneously, on Actual Weight of Organs in Experiment II*

Organs	Ovariectomized Controls	Thyroid Hormone (Large Dose)	Oestradiol B.-B. (Medium Dose)		Androsterone		
			Alone	+ Thyroid Hormone (Large Dose)	Alone	+ Thyroid Hormone	+ Thyroid Hormone + Oestradiol B.-B.
Adrenals (mg.)	55	86	84	135	42	70	123
Hypophysis (mg.)	15·4	14·2	19·8	19·8	15·2	14·7	18·7
Liver (g.) ..	6·79	9·17	8·01	11·55	8·78	9·99	10·37
Kidneys (g.) ..	1·44	2·12	1·60	2·54	1·65	2·18	2·60
Heart (mg.) ..	768	1,123	813	1,200	893	1,162	1,110

Effects of Thyroid Hormone.—This hormone has both stimulating and depressing properties. The stimulation was definitely demonstrated with a suitable dose in hypertrophy of adrenals, liver, kidneys, heart, and spleen (Table I), and in the histological changes obtained. These results are in close agreement with those of previous workers, as was shown in our review of the literature on the subject (Korenchevsky and Jones, 1946, p. 327). Depressing effects have been observed in a decreased function of *thyroid gland*, a smaller gain in *body*

weight, and decreased *fat deposition*. These changes obtained in ovariectomized rats are in complete agreement with those found in the previous experiments on normal rats (Korenchevsky, Hall, and Clapham, 1943; Korenchevsky and Hall, 1944). *Uterus and vagina* remained atrophic, but their epithelium and the muscular cells were slightly better developed than those in control ovariectomized animals.

Effects of Androsterone.—The stimulating effects of androsterone are shown (Tables I and III) in increased weight of vagina, liver, kidneys, heart, and in slightly better gain in body weight and fat deposition. Histologically the following changes

TABLE II.—*Return of "Fat-free" Relative Weights of Organs Towards or Up To the Level Present at Earlier Age After Simultaneous Administration of Oestradiol B.-B., Androsterone, and a Large Dose of Thyroid Hormone in Experiment II*

Organs	Normal Intact Control Rats		Ovariectomized Rats Aged 152 Days	
	Aged 65 Days	Aged 152 Days	Controls	Treated with Three Hormones
Adrenals (mg.) ..	79	68	51	111
Thyroid (mg.) ..	20·9	16·7	13·0	15·3
Liver (g.) ..	9·8	7·7	6·3	9·5
Kidneys (g.) ..	1·8	1·7	1·3	2·3
Heart (mg.) ..	786	871	714	1,000

were found: slightly better development of still atrophic uterine epithelium, and better development of all vaginal layers; larger liver cells and a greater number of large nuclei; larger renal tubules with enlarged lumens; in thyroid—a definitely more active columnar epithelium, with less colloid in follicles (i.e., a stimulation of the gland). Androsterone, however, had a definitely depressing effect on adrenals, as shown by their small weight and the smaller size of their cells and nuclei; their lipoid content was also decreased. The involution of thymus was accelerated, as is the case with all male sex hormones.

Effects of Oestradiol Benzoate-Butyrate.—Oestradiol B.-B. (Table I) exerts varying effects, depending on the dose administered. Since it usually depresses growth and gain in body weight, the examination of the relative weights of organs be-

TABLE III.—*Return of "Fat-free" Relative Weights of Organs Towards or Up To the Level Present at an Earlier Age after Administration of Progesterone, Oestradiol B.-B., Androsterone, and a Small Dose of Thyroid Hormone in Experiment V*

	Ovariectomized Rats, aged 175 Days					Normal Intact Controls aged 52 Days
				Progesteroné		
	Controls	Androsterone	Thyroid Desicc. (Small Dose)	+ Oestradiol B.-B.	+ Oestradiol B.-B. + Androsterone + Thyroid Desicc.	
Abdominal fat (g.) ..	11·0	13·6	7·1	12·6	10·2	1·7
Adrenals (mg.) ..	44	34	59	59	62	57
Liver (g.)	6·08	7·50	6·80	8·21	7·79	10·43
Kidneys (g.)	1·15	1·44	1·56	1·42	1·69	1·96
Spleen (mg.)	842	768	984	809	1,000	1,634
Heart (mg.)	670	730	905	777	831	1,009

comes especially important. The best results were produced by medium doses, which, besides the well-known hypertrophic effect on the uterus and vagina, increased the relative weights of the adrenals, hypophysis, liver, kidneys, and, in some experiments, of the heart. Small doses might have no effect, while comparatively large doses produce a less stimulating and more toxic action. Among the toxic effects, the metaplastic changes of the uterine epithelium and glands, the development of adenoma-like structure in thymus (Ross and Korenchevsky, 1941; Plagge, 1946), and the tumour-like enlargement of the hypophysis are very important. Histologically, non-toxic doses produced in adrenals enlargement of the cortex, enlargement of the fasciculata cells, and an increase in number of large nuclei. While small and medium doses usually do not change the structure of adrenals, except for the above-mentioned hypertrophic features, the larger doses produced atrophy and degenerative changes in the reticularis cells, with a considerable hyperaemia of this zone and a lipoid depletion in the zona glomerulosa. With non-toxic doses the cells became enlarged in liver and kidneys, in some experiments significantly; likewise their nuclei. With the doses of oestradiol used no definite changes were found in thyroid structure.

Simultaneous Administration of Thyroid Hormone with Oestradiol B.-B.—This association of hormones produced a stimulating hypertrophic action on some organs which was more pronounced than with either hormone alone. This was shown in the weight of the adrenals, liver, and kidneys (Table I), and histologically in the cortex of the adrenals and, in some cases, in the liver and kidney cells.

Simultaneous Administration of Androsterone with Oestradiol or with Thyroid Hormone.—With both these combinations the two latter hormones had an important neutralizing effect on the depressing, harmful action of androsterone on the adrenals. This was shown both in weight of adrenals (Table I) and the return of their histological structure towards or up to normal. On the other hand, a neutralizing effect of androsterone was evidenced histologically by some decrease of the thyroid depression produced by small doses of thyroid hormone. The changes brought about in the thyroid by large doses of thyroid hormone were resistant to this action of androsterone. Other organs showed chiefly the effects of thyroid hormone, the latter overcoming the effects of androsterone.

Simultaneous Administration of Three Hormones—Androsterone, Oestradiol B.-B., and Thyroid Hormone.—This combination produced (Tables I and II) effects similar to those of thyroid hormone + oestradiol, and androsterone + thyroid hormone. The neutralizing action on pathological changes in the adrenals and thyroid gland was also present. Histologically the adrenals had a structure similar to that in normal rats (except for the large size of the gland and their cells). Metaplasia of the uterine epithelium and glands was still present, but otherwise, with this combination of hormones, the structure of both uterus and vagina was closest to that in normal rats.

Insufficiency of the Three Hormones Used in Obtaining Normal Anti-involutionary Effects.—Some of the toxic or pathological effects observed with the combinations of the hormones used could not be prevented by any one of them. It is known, however, that the metaplasia of uterine epithelium produced by oestrogens, or the adenoma-like transformation of uterine glands produced by a combination of oestrogens with androgens (Korenchevsky and Hall, 1938, 1940), or the development of abdominal fibroid tumours after treatment with oestrogens (Lipschütz and Schwarz, 1944; Lipschütz *et al.*, 1944) could be prevented by progesterone. Therefore it was decided to administer progesterone in various combinations with the three hormones already investigated.

Progesterone in Combination with Oestradiol B.-B.—This combination had a definite stimulating action on the thyroid, adrenal cortex, kidneys, and liver (Table III), producing hypertrophy of their cells. Liver and adrenals and, in one experiment, kidneys and heart had significantly greater weights. Involution of thymus was accelerated, and all pathological changes in the uterine epithelium and glands were prevented. *When three or four hormones*—progesterone, oestradiol B.-B., and thyroid hormone, with or without androsterone (Table III)—were administered *simultaneously* the pathological changes in uterine epithelium were also prevented; the depressing action of androsterone on adrenals was neutralized, as was to a certain extent the depressing effect of thyroid hormone on the thyroid gland; the cells and their nuclei in the fasciculata zone of adrenals, in liver, and in kidneys were hypertrophied. Histologically, the progestational changes were found in uterus and vagina, being intensified in uterus with an androsterone-containing combination.

Discussion

It was well established by previous workers that in an ageing organism it is possible to return the secondary sex organs towards or up to normal size and weight by administration of sex hormones. In the present experiments the combined administration of sex and thyroid hormones produced a similar return towards or to normal weight in such

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.

References

Donaldson, H. H. (1924). *The Rat*, p. 228. Philadelphia.
Freudenberger, C. B., and Billeter, O. A. (1935). *Endocrinology*, **19**, 347.
—— and Clausen, F. W. (1937a). *Anat. Rec.*, **68**, 133.
—— —— (1937b). Ibid., **69**, 171.
—— and Hashimoto, E. I. (1937). *Amer. J. Anat.*, **62**, 93.
—— —— (1939). *Proc. Soc. exp. Biol., N.Y.*, **41**, 530.
—— and Howard, P. M. (1937). Ibid., **36**, 144.
Jones, V. E., and Korenchevsky, V. (1946). *J. Gerontol.*, **1**, 336.
Korenchevsky, V. (1942). *J. Path. Bact.*, **54**, 13.
—— and Hall, K. (1938). *J. Obstet. Gynaec. Brit. Emp.*, **45**, 22.
—— —— (1940). *J. Path. Bact.*, **50**, 295.
—— —— (1944). Ibid., **56**, 543.
—— —— and Clapham, B. (1943). *British Medical Journal*, **1**, 245.
—— and Jones, V. E. (1946). *J. Gerontol.*, **1**, 319.
—— —— (1947). Ibid., **2**, 116.
—— —— (1948). Ibid. In press.
Lipschütz, A., and Schwarz, J. (1944). *Cancer Research*, **4**, 24.
—— Bruzzone, S., and Fuenzalida, F. (1944). Ibid., **4**, 179.
Plagge, J. C. (1946). *Arch. Path.*, **42**, 598.
Ross, M. A., and Korenchevsky, V. (1941). *J. Path. Bact.*, **52**, 349.
Warthin, A. S. (1930). *Old Age*. New York.

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