VITAMIN C IN HAEMOPOIESIS.

William McAdam, M.B., Ch.B.

ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

PREFACE.

The work on which this thesis is based was carried out while I held the post of Medical Registrar in the Southern General Hospital, Glasgow. A few of the cases were in the wards of Dr. Dick, Visiting Psychiatrist, whom I have to thank for his kindness in granting me ready access to his cases and records. The greater bulk of the cases were in the wards of Dr. Snodgrass, to whom I cannot sufficiently express my gratitude for his help and criticism, and for his encouragement when interruptions occasioned by war conditions made it seem purposeless to attempt to continue with the work.

Dr. Briggs, then Medical Superintendent of the Southern General Hospital, also helped, both by granting permission to carry out the work and by his interest in the question of diet. A few cases had been left on the ordinary hospital diet while certain investigations were proceeding. It was thought then that the ordinary hospital diet was deficient in vitamin C. The interest of Dr. Briggs and Dr. Snodgrass in/

in this question led to the discovery that the ordinary hospital diet was in itself sufficient to bring about recovery in certain cases of scurvy. Those cases that had not been submitted to full investigation before going on this diet had thus to be excluded from the series.

Finally, I have to thank Dr. (now Major) Chalmers for his criticisms of my earlier bone marrow differential counts; the sisters and nurses who took such care to see that the diet that reached the patients was that prescribed; Miss Adamson, of Killearn Hospital laboratory, who produced adequate photomicrograms with apparently inadequate apparatus: and Messrs. Roche Products who freely supplied pure hesperidin.

* These are to be found at the end of the thesis, before the tables in the appendix.

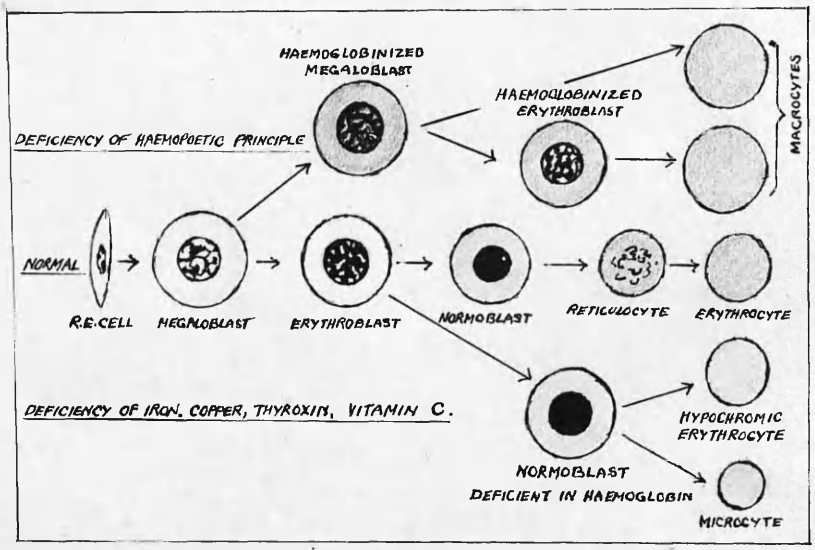
NOMENCLATURE

"Much of the confusion that mars haematological writings can be traced to the abuse of terms." (Scott, 1939). On page 8 there is a note on the terminology used in this paper, with a list and description (page 11) of the precursors of the mature leucocyte of the granular series and of the mature red cell. When one of the terms in this list is used in this paper, it is to be understood that the cell to which it applies conforms to this description; except that in a few instances, the use of the term is that of an author quoted. When this occurs, it is indicated by a statement to that effect, or by the appearance of the passage in quotations over the name of the author.

INTRODUCTION

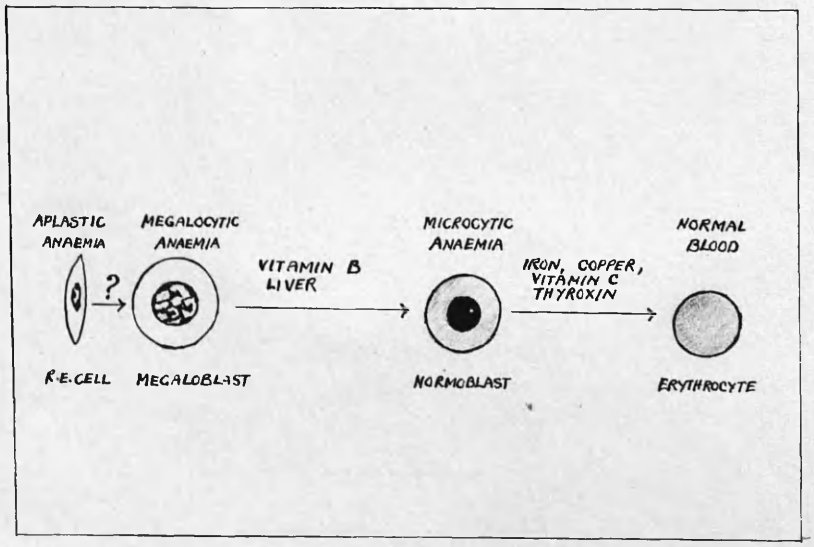
The purpose of this thesis is to determine to what extent vitamin C may be regarded as a substance of importance in the maturation of the red cell.

It was formerly commonly believed that vitamin C exercised a specific function in erythropoiesis. This view has been held by Armentano (1938), Aron (1928), Diblicek and Kucera (1938), Hojer (1942), Mettier et al.(1930), Mettier and Chew (1938), Mouriquand et al. (1934, 1938), Parsons (1938), Parsons and Small-:wood (1935), Rohmer et al. (1938) and Rohmer and Bindschedler (1938). There was difference of opinion as to the phase of maturation at which the vitamin acted. Mettier et al. (1930) and Witts (1932) considered that it acted at the phase of maturation from normoblast to erythrocyte while Whitby and Britton (1942) represented it as/



Diagrammatic representation of normal and abnormal erythropoiesis.

Whilby and Britton, (1942)



Diagrammatic representation of erythropoiesis (Wills, 1932)

as acting at the phase of maturation from erythro-:blast to normoblast. The diagrams opposite illustrate these views. (The nomenclature above is that of the authors cited). Parsons (1938), on the other hand, considered that the vitamin acted throughout the whole range of maturation, and not at a single phase only.

This work was first planned with a view to obtaining information on this question, it being accepted as already established that vitamin C was a specific erythropoietic factor. As the work progressed, however, instances appeared which were difficult to reconcile with this view. "Belief in the need for vitamin C has dwindled" (McMillan and Inglis, 1944); and it has been suggested that the anaemia of scurvy may be due to a lack of other factors than vitamin C (Croft, and Snorf, 1939).

Briefly, severe deficiency of vitamin C may occur without anaemia; so that there is difficulty in regarding vitamin C as essential to erythropoiesis. But/

But the addition of pure vitamin C to a diet on which scurvy and anaemia have developed may as efficiently correct the anaemia as remove the signs of scurvy; so that it is equally difficult not to regard the vitamin as being able to play some part in erythropoiesis.

In this thesis an attempt is made further to elucidate the role of vitamin C in erythropoiesis.

METHODS OF EXAMINATION AND TESTS EMPLOYED.

These fall into three categories: firstly, those referring to the state of the case as to the degree of vitamin C deficiency; secondly, those referring to the haematological condition; and thirdly, a number of tests not falling into either of these groups. In the first category fall, for example; an account of the diet of the subject before coming under observation; the physical examination, involving the physical diagnosis of scurvy; and chemical methods of estimating the presence or absence of vitamin C deficiency and the degree of such deficiency when present. In the second fall the examination of the blood and bone marrow. In the third are a number of diverse tests which were found to be relevant. These include gastric analysis, assessment of capillary fragility and red cell fragility.

DIET :- A number of the cases were inmates of a mental institution. In these cases the diet could be controlled; and records of the diet of the institution and of the patients' refusal of certain articles of the diet, had been kept and could be studied. In the remaining cases the diet had been so restricted, either voluntarily or because of destitution, that the patients easily recollected the limited number of articles that

it had contained.

While under investigation, each case remained on the diet to which he had been accustomed.

PHYSICAL EXAMINATION :- The following features when confirmed by the chemical tests, were taken as evidence of the presence of scurvy: follicular haemorrhages and ecchymoses, chiefly on the legs; red blood cells in the urine; dyspnoea on exertion, of recent onset, in the absence of signs of renal inadequacy or of organic heart disease. These features were common to all the cases considered to be scorbutic. In addition, one or more of the following features was usually presented: sponginess of the gums - this was found in every case in which the jaws were not edentulous; effusion into the knee joints; brawny indurated swelling in the thigh or calf muscles; moist sounds in the lung bases and oedema of the ankles; and profound weakness.

These features, although severally they might be found in a variety of conditions, were collectively considered sufficient evidence of the scorbutic state. This was supported by the fact that they disappeared with antiscorbutic treatment.

In the non-scorbutic cases none of these signs was present, though in some cases there was complaint of unusual weakness or of recent onset of dyspnoea on exertion.

Four of the thirteen cases of scurvy were found to be complicated by co-existing disease; namely, two cases of duodenal ulceration and two of rheumatoid arthritis. The effect of antiscorbutic treatment in these cases is not recorded, since the possible co-existence of anaemia unrelated to vitamin C deficiency introduces uncontrollable factors.

ASCORBIC ACID DETERMINATIONS:- Three chemical methods of assessing the ascorbic acid levels were employed. These were: Rotter's test; the estimation of the fasting plasma ascorbic acid level; and the intravenous ascorbic acid tolerance test.

Rotter's Test:- This was employed in order rapidly to obtain an approximate estimate as to whether or not there existed a material degree of vitamin C deficiency. The basis of the test is the decolorisation of a solution of 2:6 dichlorophenol-indophenol, injected intradermally, by the ascorbic acid in the skin (Rotter, 1937;

Portnoy and Wilkinson, 1938a). Absence of vitamin C deficiency is indicated by a short decolorisation time, and the time is more prolonged the more severe the deficiency.

Plasma Ascorbic Acid:- The single estimation of the fasting plasma ascorbic acid level has been held to give an estimate as to whether or not a deficiency of vitamin C existed, and as to the degree of such deficiency, sufficiently accurate for most routine purposes (Harris et al., 1936; Portnoy and Wilkinson, 1938b; Sloan, 1938).

The level was estimated by the original method of Farmer and Abt (1935). In this method the blood is deproteinised by orthophosphoric acid solution and the protein-free filtrate is titrated against 2:6 - dichlorophenol-indophenol, the titration being run within half an hour of withdrawal of the blood. The modification introduced by Pijoan and Klemperer (1937), which was designed to prevent loss of ascorbic acid in the specimen through oxidation, was avoided, as Ludden and Wright (1940) and Farmer and Abt (1938) had come to the conclusion that the modification gave false

readings and that no appreciable loss of ascorbic acid occurred if titrations were run within half an hour of withdrawal of the blood.

Intravenous Tolerance Test:- Sloan (1938) showed that the most accurate estimate of the degree of depletion of vitamin C is given by the rate of absorption from the blood stream of an injected dose of the vitamin. Harris et al. (1936) found that the response to a test dose was proportional to the fasting ascorbic acid level.

The method used in this series was that of Portnoy and Wilkinson (1938b) in which the plasma ascorbic acid levels are estimated before and at intervals after the intravenous injection of a dose of ascorbic acid. In states of depletion, no considerable rise after injection is obtained, while the level rises to a considerable height in the absence of deficiency.

BLOOD EXAMINATIONS :- The following determinations were carried out, using oxalated venous blood:

Haemoglobin (Hb) :- This was estimated in a Sahli type haemoglobinometer. The results as tabulated represent the mean of four separate readings. One hundred per cent haemoglobin is equivalent to 13.8 milligrammes per cent.

Red Cell Count. (R.B.C.)

Reticulocyte Count:- This was made on wet films stained by brilliant cresyl blue.

White Cell Count. (W.B.C.)

Schilling Count:- This is the modification of the differential count introduced by Schilling (1929)

The normal haemogram as given by Schilling is as follows:

	Basophils	Eosinophils	Neutrophils				Lymphocytes	Monocytes
			Myelocytes	Juveniles	Staffs	Segmented		
Mean	1	3	-	-	4	63	23	6
Range	0-1	2-4	-	0-1	3-5	51-67	21-35	4-8

Basophils, eosinophils, lymphocytes and monocytes are so well known as to require no further description. The other cells will be briefly described when nomenclature is discussed (page 11).

Cooke Count:- This is the Cooke modification of the Arneth polynuclear count (Cooke and Ponder, 1927). The "weighted mean" indicates the amount of lobulation

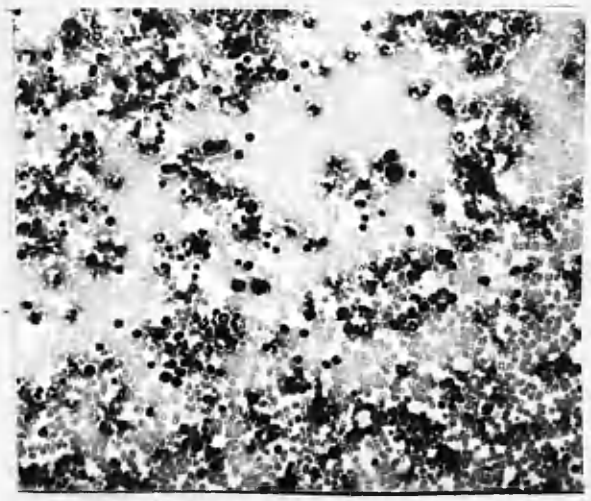


Figure 3

High Cellularity

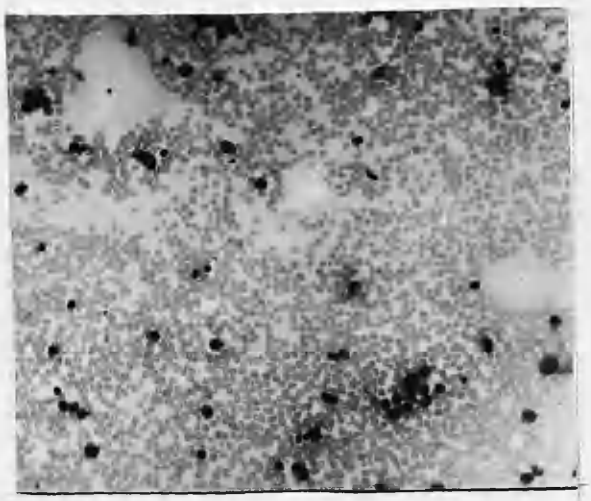


Figure 4

Medium Cellularity

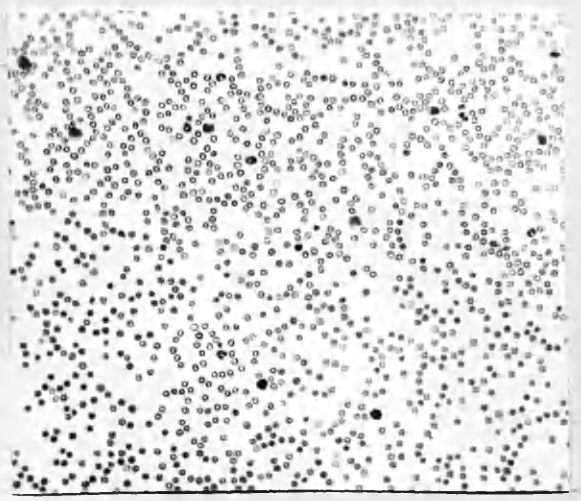


Figure 5

Low Cellularity (from a case of hypochromic anaemia in a senile individual, not in this series)

Photomicrograms of Bone Marrow Films under low Power, illustrating High, Medium and Low Cellularity Marrows.

in the polymorph nucleus. The average is 2.7; increase may be referred to as "right shift" and decrease as "left shift".

Platelet Count:- The method used was that of estimating the proportion of platelets to red cells in a wet film.

BONE MARROW EXAMINATION:- The bone marrow was obtained by sternal puncture, using a needle of the Salah type. Films were made immediately and stained with Leishman's stain. As recommended by Scott (1939) not more than 0.2 cubic centimetres of marrow were aspirated at a time, since larger amounts tend to give excessive dilution of marrow with blood.

Cellularity:- The nucleated cells in the specimen were not enumerated, but following Scott's practice, the cellularity - i.e., the number of nucleated cells in a microscope field - is recorded as being either low (approximately that of a normal blood film), medium (that of the healthy marrow) or high. The photomicrographs opposite illustrate these appearances.

Differential Count:- The nomenclature used in this paper is that of Scott (1939), who followed

Ferrata (1933), with some modifications that do not apply to the present work. The myeloid series (granuloblast) is divided into myeloblast, promyelocyte, and neutrophil granulocyte, the latter being further subdivided into the grades originally suggested by Schilling (1929) of myelocyte, juvenile, staff and segmented forms. The orthoplastic (normal) precursors of the mature red cell are known collectively as the erythroblast. The series consists of pronormoblast, and basophilic, polychromatic and orthochromatic normoblasts. The table below shows how this nomenclature appears to correspond with other authors'

Scott (1939). Wintrobe. (1942).	Whitby and Britton. (1942).	Davidson et al (1942).
Pronormoblast	Megaloblast	Erythroblast Type I
Basophilic normoblast	Erythroblast	Erythroblast Type II
Polychromatic normoblast	Late erythroblast	Erythroblast Type III
Orthochromatic normoblast	Normoblast	Erythroblast Type IV

The term "megaloblast" is reserved for the abnormal cell observed in pernicious anaemia during relapse. "Plasma cell" includes both Türck cells and bone marrow plasma cells.

The following is a brief description of the main features of the cells of the granuloblast and of the erythroblast.

Myeloblast:- This is a large cell with a basophilic cytoplasm with a deeply staining rim fading as the perinuclear zone is approached. The nucleus stains palely and contains nucleoli. It presents a little condensation of chromatin at the edge and round the margins of the nucleoli.

Promyelocytes:- The basophilia of the cytoplasm is now less intense and scattered through it are coarse violet granules. The nucleus resembles that of the myelcblast but the chromatin has undergone a little condensation to produce a little less fine stippling and the nucleoli have disappeared.

Myelocyte:- The cytoplasm is pale blue to neutral, with mature neutrophilic, basophilic or eosinophilic granules. The nucleus may be round

or oval, or slightly indented, with coarser and darker interstices.

Juveniles:- The cytoplasm may be slightly basophilic but is usually neutral and contains neutrophilic granules with a tendency to azurophilic characterestics.

Staff:- The nucleus is more slender and darker than in the juvenile and is often twisted and with indentation suggestive of beginning segmentation.

Segmented Neutrophil:- The nucleus is divided into segments connected in a chain by fine threads. The cytoplasm contains mature granules.

Pronormoblast:- The cytoplasm is deeply basophilic, with a paler perinuclear halo. The nucleus is of a fine stippled texture and contains nucleoli.

Basophilic Normoblast:- The basophilia of the cytoplasm is less intense and the nuclear pattern coarser than in the pronormoblast. The nucleus is becoming basichromatic and nucleoli have disappeared.

Polychromatic Normoblast:- The cytoplasm is slate-grey and the nuclear chromatin is in coarse clumps.

Orthochromatic Normoblast:- The cytoplasm is orthochromatic. All trace of structure in the nucleus has disappeared and it is intensely basichromatic .

Maturity Dispersal Ratios:- These were calculated in order to assess shift in maturity in successive specimens of bone marrow. In the erythroblast, the proportions of pronormoblasts, basophilic normoblasts, and polychromatic and orthochromatic normoblasts together, are calculated, the figures being given as percentages of the total erythroblast. In the granuloblast, the proportions of myeloblasts, promyelocytes, myelocytes, and juveniles are calculated as percentages of the sum of these four types.

GASTRIC ANALYSIS:- A Refuss fractional test meal examination was carried out in each case. When achlorhydria was found, the histamine test meal was performed, The fractional test meals were carried out before commencing treatment. In cases 14, 15 and 16, the histamine test meal was carried out on the day after commencing treatment.

OTHER TESTS:

CAPILLARY FRAGILITY:- This was determined by a positive pressure method, similar to that used by

Göthlin (1937). The capillary fragility is given by the number of petechiae counted, in a good light and with the aid of a hand lens, in a circle of one inch diameter on the volar aspect of the forearm, after a pressure of eighty millimetres of mercury has been maintained for fifteen minutes in the sphygmomanometer cuff round the arm. By this method, up to ten petechiae may be regarded as normal.

In most cases the following additional tests were carried out: van den Bergh reaction, the icteric index, and the urinary urobilin by Schlessinger's method. In the cases of scurvy, fragility of the red cells was estimated.

When the expression "before treatment" is used, it is to be taken to refer to investigations carried out on the case' first coming under observation, before any antiscorbutic or anti-anaemic treatment was carried out; and the expression "after treatment", to investigations carried out after the case had reached a state where no evidence of vitamin deficiency could be found.

GENERAL ACCOUNT OF THE CASES.

The cases are grouped primarily according to the presence or absence of anaemia and to the response of the anaemia to administration of ascorbic acid. Group I contains those cases in which anaemia was not a feature. None of these cases had any sign of scurvy. Group II contains those cases in which there was anaemia, remission in which took place when ascorbic acid was administered. Scurvy was present in all these cases. Group III contains those in which there was anaemia on which ascorbic acid alone had no demonstrable effect. Both scorbutic and non-scorbutic cases occur in this group.

In Group IV there are four cases of scurvy associated with anaemia. The effect of treatment is not recorded, since the picture was complicated by the presence of peptic ulceration in two cases and of rheumatoid arthritis in two others. The cases are included in order that the blood and bone marrow pictures here may be compared with those of the cases in which there was no apparent complication of the vitamin deficiency.

Group I. Cases in which no blood abnormality was found.

(Cases 1 - 6. Tables I to VI, appendix)

DIET :- These cases were schizophrenic male inmates of a mental institution, on a standard hospital diet. While this diet contained an adequacy of fresh fruit and vegetables, the cases in question had refused various articles and had had cooked food only for at least two years. It was therefore imagined that the quantity of vitamin C actually consumed would be very low. No attempt was made to estimate the actual amount.

When the examinations were complete, three hundred milligrammes of ascorbic acid were administered daily by mouth. In addition one thousand milligrammes were injected intravenously at the beginning of treatment, this being required for the carrying out of the ascorbic acid tolerance test.

PHYSICAL EXAMINATION :- Each case appeared to be in good general health. They were males of between forty and fifty years of age. There was no evidence of the scorbutic state.

ASCORBIC ACID DETERMINATIONS :-

Rotter's Test:- Before treatment, decolorisation times were prolonged. The mean time was sixteen minutes, and the range from ten to thirty-two minutes. After treatment, normal values were given, the mean decolorisation time being four and a half minutes. In no case was the time over five minutes.

Plasma Ascorbic Acid :- The level was estimated on the case first coming under observation, and again a month or more later, no ascorbic acid having been given in the meantime. There was no significant difference between the two estimations, either in the cases separately or in the mean values. The mean of the first was 0.49 milligrammes per cent, and of the second, 0.50 milligrammes per cent. The range of values was from 0.42 to 0.58 milligrammes per cent. After treatment, a considerable elevation from these was found, the mean being 1.7 and the range from 1.4 to 2.0 milligrammes per cent.

Intravenous Tolerance Test :- This test was not carried out on the case first coming under observation, as it involved injecting a large dose of ascorbic acid. This was avoided in order to observe

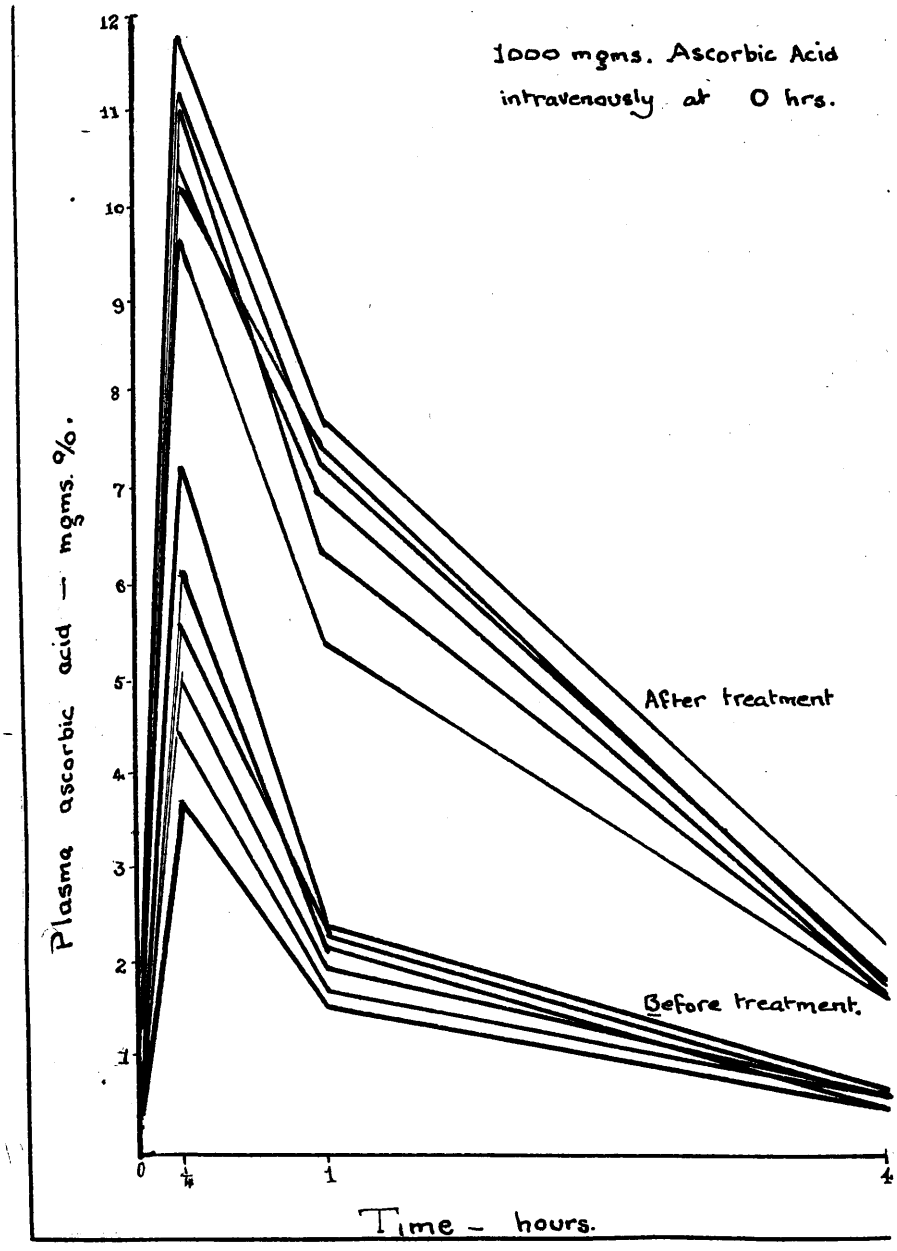


Figure 10.

Plasma ascorbic acid tolerance test, Group I. Plasma ascorbic acid curves after intravenous injection of one thousand milligrammes ascorbic acid; showing higher levels being reached after treatment.

whether or not any material change took place while the patient remained on the diet presumed to be low in ascorbic acid. The test was carried out just before treatment was begun and again after treatment. Fig. I shows the curves obtained. Before treatment, the curves are markedly lower and flatter than after treatment.

CAPILLARY FRAGILITY :- The petechial counts were low both before and after treatment, except in case 6 where the moderately high count of ten was obtained. This was not affected by treatment. The means were five petechiae before and four after treatment.

BLOOD EXAMINATIONS :-

Haemoglobin:- The levels were above ninety per cent except in one case where one reading of eighty-nine per cent was obtained. Treatment with ascorbic acid produced no demonstrable change. The mean percentages were ninety-eight before and ninety-nine after treatment.

Red Cell Count:- The lowest (case 3) was of 4.3 million per cubic millimetre.

Treatment with ascorbic acid produced no demon-

strable change in the red cell counts.

The colour index lay between 0.9 and 1.1 except in case 4 where it was 1.2. The colour index was not significantly affected by treatment.

Reticulocyte count:- Reticulocytes were counted for three days before and for seven days from the beginning of treatment. No deviation from the normal was observed.

White Cell Count:- The range, before treatment, was from 3,600 to 1,000 per cubic millimetre. No effect of ascorbic acid treatment on the white cell count could be demonstrated. The means were 6,200 before and 7,200 after treatment.

Schilling Count:- No significant deviation from the average normal, either before or after treatment could be demonstrated.

Cooke Count:- No effect of ascorbic acid could be demonstrated. The mean value for the "weighted mean" before treatment was 2.7, with a range of 2.5 to 3.0, and after treatment the mean was 2.6, one case (4) only diverging, with a weighted mean of 2.8.

Platelet Count:- One count was carried out in each case, before treatment. No abnormal values were found.

Table 1

Maturity Dispersal Ratios, Group I. Percentages before and after treatment, compared with mean normals (Scott, 1939)

	Before Treatment		After Treatment	Mean Normal (Scott)
	At beginning of control period	At end of control period.		
Granuloblast				
Myeloblast	5.5	5.7	5.5	5.1
Promyelocyte	12.9	14.9	13.9	12.6
Myelocyte	36.6	33.4	33.8	37.2
Juvenile	44.9	46.0	46.9	45.0
Erythroblast				
Pronormoblast	2.0	1.9	2.6	2.5
Normoblast-basophilic	15.1	16.5	14.9	10.8
Polychromatic and orthrochromatic	82.9	81.6	81.8	86.6

BONE MARROW :-

Cellularity: - Medium cellularity was found throughout.

Differential Count:- No gross or constant abnormality was found, and no change after treatment could be demonstrated.

Maturity Dispersal Ratios:- Table 1 opposite shows the mean percentage before and after treatment, compared with the means of six normal cases given by Scott (1939). It is apparent from this table that there is no significant deviation from the normal before, and no change after treatment with ascorbic acid in this group.

GASTRIC ANALYSIS:- The free and total hydrochloric acid curves of the fractional test meal were within normal limits in each case.

OTHER TESTS:- The van den Bergh reaction was negative, urinary urobilin could not be demonstrated, and icteric index was within normal limits in each case. These tests were carried out before treatment was begun.

Group II. Scurvy associated with anaemia; full response to ascorbic acid.

(Cases 7 to 13, tables VII to XIII, appendix)

DIET:- In all the cases in this group, the diet had been selected from the following articles; bread, biscuits, pastry, margarine, jam, sausage, fish, minced meat, pasteurised milk, tea and sugar. In no instance had any fresh fruit or vegetables been eaten for at least six months before the case came under observation.

The cases remained on the same diet during the period of observation. As soon as the necessary examinations had been carried out, ascorbic acid was administered, starting with one thousand milligrammes intravenously and continuing with three hundred milligrammes daily by mouth.

PHYSICAL EXAMINATION:- All the members of this group presented signs of scurvy. The ages ranged from fifty-one to seventy-two years. Cases 7, 9 and 10 were aged respectively sixty-eight, sixty-five and seventy-two years, and in these cases a certain amount

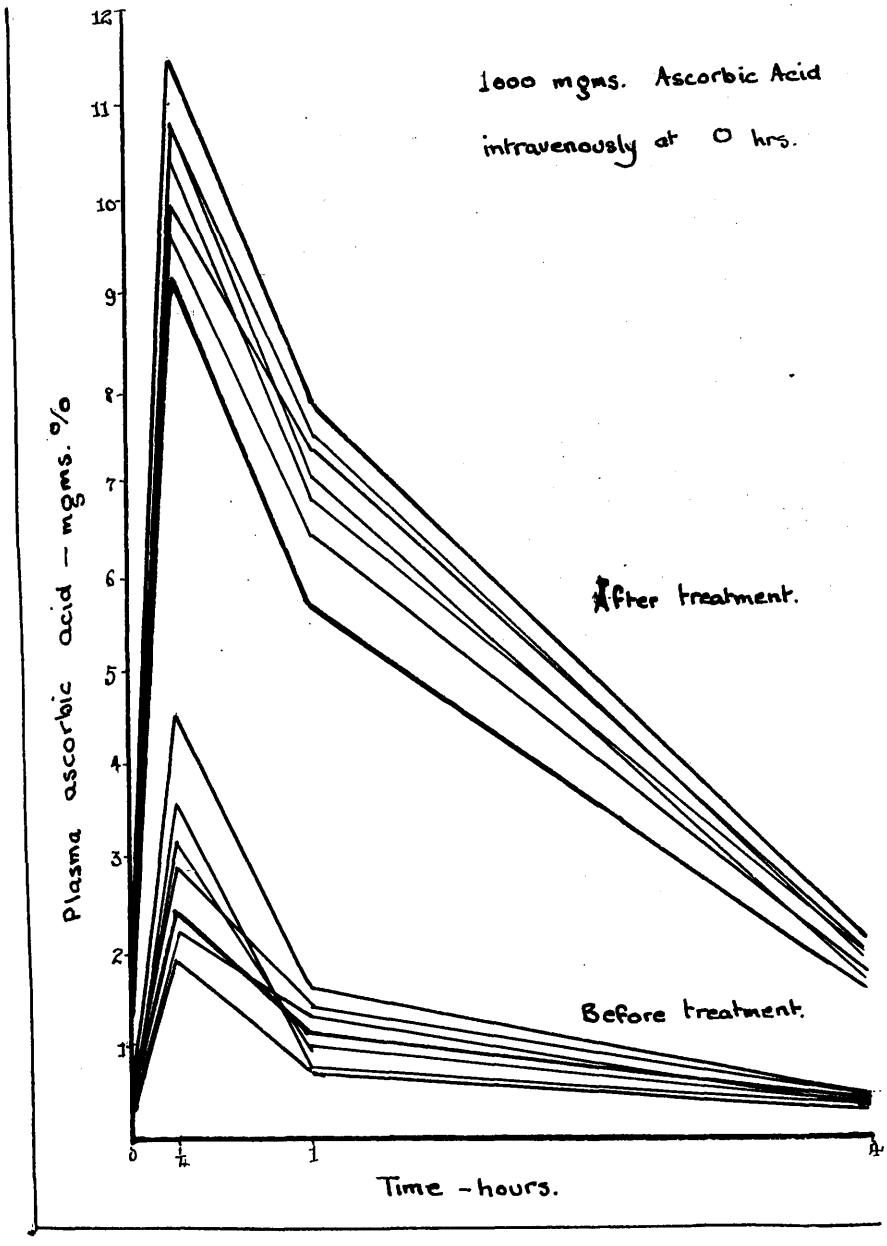


Figure 11

Plasma ascorbic acid tolerance test, Group II. Plasma ascorbic acid curves after intravenous injection of one thousand milligrammes ascorbic acid; showing higher levels being reached after treatment.

of senile cardiovascular degeneration was evident, though not to an extent greater than was to be expected at these ages. Otherwise there was no evidence of organic disease in this group after the evidence of scurvy had disappeared.

ASCORBIC ACID DETERMINATIONS:-

Rotter's Test:- Before treatment, the decolorisation times were prolonged, the shortest time being twenty minutes and the mean thirty-five minutes. After treatment, much shorter times were obtained, eight minutes being the longest and the mean being six minutes.

Plasma Ascorbic Acid:- Before treatment, low levels were obtained, the range being from 0.31 to 0.47 milligrammes per cent with a mean of 0.38 milligrammes per cent. After treatment, high levels were obtained, the range being from 1.3 to 1.9, with a mean of 1.6, milligrammes per cent.

Intravenous Tolerance Test:- The curves obtained are shown in figure 11 opposite. The curves obtained before are markedly lower and flatter than those obtained after treatment.

CAPILLARY FRAGILITY:- High capillary fragility was found in each case, the mean count, before treatment, being of sixty-eight petechiae. After treatment, normal counts were obtained, the mean being of six petechiae.

BLOOD EXAMINATIONS.

Haemoglobin and Red Cell Counts:- Every case showed some degree of anaemia. The most severe (case 7) had a haemoglobin level of forty-two per cent and 1.95 million red cells, while the least severe (case 10) had eighty-two per cent haemoglobin and 3.8 million red cells. Administration of ascorbic acid was followed by a rise in the red cells and haemoglobin. In five of the seven cases in this group, the anaemia was orthochromic; while in one (case 11) it was hyperchromic, and in another (case 12) hypochromic.

Reticulocytes:- Before treatment, the reticulocyte count was above normal, and after institution of treatment, a reticulocyte crisis was observed.

The association of the reticulocyte crisis and the rise in red cells and haemoglobin can be seen from the blood charts (figures I to VII , pages lv to lxi , appendix).

Table 2

Schilling Counts, Group II. Mean counts before and after treatment.

	Before Treatment	After Treatment
Eosinophils	0.3 per cent	0.7 per cent.
Basophils	0.2 " "	0.2 " "
Myelocytes	-	-
Juveniles	0.5 " "	1.2 " "
Staffs	1.0 " "	3.9 " "
Segmented Neutrophils	43.9 " "	53.6 " "
Lymphocytes	46.5 " "	33.0 " "
Monocytes	7.6 " "	7.5 " "

White Cell Count:- No abnormality before treatment, and no change as a result of treatment, could be demonstrated, the mean counts before and after treatment being respectively 5,100 and 5,600 per cubic millimetre.

Schilling Count:- In table 2 opposite, the mean counts before and after treatment are compared. Relatively, the Schilling count before treatment appears to show some decrease in juveniles and staffs and increase in lymphocytes.

Cooke Count:- A right shift was observed before treatment, the "weighted mean" being 3.2. This moved to the left with administration of ascorbic acid, the average after treatment being 2.7.

Platelets:- A count was made before treatment only. Normal values were found.

BONE MARROW:-

Cellularity:- Before treatment there was increased cellularity, and medium cellularity was found after treatment.

Differential Count:- In both the granuloblast and the erythroblast, certain changes were noted which are referred to under the heading "Maturity Dispersal Ratios" below. No abnormal types of cell were observed.

Megakaryocytes could be found in every specimen, though in some cases search had to be made in several films, while in others they were of more frequent occurrence. Mitotic forms of the normoblast were more commonly found during the phase of active scurvy, i.e. before treatment, than after treatment, the means being 1.3 per cent (of all the nucleated cells in the differential count) before treatment, and 0.2 per cent after treatment. It could not be clearly shown that there was any increase in the number of mitotic forms after beginning treatment. In cases 11, 12 and 13, bone marrow films were made at the time of the reticulocyte crisis that followed ascorbic acid administration. The mitotic forms were then 1.2, 2.0 and 2.0 per cent respectively for the three cases, as compared with 0.4, 1.2 and 1.6 per cent before treatment. This apparent slight increase after the institution of treatment cannot be regarded as significant, in view of the variability of the numbers of mitotic forms, the mean percentage before treatment of 1.3, with a standard deviation of 0.7 giving an indication of this variability.

Table 3

Maturity Dispersal Ratios, Group II. Mean percentages before and after treatment.

	Before Treatment	After Treatment
Myeloblasts	5.1 per cent	4.7 per cent
Promyelocytes	22.0 " "	13.2 " "
Myelocytes	37.4 " "	36.5 " "
Juveniles	35.5 " "	45.6 " "
Pronormoblast	3.3 " "	1.5 " "
Normoblast Basophilic	46.0 " "	15.8 " "
Polychromatic and orthochromatic	50.7 " "	82.7 " "

Maturity Dispersal Ratios:- Table 3 opposite shows the mean dispersions before and after treatment. In both granuloblast and erythroblast, there is a shift towards a relatively greater immaturity in the marrow from cases of active untreated scurvy. In the granuloblast, the promyelocytes showed an increase and the juveniles a decrease, relatively to the percentages found after treatment. In the erythroblast, before treatment there was a considerable increase in the basophilic normoblasts and a corresponding decrease in the polychromatic and orthochromatic forms, relatively to percentages found after treatment.

GASTRIC ANALYSIS:- The free and total hydrochloric acid curves were within normal limits in each case.

OTHER TESTS:- There was no evidence of increased haemolysis in the cases of untreated scurvy, to the extent that the van den Bergh reaction and the test for urinary urobilin were negative, and the icteric index was within normal limits. Fragility of the red cells was within normal limits.

Group III. Vitamin C deficiency associated with anaemia; poor or no response to ascorbic acid.

(Cases 14 to 17, tables XIV to XVII, appendix)

DIET:- This was similar to that of the cases in the preceding group.

In case 14, iron deficiency being suspected, iron was administered; then, as it had had no apparent effect on the anaemia or reticulocyte counts, it was discontinued and ascorbic acid and oranges added to the diet, ascorbic acid deficiency having been shown to be present; these, and also an intramuscular injection of liver extract ("Anahaemin") having been equally without effect, iron was again administered, in the same dosage as on the first occasion; a reticulocyte response and a rise in the red cells and haemoglobin now followed.

In cases 15 and 16, treatment with ascorbic acid having had no apparent effect on the anaemia, four oranges daily were added to the diet, as well as the ascorbic acid; whereupon a reticulocyte crisis and a

rise in the red cells and haemoglobin were obtained.

In case 17, hesperidin was given by intravenous injection for a week, during which the anaemia became more severe. The hesperidin was then discontinued and ascorbic acid administered, but the anaemia failed to improve. Ascorbic acid and hesperidin were then administered concurrently, when a reticulocyte crisis, followed by a rise in the red cells and haemoglobin, was obtained.

PHYSICAL EXAMINATION:- There was no sign of scurvy in cases 14 and 15, but scurvy was present in cases 16 and 17. Case 15 was a very senile individual of seventy-eight years, bedridden and mildly demented. There was no material change in this general condition after administration of vitamin C. Case 16, aged seventy-one years, was much less senile and had been accustomed to take a walk of about five miles almost daily, until six months before coming under observation when he began to experience dyspnoea on exertion, which steadily increased. On admission to hospital he had a moderate degree of congestive heart failure, with no evidence of valvular disease or hypertension, and

an electrocardiogram showing no diagnostic abnormality. No treatment of his cardiac condition was carried out, other than rest in bed for a month, and antiscorbutic treatment. He recovered to the extent of being able to resume his walks. It was considered that the vitamin C deficiency was the main factor in bringing about the cardiac failure, since it had responded so completely to a short period of rest with administration of the vitamin.

ASCORBIC ACID DETERMINATIONS:-

Rotter's Test:- Before treatment, decolorisation times were prolonged, the shortest time being twenty minutes, and the mean twenty-five. After treatment a marked drop was noted, the longest time then being six minutes and the mean five and a half minutes.

Plasma Ascorbic Acid:- Before treatment, the mean level was 0.41 milligrammes per cent, the range being from 0.35 to 0.43 milligrammes per cent. After treatment the mean level was 1.4 milligrammes per cent, and the range from 1.2 to 1.6 milligrammes,

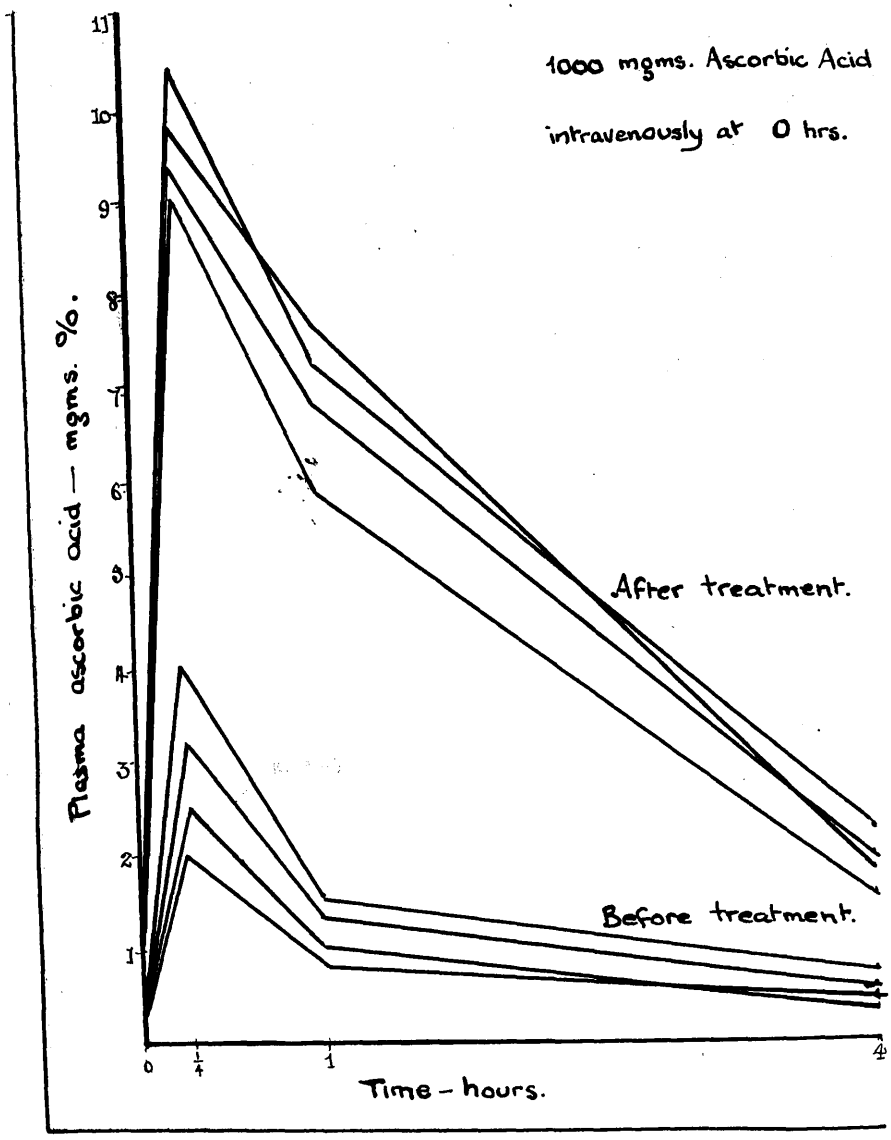


Figure 12.

Plasma ascorbic acid tolerance test, Group III. Plasma ascorbic acid curves after intravenous injection of one thousand milligrammes ascorbic acid; showing higher levels being reached after treatment.

Intravenous Tolerance Test:- Figure 12 shows the curves obtained, those before treatment being markedly lower and flatter than those after treatment.

CAPILLARY FRAGILITY:- High petechial counts were found before treatment in each case, the mean count being of fifty petechiae. After treatment, the mean count was of seven petechiae. In cases 14, 15 and 16 the counts remained high in spite of ascorbic acid administration but fell when oranges were added to the diet (figures viii to xi, pages lxii to lxv, appendix). In case 17 the petechial count fell to normal when hesperidin was added, appeared to rise slightly when hesperidin was withdrawn and ascorbic acid administered, and again fell when hesperidin was once more administered (figure XI, page lxv, appendix).

BLOOD EXAMINATIONS:-

Haemoglobin and Red Cell Counts:- Anaemia was present in all four cases. The percentage haemoglobin ranged from fifty-three to sixty-eight, and the red cell counts from 1.9 to 3.8 million per cubic millimetre. Ascorbic acid alone could not be shown to

have any effect on the anaemia, but in cases 15 and 16 improvement appeared to take place from the time that oranges were added to the diet. In case 17, improvement occurred when ascorbic acid and hesperidin were given concurrently, though separately they had had no effect on the anaemia. In case 14 it began to improve when iron was administered after the plasma ascorbic acid level had been raised and the Rotter's test decolorisation time brought down by administration of ascorbic acid and oranges, although the same dosage of iron had had no apparent effect before the vitamin C deficiency had been corrected. These changes are illustrated in the blood charts (figures VIII to XI , pages lxii to lxv , appendix).

Reticulocytes:- The reticulocyte count was somewhat raised before treatment, but appeared to be unaffected by the addition to the diet of pure ascorbic acid only. In case 14, neither iron, nor ascorbic acid and oranges, nor liver extract had any effect by themselves, but a reticulocyte crisis took place when iron was administered together with ascorbic acid and

Table 4

Schilling Counts, Group III; mean counts before and after treatment.

	Before treatment.	After treatment.
Basophils	0.9 per cent	1.3 per cent
Eosinophils	0.3 " "	1.0 " "
Myelocytes	-	-
Juveniles	0.3 " "	0.9 " "
Staffs	1.3 " "	2.8 " "
Segmented Neutrophils	50.8 " "	51.0 " "
Lymphocytes	38.7 " "	37.3 " "
Monocytes	7.8 " "	5.8 " "

oranges, after the vitamin deficiency had been at least partly corrected. In cases 15 and 16, a crisis occurred when oranges were added to the diet. In case 17 no significant change in the reticulocyte count could be shown when ascorbic acid and hesperidin were separately administered, but a crisis took place when these were administered concurrently.

White Cell Count:- No effect of vitamin C administration on the white cell count could be demonstrated. Before treatment the counts ranged from 2,400 to 7,400 per cubic millimetre, with a mean of 4,600; and after treatment, from 4,400 to 6,000, with a mean of 5,300.

Schilling Count: Table 4 opposite gives the mean counts, before and after treatment. It can be seen that there is no significant change, in this group, as a result of treatment.

Cooke Count:- Before treatment, right shift was observed, the average "weighted mean" being 3.3. It fell with treatment, the average after treatment being 2.6.

Platelets:- Counts were made before treatment only. Normal values were found.

BONE MARROW:-

Cellularity:- Before treatment, there was increased cellularity in cases 14, 16 and 17, and medium cellularity in case 15. After treatment, medium cellularity was found in 14, 16 and 17, and reduced cellularity in 15.

Differential count:- In case 14 a film was made before treatment, another after the ascorbic acid level had risen following administration of the vitamin but before the anaemia had begun to improve under iron therapy, and a third after considerable improvement had taken place under iron and vitamin C. In the first two of these, there were large numbers of small normoblasts with a densely staining nucleus showing no structural details, and a slaty-grey cytoplasm with a ragged irregular outline. These appearances are said to indicate iron deficiency (Scott, 1939). In other respects these films, and those from the other cases in this group, showed no features by which they could have been distinguished from films from the preceeding group. In case 15, the number of mitotic forms of the normoblast appeared to be higher before than after treatment. In

Table 5

Maturity Dispersal Ratios, Group III. Mean percentages before and after treatment.

	Before treatment.	After treatment.
Myeloblasts	7.8 per cent	3.2 per cent
Promyelocytes	22.0 " "	18.8 " "
Myelocytes	38.0 " "	35.7 " "
Juveniles	32.2 " "	42.4 " "
Pronormoblasts	3.7 per cent	3.2 per cent
Normoblasts Basophilic	41.3 " "	17.5 " "
Polychromatic and orthochromatic	55.0 " "	79.4 " "

the remaining cases there was no significant change in the percentage of mitotic forms before and after treatment.

Maturity Dispersal Ratios:- Table 5 opposite shows the mean percentage before and after treatment. In the granuloblast there appears to be a slight increase in the myeloblasts and promyelocytes before treatment, relatively to the percentages found after treatment. The findings are similar to those in group II (page 26). In the erythroblast there is no indication of any disturbance of the pronormoblast, but as in group II the proportion of basophilic normoblasts can be seen to be much higher before than after treatment.

GASTRIC ANALYSIS:- The fractional test meal showed achlorhydria to be present in each case. A small secretion of hydrochloric acid was obtained in response to histamine.

OTHER TESTS:- The van den Bergh reaction, the icteric index and the test for urinary urobilin, gave normal results. Fragility of the red cells was estimated in case 17 only, and was within normal limits.

Group IV. Scurvy associated with anaemia and a disorder not directly referable to vitamin C deficiency; effect of treatment not recorded.

(Cases 18 to 21, tables XVIII and XIX, appendix)

In this group, the effect of antiscorbutic treatment is not recorded because of the association of other conditions, themselves associated with anaemia and requiring treatment such that it would have been impossible to determine to what extent any observed change was to be attributed to the antiscorbutic treatment, and what to the treatment of the other condition.

DIET:- The diet of these cases resembled that of the preceding two groups.

PHYSICAL EXAMINATION:- In cases 18 and 19 there were signs of rheumatoid arthritis of long standing. In cases 20 and 21 a history suggestive of duodenal ulceration with blood loss of a fairly severe degree, was obtained and the diagnosis radiologically confirmed. There were signs of scurvy in each case.

ASCORBIC ACID DETERMINATIONS:-

Rotter's Test:- Very prolonged decolorisation times were obtained, the mean time being twenty-eight minutes.

Plasma Ascorbic Acid:- The range of levels was from 0.3 to 0.4 milligrammes per cent, the mean being 0.34 milligrammes per cent.

Intravenous Tolerance Test:- This was not carried out on these cases.

CAPILLARY FRAGILITY:- In the two cases of rheumatoid arthritis (cases 18 and 19) this was high, but in the two of peptic ulceration (cases 20 and 21) the capillary fragility was not above normal limits.

BLOOD EXAMINATIONS:-

Haemoglobin and Red Cell Count:- There was a moderate degree of anaemia in each case, haemoglobin values lying between sixty and sixty-five per cent. In one of the cases of rheumatoid arthritis (case 19) the anaemia was of the orthochromic type. In the three remaining cases it was hypochromic.

White Cell Count:- The white cell counts were within normal limits, the mean being 7,200 per cubic millimetre.

Schilling Count:- No definite shift could be made out.

Cooke Count:- There was a shift to the right, with a "weighted mean" of 3.2.

Platelet Count:- The platelet counts were within normal limits.

BONE MARROW

Cellularity:- There was medium cellularity in case 18. It was raised in the other cases.

Differential Count:- The small normoblasts with slaty-grey cytoplasm and dense nucleus, noted already in case 14 (page 33) and regarded as indicative of iron deficiency, were found more commonly in this group than in any of the others and were of frequent occurrence in cases 20 and 21. No other abnormality was noted, except that recorded below.

Maturity Dispersal Ratios:- In the granuloblast, no significant deviation from the normal was observed. In the erythroblast, there was a definite increase in the basophilic normoblasts.

GASTRIC ANALYSIS:- Achlorhydria to the Refuss meal, with some response to histamine, was found in the cases of rheumatoid arthritis, and hyperchlorhydria was found in the cases of duodenal ulceration.

ANALYSIS AND CORRELATION OF RESULTS

Certain features in the foregoing have now to receive some elaboration and a number of relationships have to be made out.

ASCORBIC ACID DETERMINATIONS

Rotter's Test:- According to Rotter (1937, 1938) a decolorisation time of five minutes or less indicates a state of adequate vitamin C nutrition, while more than ten minutes indicates a state of "desaturation". The mean decolorisation time after treatment, in this series, was five minutes, with a standard deviation (S.D.) of 1.5. The mean decolorisation time before treatment in group 1 was sixteen minutes (S.D. = 7.2), and in groups II and III together, twenty-eight minutes (S.D. =6.8). Thus a deficiency in each group is indicated, but this is less severe in group I than in groups II and III. A definite improvement was effected by treatment in all cases.

Plasma Ascorbic Acid: The normal values are given by Abt and Farmer (1938) as from 0.7 to 1.5 milligrammes per hundred cubic centimetres of plasma. Portnoy and Wilkinson (1938b) give 0.60 to 1.85 milligrammes. van Eekelen (1937) considered that a level of 0.4 to 0.8 milligrammes indicated a moderate, 0.8 to 1.2 a very good and above 1.2 an excellent state of nutrition as

to vitamin C. Sloan (1938) found the lower limit of the normal to be 0.5 milligrammes, the average normal being between 0.8 and 1.0. In scurvy, Ingalls (1937) found the levels to be from nil to 0.15 milligrammes. Wortis et al. (1938) found the range to be from 0.22 to 0.3 milligrammes. Abt and Farmer (1938) found levels of 0.4 to 0.5 in scurvy. They thought it possible that the very low values recorded by Ingalls might be attributed to the fact that in his cases potassium cyanide was added to the blood sample, after which it was allowed to stand, whereas they had shown (Farmer and Abt, 1938) that the addition of potassium cyanide did not delay destruction of ascorbic acid in the blood sample.

In view of the fact that different authors have given such different ranges of values, it seemed most reasonable to accept the standards of Abt and Farmer (1938), since it was their method of estimating the ascorbic acid level (Farmer and Abt, 1935) that was used in this study. According to these standards, the ascorbic acid level before treatment in group I of this series was about the upper limit of the scorbutic range, with a mean level of 0.49 milligrammes

(S.D. = 0.05). In groups II and III the mean level was lower, being 0.39 milligrammes (S.D. = 0.04). The highest level found was of 0.45 milligrammes, which is within the scorbutic range, whereas in group I, the level in case 4 was above and in cases I and 5 at the upper limit of the scorbutic range. After treatment, the mean level of the series was 1.6 milligrammes per cent (S.D. = 0.23), and the lowest level obtained was of 1.2 milligrammes.

By the standards accepted, therefore, the plasma ascorbic acid levels were sufficiently low to confirm the diagnosis of scurvy where that had been made on clinical grounds. The levels were equally low in four cases (2, 6, 14 and 15) in which no clinical sign of scurvy was noted. In those cases (1,3,4 and 5) where the levels were somewhat higher than in those manifestly scorbutic, they were nevertheless still very low. After treatment, in all cases, the levels were found to have risen to normal.

Intravenous Tolerance Test:- Abt (1937) described an oral ascorbic acid tolerance test, in which in scurvy the plasma ascorbic acid level rose only slightly after administration of the test dose of ascorbic acid, while

Table 6

Intravenous Tolerance Test. Mean values in milligrammes ascorbic acid per hundred cubic centimetres of plasma; from present series and from Portnoy and Wilkinson (1938b)

		Before injection of ascorbic acid	After injection of ascorbic acid		
		Fasting Level	15 minutes	1 hour	4 hours
Present Series	Group I before treatment	0.49	5.37	2.06	0.50
	Groups II & III before treatment	0.39	2.90	1.09	0.34
	All cases, after treatment	1.6	10.27	6.89	1.84
Portnoy and Wilkinson (1938)		Resting Level	18 minutes	1 hour	4 hours
	Deficient Group	0.36	4.45	1.69	0.51
	Normal Group	1.20	10.12	5.62	1.55

during recovery from the scurvy the peaks after the test dose became higher as recovery proceeded. Portnoy and Wilkinson (1938b) described the intravenous tolerance test, which with slight modification was used in this series. Table 6 opposite shows the figures obtained by Portnoy and Wilkinson (1938b), in a group of subjects whose diet had been deficient in vitamin C, and in a normal group; their figures are shown alongside those obtained in the present series. It can be seen that the levels in group I of this series, before treatment, are somewhat higher, while those in groups II and III are somewhat lower, than those in Portnoy and Wilkinson's "deficient group"; and that all these are definitely lower than in their "normal group". The levels in their normal group corresponds closely with those obtained after treatment in the present series. The graphs of the tolerance test (figures 10, 11 and 12, facing pages 18, 22 and 30) show the differences between the curves obtained before and after treatment. In cases 5 and 6 (figure 10) and 14 and 15 (figure 12) in which there was no sign of scurvy, the curves obtained before treatment were as low as some of those

found in manifest scurvy.

This test shows that a severe degree of vitamin C deficiency was present in every case and that the deficiency disappeared with treatment. In group I, the deficiency was, generally speaking, less severe than in the other groups.

Taking the results of Rotter's test, the plasma ascorbic acid levels, and the tolerance test together, it may be concluded that a severe degree of vitamin C deficiency existed in every case. In general, however, it was less severe in those in which there was no anaemia than in the others. In only two of the non-anaemic cases (5 and 6) was the deficiency fully as great as that seen in the cases of scurvy. Even in these, the tests employed seemed to indicate that the deficiency was towards the upper limit of the scorbutic range.

The finding of two cases in which there was no scurvy and no anaemia, with ascorbic acid values as low as those found in some cases of scurvy, might be taken as suggesting that ascorbic acid deficiency alone is not sufficient to bring about anaemia.

On the other hand, the ascorbic acid values in these two cases being higher than those in most of the cases in which anaemia was found may indicate merely that the deficiency in these non-anaemic cases was not sufficiently severe to bring about anaemia. For want of sufficient data this question must be left unsettled at present.

CAPILLARY FRAGILITY:- * This test has been regarded as one that gave evidence as to the state of nutrition as to vitamin C. Thus Gothlin (1937) and Sloan (1938) have stated it as their opinion that the test gave valuable information as to whether or not a severe state of vitamin C deficiency existed, and Bourne (1938) in cases of gastric ulcer, found lowered capillary resistance which he believed to be traceable to deficiency of antiscorbutic vitamins in the diet. Bell et al.(1940) found that high capillary fragility was related to low ascorbic acid values. However, in a quarter of their cases, the high capillary fragility was not affected by the administration of ascorbic acid. In a further communication (Munro et al., 1942) they indicated the possibility that there may be no close relationship between

* Summary on page 49

vitamin C and capillary fragility. Greene (1934), Molitch (1935) and Abt et al. (1936) found that tests of capillary fragility could not necessarily be related to states of vitamin C deficiency.

While pure ascorbic acid given by mouth had been found to be an efficient antiscorbutic agent (Svensgaard, 1934; Bell, 1935; Schultzer, 1938), occasional failures occurred (Elmby and Warburg, 1937; Lauber and Bersin, 1939). Szent-Gyorgyi and his co-workers (Bentsáth et al., 1936) introduced "vitamin P" as a factor regulating capillary fragility, reporting that "citrin", a mixture of hesperidin and an eriodyctiol glucoside (Bruckner and Szent-Gyorgyi, 1936) would reduce the number of haemorrhages. They thought that deficiency of vitamin P might be partly responsible for the haemorrhages of scurvy. Croft and Snorf (1939) found, in man, ascorbic acid values as low as those found in scurvy, yet scurvy was not present. They thought that this indicated that some factor other than ascorbic acid deficiency was involved in the aetiology of scurvy. Elmby and Warburg (1937) found

that to effect a cure in some of a series of cases with haemorrhagic diatheses and low ascorbic acid values, it was necessary to give orange juice, ascorbic acid alone, by mouth or by injection, having failed to effect a cure though it had done so in other cases in the series. Histories of gastrointestinal disease of long standing were obtained from the cases which had failed to respond to ascorbic acid. They though that a co-vitamin, perhaps P, might be necessary for vitamin C to exercise its effect. In a case of scurvy described by Lauber and Bersin (1939) ascorbic acid failed to effect any improvement either in the scurvy or in the accompanying anaemia until a blood transfusion had been given.

Thus there is support for the view that ascorbic acid deficiency alone is not responsible for the full scorbutic picture. On the other hand, Szent-Gyorgyi (1938) was unable to repeat his original experiments with citrin, and Zilva (1937) and Moll (1937) also had been unable to confirm Szent-Gyorgyi's original work. Scarborough and Stewart (1938) however, found that hesperidin, one of the substances present in citrin, could reduce the number of skin

haemorrhages in patients with vitamin deficiencies, and that the effect was apparently independent of vitamin C. Scarborough (1939) showed that oranges and lemons contained a substance which could increase capillary resistance even when ascorbic acid had failed to do so. Jersild (1939) found that in certain cases citrin could increase capillary resistance, the effect being apparently independent of ascorbic acid. Gorrie (1940) obtained similar effects from the use of hesperidin. Scarborough (1940) found that the subcutaneous haemorrhages of scurvy were corrected by ascorbic acid, but that it did not affect the capillary fragility, which was improved by vitamin P. He regarded it as established that "there is a substance or substances present in fruits and their juices and in certain extracts made therefrom which is capable in man of increasing the resistance of capillary walls to the application of pressure. The substance is not ascorbic acid . . " (Scarborough, 1942).

Armentano (1938) found that citrin had no effect on the anaemia of scorbutic guinea pigs, and Scarborough (1940) found that hesperidin had no effect

on the anaemia of human scurvy. Crandon et al. (1941) reported on a case of experimental human scurvy, in which the capillary fragility was not raised and in which anaemia failed to develop. Fox et al. (1940) had not found increase in the capillary fragility in a number of Bantu Labourers who developed scurvy. It was suggested, however, that Bantus might not be comparable with Europeans in respect of capillary fragility.

In the present series, normal capillary fragility was found in the cases in group I. In group II and III, it was considerably raised. In the seven cases in group II, it fell to normal with the administration of ascorbic acid. In three cases in group III (cases 14, 15 and 16) it remained high despite the administration of ascorbic acid, but fell to normal when oranges were added to the diet. In case 17, it fell to normal with the administration of hesperidin, rose slightly when hesperidin was discontinued and ascorbic acid administered, and fell to normal again when hesperidin and ascorbic acid were administered

concurrently. These changes are indicated in the blood charts (figures VIII to XI, pages lxii to lxv, appendix). In groups I and II there was no clinical evidence of gastrointestinal disease and normal amounts of free hydrochloric acid were found in the test meal. In group III however, in which the high capillary fragility was apparently unaffected by ascorbic acid, achlorhydria was present in each case.

Low capillary fragility in scurvy has been recorded by Lazarus (Munro et al., 1942) and Crandon et al. (1941). It was observed in two cases (18 and 19) in the present study.

In group II of the present series, the capillary fragility, high before treatment, came down while ascorbic acid was being administered. In group III, in cases 14, 15 and 16, the capillary fragility remained high while ascorbic acid was being administered, but fell on oranges being added to the diet. The response of the capillary fragility to hesperidin and to ascorbic acid in case 17 has already been noted (page 30). In all the cases of anaemia, the red cell count and haemoglobin level rose in association with

the fall in capillary fragility, except in cases 14 and 17. In the first of these, iron deficiency is considered to have been a factor in preventing improvement in the anaemia (page 31) while in the second, the rise in red cells and haemoglobin took place when the high capillary fragility and low ascorbic acid values were simultaneously corrected, although there had been no such rise when an attempt was made to correct these errors separately (page 30).

The findings as to capillary fragility and the effect of treatment thereon, and the relationship of these to the anaemia, may now be summarised:

1. Normal capillary fragility was found in two cases of scurvy, although in most cases of scurvy the capillary fragility was high.

2. In one case of scurvy, hesperidin reduced the high capillary fragility, independently of ascorbic acid.

3. Ascorbic acid restored to normal the high capillary fragility in seven cases of scurvy, but failed to do so in two cases of scurvy and in two cases of severe ascorbic acid deficiency without scurvy.

4. Achlorhydria was present in each of the four cases in which ascorbic acid failed to restore the high capillary fragility to normal. In three of these cases the high capillary fragility fell to normal on the addition of oranges, and in the remaining case, of hesperidin.

5. In seven cases of scurvy, a reticulocyte crisis followed by a rise in the red cell count and haemoglobin level were obtained by the administration of pure ascorbic acid, but ascorbic acid was ineffective in two cases of scurvy, in one of which the addition of oranges had the desired effect; in the other, neither ascorbic acid nor hesperidin separately had any effect, but they were effective when administered together. In one case of severe ascorbic acid deficiency without clinical scurvy, ascorbic acid had no effect on the anaemia but the addition of oranges was effective.

This summary may be compared with the following, compiled from the literature referred to on pages 43 to 48.

1. Capillary fragility in scurvy is often high but is sometimes normal.

2. Vitamin P may cure the raised capillary fragility of scurvy, this effect being apparently independent of ascorbic acid.

3. In most cases, ascorbic acid effects a cure in scurvy. Occasionally it fails to do so.

4. This failure has been noted in some cases to be associated with an unhealthy state of the alimentary tract. In such cases, a factor, not ascorbic acid but present in lemon juice, is also necessary to effect a cure.

5. Usually, ascorbic acid will cure the anaemia of scurvy. Vitamin P has no such effect.

From a comparison of these two summaries it can be seen that there are reasonable grounds for accepting vitamin P as giving a plausible explanation of the fact that ascorbic acid was an effective anti-anaemic substance in certain cases of vitamin C deficiency, while in other cases of vitamin C deficiency, in which there was apparently no significant difference from the

first as to the blood and bone-marrow pictures, it was ineffective. If vitamin P is a necessary co-vitamin with vitamin C and if additional amounts of vitamin P must be provided in certain unhealthy states of the gastrointestinal tract, the failure of ascorbic acid in group III, until some substance that lowered the capillary fragility was administered, would be explained.

In some cases of scurvy, faulty absorption of ascorbic acid may be a factor in the failure to respond to oral ascorbic acid therapy (Hagman, 1937). Alt et al. (1937) showed that there was a tendency for ascorbic acid to be low in achlorhydric patients, and Stepp (1937) and Kendall and Chinn (1938) showed that certain bacteria from the stomach and gastrointestinal tract can destroy ascorbic acid. Faulty absorption, however, is not likely to be a factor in the failure of some cases in the present series to respond to ascorbic acid, since those cases which showed such failure to respond had received an intravenous injection of one thousand milligrammes of ascorbic acid, on the occasion of carrying out the intravenous tolerance test. This dose is from a quarter to a sixth of the total amount required to saturate the case of experimental adult scurvy reported by

Crandon et al. (1941). Schultzer (1937) found that forty milligrammes of ascorbic acid daily was an adequate curative dose in scurvy. Also, Goettsch (1935) has shown that a single massive dose permits the healing of scurvy as effectively as the same amount of vitamin in divided doses. If failure of absorption of ingested ascorbic acid had been alone responsible for the absence of response to ascorbic acid therapy in the cases in group III of this series, the intravenous dose might have been expected to produce some improvement, and no such response was obtained.

BLOOD EXAMINATION:-

Haemoglobin and Red Cell Count:- It appears from the varying accounts in the literature that hypochromic, orthochromic and hyperchromic types of anaemia can all be found in scurvy. Piney (1932) and Turnbull (1936) stated that the anaemia was hypochromic. Boyd (1938) stated that it was "secondary", and described the blood picture in secondary anaemia as being of the hypochromic microcytic type. Gulland and Goodall (1925), Still (1934) and Hutchison (1937) also stated that the anaemia was of the "secondary" type. Dunlop and Scarborough (1938) and Whitby and Britton (1942b) stated that a hypochromic

or normochromic anaemia was usual, though not constant. Bondurant (1934) and Parsons and Smallwood (1934) said that the anaemia was usually orthochromic. Cases of hypochromic anaemia have been described by Comrie (1920), Gichner and Sherry (1930) and Young (1938); of orthochromic anaemia, by Gichner and Sherry (1930), Wood (1935), Archer and Graham (1936), Jennings and Glazebrook (1938) and Dunlop and Scarborough (1938); of hyperchromic anaemia, by Nisenson and Cohen (1937) and Jennings and Glazebrook (1938). Parsons (1938) stated that he found cases of hypochromic, orthochromic and hyperchromic anaemia in scurvy. As to cell size, the anaemia is said usually to be normocytic, though it may occasionally be macrocytic (Whitby and Britton, 1942; Parsons, 1938; Parsons and Smallwood, 1935).

In the present series, anaemia was found in all the cases of scurvy. In seven cases, the anaemia was orthochromic (i.e. with a colour index of between 0.9 and 1.1): in two it was hyperchromic, and in one hypochromic. In each case the anaemia is considered to be definitely related to scurvy, since great improvement took place

on the addition to the diet of ascorbic acid, in some cases with the addition of oranges or hesperidin, the diet being in other respects identical with that on which scurvy had appeared. In two cases in which there were no clinical signs of scurvy but in which ascorbic acid values as low as those of scurvy were found, anaemia was present. In one of these it was hyperchromic, and responded to ascorbic acid and oranges. In the other it was hypochromic. It did not at first respond to iron, but responded to iron after a considerable amount of vitamin C had been administered. In this case, the anaemia, though in the main due to iron deficiency, is thought to be directly related to the vitamin deficiency (page 27). Rohmer and Binaschedler (1932) have reported on similar cases, which required both iron and vitamin C for the cure of the anaemia.

Jennings and Glazebrook (1938) described two cases of scurvy, in one of which there was severe megalocytic anaemia associated with low ascorbic acid values, while in the other there was moderate normocytic anaemia and the degree of vitamin deficiency was less severe. This led

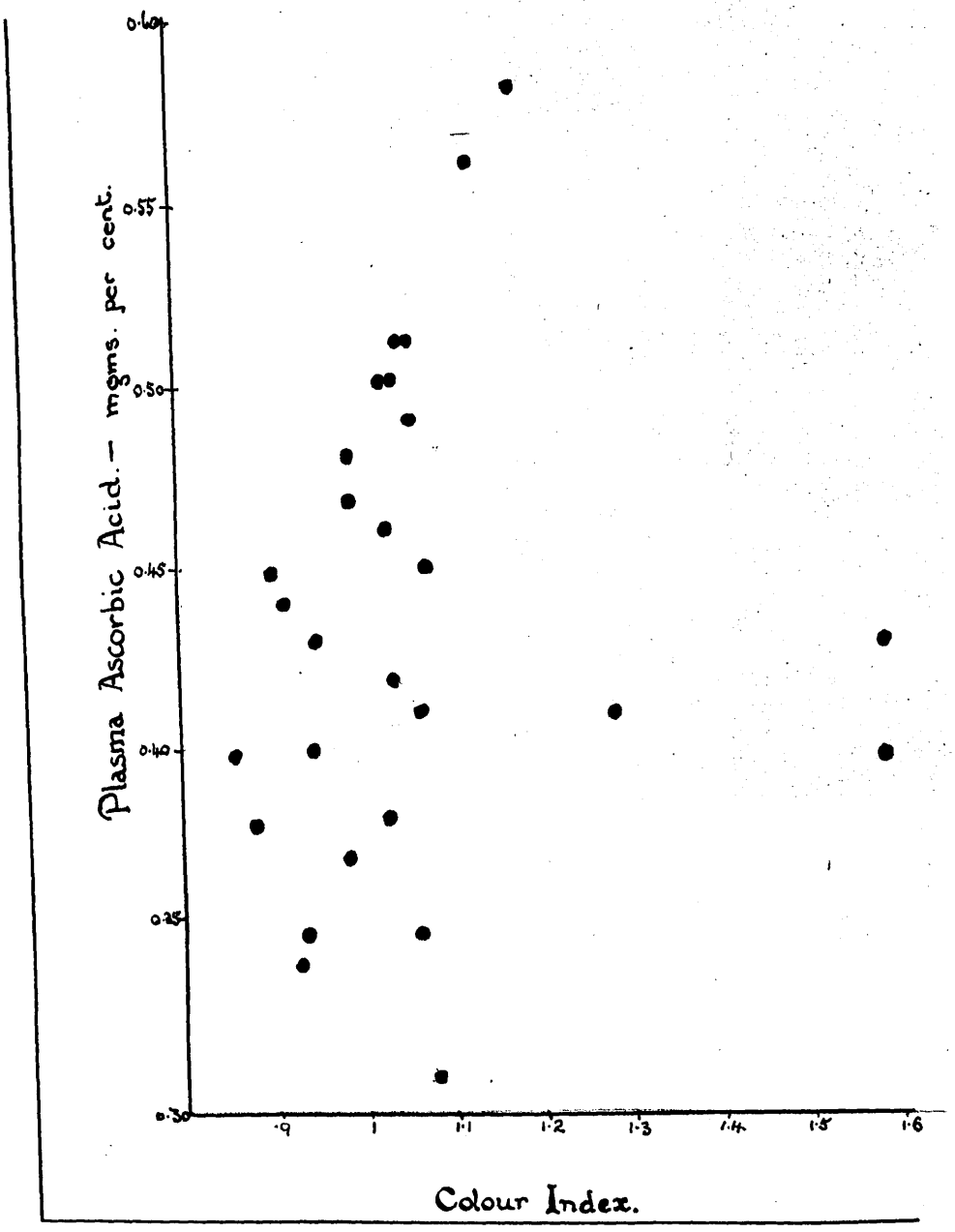


Figure 13

Scatter diagram showing lack of correlation between plasma ascorbic acid level and colour index in vitamin C deficiency.

them to suggest that there might be some relationship between the degree of vitamin C deficiency and the point at which marrow cell maturation is chiefly affected. In the present series, red cell size was not measured; but no correlation could be made out between the colour index and ascorbic acid level, as the diagram (figure 13) indicates.

Reticulocytes:- It has been reported that the numbers of reticulocytes in untreated scurvy may be above normal (Mettier and Chew, 1932; Euler and Malmberg, 1937; Nisenson and Cohen, 1937; Jennings and Glazebrook, 1938; Dunlop and Scarborough, 1938). Armentano (1938) found that the number of reticulocytes increased as the anaemia became more severe in scorbutic guinea pigs. Respecting the effect of administration of vitamin C, Ungley (1938), who observed a "spontaneous reticulocytosis" in scurvy, was unable to demonstrate the specific effect of vitamin C in the anaemia of scurvy; but a reticulocyte response following the administration of vitamin C was observed by Dunlop and Scarborough (1938), Jennings and Glazebrook (1938) and Mettier and his co-workers (Mettier

TABLE 7

Relationship between red cell count and reticulocyte count before institution of treatment, and reticulocyte count at peak of crisis following institution of treatment, in anaemia of vitamin C deficiency.

Case	Red Cell Count before treatment. (millions/cu.mm.)	Reticulocytes		
		Before treatment per cent.	At peak per cent	Day of reaching peak.
10	3.8	0.8	3.6	5
16	3.6	1.2	4.2	9
8	3.5	0.8	3.8	5
11	3.21	0.9	3.4	6
17	2.78	2.4		
12	2.7	2.6	6.5	4
15	2.48	2.4	8.2	7
9	2.26	3.0	15.2	6
17	2.0	3.9	25.2	5
7	1.95	1.9	14.6	5
15	1.9	1.6	2.5	5

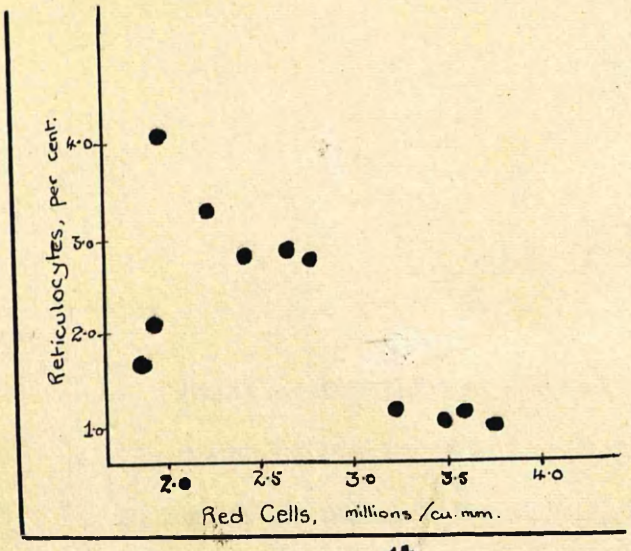


Figure 14.

Scatter diagram showing correlation between reticulocyte count and red cell count in untreated vitamin C deficiency.

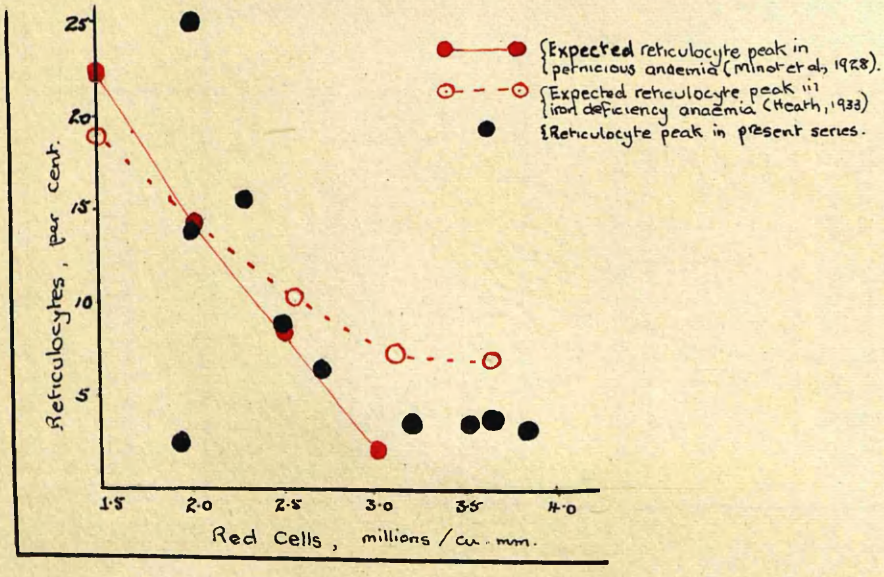


Figure 15

Scatter diagram showing correlation between red cell count before treatment and reticulocyte count at peak of crisis following institution of treatment, in vitamin C deficiency. The "expected reticulocyte peak" in iron deficiency anaemia and in pernicious anaemia responding to treatment are shown for comparison.

et al., 1930: Mettier and Chew, 1932). Ascorbic acid has no such effect on the reticulocyte count in normal individuals (Gingold, 1936, 1937).

In the present series also, it was observed that the reticulocyte count was raised in all the anaemic cases, and it varied roughly in inverse proportion to the red cell count, as the scatter diagram (figure 14) indicates. In the seven cases of scurvy in group II, a reticulocyte crisis followed the administration of ascorbic acid, and in three of the four cases in group III (the fourth, having an iron deficiency, being excluded at present) a reticulocyte crisis followed administration of ascorbic acid with the addition of oranges or hesperidin. The height to which this crisis rose was inversely proportional to the red cell count, as the scatter diagram (figure 15) indicates. From this diagram it can be seen that the crisis which follows the initiation of successful treatment in the anaemia of vitamin C deficiency is comparable with the crisis under similar circumstances in other types of deficiency anaemia.

Mettier et al. (1930) reported that the reticulocyte crisis in treated scurvy occurred sooner than

that in pernicious anaemia. They considered that this could be explained by the presumably longer process of maturation from megaloblast to erythrocyte in pernicious anaemia, whereas in scurvy, maturation would have to proceed through the shorter process from normoblast to erythrocyte. But there does not in fact seem to be any material difference between the times taken for maturation from the megaloblast and from the normoblast, because the length of time between initiation of treatment and reticulocyte crisis is about the same for pernicious anaemia and for iron deficiency anaemia. According to Wintrobe (1942b) the increase in reticulocytes in iron deficiency anaemia is maximal on the fifth to the tenth day after institution of iron therapy, and according to Whitby and Britton (1942) the reticulocyte response in pernicious anaemia reaches a peak on the third to the tenth day; in a series of twelve cases of pernicious anaemia described by Davidson et al. (1942) the peak was reached on the fourth to the sixth (mean =fifth) day. In the present series (of cases of the anaemia of vitamin C deficiency), the peak was found to occur on the fourth to the ninth (mean = sixth) day after institution of vitamin C therapy. Thus, maturation appears

Table 8

Schilling Count: mean values and standard deviation (S.D.) before and after treatment

	Before Treatment				After Treatment	
	Group I		Groups II and III		All Groups	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
Basohpils	0.9		0.5	0.7	0.7	1.1
Eosinophils	1.5	1.4	0.2	0.3	0.6	0.7
Juveniles	0.7	0.4	0.5	0.4	1.0	0.5
Staffs	3.0	0.4	1.1	0.7	3.2	0.4
Segmented Neutrophils	51.0	6.7	46.4	10.9	51.9	7.1
Lymphocytes	35.3	6.5	43.7	7.1	35.7	6.9
Monocytes	8.6	1.4	7.6	2.4	6.9	2.5

to take about the same length of time in the anaemias of iron and of vitamin C deficiency and in pernicious anaemia under appropriate treatment.

White Cell Count: - Gulland and Goodall (1925) stated that in scurvy the number of white cells was diminished, in the absence of recent haemorrhage, while Piney (1932) stated that sometimes a leucocytosis occurred, but that oftener the number of white cells was normal. Mettier et al. (1930) gave the number of white cells in uncomplicated cases as from four to six thousand per cubic millimetre. Parsons and Smallwood (1935) found no constant change. In guinea pigs with experimental scurvy, Diblicek and Kucera found a leucopenia, while Mouriquand et al. (1938) found that there was first a leucocytosis, then a leucopenia as the scurvy advanced.

No constant changes were found in the present series. The mean white cell count, of all the cases in which there was anaemia, was rather low, being 4,900 per cubic millimetre. The high standard deviation (= 1,250) indicates the variability of the individual counts.

Schilling Count: - Schilling (1929) described right

shift with neutropenia in scurvy. Comrie (1920) stated that there was a slight relative lymphocytosis, with no increase in monocytes, often a few myelocytes, and a scarcity of basophils. In guinea pigs, Mouriquand found that the numbers of monocytes increased as the scurvy became more severe; and Diblicek and Kucera (1933) found an increase in basophils and eosinophils.

Table 8 shows the mean values in the present series. From this table it can be seen that the Schilling count in group 1 showed no abnormality despite the vitamin deficiency. Taking as standard the mean of all seventeen cases after treatment, it appears that the proportions of segmented neutrophils and monocytes were not significantly affected by the vitamin deficiency. No statement can be made concerning alterations in the proportions of eosinophils and basophils, on account of their variability; but the rarity of basophils in untreated scurvy, to which Mettier et al. (1930) referred, was not apparent. There was a diminution in the numbers of juveniles and staffs; the difference between the mean values before and after treatment/

treatment being more than twice the standard error (S.E.) in the case of the juveniles (S.E. = 0.2) and more than four times in the case of the staffs (S.E. = 0.4). There appeared to be a slight lymphocytosis before treatment, the difference between the numbers before and after treatment being more than twice the standard error (= 2.7) These figures suggest that there was a slight degree of "right shift" in those cases of vitamin C deficiency in which anaemia, presumably attributable to the deficiency, was found.

The formula used for the calculation of the standard error was $S.E. = \sqrt{\frac{(S.D.)_1^2}{n_1} + \frac{(S.D.)_2^2}{n_2}}$ The sample was small; n_1 (the number of cases in groups II and III) being eleven, and n_2 (the total number of cases treated) being seventeen.

Cooke Count: - A shift to the right in the Arneth count, of which this is a modification, is said to occur in scurvy (Schilling 1929) and was found in the cases in groups II and III in this series, the mean "weighted mean" being 3.2 (S.D. = 0.2) before treatment, and 2.6 after treatment.

BONE/

BONE MARROW: -

Cellularity: - Post-mortem studies of the bone marrow have been reported by Naegeli (1932), Harris (1927), Shipley (1933), Holt and McIntosh (1933) and MacCallum (1938), who describe the disappearance of the blood-forming tissues and their replacement by fibrous tissue. Piney (1932) stated that the marrow was hypoplastic. Dalldorf (1938) stated that atrophy occurred. Wolbach (1937) described large areas of an amorphous material resembling amyloid. In biopsy material, hyperplasia has been described. Mettier et al. (1930) and Jennings and Glazebrook (1938) described hyperplasia in bone marrow removed by sternal puncture. Markedly increased cellularity was noted, in the bone marrow of guinea pigs that had died of scurvy, by Mettier and Chew (1932).

Increased cellularity was a constant feature in the anaemic cases in the present series. The photo-micrographs (figures 3 and 4, facing page 9) illustrate the difference between the cellularity of the films from one case of scurvy before and after treatment.

Differential Count: -/

Differential Count:- Mettier et al. (1930) carried out sternal puncture on a case of scurvy before treatment, and on another at the height of the reticulocyte crisis following ascorbic acid administration. In the first they found scattered, small, varying-sized groups of nucleated red cells, many myelocytes among which were many of the eosinophilic variety, adult polymorphs and megakaryocytes in moderate numbers, and no evidence of fibrosis. In the second there were quantitatively more nucleated red cells, and in each field there were mitotic figures in the red cell precursors, a feature that had not been apparent in the first case. Jennings and Glazebrook (1938), in two cases, found in both, a relative increase in the numbers of the earlier red cell precursors, and in the more severe case, "definite hyperplasia, the early red cells being more affected than the white cells". Mettier and Chew (1932) found that the bone marrow of guinea pigs that had died of scurvy contained "large numbers of erythrogenic cells, mainly normoblasts, which showed little evidence of active maturation", but when/

when remission had been induced by giving orange juice, there were relatively more adult red cells than in the marrow of untreated cases.

To summarise, it has been stated that there is an increase in the numbers of nucleated red cells, sometimes affecting to a greater extent the earlier types, during untreated scurvy; during treatment there is an increase in mitotic activity in the red cell precursors. An increase in myelocytes has been observed in the untreated phase.

In the present series, increased numbers of the earlier types of red cell precursors and of pre myelocytes were observed in the cases of scurvy, before treatment. These changes are made clearer by the calculation of the maturity dispersions, and are referred to below. In cases 11, 12 and 13 marrow was aspirated during the reticulocyte crisis that took place after treatment was begun. It could not be clearly shown that the numbers of mitotic forms of the normoblasts were higher than they had been before treatment, though the numbers were definitely/

TABLE 9

Maturity Dispersal Ratios: Granuloblast and Erythroblast before and after treatment. The standard error (S.E.) is that of the difference between groups II and III before treatment, and groups I, II and III after treatment.

	Before treatment				After treatment		
	Group I		Groups II and III		Groups I, II and III		
	Mean	S.D.	Mean	S.D.	Mean	S.D.	S.E.
Granuloblast.							
Myeloblasts	5.5	1.6	6.1	6.4	4.6	2.0	2.0
Promyelocytes	13.0	1.9	22.3	4.5	14.5	4.4	1.7
Myelocytes	36.6	2.8	38.3	5.5	35.6	3.6	
Juveniles	44.9	4.2	34.3	6.9	45.3	5.2	1.3
Erythroblast.							
Pronormoblast	2.0	1.1	3.4	1.8	2.3	1.2	0.6
Basophilic normoblasts	15.1	5.2	44.3	9.1	16.1	6.0	3.1
Polychromatic and Orthochromatic normoblasts	82.9	4.9	52.3	7.2	81.6	5.9	2.6.

definitely higher during the crisis than after treatment. Megakaryocytes were always found, though in some specimens they had to be sought in several films.

Maturity Dispersal Ratios: - Table 9 shows how the means compare, before and after treatment. From this table, it is seen that the maturity dispersions of both granuloblast and erythroblast in group I were within normal limits. In groups II and III, however, certain deviations from the normal were noted as follows: -

Granuloblast: - There was no demonstrable change in the percentages of myeloblasts or myelocytes, but there was a significant increase in the promyelocytes and a corresponding reduction in the juveniles.

Erythroblast: - There was no demonstrable change in the pronormoblasts. There was a definite normoblastic reaction, in the form of a significant increase in the basophilic forms of the normoblast, with a corresponding decrease in the polychromatic and orthochromatic forms.

In six cases of iron deficiency anaemia with haemoglobin levels that gave a mean near that of the vitamin/

TABLE 10

Comparison of maturity dispersion of erythroblast in vitamin C deficiency anaemia (cases 7 to 17) and iron deficiency anaemia (six cases).

		Vitamin C deficiency.	Iron deficiency.
Mean Values	Haemoglobin, per cent.	59	52
	Red cell count (millions/cu.mm.)	2.9	3.7
	Pronormoblasts	3.4	4.4
	Normoblasts		
	Basophilic	44.3	17.2
	Polychromatic and Orthochromatic	52.3	78.3

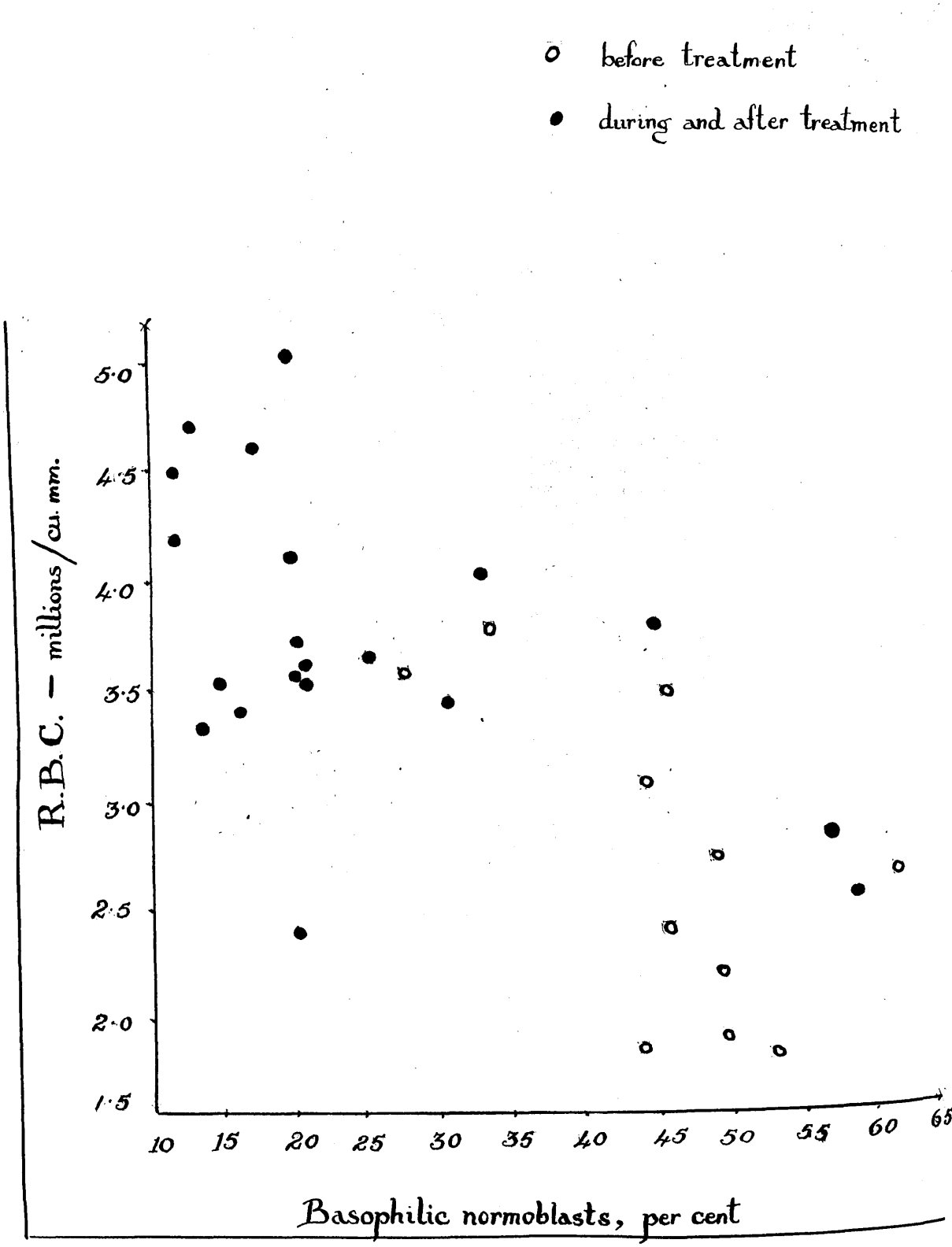


Figure 16

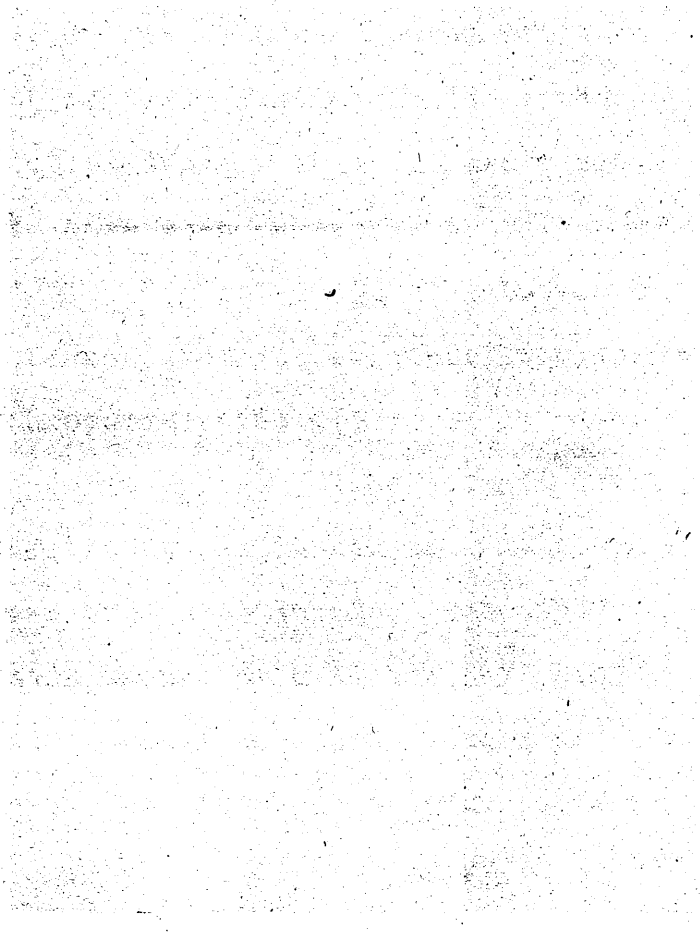
Scatter diagram showing inverse relationship between red cell count and percentage of basophilic normoblasts (as percentage of total erythroblast) in anaemia in vitamin C deficiency.

vitamin C deficient cases of groups II and III, this increase in basophilic normoblasts was not a feature, as can be seen from table 10 . However, increased numbers of basophilic normoblasts are known to be a feature of iron deficiency anaemia (Piney 1941) so that the probability is that the means of the iron deficient and vitamin C deficient anaemias in table 10 are not comparable, since the cell count in the iron deficient cases is higher than in the vitamin C deficient. This is partly supported by the finding that in vitamin C deficiency anaemia, there is an inverse relationship between the red cell count and the percentage of baso-:philic normoblasts (figure 16).

While there was an increase in the percentage of basophilic normoblasts before treatment, no further increase with the institution of treatment was observed; there was rather a gradual return to normal. Similar findings have been reported of post-haemorrhagic anaemia during treatment (Piney, 1941).

GASTRIC ANALYSIS: - Achlorhydria was a feature in the/

the four cases that failed to respond to ascorbic acid, whereas there were normal amounts of free hydrochloric acid in the cases that did respond.



DISCUSSION.

It is commonly accepted that vitamin C plays some part in erythropoiesis. Difference of opinion exists as to the actual part itplays. Thus it has been thought to be a stimulant to red cell formation (Lichwitz, 1942). Others have thought it to be a specific erythropoietic factor, in the absence of which maturation cannot proceed; while others again have thought it to be no more than an adjuvant, which may be taken as meaning that it facilitates the utilisation of erythropoietic substances, but is not itself indispensable as an erythropoietic factor.

It is unlikely that vitamin C merely stimulates maturation since it has no demonstrable effect on the normal subject (Gingold, 1936, 1937). But there is a certain amount of evidence for both the view that it is a specific erythropoietic factor, and for that that it is an adjuvant, and this evidence must be considered.

The characteristic response to the administration of a/

a specific erythropoietic substance which has been lacking, is a reticulocyte response followed by a rise in red cells and haemoglobin (Israels and Wilkinson, 1936). Such a response to the administration of vitamin C in the anaemia of scurvy has been observed (Jennings and Glazebrook, 1938; Mettier and Chew, 1932; Parsons and Smallwood, 1935). It was observed in the present series also, and the charts (pages lv to lxv, appendix) illustrate the type of response, while figure 14 (facing page 57) shows that the reticulocyte response was comparable with that of other types of anaemia under adequate treatment.

It may be accepted, then, that the vitamin plays a part in erythropoiesis. But there are objections to regarding it as a specific erythropoietic factor. Thus, the presence or absence of anaemia is not related to the degree of vitamin C deficiency, as scurvy may occur without anaemia (Rohmer and Bindschedler, 1932; Crandon et al. 1941), and ascorbic acid values as low as those of scurvy may occur in the absence of either scurvy or anaemia/

anaemia (Croft and Snorf, 1939). The latter observation has been made in this series (page 40). Again, the response of the anaemia of scurvy to vitamin C is not always of the specific type; thus, Ungley (1938) observed a "spontaneous reticulocytosis" in scurvy and was unable to demonstrate the specific effect of vitamin C, while McMillan and Inglis (1944) failed to observe a reticulocyte response although the red cells and haemoglobin rose on the administration of the vitamin. Finally, vitamin C, in the form of pure ascorbic acid, has sometimes failed to effect any change in the anaemia of scurvy until some other factor was added (page 45), and Rohmer and Bindschedler (1932) found that in some cases both iron and vitamin C were necessary. In the present series, there were four cases of severe vitamin C deficiency with anaemia which failed to respond to ascorbic acid; in two cases, response was obtained on the addition of oranges; in the other two, it appeared that iron in the one, and vitamin P in the other, were required as well as ascorbic acid (pages 31) a

it/

It is therefore probable that vitamin C is a factor of some importance in erythropoiesis, but that it is of secondary importance, in that it facilitates the utilisation of other, erythropoietic substances; while erythropoiesis can proceed, in spite of gross ascorbic acid deficiency, if there is an adequate supply of these other substances.

The blood and bone marrow in the anaemia of vitamin C deficiency, and changes in these as a result of treatment, will now be considered for the purpose of reaching a conclusion as to the level or levels at which erythropoiesis is held up in the anaemia of vitamin C deficiency. This might be expected to give information supporting one or other of the theories discussed above. Thus, if there was a specific anaemia of vitamin C deficiency, one might expect to find some constant and possibly also characteristic type of response to both the deficiency itself and the treatment of it. If vitamin C acts as an adjuvant only, one would expect to find a variable/

variable picture in the deficiency, and a variable response to treatment; or if a constant picture was found, that it would be such as could be found in other types of anaemia.

The anaemia of vitamin C deficiency will be compared with other types of anaemia, in which the erythropoietic factors act at different levels; for example with pernicious anaemia and with iron deficiency anaemia. Comparisons will be made in respect of the following (a) colour index and cell size; (b) response to treatment; (c) bone marrow picture; and (d) response of bone marrow to treatment.

(a) Colour index and cell size: - It is commonly accepted that the anaemia is usually orthochromic, though hyperchromic and hypochromic types also occur (page 53). This was found to be the case in the present series. It is stated also that the anaemia is usually normocytic though it may occasionally be macrocytic (Whitby and Britton, 1942). Jennings and Glazebrook (1938) considered that this variation indicated that the vitamin/

vitamin acts through a wide range of maturation, but that a severe deficiency might lead to maturation being held up at an earlier phase and so giving rise to macrocytosis. Wintrobe (1942) stated that macrocytosis may occur, in anaemias usually normocytic, if blood formation is stimulated, since young red cells are larger than the older cells. This may partly account for the occasional finding of macrocytosis in the anaemia of vitamin C deficiency, as there is often an increased reticulocyte count in the more severe anaemias (page 56). It fails to account for the occurrence of macrocytosis with hyperchromia. Since the hold up in maturation of the megaloblast in pernicious anaemia gives rise to a large-celled anaemia, while in iron deficiency the hold up in maturation of the normoblast gives rise to a small-celled anaemia, one assumes that in dyshaemopoietic anaemias, the larger-celled anaemias are due to a hold up in maturation at an earlier phase than in the case of the smaller-celled anaemias. If this is true, it would imply that in the anaemia of vitamin C deficiency/

deficiency in some cases the hold up is at an earlier phase than in others.

(b) Response to treatment: - The curve correlating the red cell count before treatment with the percentage of reticulocytes at the peak of the crisis in pernicious anaemia is different from that in iron deficiency anaemia. The difference, however, is small. In the present series the relationship did not give a sufficiently clear curve or a sufficiently close approximation to either the pernicious anaemia or the iron deficiency anaemia curve to allow of any conclusion being drawn from this comparison (figure 15, facing page 57).

Mettier et al. (1930) have stated that the interval between initiation of treatment and the reticulocyte crisis is shorter in scurvy than in pernicious anaemia. They have offered as an explanation that in scurvy the erythrocyte has only to undergo the relatively short process of maturation from the normoblast, whereas in pernicious anaemia it has to undergo the longer process of/

of maturation from the megaloblast. It appears, however, that there is no material difference between the interval in pernicious anaemia and that in iron deficiency anaemia, and in scurvy the interval was found to be of the same order (page 58). Thus no conclusion can be based on observations of the interval between the initiation of treatment and the reticulocyte response.

(c) Bone marrow: - In all the anaemic cases described in this paper - fifteen in number - the erythroblast showed a very constant change: namely, an increase in basophilic normoblasts with a corresponding decrease in the orthochromatic and polychromatic forms. There was no material change in the pronormoblasts. This picture appears to resemble that of iron deficiency in which Piney (1942) described an increase in the basophilic normoblasts. It bears no resemblance to the megaloblastic marrow of untreated pernicious anaemia, although it resembles the picture early in the course of treatment of pernicious anaemia, just after the megaloblastic has given place to a/

a normoblastic picture.

(d) Response of bone marrow to treatment: - As in the case of iron deficiency under treatment (Piney, 1933) no increase in the number of basophilic normoblasts took place with the institution of treatment, but there was rather a gradual return to normal. In this respect again there was no resemblance to pernicious anaemia in which there is a rapid change from a megaloblastic to a normoblastic picture, followed by a steady return to normal (Davidson et al., 1932).

From the foregoing it appears, from the general similarities with iron deficiency anaemia, that a parallel may be drawn between that and vitamin C deficiency. The point of action of iron must therefore be considered.

Piney (1942) deduced that iron was needed for complete maturation of the erythroblast and not as a stimulant to erythropoiesis, because the great excess of immature normoblasts in the bone marrow of the untreated case did not further increase after iron therapy had been instituted./

instituted. Presumably, the administration of iron allows erythropoiesis to proceed beyond the point at which it had been held up when iron was deficient. "Iron is essential for the proper production of fully haemoglobinised red corpuscles and a deficiency affects that stage of erythropoiesis at which haemo-:globin is being rapidly assimilated by the ripening corpuscles" (Whitby and Britton, 1942). In the nomenclature used in this paper, the point of action would be at the phase of maturation from the basophilic normoblast to the orthochromatic normoblast. A hold up at this point would yield an increase in basophilic normoblasts, either relatively, or absolutely, in an attempt to compensate for decreased production of later forms.

Similarly, in the case of vitamin C deficiency anaemia the observed increase in basophilic normoblasts could be taken to indicate that the vitamin acts chiefly at the point of maturation from the basophilic to the polychromatic form. The progressive decrease in the percentage of basophilic forms after the institution of/

of treatment would indicate that the vitamin did not act as a stimulant to erythropoiesis, but by allowing some deficiency to be filled, allowed maturation to proceed. The occasional variation in the colour index could be taken to indicate that the point of action could vary to a certain extent within the normoblastic range.

It has been thought that vitamin C would act throughout the whole range of maturation, because vitamin C is essential for cell metabolism (Parsons and Smallwood, 1935). But iron also can be regarded as acting through the whole range of erythropoiesis; because haemoglobin can be detected in the ortho-:plastic pronormoblast (Wintrobe, 1942). Despite this, it is apparently at the early normoblastic level that both iron and vitamin C have their chief effect. This is probably related to the fact that it is at this level that the most active cell division takes place, as is stated by Doan, Cunningham and Sabin (1925); as the cells are proliferating more actively at this level/

level, they would require larger amounts of vitamin C and iron, as well as other factors.

Thus there is nothing characteristic about the anaemia of vitamin C deficiency. The constant finding of increased numbers of basophilic normoblasts appears to be such a finding as might be expected in an anaemia in which the blood-forming tissues were reacting and giving a raised reticulocyte count; just as acute haemolytic anaemia may give a high reticulocyte count and a marrow showing extreme normoblastic "hyperplasia", and acholuric jaundice give a marrow showing "erythro-:poietic nyperplasia of the normoblastic type" (Wintrobe 1942).

The findings as to the blood and bone marrow and their reponse to treatment therefore favour the view that vitamin C is an adjuvant to erythropoiesis, since the variable type of anaemia suggests that the hold up in maturation may be at different levels in different cases. The reticulocyte response, the bone marrow picture and its response to treatment, are in no way/

way characteristic of vitamin C deficiency, but are such as may be found in several other conditions.

The polymorphonuclear neutrophils show a similarly uncharacteristic picture. Leucopenia is frequent but inconstant (page 59) and there is generally a right shift, because of the large proportion of multilobed (and so presumably senile) polymorphs (page 59). The bone marrow shows a correspondingly increased proportion of promyelocytes in many cases (page 65). It seems likely that the deficiency of vitamin C leads to delayed formation of polymorphonuclear neutrophils; this would account for the common neutropenia and the decreased numbers of young forms in the peripheral blood.

It is likely that vitamin C is a substance of importance in cell metabolism, by regulating tissue respiration (Euler and Klussman, 1933) so that there is nothing inherently improbable about the vitamin's having an action on both red cell and while cell formation; it may be that the diminished respiration and metabolism during the vitamin deficiency are the cause of the imperfect utilisation of erythropoietic substances and of the delayed formation of polymorphonuclear neutrophils.

CONCLUSIONS

Vitamin C has an effect on red cell and on white cell formation.

It is probable that it acts as an adjuvant to red cell formation, by facilitating the utilisation of other haemopoietic factors.

On both red cell and white cell (neutrophil granulocyte) formation the action of the vitamin is non-specific and may be related to the postulated role of the vitamin in cell metabolism.

SUMMARY.

Twenty one cases of severe vitamin C deficiency, including thirteen cases of scurvy, are studied.

The blood and bone marrow pictures and the effects of treatment are considered.

Theories as to whether or not vitamin C is an erythropoietic factor are discussed.

Reasons are given for concluding that the vitamin does not play a specific part in erythropoiesis.

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A P P E N D I X

Protocols of all cases of vitamin C deficiency in the series: tables I - XIX; pp i to liv.

Blood charts, cases 7 to 17; pp lv to lxv.

Table I

Case 1. Male aged 43 years. No sign of scurvy or other physical disease.
Treatment:- One thousand milligrammes ascorbic acid intravenously on 26.ix; and three hundred milligrammes ascorbic acid daily by mouth, from 26.ix

Date	28.vii	26.ix	5.i
ASCORBIC ACID DETERMINATIONS			
Rotter's Test (time, minutes)	12	12	5
Plasma ascorbic acid (mgms. per cent)	0.51	0.49	1.5
CAPILLARY FRAGILITY	3	4	2
BLOOD EXAMINATIONS.			
Haemoglobin (%)	102	101	102
Colour Index	1.06	1.06	1.03
White cell count (/cu.mm.)	8,600	5,400	5,800
Schilling Count			
Basophils	0.5	0.5	1.0
Eosinophils	-	0.25	0.25
Myelocytes	-	-	-
Juveniles	1.0	1.0	1.0
Staffs	3.5	3.75	2.25
Segmented Neutrophils	60.0	58.0	56.0
Lymphocytes	24.0	27.5	31.0
Monocytes	11.0	9.0	8.5
Cooke Count - weighted mean	2.7	2.7	2.6
Platelet Count (/cu.mm.)	275,000		

Table I (contd.)

Date	28.vii	26.ix	5.i
BONE MARROW			
Cellularity			
Differential Count			
Myeloblasts	1.6	1.2	1.2
Promyelocytes	3.6	3.2	2.4
Neutrophil myelocytes	9.6	7.2	8.0
" juveniles	12.0	10.8	13.6
" staffs	11.2	11.6	12.4
" segmented	13.6	14.0	13.2
Eosinophil myelocytes	-	-	0.4
" segmented	0.4	-	0.4
Basophil myelocytes	0.4	0.4	-
" segmented	0.4	1.2	0.4
Lymphocytes	8.0	8.8	6.4
Monocytes	2.0	2.0	1.6
Plasma cells	1.6	2.0	1.2
Pronormoblasts	0.8	0.4	0.8
Normoblasts			
Basophilic	2.8	2.8	1.6
Polychromatic	30.0	34.4	33.2
Orthochromatic	2.0	-	3.2
Mitotic forms	0.4	0.4	-
Maturity Dispersal Ratios			
Granuloblast			
Myeloblasts	5.9	5.4	4.7
Promyelocytes	13.1	14.2	9.4
Myelocytes	36.8	32.4	32.7
Juveniles	44.2	48.0	53.2
Erythroblast			
Pronormoblast	2.2	1.2	2.0
Normoblast - basophilic	7.8	7.4	4.0
" polychromatic and orthochromatic	90.0	91.4	94.0

Table II

Case 2. Male aged 43 years. No sign of scurvy or other physical disease.
Treatment:- One thousand milligrammes ascorbic acid intravenously on 7.xii; and three hundred milligrammes ascorbic acid daily by mouth from 7.xii.

Date	7.viii	7.xii	8.i
ASCORBIC ACID DETERMINATIONS			
Rotter's Test (time, minutes)	14	11	5
Plasma ascorbic acid (mgms. per cent)	0.46	0.48	1.4
CAPILLARY FRAGILITY			
BLOOD EXAMINATIONS			
Haemoglobin (%)	92	93	92
Colour Index	1.03	0.99	1.0
White cell count (/cu.mm.)	5,600	5,800	5,000
Schilling Count			
Basophils	-	-	-
Eosinophils	2.5	2.0	1.25
Myelocytes	-	-	-
Juveniles	1.0	1.25	-
Staffs	2.5	2.0	2.5
Segmented Neutrophils	55.25	50.0	48.0
Lymphocytes	31.75	38.0	41.25
Monocytes	7.0	6.75	8.0
Cooke Count - weighted mean	2.5	2.6	2.6
Platelet Count (/cu.mm.)	350,000		

Table II (contd.)

Date	7.viii	7.xii	8.i
BONE MARROW			
Cellularity			
Differential Count			
Myeloblasts	2.0	2.0	1.2
Promyelocytes	2.4	5.2	4.0
Neutrophil myelocytes	8.4	8.0	9.2
" juveniles	12.0	9.6	10.0
" staffs	17.2	15.6	17.6
" segmented	18.0	17.2	20.4
Eosinophil myelocytes	-	0.8	0.4
" segmented	0.8	-	-
Basophil myelocytes	-	-	-
" segmented	-	-	0.4
Lymphocytes	4.0	2.0	2.0
Monocytes	1.2	1.6	0.4
Plasma cells	0.8	0.8	0.8
Pronormoblasts	-	0.4	0.8
Normoblasts			
Basophilic	3.2	5.6	5.2
Polychromatic	26.0	30.0	25.6
Orthochromatic	4.0	1.2	2.0
Mitotic forms	-	-	0.4
Maturity Dispersal Ratios			
Granuloblast			
Myeloblasts	8.0	7.7	4.8
Promyelocytes	9.7	20.3	16.4
Myelocytes	33.9	34.4	38.4
Juveniles	48.4	37.6	40.4
Erythroblast			
Pronormoblast	-	1.1	2.4
Normoblast - basophilic	9.5	15.1	15.3
polychromatic and orthochromatic	90.5	83.8	82.3

Table. III

Case 3. Male aged 49 years. No sign of scurvy or other physical disease.
Treatment:- One thousand milligrammes ascorbic acid on 15.ii; and three hundred milligrammes ascorbic acid daily by mouth from 15.ii

Date	9.viii	15.ii	21.iii
ASCORBIC ACID DETERMINATIONS			
Rotter's Test (time, minutes)	14	9	3
Plasma ascorbic acid. (mgms. per cent.)	0.5	0.51	1.8
CAPILLARY FRAGILITY	2	4	-
BLOOD EXAMINATIONS			
Haemoglobin (%)	91	89	94
Colour Index	1.04	1.05	0.9
White cell count (/cu.mm.)	4,000	3,600	9,500
Schilling Count			
Basophils	-	-	-
Eosinophils	0.25	0.5	0.5
Myelocytes	-	-	-
Juveniles	1.0	-	1.5
Staffs	3.0	5.75	3.0
Segmented Neutrophils	51.0	60.0	57.25
Lymphocytes	36.0	27.75	31.0
Monocytes	8.75	9.0	7.0
Cooke Count - weighted mean	2.6	2.7	2.6
Platelet Count (/ cu.mm.)	250,000		

Table III (contd.)

Date	9.viii	15.ii	21.iii
BONE MARROW			
Cellularity			
Differential Count			
Myeloblasts	1.6	1.2	1.6
Promyelocytes	4.0	3.6	3.2
Neutrophil myelocytes	9.6	8.4	9.2
" juveniles	10.0	11.6	10.8
" staffs	12.0	13.2	11.6
" segmented	15.6	16.4	15.2
Eosinophil myelocytes	0.8	-	-
" segmented	0.4	-	-
Basophil myelocytes	-	-	0.4
" segmented	-	-	0.4
Lymphocytes	4.4	4.0	3.6
Monocytes	1.6	0.8	1.6
Plasma cells	0.8	1.6	1.2
Pronormoblasts	1.2	0.8	0.8
Normoblasts			
Basophilic	7.2	8.0	8.0
Polychromatic	27.2	28.4	31.2
Orthochromatic	3.6	2.0	1.2
Mitotic forms	0.8	-	-
Maturity Dispersal Ratios			
Granuloblast			
Myeloblasts	6.1	4.8	6.4
Promyelocytes	15.4	14.6	12.9
Myelocytes	40.0	33.8	37.1
Juveniles	38.5	46.8	43.6
Erythroblast			
Pronormoblast	3.0	2.0	1.9
Normoblast - basophilic polychromatic and orthochromatic	18.0 79.0	20.4 77.6	19.3 78.8

Table IV

Case 4. Male aged 41 years. No sign of scurvy or other physical disease.
Treatment:- One thousand milligrammes ascorbic acid intravenously on 23.ii; and three hundred milligrammes ascorbic acid daily by mouth from 23.ii

Date	14.i	23.ii	2.iv
ASCORBIC ACID DETERMINATIONS			
Rotter's Test (time, minutes)	10	10	4
Plasma ascorbic acid. (mgms per cent.)	0.58	0.56	1.6
CAPILLARY FRAGILITY	3	2	2
BLOOD EXAMINATIONS			
Haemoglobin (%)	110	107	107
Colour Index	1.18	1.13	1.21
White cell count (/cu.mm.)	9,800	11,000	8,600
Schilling Count			
Basophils	-	6.25	-
Eosinophils	3.75	-	3.0
Myelocytes	-	-	-
Juveniles	-	1.0	0.25
Staffs	2.75	2.0	2.75
Segmented Neutrophils	43.0	40.0	43.75
Lymphocytes	41.75	36.5	38.0
Monocytes	8.75	14.25	12.25
Cooke Count - weighted mean	3.0	2.9	2.8
Platelet Count (/cu.mm.)	400,000		

Table IV (contd.)

Date	14.i	23.ii	2.iv
BONE MARROW			
Cellularity			
Differential Count			
Myeloblasts	1.2	2.0	2.0
Promyelocytes	4.0	3.2	4.4
Neutrophil myelocytes	9.6	8.0	9.2
" juveniles	13.2	13.6	15.6
" staffs	10.4	14.8	9.6
" segmented	14.4	17.2	12.4
Eosinophil myelocytes	0.8	-	-
" segmented	0.4	0.4	-
Basophil myelocytes	-	0.4	-
" segmented	-	-	-
Lymphocytes	2.4	5.6	3.6
Monocytes	1.6	2.0	1.2
Plasma cells	0.8	2.0	1.2
Pronormoblasts			
Normoblasts	7.2	7.2	6.8
Basophilic	31.2	31.2	31.6
Polychromatic	1.2	2.0	1.6
Orthochromatic			
Mitotic forms	0.4	-	-
Maturity Dispersal Ratios			
Granuloblast			
Myeloblasts	4.1	5.9	5.4
Promyelocytes	13.8	11.9	14.3
Myelocytes	36.1	31.3	29.8
Juveniles	45.8	50.9	50.5
Erythroblast			
Pronormoblast	2.0	1.9	2.9
Normoblast - basophilic	17.6	17.6	16.6
Polychromatic and orthochromatic	80.4	80.5	80.5

Table V

Case 5. Male aged 49 years. No sign of scurvy or other physical disease.
Treatment:- One thousand milligrammes ascorbic acid intravenously on 2.xi; and three hundred milligrammes ascorbic acid daily by mouth from 2.xi

Date	24.vii	2.xi	2.xii
ASCORBIC ACID DETERMINATIONS			
Rotter's Test (time, minutes)	14.	15	5
Plasma ascorbic acid. (mgms. per cent.)	0.47	0.5	2.0
CAPILLARY FRAGILITY	7	9	8
BLOOD EXAMINATIONS			
Haemoglobin: (%)	99	97	100
Colour Index	0.99	1.03	0.99
White cell count (/cu.mm.)	4,800	5,800	6,200
Schilling Count			
Basophils	5.2	7.0	3.5
Eosinophils	1.4	-	1.0
Myelocytes	-	-	-
Juveniles	0.4	0.25	0.5
Staffs	3.4	2.25	3.75
Segmented Neutrophils	43.6	59.5	42.0
Lymphocytes	38.2	25.5	38.5
Monocytes	7.8	5.5	5.75
Cooke Count - weighted mean	2.7	2.8	2.6
Platelet Count (/cu.mm.)	220,000		

Table V (contd.)

Date	24.vii	2.xi	2.xii
BONE MARROW			
Cellularity			
Differential Count			
Myeloblasts	1.2	2.0	2.0
Promyelocytes	4.0	4.8	4.8
Neutrophil myelocytes	11.6	8.0	9.2
" juveniles	13.2	12.4	12.0
" staffs	9.6	9.2	11.2
" segmented	12.0	12.0	14.0
Eosinophil myelocytes	0.4	0.8	-
" segmented	-	-	-
Basophil myelocytes	-	0.4	-
" segmented	-	-	-
Lymphocytes	4.0	4.4	3.2
Monocytes	1.6	2.0	1.2
Plasma cells	1.2	1.6	1.2
Pronormoblasts	0.8	1.2	1.2
Normoblasts			
Basohpilic	7.2	8.0	7.6
Polychromatic	30.0	31.6	30.0
Orthochromatic	3.2	1.6	2.0
Mitotic forms	-	0.8	0.4
Maturity Dispersal Ratios			
Granuloblast			
Myeloblasts	3.9	7.1	7.1
Promyelocytes	13.1	17.1	17.1
Myelocytes	39.5	31.5	32.8
Juveniles	43.5	44.3	43.0
Erythroblast			
Pronormoblast	1.9	2.6	2.9
Normoblast - basophilic	17.7	18.6	18.2
polychromatic and orthochromatic	80.4	78.8	78.9

Table VI

Case 6. Male aged 45 years. No sign of scurvy or other physical disease.
Treatment:- One thousand milligrammes ascorbic acid intravenously on 23.ix; and three hundred milligrammes ascorbic acid daily by mouth from 23.ix

Date	27.vii	23.ix	23.x
ASCORBIC ACID DETERMINATIONS			
Rotter's Test (time, minutes)	30	35	5
Plasma ascorbic acid. (mgms. per cent)	0.42	0.44	1.9
CAPILLARY FRAGILITY	10	7	10
BLOOD EXAMINATIONS			
Haemoglobin (%)	97	95	98
Colour Index	1.04	0.91	0.98
White cell count (/cu.mm.)	5,200	4,600	7,800
Schilling Count			
Basophils	-	-	0.5
Eosinophils	1.0	2.0	1.0
Myelocytes	-	-	-
Juveniles	1.0	0.5	0.5
Staffs	3.0	4.0	2.5
Segmented Neutrophils	47.0	47,25	38.25
Lymphocytes	40.0	37.5	47.0
Monocytes	8.0	8,75	10.75
Cooke Count - weighted mean	2.5	2.7	2.6
Platelet Count (/cu.mm.)	195,000		

Table VI (contd.)

Date	27.viii	23.ix	23.x
BONE MARROW			
Cellularity			
Differential Count			
Myeloblasts	1.2	0.8	1.2
Promyelocytes	3.2	2.8	3.6
Neutrophil myelocytes	8.4	8.8	8.0
" juveniles	12.4	12.0	13.2
" staffs	11.2	9.2	13.2
" segmented	12.8	10.8	13.6
Eosinophil myelocytes	-	0.4	-
" segmented	0.4	-	-
Basophil myelocytes	-	-	0.4
" segmented	-	0.4	-
Lymphocytes	5.2	6.0	4.8
Monocytes	1.6	2.4	2.0
Plasma cells	2.0	2.0	-
Pronormoblasts	1.2	1.2	1.6
Normoblasts			
Basophilic	8.4	9.2	8.0
Polychromatic	28.8	31.2	27.6
Orthochromatic	3.2	2.0	2.8
Mitotic forms	-	0.8	-
Maturity Dispersal Ratios			
Granuloblast			
Myeloblasts	4.8	3.2	4.6
Promyelocytes	12.7	11.2	13.6
Myelocytes	33.3	37.1	31.9
Juveniles	49.2	48.5	50.9
Erythroblast			
Pronormoblast	2.8	2.6	4.0
Normoblast - basophilic polychromatic and orthochromatic	20.2	19.6	20.0
	77.0	77.8	76.0

Table VII

Case 7. Female, aged 68 years; moderately arteriosclerotic, with signs of scurvy - follicular haemorrhages and ecchtmoses on legs and red cells in urine.
Treatment:- One thousand milligrammes ascorbic acid intravenously on 20.vii; and three hundred milligrammes ascorbic acid daily by mouth from 20.vii

Date	20.vii	28.vii	10.viii	10.ix	20.xi
ASCORBIC ACID DETERMINATIONS					
Rotter's Test (time, minutes)	40		5	4	5
Plasma ascorbic acid (mgms. per cent.)	0.31				1.3
CAPILLARY FRAGILITY	65	54		8	3
BLOOD EXAMINATIONS					
Haemoglobin (%)	42	45	54	80	98
Colour Index	1.08	1.07	0.90	0.98	0.94
White cell count (/cu.mm.)	4,600	4,400	5,200	4,600	5,000
Schilling Count					
Basophils	-	-	0.25	-	-
Eosinophils	0.5	-	-	0.5	-
Myelocytes	-	-	-	-.	-
Juveniles	1.0	0.25	1.5	2.25	2.0
Staffs	1.0	2.0	5.5	5.5	3.25
Segmented Neutrophils	40.5	42.0	45.5	45.5	55.75
Lymphocytes	48.5	48.0	41.25	38.5	31.75
Monocytes	8.5	7.75	6.0	7.75	9.25
Cooke Count - weighted mean	3.1	2.8	2.7	2.4	2.7
Platelet Count (/cu.mm.)	650,000				

Table VII (contd.)

Date	20.vii	20.xi
BONE MARROW		
Cellularity		
Differential Count		
Myeloblasts	0.8	1.2
Promyelocytes	6.4	4.0
Neutrophil myelocytes	10.4	9.6
" juveniles	12.0	15.6
" staffs	12.8	10.4
" segmented	12.4	11.6
Eosinophil myelocytes	0.4	0.4
" segmented	-	-
Basophil myelocytes	-	-
" segmented	-	-
Lymphocytes	1.0	5.2
Monocytes	0.8	2.8
Plasma cells	-	1.6
Pronormoblasts	2.8	0.4
Normoblasts		
Basophilic	21.6	6.4
Polychromatic	16.4	28.0
Orthochromatic	2.0	2.0
Mitotic forms	2.4	0.4
Maturity Dispersal Ratios		
Granuloblast		
Myeloblasts	2.7	3.9
Promyelocytes	21.3	13.0
Myelocytes	36.0	32.4
Juveniles	40.0	50.7
Erythroblast		
Pronormoblast	6.4	0.9
Normoblast - basophilic	49.8	13.6
polychromatic and orthochromatic	43.8	85.5

Table VIII

Case 8. Male, aged 52 years, with signs of scurvy - follicular haemorrhages on legs and thighs, ecchymoses on legs, red cells in urine, sponginess of gums.
Treatment:- One thousand milligrammes ascorbic acid intravenously on 13. viii and three hundred milligrammes ascorbic acid daily by mouth from 13.viii.

Date	12.viii	17.viii
ASCORBIC ACID DETERMINATIONS		
Rotter's Test (time, minutes)	30	23
Plasma ascorbic acid. (mgms. per cent)	0.35	
CAPILLARY FRAGILITY	85	70
BLOOD EXAMINATIONS		
Haemoglobin (%)	65	72
Colour Index	0.93	0.97
White Cell count (/cu.mm.)	5,600	5,000
Schilling Count		
Basophils	-	-
Eosinophils	-	-
Myelocytes	-	0.25
Juveniles	0.75	1.5
Staffs	0.25	3.5
Segmented Neutrophils	42.5	45.25
Lymphocytes	47.5	40.75
Monocytes	9.0	8.75
Cooke Count - weighted mean.	3.3	3.0
Platelet Count (/cu.mm.)	450,000	

Table VIII (contd.)

Date	30.viii	18.ix
ASCORBIC ACID DETERMINATIONS		
Rotter's Test (time, minutes)	5	5
Plasma ascorbic acid. (mgms. per cent)		1.9
CAPILLARY FRAGILITY	4	5
BLOOD EXAMINATIONS		
Haemoglobin (%)	75	95
Colour Index	0.89	1.03
White cell count (/cu.mm.)	6,200	6,800
Schilling Count		
Basophils	-	-
Eosinophils	0.25	0.5
Myelocytes	-	-
Juveniles	3.0	1.5
Staffs	3.0	4.75
Segmented Neutrophils	52.0	48.75
Lymphocytes	35.25	37.5
Monocytes	6.5	7.0
Cooke Count - weighted mean	2.8	2.7
Platelet Count (/cu.mm.)	450,000	

Table VIII (contd.)

Date	12.viii	18.ix
BONE MARROW		
Cellularity		
Differential Count		
Myeloblasts	0.8	1.2
Promyelocytes	6.4	2.4
Neutrophil myelocytes	10.4	9.2
" juveniles	9.6	11.2
" staffs	8.0	12.0
" segmented	9.6	14.0
Eosinophil myelocytes	-	0.4
" segmented	-	-
Basophil myelocytes	-	-
" segmented	-	-
Lymphocytes	6.4	6.4
Monocytes	1.6	0.8
Plasma cells	2.8	2.0
Pronormoblasts	1.2	0.8
Normoblasts		
Basophilic	20.0	7.2
Polychromatic	22.4	32.0
Orthochromatic	0.8	0.4
Mitotic forms	0.8	-
Maturity Dispersal Ratios		
Granuloblast		
Myeloblasts	2.8	4.9
Promyelocytes	23.6	9.7
Myelocytes	38.3	39.4
Juveniles	35.3	46.0
Erythroblast		
Pronormoblast	2.7	2.0
Normoblast - basophilic	45.3	17.8
polychormatic and orthochromatic	52.0	80.2

Table IX

Case 9. Male aged 65 years. Moderately arteriosclerotic with signs of scurvy - follicular haemorrhages and ecchymoses on legs and thighs and red cells in urine; complaint of unusual dyspnoea on slight exertion for a week before admission.
Treatment:- One thousand milligrammes ascorbic acid intravenously on 30.xi and three hundred milligrammes ascorbic acid daily by mouth from 30.xi

Date	29.xi	5.xii	28.xii
ASCORBIC ACID DETERMINATIONS			
Rotter's Test (time, minutes)	30		3
Plasma ascorbic acid (mgms. per cent.)	0.34		1.7
CAPILLARY FRAGILITY	55		5
BLOOD EXAMINATIONS			
Haemoglobin (%)	42	44	56
Colour Index	0.92	0.95	0.84
White cell count (/cu.mm.)	5,200	5,800	4,200
Schilling Count			
Basophils	-	0.25	-
Eosinophils	-	-	-
Myelocytes	-	-	-
Juveniles	1.0	2.25	1.75
Staffs	1.5	4.5	3.0
Segmented Neutrophils	42.5	43.0	53.75
Lymphocytes	48.75	41.5	35.25
Monocytes	6.25	8.5	6.25
Cooke Count - weighted mean	2.9	2.7	2.7
Platelet Count (/cu.mm.)	520,000		

Table IX (contd.)

Date	29.xi	8.xii
BONE MARROW		
Cellularity		
Differential Count		
Myeloblasts	0.4	1.6
Promyelocytes	5.6	3.6
Neutrophil myelocytes	11.2	9.2
" juveniles	10.8	10.8
" staffs	9.2	11.6
" segmented	7.6	14.4
Eosinophil myelocytes	-	-
" segmented	-	-
Basophil myelocytes	-	0.4
" segmented	-	-
Lymphocytes	4.4	6.4
Monocytes	2.4	1.6
Plasma cells	1.2	0.8
Pronormoblasts	0.8	0.8
Normoblasts		
Basophilic	24.0	5.2
Polychromatic	20.8	30.4
Orthochromatic	1.6	3.2
Mitotic forms	1.6	-
Maturity Dispersal Ratios		
Granuloblast		
Myeloblasts	1.5	6.3
Promyelocytes	20.0	14.0
Myelocytes	40.0	37.5
Juveniles	38.5	42.2
Erythroblast		
Pronormoblast	1.6	2.0
Normoblast - basophilic	49.2	13.1
polychromatic and orthochromatic	49.2	84.9

Table X

Case 10. Female, aged 72 years. Arteriosclerotic and mildly demented. Petechial haemorrhages on legs, ecchymoses on legs and thighs, effusion in left knee, brawny swelling of left calf, red cells in urine.
Treatment:- One thousand milligrammes ascorbic acid intravenously on 23.vii, and three hundred milligrammes daily by mouth from 23.vii.

Date	22.vii	16.viii
ASCORBIC ACID DETERMINATIONS		
Rotter's Test (time, minutes)	20	8
Plasma ascorbic acid (mgms. per cent)	0.45	1.8
CAPILLARY FRAGILITY	85	14
BLOOD EXAMINATIONS		
Haemoglobin (%)	82	102
Colour Index	1.08	1.02
White cell count (/cu.mm.)	4,200	4,800
Schilling Count		
Basophils	-	0.25
Eosinophils	0.25	-
Myelocytes	-	-
Juveniles	0.25	1.5
Staffs	1.5	3.0
Segmented Neutrophils	47.5	47.25
Lymphocytes	41.5	39.25
Monocytes	9.0	8.75
Cooke Count - weighted mean	3.4	3.0
Platelet Count (/cu.mm.)	350,000	

Table X (contd.)

Date	22.vii	16.viii
BONE MARROW		
Cellularity		
Differential Count		
Myeloblasts	0.4	1.6
Promyelocytes	4.0	3.6
Neutrophil myelocytes	11.6	7.2
" juveniles	9.6	11.6
" staffs	8.0	14.0
" segmented	7.6	18.0
Eosinophil myelocytes	-	1.2
" segmented	0.4	-
Basophil myelocytes	-	0.8
" segmented	-	0.8
Lymphocytes	5.2	3.2
Monocytes	2.4	0.4
Plasma cells	1.6	0.8
Pronormoblasts	2.0	0.8
Normoblasts		
Basophilic	16.8	5.2
Polychromatic	28.8	29.2
Orthochromatic	1.6	1.6
Mitotic forms	0.8	-
Maturity Dispersal Ratios		
Granuloblast		
Myeloblasts	1.6	6.2
Promyelocytes	15.6	13.8
Myelocytes	45.3	35.4
Juveniles	37.5	44.6
Erythroblast		
Pronormoblast	4.0	2.2
Normoblast - basophilic	33.6	14.1
polychromatic and orthochromatic	62.4	83.7

Table XI

Case 11. Male aged 51 years, with signs of scurvy - follicular haemorrhages and ecchymoses on legs and thighs, red cells in urine, spongy gums, slight oedema of ankles.
Treatment:- One thousand milligrammes ascorbic acid intravenously on 5.viii, and three hundred milligrammes ascorbic acid daily by mouth, from 5,viii.

Date	1.viii	4.viii	7.viii
ASCORBIC ACID DETERMINATIONS			
Rotter's Test (time, minutes)	25		
Plasma ascorbic acid (mgms, per cent.)	0.41	0.43	
CAPILLARY FRAGILITY	55		49
BLOOD EXAMINATIONS			
Haemoglobin (%)	82	83	93
Colour Index	1.28		1.22
White cell count (/cu.mm.)	4,800		4,600
Schilling Count			
Basophils	1.25		1.75
Eosinophils	0.5		-
Myelocytes	-		-
Juveniles	0.25		1.0
Staffs	0.25		3.5
Segmented Neutrophils	69.75		55.0
Lymphocytes	24.5		34.5
Monocytes	3.5		4.25
Cooke Count - weighted mean	3.1		2.6
Platelet Count (/cu.mm.)	450,000		

Table XI (contd.)

Date	14.viii	21.viii
ASCORBIC ACID DETERMINATIONS		
Rotter's Test (time, minutes)		4
Plasma ascorbic acid (mgms. per cent.)		1.6
CAPILLARY FRAGILITY		4
BLOOD EXAMINATIONS		
Haemoglobin (%)	96	96
Colour Index	1.19	1.19
White cell count (/cu.mm.)	6,400	6,600
Schilling Count		
Basophils	0.75	1.5
Eosinophils	-	0.25
Myelocytes	-	-
Juveniles	1.25	1.0
Staffs	5.0	5.25
Segmented Neutrophils	47.75	71.25
Lymphocytes	42.0	17.0
Monocytes	3.25	3.75
Cooke Count - weighted mean	2.3	2.6

Table XI (contd.)

Date	I.viii	4.viii	7.viii
BONE MARROW			
Cellularity			
Differential Count			
Myeloblasts	2.8	4.0	1.2
Promyelocytes	4.8	5.6	4.0
Neutrophil myelocytes	3.2	4.0	5.6
" juveniles	3.6	3.6	7.6
" staffs	7.2	2.0	2.0
" segmented	4.0	3.2	4.4
Eosinophil myelocytes	0.8	0.4	0.8
" segmented	0.8	0.8	0.8
Basophil myelocytes	0.8	-	0.4
" segmented	-	-	-
Lymphocytes	3.2	3.6	6.2
Monocytes	0.8	1.6	2.4
Plasma Cells	0.4	0.8	0.4
Pronormoblasts	3.2	2.4	2.8
Normoblasts			
Basophilic	24.8	32.8	29.4
Polychromatic	39.6	32.4	31.6
Orthochromatic	-	2.8	0.4
Mitotic forms	0.4	1.2	1.2
Maturity Dispersal Ratios.			
Granuloblast			
Myeloblasts	17.5	22.7	6.1
Promyelocytes	30.0	31.8	20.2
Myelocytes	30.0	25.0	34.8
Juveniles	22.5	20.5	38.9
Erythroblast			
Pronormoblast	4.7	3.4	4.3
Normoblast - basophilic	36.7	45.8	46.0
" polychromatic and orthochromatic	58.6	50.8	49.7

Table XI (contd.)

Date	14.viii	21.viii
BONE MARROW		
Cellularity		
Differential Count		
Myeloblasts	1.2	2.0
Promyelocytes	3.6	4.4
Neutrophil myelocytes	5.6	8.0
" juveniles	9.2	8.8
" staffs	5.2	11.2
" segmented	16.8	16.6
Eosinophil myelocytes	0.4	0.4
" segmented	0.4	-
Basophil myelocytes	-	0.4
" segmented	-	0.4
Lymphocytes	6.4	7.4
Monocytes	2.4	0.8
Plasma cells	0.4	0.7
Pronormoblasts	1.2	-
Normoblasts		
Basophilic	13.2	7.6
Polychromatic	21.6	29.0
Orthochromatic	2.4	2.0
Mitotic forms	2.0	-
Maturity Dispersal Ratios.		
Granuloblast		
Myeloblasts	6.0	7.6
Promyelocytes	18.0	18.8
Myelocytes	30.0	36.8
Juveniles	46.0	36.8
Erythroblast		
Pronormoblast	3.0	-
Normoblast - basophilic	33.0	19.8
polychromatic and orthochromatic	64.0	80.2

Table XII

Case 12. Male aged 55 years, with signs of scurvy - follicular haemorrhages on legs and thighs, ecchymosis over and indurated swelling in left calf, red cells in urine, spongy gums, moist sounds at lung bases, slight oedema of ankles.
Treatment:- One thousand milligrammes ascorbic acid intravenously on 25.ii and three hundred milligrammes ascorbic acid daily from 26.ii

Date	25.ii	29.ii
ASCORBIC ACID DETERMINATIONS		
Rotter's Test (time, minutes)	35	
Plasma ascorbic acid (mgms. per cent.)	0.37	
CAPILLARY FRAGILITY	62	
BLOOD EXAMINATIONS		
Haemoglobin (%)	45	52
Colour Index	0.~~38~~	1.0
White cell count (/cu.mm.)	5,200	6,000
Schilling Count		
Basophils	0.25	-
Eosinophils	-	-
Myelocytes	-	-
Juveniles	0.5	-
Staffs	1.25	2.0
Segmented Neutrophils	28.0	23.8
Lymphocytes	59.0	61.4
Monocytes	11.0	12.8
Cooke Count - weighted mean	3.6	3.2
Platelet Count (/cu.mm.)	500,000	

Table XII (contd.)

Date	4.iii	15.iv
ASCORBIC ACID DETERMINATIONS		
Rotter's Test (time, minutes)	5	6
Plasma ascorbic acid (mgms. per cent.)		1.4
CAPILLARY FRAGILITY+	2	3
BLOOD EXAMINATIONS		
Haemoglobin (%)	60	105
Colour Index	1.03	1.04
White cell count (/cu.mm.)	5,200	5,400
Schilling Count		
Basophils	-	2.75
Eosinophils	-	-
Myelocytes	-	-
Juveniles	2.0	0.5
Staffs	4.25	3.5
Segmented Neutrophils	50.5	51.75
Lymphocytes	32.75	31.5
Monocytes	10.5	10.0
Cooke Count - weighted mean	2.8	2.6

Table XII (contd.)

Date	25.ii	29.ii
BONE MARROW		
Cellularity		
Differential Count		
Myeloblasts	1.2	1.6
Promyelocytes	5.2	5.2
Neutrophil myelocytes	8.4	7.6
" juveniles	8.4	8.4
" staffs	4.8	4.4
" segmented	6.0	6.4
Eosinophil myelocytes	0.4	0.4
" segmented	-	0.8
Basophil myelocytes	0.8	0.4
" segmented	-	-
Lymphocytes	5.2	5.0
Monocytes	2.4	1.6
Plasma cells	1.2	1.2
Pronormoblasts	1.2	1.2
Normoblasts		
Basophilic	35.2	34.0
Polychromatic	16.0	17.6
Orthochromatic	3.6	4.0
Mitotic forms	1.2	1.6
Maturity Dispersal Ratios		
Granuloblast		
Myeloblasts	4.9	6.8
Promyelocytes	21.3	22.0
Myelocytes	34.4	35.6
Juveniles	39.4	35.6
Erythroblast		
Pronormoblast	2.1	2.1
Normoblast - basophilic	61.5	58.2
" polychromatic and orthochromatic	36.4	39.7

Table XII (contd.)

Date	4.iii	15.iv
BONE MARROW		
Cellularity		
Differential Count		
Myeloblasts	1.2	0.4
Promyelocytes	5.6	2.0
Neutrophil myelocytes	10.8	9.2
" juveniles	12.8	10.0
" staffs	6.4	9.2
" segmented	6.8	9.6
Eosinophil myelocytes	-	0.4
" segmented	-	0.4
Basophil myelocytes	-	1.2
" segmented	-	0.8
Lymphocytes	7.6	5.6
Monocytes	4.0	2.4
Plasma cells	2.0	0.4
Pronormoblasts	1.6	1.2
Normoblasts		
Basophilic	26.4	9.6
Polychromatic	12.4	36.0
Orthochromatic	4.4	1.6
Mitotic forms	2.0	0.8
Maturity Dispersal Ratios		
Granuloblast		
Myeloblasts	3.9	1.7
Promyelocytes	18.4	8.6
Myelocytes	43.1	43.1
Juveniles	34.6	46.6
Erythroblast		
Pronormoblast	3.4	2.4
Normoblast - basophilic	56.4	19.5
" polychromatic and orthochromatic	40.2	78.1

Table XIII

Case 13. Male, aged 58 years, with signs of scurvy - follicular haemorrhages on legs, sponginess of gums, red cells in urine. Treatment:- One thousand milligrammes ascorbic acid intravenously on 14.iv and three hundred milligrammes ascorbic acid daily by mouth from 14.iv.

Date	5.iv	9.iv	14.iv
ASCORBIC ACID DETERMINATIONS			
Rotter's Test (time, minutes)	25		
Plasma ascorbic acid (mgms. per cent)	0.41		0.38
CAPILLARY FRAGILITY	65		60
BLOOD EXAMINATIONS			
Haemoglobin (%)	52	52	53
Colour Index	1.06	1.04	1.02
White Cell count (/cu.mm.)	6,000		
Schilling Count			
Basophils	0.8	-	-
Eosinophils	-	-	-
Myelocytes	-	-	-
Juveniles	-	0.25	0.75
Staffs	1.2	2.75	1.5
Segmented Neutrophils	36.4	37.25	41.25
Lymphocytes	56.0	52.0	50.0
Monocytes	5.6	7.75	6.5
Cooke Count - weighted mean.	3.2	3.0	3.1
Platelet Count (/cu.mm.)	400,000		

Table XIII (contd.)

Date	4.V	20.V	30.V
ASCORBIC ACID DETERMINATIONS			
Rotter's Test (time, minutes)		12	10
Plasma ascorbic acid (mgms. per cent)	0.60		1.5
CAPILLARY FRAGILITY		8	8
BLOOD EXAMINATIONS			
Haemoglobin (%)		99	100
Colour Index		1.1	1.06
White cell count (/cu.mm.)		5,400	6,600
Schilling Count			
Basophils		-	0.4
Eosinophils		2.0	0.4
Myelocytes		-	-
Juveniles		2.0	0.4
Staffs		10.0	4.6
Segmented Neutrophils		45.6	48.6
Lymphocytes		36.4	38.4
Monocytes		5.2	7.2
Cooke Count - weighted mean		2.7	2.8
Platelet Count (/cu.mm.)			

Table XIII (contd.)

Date	5.iv	4.v	30.v
BONE MARROW			
Cellularity			
Differential Count			
Myeloblasts	0.8	0.4	0.4
Promyelocytes	4.0	2.8	2.4
Neutrophil myelocytes	6.0	6.8	4.4
" juveniles	6.4	11.2	8.8
" staffs	6.0	6.8	2.0
" segmented	8.4	6.4	12.4
Eosinophil myelocytes	0.4	0.4	0.4
" segmented	0.8	0.4	0.4
Basophil myelocytes	0.4	0.4	0.4
" segmented	-	0.4	0.8
Lymphocytes	6.4	4.0	4.4
Monocytes	3.2	0.8	2.0
Plasma cells	2.0	2.0	0.8
Pronormoblasts	0.8	1.6	0.4
Normoblasts			
Basophilic	26.0	13.6	6.4
Polychromatic	26.0	40.0	39.6
Orthochromatic	2.4	2.0	4.0
Mitotic forms	1.6	2.0	0.4
Maturity Dispersal Ratios			
Granuloblast			
Myeloblasts	4.4	1.8	2.4
Promyelocytes	22.4	12.7	14.2
Myelocytes	37.8	34.5	30.9
Juveniles	35.4	51.0	52.4
Erythroblast			
Pronormoblast	1.4	2.7	0.8
Normoblast - basophilic	45.8	23.0	12.6
polychromatic and orthochromatic	52.8	74.3	86.6

Table XIV

Case 14. Female, aged 60 years. No sign of scurvy. No physical abnormality noted other than marked pallor, and moist sounds at lung bases.
Treatment:- Ferrous sulphate, gr. vi t.i.d., from 17.i to 1.ii and from 7.iii to 3.iv; ascorbic acid, one thousand milligrammes intravenously on 26.i, and three hundred milligrammes daily by mouth from 26.i, "Anahaemin", 4 c.c. intramuscularly on 14.ii; and four oranges daily from 22.iii

Date	17.i	26.i	26.ii
ASCORBIC ACID DETERMINATIONS			
Rotter's Test (time, minutes)		25	
Plasma ascorbic Acid (mgms. per cent)		0.4	
CAPILLARY FRAGILITY		40	48
BLOOD EXAMINATIONS			
Haemoglobin (%)	53	53	55
Colour Index	0.8	0.85	0.79
White cell count (/cu.mm.)	4,600	6,000	5,400
Schilling Count			
Basophils	0.5	0.5	-
Eosinophils	-	-	-
Myelocytes	-	-	-
Juveniles	0.25	1.0	1.0
Staffs	2.25	1.25	2.75
Segmented Neutrophils	46.0	39.25	36.5
Lymphocytes	41.0	48.5	46.25
Monocytes	10.0	9.5	13.5
Cooke Count - weighted mean	3.2	3.2	2.8
Platelet Count (/cu.mm.)		350,000	

Table XIV (contd.)

Date	28.ii	8.iii	14.iii
ASCORBIC ACID DETERMINATIONS			
Rotter's Test (time, minutes)	12		5
Plasma ascorbic acid (mgms. per cent)		0.7	
CAPILLARY FRAGILITY	30	8	10
BLOOD EXAMINATIONS			
Haemoglobin (%)	55	55	57
Colour Index	0.79	0.85	0.85
White cell count (/cu.mm.)	5,600		5,400
Schilling Count			
Basophils		0.5	1.0
Eosinophils		-	-
Myelocytes		0.25	-
Juveniles		2.75	-
Staffs		3.0	1.25
Segmented Neutrophils		43.75	38.5
Lymphocytes		41.25	40.0
Monocytes		8.0	15.0
Cooke Count - weighted mean		2.4	2.1

Table XIV (contd.)

Date	27.iii	3.iv
ASCORBIC ACID DETERMINATIONS		
Rotter's Test (time, minutes)		5
Plasma ascorbic acid (mgms. per cent.)		1.2
CAPILLARY FRAGILITY		7
BLOOD EXAMINATIONS		
Haemoglobin (%)	72	81
Colour Index	0.95	0.99
White cell count (/cu.mm.)	5,400	6,000
Schilling Count		
Basophils	-	
Eosinophils	-	
Myelocytes	-	
Juveniles	1.25	
Staffs	2.5	
Segmented Neutrophils	47.25	
Lymphocytes	40.25	
Monocytes	8.75	
Cooke Count - weighted mean	2.1	
Platelet Count (/cu.mm.)		400,000

Table XIV (contd.)

Date	16.i	8.iii	3.iv
BONE MARROW			
Cellularity			
Differential Count			
Myeloblasts	3.2	1.6	2.0
Promyelocytes	3.6	3.6	4.0
Neutrophil myelocytes	4.8	9.2	9.6
" juveniles	5.6	8.6	11.4
" staffs	14.0	18.8	14.0
" segmented	17.2	13.2	14.4
Eosinophil myelocytes	-	-	-
" segmented	-	-	-
Basophil myelocytes	0.4	0.8	0.4
" segmented	-	-	-
Lymphocytes	4.0	5.2	5.6
Monocytes	2.4	2.4	2.8
Plasma cells	1.6	1.6	1.2
Pronormoblasts	2.8	1.6	2.0
Normoblasts			
Basophilic	19.2	5.2	4.0
Polychromatic	15.6	27.8	25.0
Orthochromatic	5.6	0.4	3.6
Mitotic forms	0.4	-	0.4
Maturity Dispersal Ratios			
Granuloblast			
Myeloblasts	18,2	6.7	6.6
Promyelocytes	20.4	15.1	13.1
Myelocytes	29.6	42.0	32.9
Juveniles	31.8	36.0	47.4
Erythroblast			
Pronormoblast	6.4	4.6	5.7
Normoblast - basophilic	44.1	32.0	11.4
polychromatic and orthochromatic	49.5	63.4	82.9

Table XV

Case 15. Male, aged 78 years. No sign of scurvy. Bedridden, mildly demented, arteriosclerotic.
Treatment:- One thousand milligrammes ascorbic acid intravenously on 25.v, and three hundred milligrammes daily by mouth from 25.v; four oranges daily from 17.vi

Date	25.v	29.v
ASCORBIC ACID DETERMINATIONS		
Rotter's Test (time, minutes)	20	18
Plasma ascorbic acid (mgms. per cent)	0.4	0.43
CAPILLARY FRAGILITY	56	59
BLOOD EXAMINATIONS		
Haemoglobin (%)	60	60
Colour Index	1.58	1.58
White cell count (/cu.mm.)	2,400	2,200
Schilling Count		
Basophils	-	1.25
Eosinophils	-	-
Myelocytes	-	-
Juveniles	0.5	0.5
Staffs	1.25	1.75
Segmented Neutrophils	49.75	50.75
Lymphocytes	41.5	30.0
Monocytes	7.0	5.25
Cooke Count - weighted mean	3.2	3.4
Platelet Count (/cu.mm.)		650,000

Table XV (contd.)

Date	17.vi	18.viii
ASCORBIC ACID DETERMINATIONS		
Rotter's Test (time, minutes)	14	6
Plasma ascorbic acid (mgms. per cent.)		1.5
CAPILLARY FRAGILITY	50	8
BLOOD EXAMINATIONS		
Haemoglobin (%)	61	88
Colour Index	1.49	1.3
White cell count (/cu.mm.)	2,900	4,400
Schilling Count		
Basophils	2.0	2.5
Eosinophils	0.5	0.75
Myelocytes	-	-
Juveniles	-	0.25
Staffs	2.5	3.0
Segmented Neutrophils	50.0	57.0
Lymphocytes	40.0	33.25
Monocytes	5.0	3.25
Cooke Count - weighted mean	3.2	2.8

Table XV (contd.)

Date	25.v	31.v
BONE MARROW		
Cellularity		
Differential Count		
Myeloblasts	2.8	0.3
Promyelocytes	6.8	4.6
Neutrophil myelocytes	11.2	12.3
" juveniles	6.4	11.0
" staffs	4.8	5.0
" segmented	6.0	5.0
Eosinophil myelocytes	-	-
" segmented	-	0.6
Basophil myelocytes	2.0	1.3
" segmented	2.0	1.6
Lymphocytes	0.8	2.0
Monocytes	-	3.4
Plasma cells	1.2	1.0
Pronormoblasts	1.6	1.3
Normoblasts		
Basophilic	25.2	21.6
Polychromatic	26.4	25.0
Orthochromatic	2.8	4.0
Mitotic forms	1.6	3.0
Maturity Dispersal Ratios		
Granuloblast		
Myeloblasts	9.6	1.0
Promyelocytes	23.1	15.6
Myelocytes	45.0	46.1
Juveniles	21.9	37.2
Erythroblast		
Pronormoblast	2.9	2.4
Normoblast - basophilic	45.0	37.5
polychromatic and orthochromatic	52.1	58.3

Table XV (contd.)

Date	18.vi	18.viii
BONE MARROW		
Cellularity		
Differential Count		
Myeloblasts	0.4	0.4
Promyelocytes	4.0	5.2
Neutrophil myelocytes	7.2	11.2
" juveniles	9.2	12.4
" staffs	9.6	8.0
" segmented	8.0	6.4
Eosinophil myelocytes	1.2	-
" segmented	-	-
Basophil myelocytes	-	0.4
" segmented	-	1.2
Lymphocytes	6.4	5.2
Monocytes	3.2	0.4
Plasma cells	3.6	1.2
Pronormoblasts	0.8	1.6
Normoblasts		
Basophilic	15.2	15.2
Polychromatic	26.8	26.8
Orthochromatic	4.4	4.4
Mitotic forms	1.2	0.4
Maturity Dispersal Ratios		
Granuloblast		
Myeloblast	1.9	1.4
Promyelocytes	18.9	17.6
Myelocytes	38.2	39.2
Juveniles	42.0	41.8
Erythroblast		
Pronormoblast	1.5	3.3
Normoblast - basophilic	35.6	31.4
polychromatic and orthochromatic	63.0	65.3

Table XVI

Case 16. Male, aged 71 years, with signs of scurvy - follicular haemorrhages and ecchymoses on legs, red cells in urine, oedema of ankles and legs, moist sounds at lung bases.
Treatment:- One thousand milligrammes ascorbic acid intravenously on 20.v, and three hundred milligrammes daily by mouth from 20.v; four oranges daily from 23.vi

Date	21.v	27.v	31.v
ASCORBIC ACID DETERMINATIONS			
Rotter's Test (time, minutes)	20		
Plasma ascorbic acid (mgms. per cent)	0.45	0.43	
CAPILLARY FRAGILITY	58		
BLOOD EXAMINATIONS			
Haemoglobin (%)	68	69	65
Colour Index	0.9	0.96	0.9
White cell count (/cu.mm.)	4,000	8,200	5,400
Schilling Count			
Basophils	1.5		1.0
Eosinophils	0.5	0.5	-
Myelocytes	-	-	-
Juveniles	0.5	0.5	0.5
Staffs	1.5	1.0	2.0
Segmented Neutrophils	57.0	51.0	46.0
Lymphocytes	34.0	40.5	41.5
Monocytes	5.0	6.0	9.0
Cooke Count - weighted mean	3.5	3.3	3.4
Platelet Count (/cu.mm.)	300,000		

Table XVI (contd.)

Date	17.vi	22.vi
ASCORBIC ACID DETERMINATIONS		
Rotter's Test (time, minutes)	15	
Plasma ascorbic acid (mgms. per cent.)		
CAPILLARY FRAGILITY	51	
BLOOD EXAMINATIONS		
Haemoglobin (%)	68	67
Colour Index	0.97	1.0
White cell count (/cu.mm.)	5,000	4,400
Schilling Count		
Basophils	1.0	0.75
Eosinophils	0.25	1.75
Myelocytes	-	-
Juveniles	0.25	0.5
Staffs	2.75	3.0
Segmented Neutrophils	41.25	49.5
Lymphocytes	47.75	37.0
Monocytes	7.75	7.5
Cooke Count - weighted mean	3.4	3.2

Table XVI (contd.)

Date	30.vi	20.viii
ASCORBIC ACID DETERMINATIONS		
Rotter's Test (time, minutes)		5
Plasma ascorbic acid (mgms. per cent.)	0.7	1.4
CAPILLARY FRAGILITY	50	11
BLOOD EXAMINATIONS		
Haemoglobin (%)	70	88
Colour Index	0.99	0.98
White cell count (/cu.mm.)	5,200	5,600
Schilling Count		
Basophils	0.75	0.75
Eosinophils	0.75	1.75
Myelocytes	-	-
Juveniles	0.25	1.25
Staffs	3.75	4.0
Segmented Neutrophils	48.5	50.25
Lymphocytes	38.75	35.5
Monocytes	8.25	6.5
Cooke Count - weighted mean	3.1	2.6

Table XVI (contd.)

Date	21.v	27.v
BONE MARROW		
Cellularity		
Differential Count		
Myeloblasts	0.8	0.4
Promyelocytes	5.2	4.4
Neutrophil myelocytes	12.8	13.8
" juveniles	14.4	13.2
" staffs	5.2	8.0
" segmented	17.2	17.2
Eosinophil myelocytes	-	-
" segmented	1.2	0.4
Basophil myelocytes	0.4	0.4
" segmented	0.4	1.6
Lymphocytes	8.0	6.8
Monocytes	2.4	0.8
Plasma cells	1.2	1.6
Pronormoblasts	0.8	-
Normoblasts		
Basophilic	8.4	6.4
Polychromatic	20.4	24.8
Orthochromatic	1.2	0.4
Mitotic forms	-	0.4
Maturity Dispersal Ratios		
Granuloblast		
Myeloblasts	2.4	1.3
Promyelocytes	15.5	13.7
Myelocytes	39.1	43.7
Juveniles	43.0	41.3
Erythroblast		
Pronormoblast	2.6	-
Normoblast - basophilic	27.3	20.0
polychromatic and orthochromatic)	70.1	80.0

Table XVI (contd.)

Date	31.v	17.vi	20.viii
BONE MARROW			
Cellularity			
Differential Count			
Myeloblasts	0.4	-	0.8
Promyelocytes	4.4	4.4	4.0
Neutrophil myelocytes	14.8	9.2	8.0
" juveniles	14.0	14.8	10.4
" staffs	6.0	5.6	16.0
" segmented	12.0	15.2	18.0
Eosinophil myelocytes	0.4	-	-
" segmented	0.4	0.8	-
Basophil myelocytes	0.8	0.4	0.4
" segmented	-	1.2	-
Lymphocytes	6.4	8.0	7.6
Monocytes	0.4	1.2	1.2
Plasma cells	0.8	0.8	1.6
Pronormoblasts	-	0.8	0.8
Normoblasts			
Basophilic	10.0	8.0	3.6
Polychromatic	27.6	28.4	26.0
Orthochromatic	2.0	1.2	1.6
Mitotic forms	-	0.4	-
Maturity Dispersal Ratios			
Granuloblast			
Myeloblasts	1.2	-	3.4
Promyelocytes	12.8	15.2	16.9
Myelocytes	45.3	33.4	35.6
Juveniles	40.7	51.4	44.1
Erythroblast			
Pronormoblast	-	2.1	2.5
Normoblast - basophilic	25.3	20.6	11.2
polychromatic and orthochromatic	74.7	77.3	86.3

Table XVII

Case 17. Female aged 43 years, with signs of scurvy - follicular haemorrhages on legs, extensive ecchymosis on legs and thighs, red cells in urine, sponginess of gums, moist sounds at lung bases.
Treatment:- Hespiridin, forty milligrammes intravenously daily from 7.ix to 14. ix and from 21.ix to 6.x; ascorbic acid, one thousand milligrammes intravenously on 14.ix, and three hundred milligrammes daily by mouth from 14.ix.

Date	I.ix	7.ix	10.ix
ASCORBIC ACID DETERMINATIONS			
Rotter's Test (time, minutes)	35		
Plasma ascorbic acid (mgms. per cent.)	0.4		
CAPILLARY FRAGILITY	45	53	
BLOOD EXAMINATIONS			
Haemoglobin (%)	53	46	41
Colour Index	0.95	1.01	1.1
White cell count (/cu.mm.)	7,400	6,800	2,800
Schilling Count			
Basophils	1.5		3.5
Eosinophils	0.75		-
Myelocytes	-		0.25
Juveniles	-		2.25
Staffs	-		3.75
Segmented Neutrophils	50.5		56.0
Lymphocytes	38.25		24.5
Monocytes	9.0		9.75
Cooke Count - weighted mean	3.3		2.9
Platelet Count (/cu.mm.)			600,000

Table XVII (contd.)

Date	12.ix	14.ix	17.ix
ASCORBIC ACID DETERMINATIONS			
Rotter's Test (time, minutes)	38		
Plasma ascorbic acid (mgms. per cent.)		0.35	
CAPILLARY FRAGILITY		3	
BLOOD EXAMINATIONS			
Haemoglobin (%)	43	40	46
Colour Index	1.0	1.06	1.08
White cell count (/cu.mm.)	2,600	3,800	2,600
Schilling Count			
Basophils	1.75	0.75	2.25
Eosinophils	0.25	2.0	0.25
Myelocytes	0.25	-	-
Juveniles	1.75	1.0	1.25
Staffs	2.75	0.75	2.5
Segmented Neutrophils	44.0	33.5	48.75
Lymphocytes	36.75	45.25	31.25
Monocytes	13.5	16.75	9.5
Cooke Count - weighted mean	2.8	2.7	2.8

Table XVII (contd.)

Date	21.ix	23.ix	17.x
ASCORBIC ACID DETERMINATIONS			
Rotter's Test (time, minutes)			6
Plasma ascorbic acid (mgms. per cent.)			1.6
CAPILLARY FRAGILITY	15		2
BLOOD EXAMINATIONS			
Haemoglobin (%)	37	48	86
Colour Index	1.0	0.99	0.92
White cell count (/cu.mm.)	4,000	4,200	5,000
Schilling Count			
Basophils	0.5	2.0	
Eosinophils	-	1.5	
Myelocytes	0.25	-	
Juveniles	3.25	1.0	
Staffs	2.5	1.5	
Segmented Neutrophils	43.75	49.5	
Lymphocytes	40.25	40.0	
Monocytes	4.5	4.5	
Cooke Count - weighted mean	2.7	2.7	

Table XVII (contd.)

Date	1.ix	17.ix
BONE MARROW		
Cellularity		
Differential Count		
Myeloblasts	0.4	0.4
Promyelocytes	10.8	6.8
Neutrophil myelocytes	13.2	13.2
" juveniles	12.0	12.8
" staffs	3.2	3.6
" segmented	4.0	6.4
Eosinophil myelocytes	0.8	0.8
" segmented	2.8	0.4
Basophil myelocytes	0.4	-
" segmented	-	-
Lymphocytes	5.6	1.2
Monocytes	1.2	0.4
Plasma cells	1.2	1.2
Pronormoblasts	1.2	0.8
Normoblasts		
Basophilic	22.0	28.0
Polychromatic	21.2	24.0
Orthochromatic	-	-
Mitotic forms	0.8	0.4
Maturity Dispersal Ratios		
Granuloblast		
Myeloblast	1.1	1.2
Promyelocytes	28.8	20.0
Myelocytes	38.2	41.2
Juveniles	31.9	37.6
Erythroblast		
Pronormoblast	2.7	1.5
Normoblast - basophilic	48.9	52.6
polychromatic and orthochromatic	48.4	45.9

Table XVIII (contd.)

Date	23.ix	29.ix
BONE MARROW		
Cellularity		
Differential Count		
Myeloblasts	1.2	0.4
Promyelocytes	4.0	9.2
Neutrophil myelocytes	9.6	10.0
" juveniles	10.8	12.0
" staffs	6.0	13.2
" segmented	5.2	10.0
Eosinophil myelocytes	0.4	0.4
" segmented	0.8	-
Basophil myelocytes	-	1.6
" segmented	-	1.6
Lymphocytes	5.2	2.8
Monocytes	2.0	0.8
Plasma cells	0.4	0.8
Pronormoblasts	0.4	0.4
Normoblasts		
Basophilic	11.2	6.0
Polychromatic	35.6	30.0
Orthochromatic	7.2	0.8
Mitotic forms	-	0.4
Maturity Dispersal Ratios		
Granuloblast		
Myeloblasts	4.6	1.2
Promyelocytes	15.4	27.6
Myelocytes	38.4	35.0
Juveniles	41.6	36.2
Erythroblast		
Pronormoblast	0.7	1.1
Normoblast - basophilic	20.6	16.0
polychromatic and orthochromatic	78.9	82.9

Table XVIII

Two cases of scurvy associated with rheumatoid arthritis. Effects of antiscorbutic treatment not recorded

Case	18	19
ASCORBIC ACID DETERMINATIONS		
Rotter's Test (time, minutes)	35	23
Plasma ascorbic acid (mgms. per cent.)	0.3	0.4
CAPILLARY FRAGILITY	55	62
BLOOD EXAMINATIONS		
Haemoglobin (%)	65	60
Colour Index	0.9	1.05
White cell count (/cu.mm.)	5,600	7,200
Schilling Count		
Basophils	-	-
Eosinophils	0.25	-
Myelocytes	-	-
Juveniles	0.5	0.4
Staffs	1.5	1.8
Segmented neutrophils	55.0	41.0
Lymphocytes	35.0	48.2
Monocytes	7.75	8.6
Cooke Count - weighted mean	3.4	3.2
Platelet Count (/cu.mm.)	450,000	540,000

Table XVIII (contd.)

Case	18	19
BONE MARROW		
Cellularity		
Differential Count		
Myeloblasts	1.6	0.8
Promyelocytes	3.6	4.0
Neutrophil myelocytes	6.0	6.0
" juveniles	8.4	8.8
" staffs	14.0	12.4
" segmented	16.4	18.4
Eosinophil myelocytes	-	-
" segmented	0.8	-
Basophil myelocytes	-	0.8
" segmented	0.8	-
Lymphocytes	7.2	6.4
Monocytes	2.4	3.6
Plasma cells	0.8	0.8
Pronormoblasts	3.2	2.8
Normoblasts		
Basophilic	19.2	7.6
Polychromatic	11.2	23.2
Orthochromatic	2.8	4.4
Mitotic forms	1.6	2.0
Maturity Dispersal Ratios		
Granuloblast		
Myeloblasts	8.2	3.9
Promyelocytes	18.6	19.6
Myelocytes	30.6	33.3
Juveniles	42.6	43.2
Erythroblast		
Pronormoblast	8.4	7.5
Normoblast - basophilic	53.6	19.7
polychromatic and orthochromatic	38.0	72.8

Table XIX (contd.)

Two cases of scurvy associated with duodenal ulceration, with history of haematemeses and melaena.
Effects of antiscorbutic treatment not recorded.

Case	20	21
ASCORBIC ACID DETERMINATIONS		
Rotter's Test (time, minutes)	30	25
Plasma ascorbic acid (mgms. per cent.)	0.3	0.35
CAPILLARY FRAGILITY	5	9
BLOOD EXAMINATIONS		
Haemoglobin (%)	50	62
Colour Index	0.75	0.8
White cell count (/cu.mm.)	8,400	7,600
Schilling Count		
Basophils	-	-
Eosinophils	0.5	-
Myelocytes	-	-
Juveniles	0.5	-
Staffs	1.75	1.75
Segmented neutrophils	31.25	40.0
Lymphocytes	46.0	50.75
Monocytes	10.0	7.25
Cooke Count - weighted mean	3.0	3.1
Platelet Count (/cu.mm.)	350,000	580,000

Table XIX (contd.)

Case	20	21
BONE MARROW		
Cellularity		
Differential Count		
Myeloblasts	0.8	-
Promyelocytes	6.0	2.0
Neutrophil myelocytes	10.4	14.0
" juveniles	12.0	16.4
" staffs	9.6	10.4
" segmented	10.4	12.0
Eosinophil myelocytes	-	-
" segmented	-	-
Basophil myelocytes	1.6	-
" segmented	-	-
Lymphocytes	6.4	8.8
Monocytes	3.2	1.6
Plasma cells	0.4	0.8
Pronormoblasts	2.0	1.2
Normoblasts		
Basophilic	9.6	11.2
Polychromatic	18.0	20.0
Orthochromatic	9.6	1.6
Mitotic forms	1.2	1.6
Maturity Dispersal Ratios		
Granuloblast		
Myeloblasts	2.6	-
Promyelocytes	19.4	6.2
Myelocytes	39.0	43.2
Juveniles	39.0	50.6
Erythroblast		
Pronormoblast	4.8	4.3
Normoblast - basophilic	24.3	32.5
polychromatic and orthochromatic	70.9	63.2

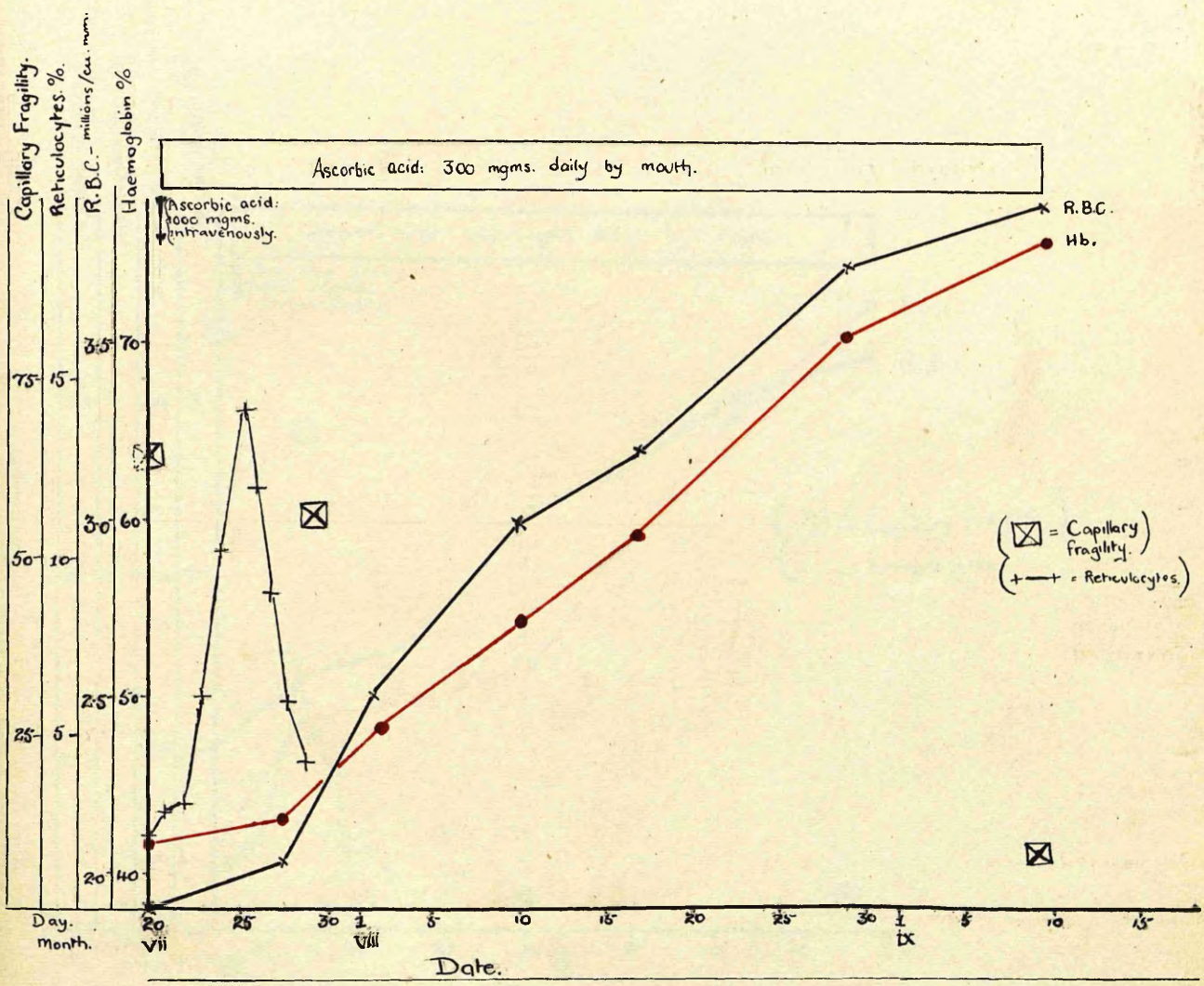

FIGURE I.

Blood chart, case 7; showing reticulocyte response, rise in red cells and haemoglobin, and fall in capillary fragility, on administration of ascorbic acid.

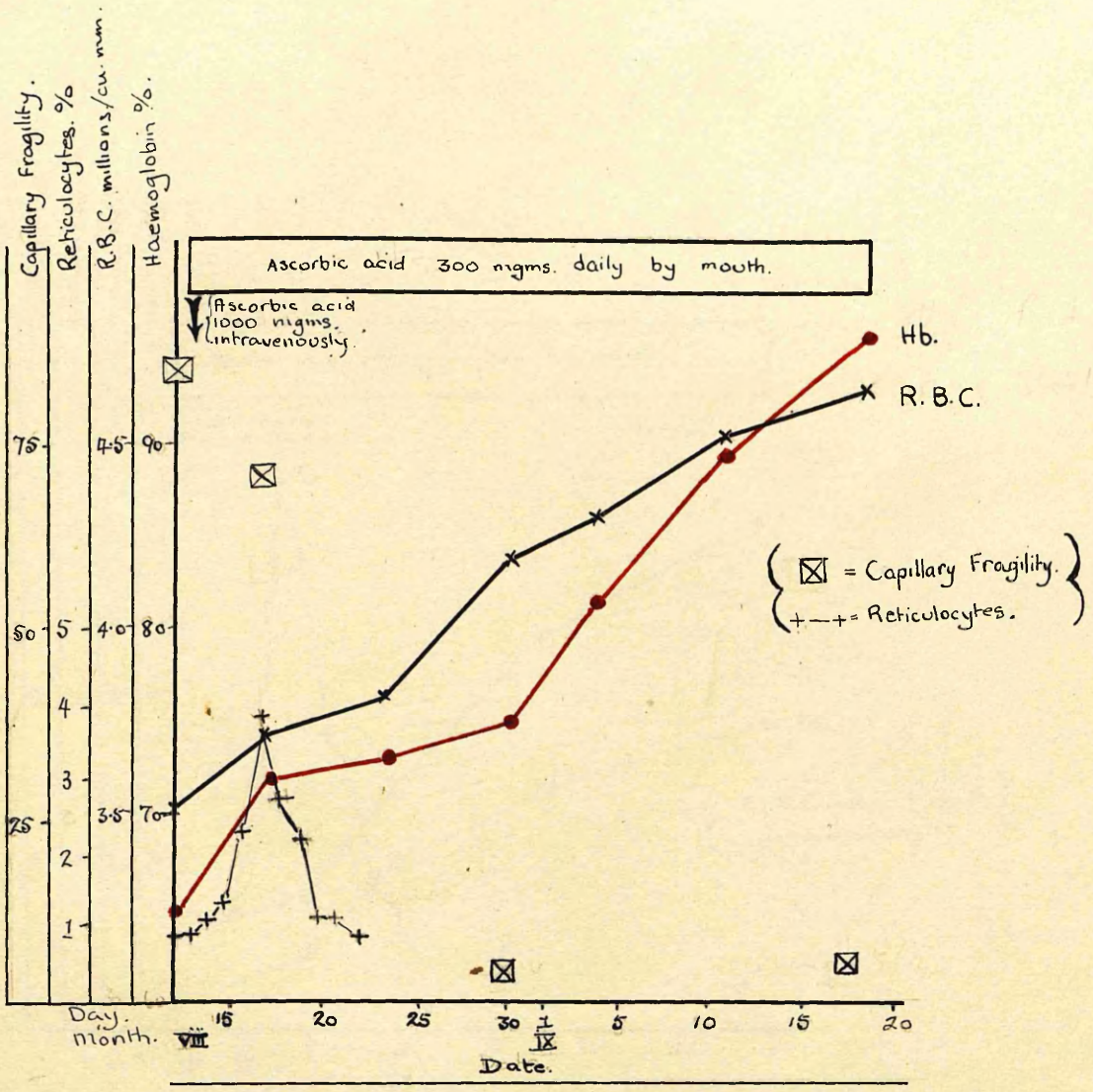

FIGURE II.

Blood chart, case 8; showing reticulocyte response, rise in red cells and haemoglobin, and fall in capillary fragility, on administration of ascorbic acid.

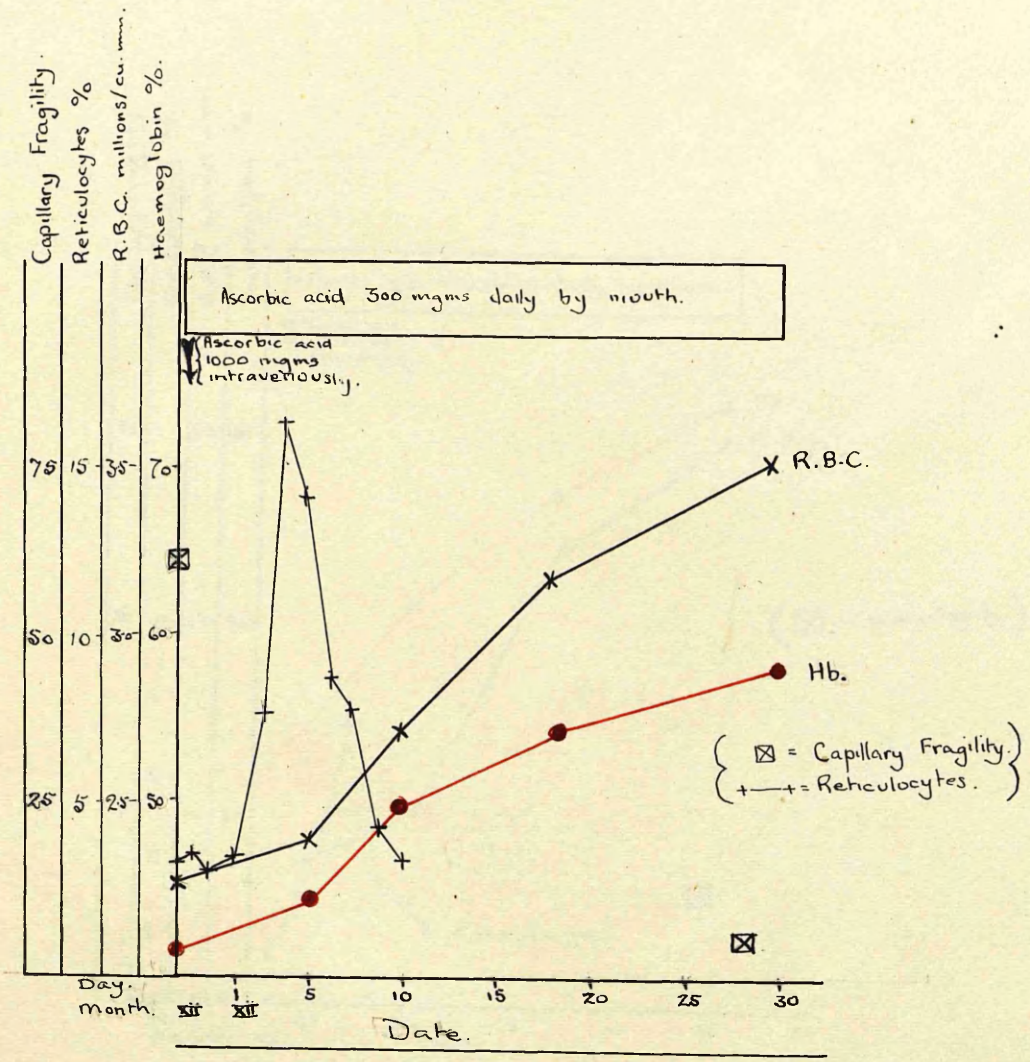

FIGURE III.

Blood chart, case 9; showing reticulocyte response, rise in red cells and haemoglobin, and fall in capillary fragility, on administration of ascorbic acid.

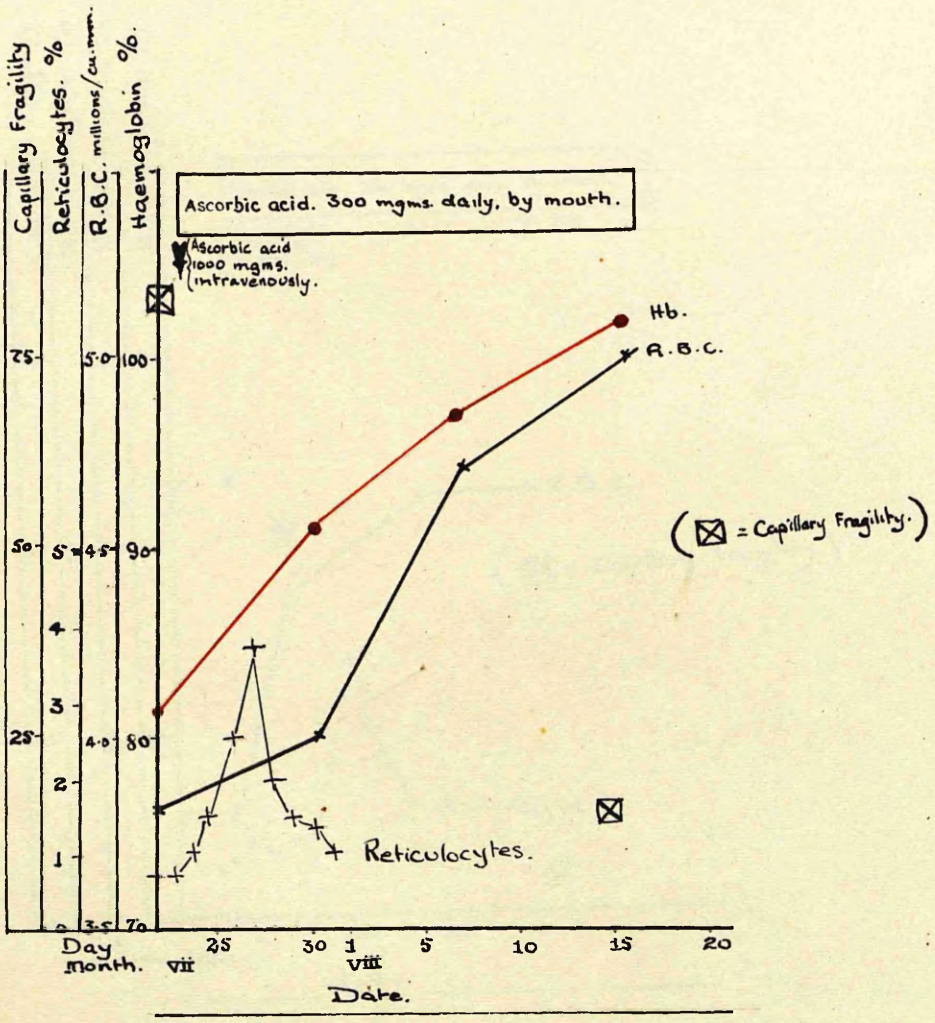

FIGURE IV.

Blood chart, case 10; showing reticulocyte response, rise in red cells and haemoglobin, and fall in capillary fragility, on administration of ascorbic acid.

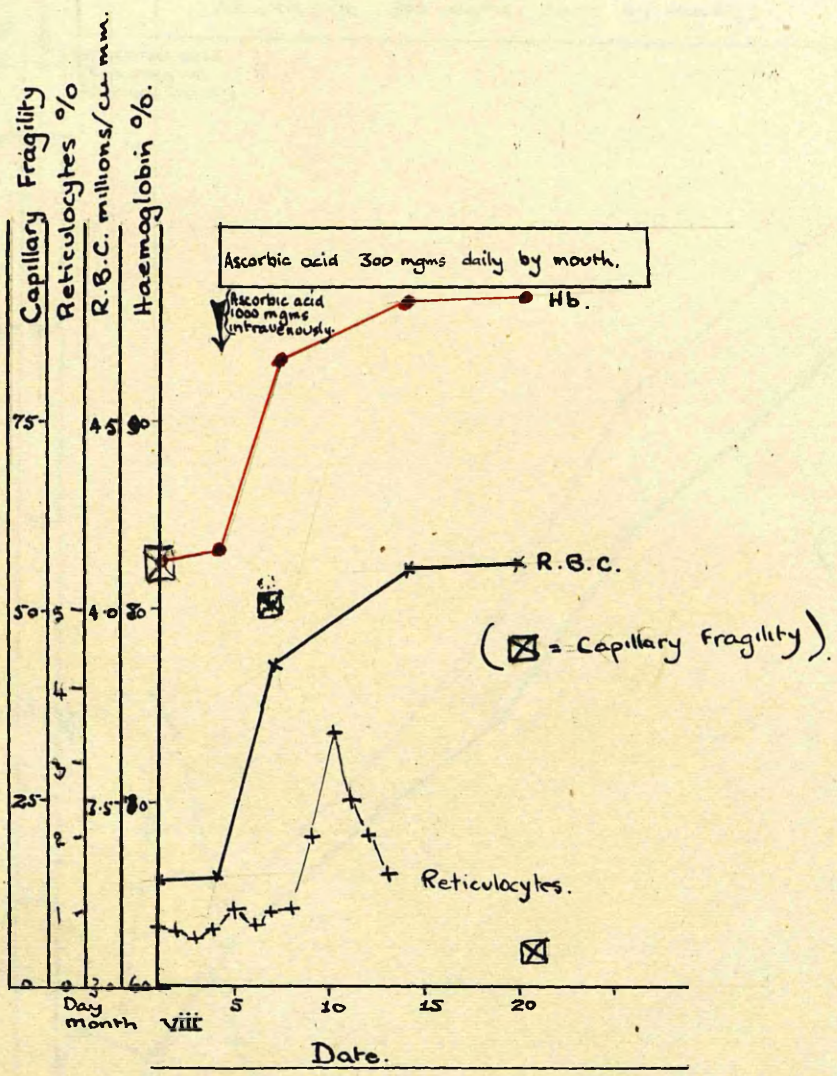

FIGURE V.

Blood chart, case 11; showing reticulocyte response, rise in red cells and haemoglobin, and fall in capillary fragility, on administration of ascorbic acid.

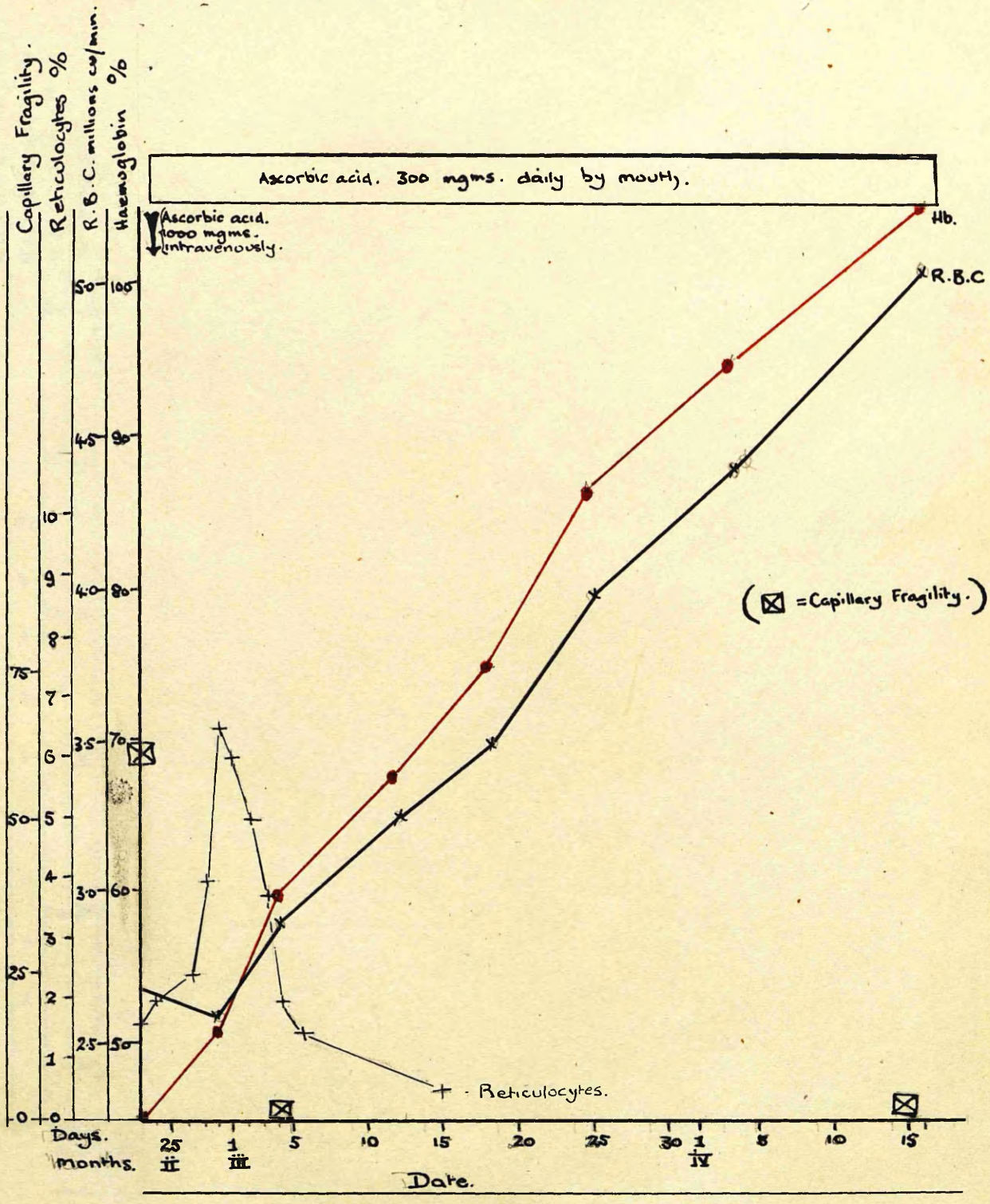

FIGURE VI.

Blood chart, case 12; showing reticulocyte response, rise in red cells and haemoglobin, and fall in capillary fragility, on administration of ascorbic acid.

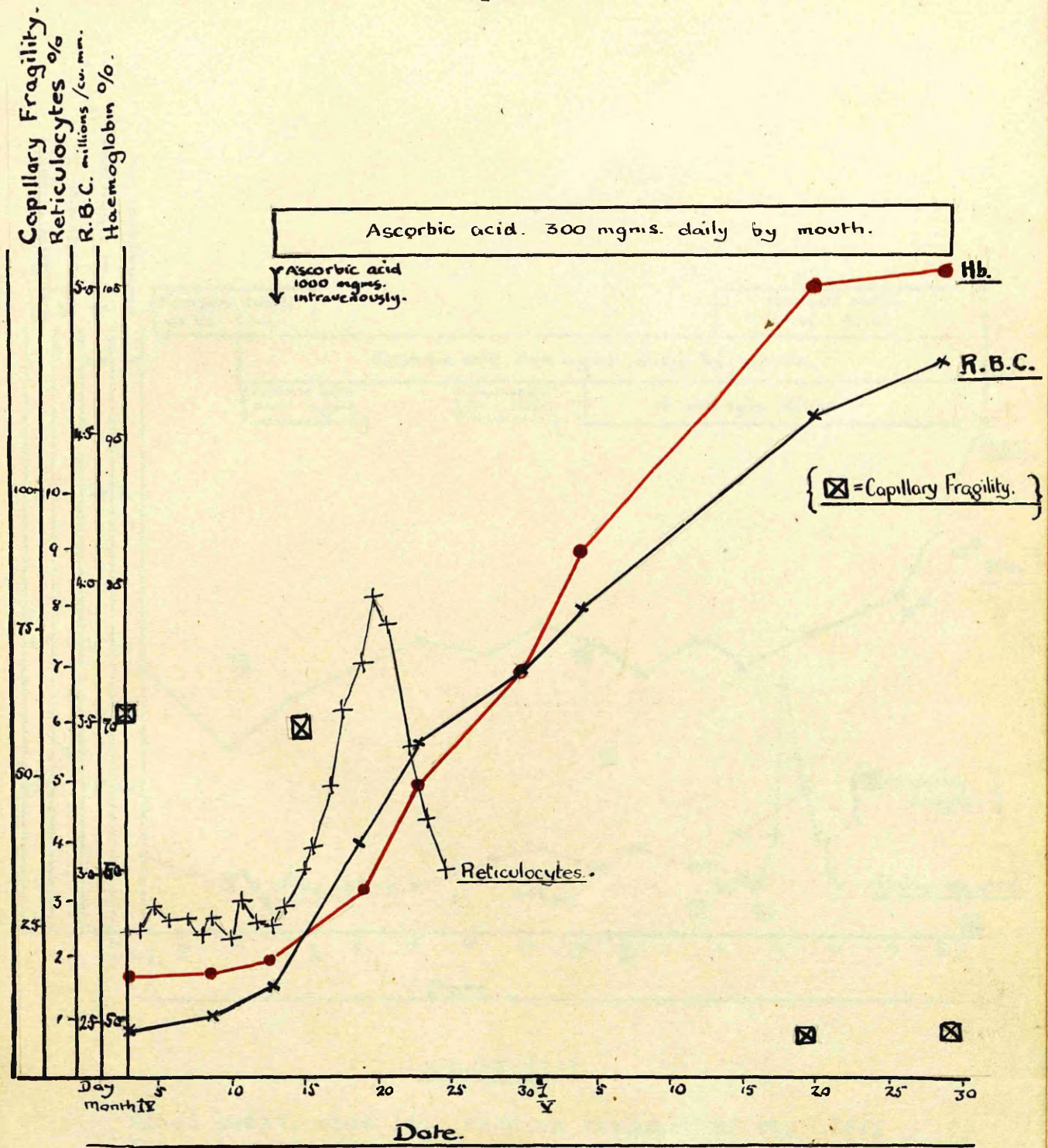

FIGURE VII.

Blood chart, case 13; showing reticulocyte response, rise in red cells and haemoglobin, and fall in capillary fragility, on administration of ascorbic acid.

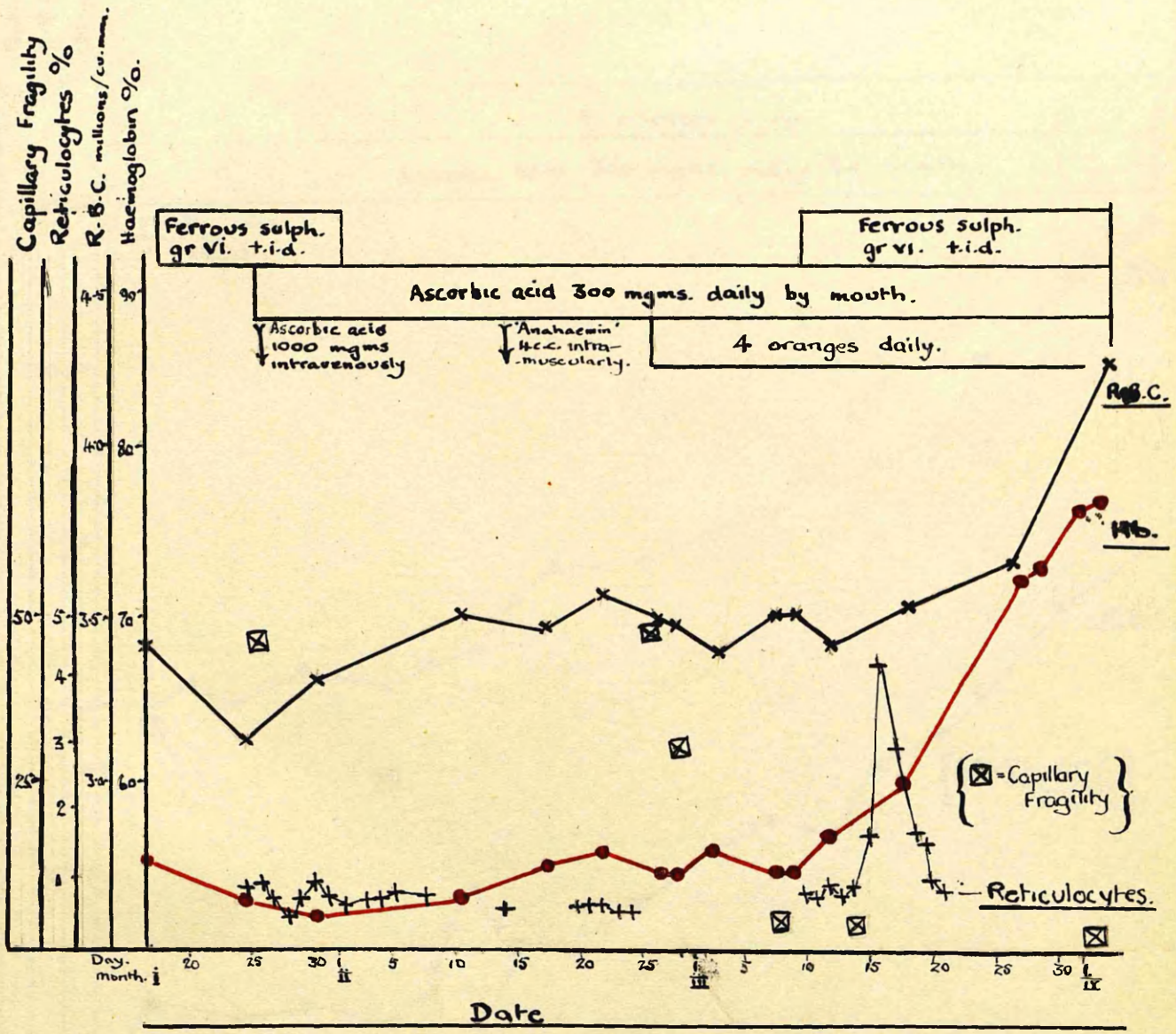

FIGURE VIII.

Blood chart, case 14; showing response of capillary fragility to administration of oranges and lack of response to ascorbic acid, ultimate response to iron with initial absence of such response associated with high capillary fragility (and low ascorbic acid values not shown here).

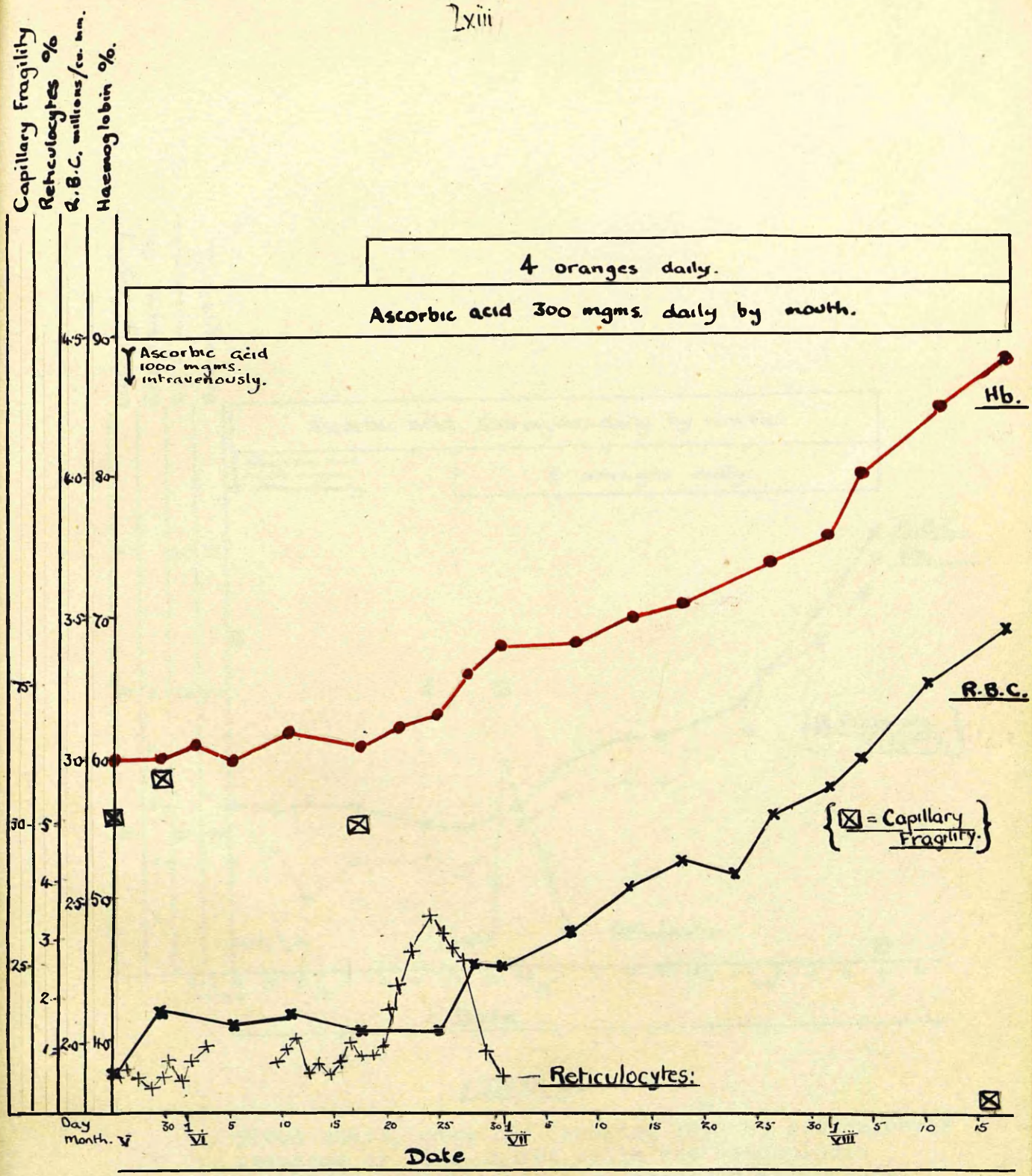

FIGURE IX.

Blood chart, case 15; showing lack of reticulocyte response and indefinite response of red cells and haemoglobin to ascorbic acid alone; reticulocyte response and rise in red cells and haemoglobin following addition of oranges.

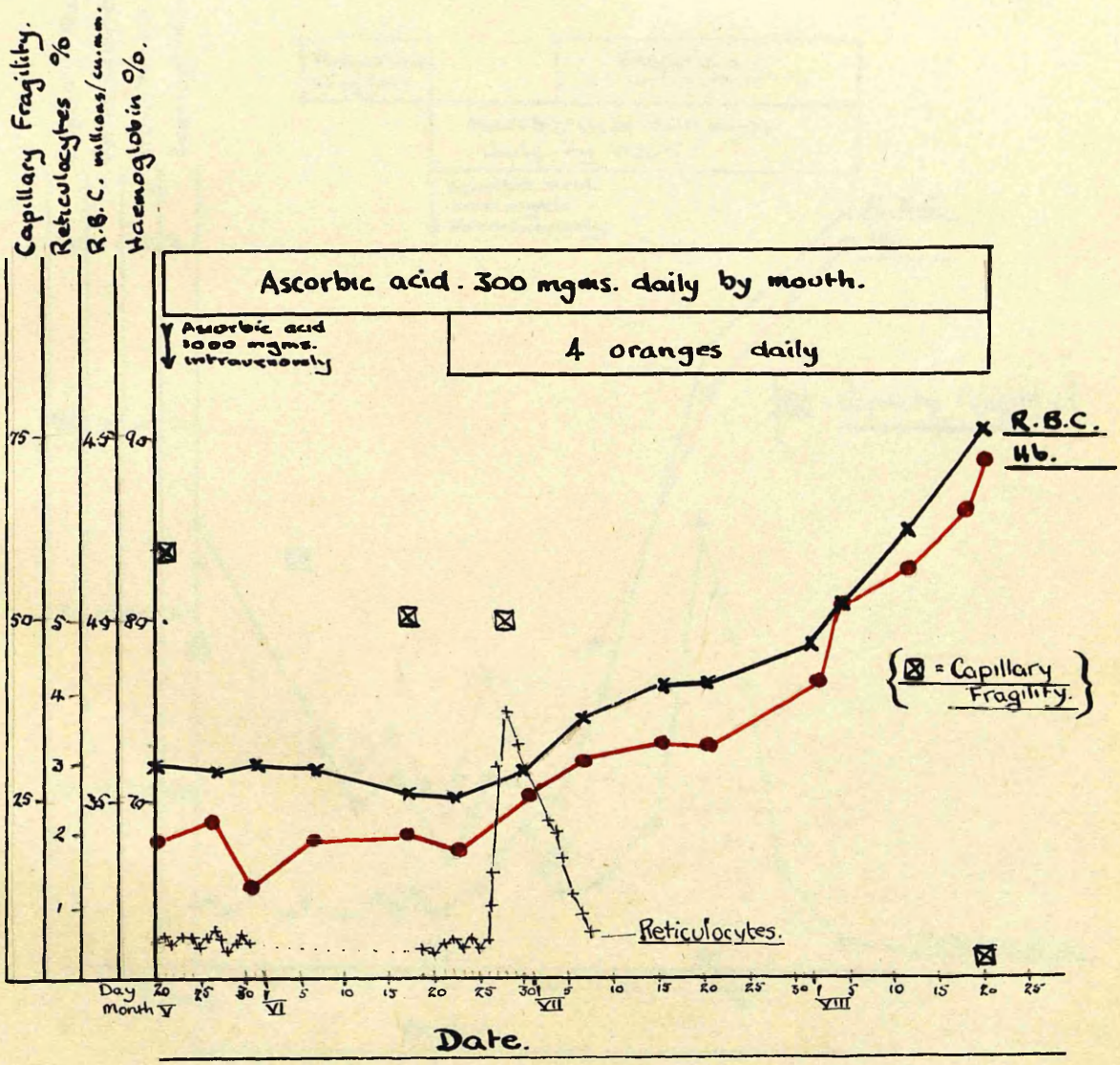

FIGURE X.

Blood chart, case 16; showing lack of reticulocyte response or rise in red cells and haemoglobin following administration of ascorbic acid alone; reticulocyte response and rise in red cells and haemoglobin following addition of oranges.

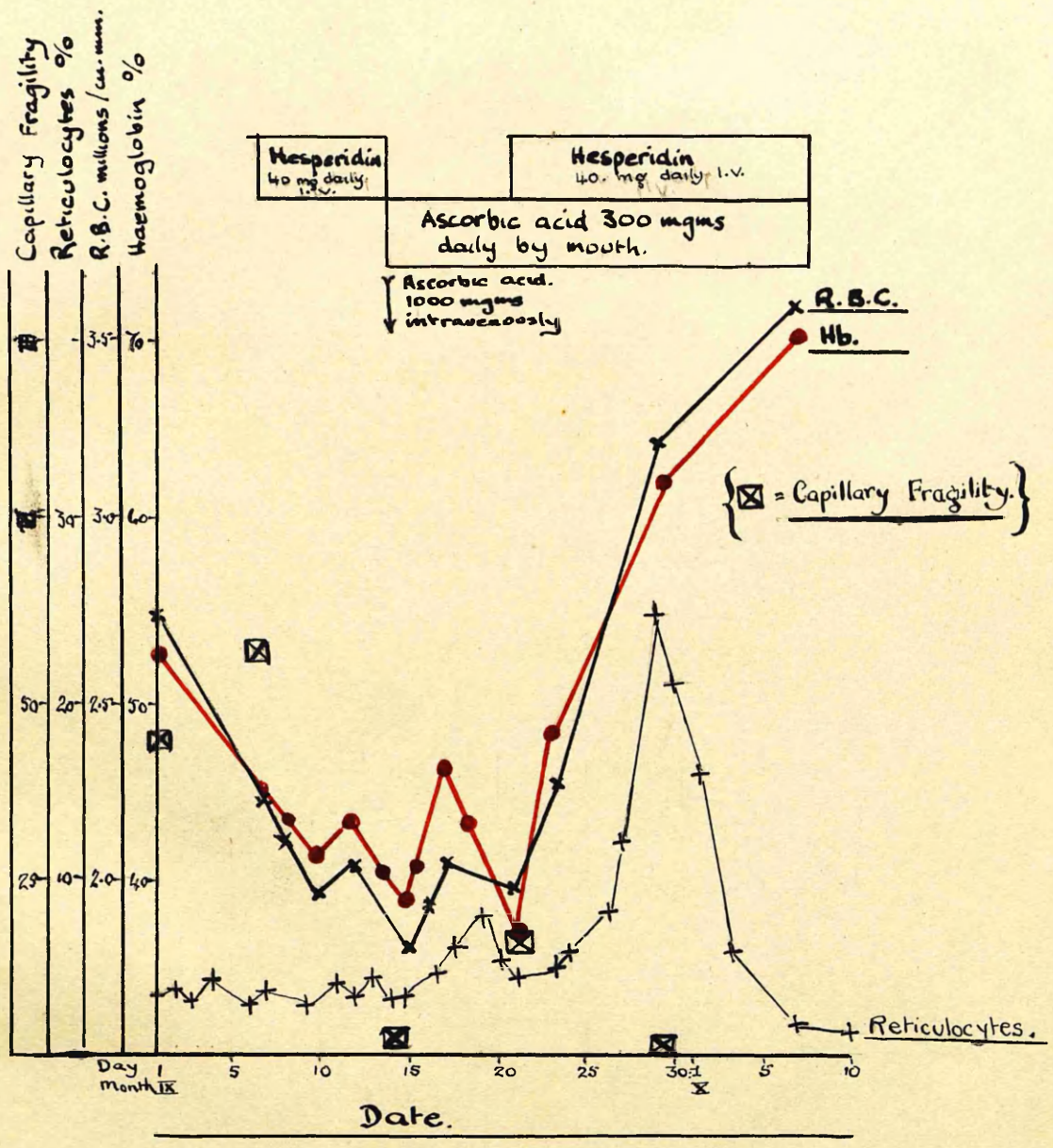

FIGURE XI.

Blood chart, case 17; showing reticulocyte response and rise in red cells and haemoglobin during the administration of hesperidin and ascorbic acid concurrently, with absence of such response to either when administered separately.