CLINICAL PATTERNS AND COURSE OF ANAEMIAS IN GENERAL PRACTICE

BY

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Anaemia is an important clinical condition in general practice for three very good resons: (1) it is frequent —according to French and Israëls (1955) an average G.P. may expect to meet 40–50 new cases each year; (2) it is the cause of much "sub-health"; and (3) it is eminently controllable. However, in spite of this importance it is probable that many anaemic patients remain undiagnosed and ineffectively treated.

The family doctor should play an important part in the control of anaemia. Obviously he must be constantly on the look-out for new cases, and must have readily available laboratory facilities to confirm his clinical suspicions. Having made the diagnosis, he must then plan and carry out long-term treatment and observation to ensure complete correction of the anaemia.

How far these ideals apply in actual practice is not known because of lack of any reliable information. Apart from the work of enthusiasts such as French (1948, 1953), French and Israëls (1955), and Semmence (1959), there are few reliable reports on anaemia in general practice.

Present Investigation

Because of the lack of such information this study was planned to review cases of anaemia in a general practice during a period of 10 years (1950–60).

The objects of the study were: (1) to collect cases for five years (1950–5) and then to follow them up for another five to ten years; (2) to estimate the incidence of anaemia in a general practice; (3) to define the common clinical types of anaemia; (4) to discuss the management, including the scope of a family doctor who has full diagnostic facilities available; and (5) to describe the course of the disease and the situation of the patients after five to ten years.

The practice is situated in a middle-class suburb in south London and its average size during the period 1950–5 is as shown in Table I.

TABLE I.—*Average Population at Risk* (1950-5)

Age:	0–	10–	20–	30–	40–	50–	60–	70+	Total
Males	405	246	349	380	398	302	173	127	2,380
Females	379	351	350	397	403	322	218	142	2,562

Diagnostic Facilities and Criteria

In this area all the family doctors have full and complete access to the pathological and radiological departments of the local hospitals. After a pilot study it was decided to restrict the types of cases to be studied to those in which "anaemia" presented as the main clinical feature. The decision to investigate the patient was based on clinical judgment. Pallor, debility, and shortness of breath were the most frequent reasons. Although the results cannot by reason of such clinical assessments give a true incidence of anaemia in practice, it must be appreciated that it is in just this way that medicine is practised and that it is not really practicable to carry out routine investigations on every patient seen.

Excluded from this review and follow-up were (*a*) those cases of anaemia that were picked up incidentally through routine blood tests during pregnancy (these cases were excluded because subsequent follow-up was difficult), and (*b*) those in which anaemia developed during the later stages of already established diseases.

"Anaemia" was regarded as being present when the level of haemoglobin reported was below 80% (100% = 14.8 g./100 ml.). Since only the one hospital laboratory was used during this study there was no variation in technique to be accounted for. Screening tests were not carried out; the patient was referred to the laboratory when anaemia was suspected, and the haemoglobin level, red-cell count, and erythrocyte sedimentation rate were estimated.

Methods

The methods of recording were simple. As each new case was diagnosed a card was made out and clinical details and haematological findings were recorded. These cards were then filed in small card-index boxes. The patients were all seen fairly regularly. Since the average yearly attendance rate in this practice was between three and four attendances per patient per annum no special reminders were necessary for patients to reattend. During the years 1950–60, five to ten years from the beginning of the study, those patients who were still in the practice were seen and re-examined.

Results

Incidence.—During the period of "collection" (1950–5) 222 patients (44 males, 178 females) were seen with anaemia as the main clinical feature. Records were also kept of the other clinical types of anaemia that occurred in the practice during this same time, and these amounted to 164 anaemias diagnosed during pregnancy by routine blood test, and 47 anaemias occurring in the later stages of other diseases (males 20, females 27). The incidence of *all* types of anaemia over the five years was therefore 433 cases (8.7%), and the *annual incidence was approximately 17.5 per 1,000.* This means that the average family doctor with a list of 2,500 may expect to meet some 52 patients with anaemia each year, a figure very close to that of French and Israëls (1955). It is of some interest to observe that on average about 100 patients are referred for haematological investigations each year, so that anaemia was present in some 86% of those investigated. For reasons already given only those patients who presented anaemia as the main clinical feature were followed up, and it is this group only that is discussed.

Age-and-Sex Distribution.—There was a fourfold predominance of females. The age-and-sex distribution is given in Table II. The sex differences of anaemia are well known, but the differing age distributions in the two sexes are less so. In males anaemia was most frequent in boys under 10 and in men over 50. The incidence of anaemia in these young boys was higher even than that in girls—the only period in which this was the case. In females the pattern was rather

TABLE II.—*Age-and-Sex Distribution of* 222 *Patients with Anaemia*

Age:	0–	10–	20–	30–	40–	50–	60–	70+	Total
Males	14	2	—	2	2	10	5	9	44
Females	7	9	26	36	46	22	19	13	178
				Rate per 1,000					
Males	35	8	—	5	5	33	29	71	
Females	20	26	74	90	115	68	87	91	

different. The peak occurred in the fifth decade, but the rates were high from the age of 20 onwards. This was probably connected with the menstrual blood loss during the reproductive phase.

Clinical Types

Two main types of anaemia were differentiated—hyperchromic and hypochromic (iron-deficiency). The hypochromic anaemia cases (with the colour index below 1) were further subdivided clinically into those where subsequent investigation revealed a definite underlying cause for the anaemia and those in which no obvious cause was evident. The distribution of these groups is shown in Table III. A number of interesting facts emerge from these distributions.

If we distinguish the two subgroups of hypochromic anaemias—that is, those with and those without obvious underlying disease—their proportions in males and females were very different. In 46% of the males no obvious underlying disease was discovered, whereas this group accounted for 83% of the females. The numbers in the various age-groups were very different. In males it was in infancy and early childhood that most of these cases of hypochromic anaemia were found. These anaemic boys accounted for 70% of this type of anaemia. It is very likely that nutritional deficiencies were the cause. In females the peak age-periods were at 30–49—that is, in the later reproductive phase—and the cause here must have been the negative iron balance from excessive menstrual blood loss.

The underlying conditions causing hypochromic anaemia included direct bleeding from a peptic ulcer in eight and hypochromic anaemia some years after a gastrectomy in a further seven. Other prominent conditions were new growths, usually in either the stomach or the colon, and rheumatoid arthritis; these accounted for a further 14 patients.

Since subclinical gastric haemorrhage has been shown to occur with aspirin tablets a note was made of the patients who were in the habit of consuming aspirin regularly. These amounted to 22 in all, 10 women and 1 man in the group with no obvious underlying disease, and in 11 patients (7 women and 4 men) with obvious underlying disease—that is, new growths, myeloma, and rheumatoid arthritis.

During the five-year period 14 patients were under treatment for pernicious anaemia. This represents a rate of 2.8 per 1,000, which is much higher than the national average of 1.3 quoted by Scott (1960).

Comment.—It is quite clear that in general practice hypochromic anaemias, associated with iron-deficiency, of one cause or another, are by far the most common types. Of the 222 cases, 205 (92%) were of iron-deficiency anaemia, and only 14 (7%) of pernicious anaemia and 3 (1%) of haemolytic anaemia. Considering the many varied conditions that were associated with the anaemia, it is important to realize that "anaemia" of itself was no definitive diagnosis. It was merely a sign and the result of some defect in blood formation, loss, or obstruction. In each case a careful clinical assessment and a search for the cause had to be made.

Severity

It was surprising how human beings could go about their daily tasks with anaemias of great severity. Of the 222 cases, 41 (18%) had initial haemoglobin levels below 50% (Table IV), and five (2%) had levels below 30%.

TABLE IV.—*Distribution of 41 Cases with Initial Haemoglobin Below 50%*

	Hypochromic		Hyperchromic		Total
	No Obvious Cause	Underlying Disease	P.A.	Haemolytic	
Males ..	2	4	1	1	8
Females ..	15	14	3	1	33

Management

Diagnosis.—As a first step in management the correct diagnosis had to be made, for, as already stated, "anaemia" was of itself an inadequate label. When the haemoglobin was below the critical level of say 80%, a search had next to be made for the cause and type of the anaemia. Co-operation with the haematologist will help to define the type, but a careful clinical assessment is required, especially when dealing with hypochromic anaemia, to discover any underlying disease. For this purpose a clinical examination, including rectal and pelvic examinations, followed by radiographs of the digestive tracts and tests for occult blood in the faeces may be required.

Referral to Consultant.—In this practice, with full access to all pathological and radiological examinations, only 18 out of the 222 patients reviewed, or 8% of the total, had to be referred to a consultant physician for elucidation of the anaemia and advice on its management. Of course, others were referred for treatment of their underlying disease—for example, new growths and peptic ulcers—after the exact diagnosis had been made. The fact that in this particular practice 92% of anaemias were diagnosed and elucidated by the family doctor without the aid of a consultant physician, but

TABLE III.—*Distribution of Types of Anaemia*

	Males									Females								
Age:	0–	10–	20–	30–	40–	50–	60–	70+	Total	0–	10–	20–	30–	40–	50–	60–	70+	Total
Hypochromic:																		
No obvious cause ..	14	2	—	—	—	2	2	—	20 (46%)	7	8	25	33	42	18	7	6	146 (83%)
Underlying disease ..									17 (38%)									22 (12%)
Peptic ulcer	—	—	—	—	—	1	2	1	4	—	—	—	1	1	—	2	—	4
Post-gastrectomy ..	—	—	—	1	1	2	—	1	5	—	—	—	—	—	1	1	—	2
Hiatus hernia	—	—	—	—	—	—	—	1	1	—	—	—	—	—	—	2	—	2
New growth	—	—	—	—	—	—	1	2	3	—	—	—	1	—	—	2	3	6
Leukaemia	—	—	—	1	—	1	—	—	2	—	—	—	—	—	—	1	—	1
Myeloma	—	—	—	—	—	—	—	1	1	—	—	—	—	—	1	—	1	2
Rheumatoid arthritis ..	—	—	—	—	1	—	—	—	1	—	—	—	—	2	2	—	—	4
Chronic nephritis ..	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	1
Hyperchromic:																		
Pernicious anaemia ..	—	—	—	—	—	4	—	1	5 (11%)	—	—	—	1	1	—	4	3	9 (4%)
Haemolytic ,, ..	—	—	—	—	—	—	—	2	2 (5%)	—	—	1	—	—	—	—	—	1 (1%)
Total	14	2	—	2	2	10	5	9	44 (100%)	7	9	26	36	46	22	19	13	178 (100%)

with the full co-operation and support of the local hospital diagnostic services, shows that the control of anaemia in the community is essentially a matter for the family doctor, provided he has the diagnostic facilities at his disposal. The 18 referred to a consultant physician were six males—two each with hyperchromic anaemia, leukaemia, and haemolytic anaemia; and 12 females—three with hyperchromic anaemia, two each with hiatus hernia and new growths, and one each with rheumatoid arthritis, chronic nephritis, myeloma, hypochromic anaemia, and haemolytic anaemia. The severity of the anaemia was not in itself a primary factor in deciding whether the patient was to be referred to a consultant. In fact, three of the five patients with haemoglobin levels below 30% were managed at home.

Treatment

The treatment naturally depended on the type and cause of the anaemia. Underlying disease required treatment—for example, peptic ulcer, new growth, etc. —but even here correction of the anaemia was an urgent primary matter. No patients treated at home were thought to require blood transfusions, although some of those admitted to hospital for elective treatment of underlying disease did receive blood as part of their management.

Hypochromic anaemia was treated with iron. Oral iron in the form of the standard ferrous sulphate preparations was given in the first instance where the haemoglobin was between 50 and 80%, and where the haemoglobin level was below 50% additional intramuscular iron ("imferon") was used on occasion. It is of interest to note that the intolerance rate of ferrous sulphate was as high as 20%. Most of these patients, however, were able to tolerate the gluconate or fumarate compounds. Follow-up was maintained for as long as possible with regular blood checks, but once patients felt better many were loath to continue to attend over the years, and no special efforts were made to pick up the defaulters until the results of the study were known.

Hyperchromic anaemia cases had first to be accurately diagnosed by gastric analyses and marrow examination. Since all but three of these were pernicious anaemia the management was relatively simple, with regular vitamin B_{12} injections. Follow-up with regular three-monthly blood checks was easily maintained in this group because the patients had to attend for injections.

Course and Follow-up

Patients still in the practice in 1959–60 (5–10 years from beginning the study) were seen, examined, and their haemoglobin levels estimated. During the follow-up period 15 patients (7%) (3 males and 12 females) had moved out of the practice. A further 18 had died from the following: males—new growths (3), leukaemia (2), myeloma (1), haemolytic anaemia (1), and one man with a gastric ulcer who died from a cerebral haemorrhage; females—new growths (6), myeloma (2), chronic nephritis (1), and rheumatoid arthritis (1).

There were therefore 189 patients who were reassessed in 1959–60. Analysis of the haemoglobin figures at follow-up showed that anaemia (Hb below 80%) was still present in 61 (32%). The distribution of these patients is shown in Table V. It was far from satisfactory to find that at follow-up one-third of the patients were still anaemic. Who were they? Why were they still anaemic? What should be done about this situation?

Who were they?—Patients with hypochromic anaemia with no major underlying disease accounted for 55 out of the 61, and 50 of these were females. Women aged between 30 and 60 were most liable to relapse, but three out of the five males who relapsed were children. The hyperchromic anaemias presented few problems. Those who relapsed were two patients with haemolytic anaemia whose course is known to fluctuate and one old woman with pernicious anaemia who required iron and folic acid to maintain her haemoglobin level at over 90%.

Why were they anaemic?—All the patients with hypochromic anaemia who relapsed had either stopped taking oral iron or were women who were having very heavy menstrual losses and in whom there was a negative iron balance in spite of their taking iron.

What should be done?—Patients with hypochromic iron-deficiency anaemia, by far the most common type of anaemia in the community, should be under constant medical supervision with regular haemoglobin estimations, and they should be seen at regular intervals to ensure that they continue to take the iron that is so necessary for the control of their anaemia. They should be seen at least two or three times a year to check their haemoglobin levels.

When can treatment be stopped safely in iron-deficiency anaemias?—This is an individual matter in each case. As a general rule it is unwise to stop therapy until well after the menopause in women with hypochromic anaemias. Where underlying diseases have been cured treatment can cease once normal haemoglobin levels have been maintained for over a year. However, all patients who have been on treatment should have haemoglobin estimations after six months of ceasing iron therapy to make sure that all is still well.

Discussion

The importance of "anaemia" as a frequent cause of "sub-health" has already been referred to in a general way. The subject can now be discussed in relation to the findings of this study. The estimated annual incidence of all forms of anaemia was 17.5 per 1,000. This is a high figure, representing about one new case to be diagnosed and managed each week of the year in an average-sized British practice. The family doctor has therefore to be alive to the condition and be given opportunities for early diagnosis and encouragement in supervision of his patients. Unless this awareness is present and these facilities are available the diagnosis will not be made and many patients will suffer unnecessarily.

TABLE V.—*Patients with Haemoglobin Level of Less than 80% at Follow-up*

	Males									Females								
Age:	0–	10–	20–	30–	40–	50–	60–	70+	Total	0–	10–	20–	30–	40–	50–	60–	70+	Total
Hypochromic:																		
No obvious cause ..	3	1	—	—	—	—	1	—	5/17 (30%)	1	2	5	12	14	11	2	3	50/138 (36%)
Underlying disease ..	—	—	—	—	—	—	—	2	2/12 (17%)	—	—	—	—	—	1	—	—	1/11 (9%)
Hyperchromic	—	—	—	—	—	—	—	1	1/4 (25%)	—	—	—	1	—	—	—	1	2/7 (29%)

As with many other conditions, hospital experiences cannot be applied to general practice. The types of anaemia seen most often in the community, and therefore in general practice, have quite a different slant and pattern from those seen in hospital.

In this series of 222 patients who presented clinically with anaemia as the major feature, hypochromic anaemia accounted for 92% and hyperchromic anaemia for 8%.

In 17% the hypochromic anaemia was found to be the result of some obvious underlying disease; in 75% there was no very obvious cause for the hypochromic anaemia, but it was probably the result of excessive blood loss—for example, menstrual—and inadequate nutrition.

The importance of hypochromic anaemia in pregnancy must also be remembered. Although this type was not specially studied here, during the five years 167 expectant mothers were found to have a haemoglobin level below 80% (out of nearly 400 deliveries in the practice during this time), a rate of 42%. Giles and Burton (1960), in Stoke, reported a rate of 66%.

The most vulnerable groups of patients were women from 30 upwards, young male infants, and old men. This liability of male infants to iron-deficiency anaemia is interesting in that it fits in with the generally excessive morbidity of male children. The vulnerability of the women in the 30–60 period was undoubtedly related to the negative iron balance from excessive menstrual losses. In the elderly of both sexes the anaemias were much more likely to be associated with some underlying diseases.

Hyperchromic anaemia was most frequent in those over 50. No case of hyperchromic anaemia occurred during pregnancy.

Reference has been made to the amazing tolerance and adaptive powers of the human body in regard to anaemia. During this study 41 patients (18%) had a haemoglobin of less than 50% at the time of diagnosis. In 5 (2%) the initial level was between 20 and 30%, and yet these patients were able, with difficulty admittedly, to carry on their daily tasks. This is also a reflection of the delay of the diagnosis. The blame for this delay was very often the patient's, because the diagnosis was usually made by the doctor at the first consultation.

The management of these anaemic patients must follow a definite pattern in order to be successful. A confirmatory blood examination is necessary to make the diagnosis of "anaemia." This, however, is merely the beginning. The patient has next to be clinically examined to exclude or discover any underlying disease. Further investigations, both radiological and pathological, may also be required before the type of anaemia and its cause can be ascertained. Given the facilities for investigation, the family doctor should be able to assess most of his anaemic patients.

Treatment should be kept as simple as possible, and stress must be laid on the necessity for long-term supervision. The importance of such supervision is evident from an examination of the results of reassessment at the end of 5 to 10 years. In one-third (32%) anaemia was still present. The results were particularly poor in women aged 30 to 60 with hypochromic anaemia. In view of these unsatisfactory results certain conclusions and recommendations can be made.

Conclusions

Hospital pathological laboratories and *x*-ray departments should be open to all local family doctors. Unless they are it is impossible for the family doctor to diagnose anaemia early, and difficult to supervise and maintain satisfactory treatment.

It is important to make students and doctors aware of the high frequency of the common types of anaemia and of the principles of management.

In management the most important points are: the need for an accurate initial diagnosis, particular care being taken to exclude any underlying disease as the cause of the anaemia; to appreciate that satisfactory results can be obtained by very simple treatment; and to realize that long-term supervision of the patient must be maintained with regular haemoglobin estimations extending over many years. If this supervision is neglected the tendency for relapse is great.

Summary

Anaemia is a very important illness in our community because of its high prevalence and the ill-health that it causes; it is so easily remedied.

A study is reported from a London general practice of 5,000 patients. Full facilities are available in the area for family doctors to investigate their patients. Cases of anaemia were recorded to assess the incidence, the distribution of the common varieties, and the level of haemoglobin at the end of 5 to 10 years.

"Anaemia" was regarded as being present when the haemoglobin level was below 80%. Only those cases where the anaemia was the chief presenting clinical feature were studied. There were 222 of these in five years (1950–5). Excluded were 164 women in whom the anaemia was diagnosed incidentally during pregnancy, and 47 patients in whom anaemia developed during the later stages of other diseases.

The total incidence rate (including all cases and types) of anaemia worked out at 17.5 per 1,000 per annum.

There was a 4:1 female predominance (178 females and 44 males) of anaemia. The most vulnerable age periods were: in males, children under 10 and men over 60; and in women, all age-groups over 30, with a peak at 50–59.

Hypochromic anaemias (iron-deficiency) accounted for 92% (205 patients) of all types. In 17% (39) of these an obvious underlying disease was present at the time the diagnosis was first made. In the other 83% (166) cases of hypochromic anaemia no serious underlying disease was detected. The proportion of cases with underlying disease was much higher in males (54%) than in females (17%), and in the elderly of both sexes. Pernicious anaemia was present in 14 patients—a rate of 2.8 per 1,000.

Many patients were severely anaemic when first diagnosed. In 41 (18%) the initial haemoglobin level was below 50% and in 5 (2%) it was below 30%.

With the full diagnostic facilities 92% of these patients had their anaemias investigated, diagnosed, and managed by the family doctor alone.

The routine treatment in hypochromic anaemias was oral iron. (There was a 20% intolerance rate to ferrous sulphate.)

At the end of 5 to 10 years, in 1959–60, there were 189 patients still in the practice (15 had moved and 18

had died), and these were all reassessed. In 61 (32%) the haemoglobin level was below 80%. Hypochromic anaemias, of the non-specific variety, accounted for 55 (50 in females). The reasons for these relapses were generally failure to continue with iron therapy.

As a result of this study it is recommended that full facilities for investigations be given to all family doctors in at least one hospital in each local hospital group; that more teaching be given to undergraduates and post-graduates (in general practice) on the frequency of anaemia and on the principles of successful management; and that the importance of the long-term treatment and follow-up of the particularly vulnerable group of women in their later reproductive phase (that is, 30–50) is appreciated. It is quite useless to treat those women by a prescription for 100 iron tablets and then to forget all about them. Treatment, with regular blood tests, is necessary right up to and well past the menopause.

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PREVALENCE OF ANAEMIA IN THE GENERAL POPULATION

A RURAL AND AN INDUSTRIAL AREA COMPARED

BY

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The results of a study of the prevalence of anaemia in an industrial community, the Rhondda Fach, have already been published (Kilpatrick and Hardisty, 1961), and in the present paper the findings are given of a survey carried out for comparative purposes in a rural area, Wensleydale, the largest of the Yorkshire dales.

The inhabitants of Wensleydale had previously been the subject of epidemiological studies by Dr. Pickles, of Aysgarth, and the decision to sample this population was made easy by a fortunate coincidence: Dr. J. S. Lawrence and his colleagues of the Empire Rheumatism Council Field Research Unit had elected to go there to study rheumatic conditions in an agricultural community, and it was decided to join them to determine the prevalence of anaemia in their sample.

Sample and Methods

Wensleydale is about 35 miles (56 km.) long, and the size of the valley with its scattered population (about 0.04 person per acre) made it impracticable to work on a random sample of the whole population; a representative area was therefore selected. After a private census had been made it was decided to study the population of both sexes, aged 15 and over, in the southern half of the village of Hawes, in three of the near-by hamlets, and in about 40 square miles (103 sq. km.) of the surrounding farming area in the upper end of the dale. Because of the knowledge of the structure of the population in this area it is thought that the subjects studied were a fair but perhaps not an impeccable sample of the population as a whole. The total available population was 547, of whom 412 (75%) were examined. This survey was planned for August and September, 1958, in the hope that the hay harvest would be completed before then, but because of bad weather the harvest was late, and the response rate was therefore lower than in the previous survey. The numbers included in the survey are shown in Table I.

Our base was in the centre of Hawes, where the Manchester University Survey van and trailer provided an almost self-contained unit in which some 30 people were seen each day. Because it was impossible to have full facilities in the van for blood-counting, and so that the findings of this survey would be comparable to the previous studies, the blood taken by venepuncture during one day was each evening taken by road to Kendal and put on the night train so that the samples arrived at the laboratory in Cardiff Royal Infirmary the next morning. The specimens were then examined in exactly the same way as during the Rhondda survey (Kilpatrick and Hardisty, 1961). The arbitrary levels of haemoglobin chosen for "anaemia" were the same—12.5 g./100 ml. (85%) or less for men and 12 g./100 ml. (81%) or less for women.

TABLE I.—*Details of Population Studied*

Age-group	Men		Women	
	No. Living in Area	No. Examined	No. Living in Area	No. Examined
15–24	53	29 (55%)	45	32 (71%)
25–34	37	26 (70%)	51	40 (78%)
35–44	54	34 (63%)	52	45 (86%)
45–54	48	36 (75%)	42	34 (81%)
55–64	33	25 (76%)	38	32 (84%)
65–74	27	20 (74%)	37	33 (89%)
75+	13	12 (92%)	17	14 (82%)
	265	182 (69%)	282	230 (82%)

Because this survey was planned purely as a prevalence study no further investigation or treatment was done, but the name of each person found to be anaemic was immediately sent to the general practitioner concerned.

Results

In men the mean level of each index, except P.C.V., declines fairly steadily with age; there is no fall in P.C.V. until the 55–64 year age-group, but the means thereafter are much lower (Table II). The scatter of values of each index, as measured by the standard deviation, shows a tendency to increase with age, except in the case of the serum iron. This is almost certainly a reflection of an increased proportion of subjects with low values in the higher age-groups.

In women the levels for all indices are lower than those for men, though the differences are much less marked over the age of 65 years (Table II). There is no downward trend of values with increasing age, and