THE BLOOD PLATELET.

A clinical study and review of the literature,

being a

THESIS

submitted for the Degree of M.D.

by

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PREFACE.

Most of the literature dealing with the blood platelet is scattered throughout the journals and periodicals of a number of countries. I have attempted to review the subject and interpret the results of others in the light of my own observations, in so far as that is possible, in an effort to give some idea of the place of the blood platelet in Medicine. In order to keep the text free from the names of too many authors acknowledgment of much of the work has been made by means of numbers. I accept responsibility where any interpretation has been put on the work of others, other than that intended by them.

My own investigations were carried out in Professor W.K. Hunter's wards at the Royal Infirmary, Glasgow. With the exception of four, all the cases were treated in these wards. Cases 2, 3 and 6 attended my dispensary at the Royal Infirmary and case 13 was a private patient. The diagnosis made in each case is mine.

For convenience in referring to the case notes and charts the appendix has been bound separately.

I have pleasure in acknowledging my indebtedness to Professor W.K. Hunter for the unlimited freedom he gave me to investigate the cases under his care and I have to thank him also for his help in obtaining access to a number of papers to which I should otherwise have been unable to make reference.

My thanks are due also to Dr. A.B. McLean for information received regarding the dosage of deep X-ray therapy given to cases 10, 11, 12, 13 and 15, and also to Mr. James Taylor for permission to follow up cases 18 and 33 after they were transferred to his wards for operative treatment.

W. Mackay.

GLASGOW, June, 1930.

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INTRODUCTION.

It seems to be generally admitted that mammalian blood platelets were first seen by Donné* who, in the decade previous to 1850, called them "globulins". About that time the presence in the blood of what is now recognised as the blood platelet was also observed by Arnold* in Germany. Some 30 years later the great French hæmatologist, Hayem, thinking that they were the precursors of red blood corpuscles, named them "hématoblastes". It is to Bizzozero[43] that we owe the name "blood platelets". Because the spindle cells of amphibia and other lower animals have been regarded as corresponding to the blood platelets of mammals the platelets have also been designated "thrombocytes". In the following pages the terms "blood platelet", "platelet", and "thrombocyte" are regarded as being synonymous and will be used without discrimination.

The existence of the mammalian blood platelet as a third morphological element in the blood has been repeatedly affirmed and denied. In this country the thrombocyte has been treated with scant attention until comparatively recent years. Prominent amongst modern authors who oppose the idea that the platelet is a preformed element in the blood are Buckmaster[52] and Mathews[157], both of whom believe that the thrombocyte is

* Cited by Degkwitz.[72]

merely a precipitate formed in the altered blood plasma when it is exposed to pathological conditions, as when it is shed and coagulation occurs or when, while in the circulation, it is brought into contact with injured endothelial surfaces and foreign bodies. Marino[156] failed to observe the presence of blood platelets when blood was allowed to flow directly into absolute alcohol. In contradistinction to these observations Roskam[195] showed that the particles making up the precipitate obtained by cooling incoagulable peptone plasma, after rendering it free from all formed elements by centrifuging, bore no resemblance to blood platelets in shape,size, grouping, refraction, and staining reaction. Downey[76] observed that 100% alcohol really distorted the platelets in such a way that, though they were present, they were difficult to demonstrate. Further, Bedson[30] showed that the specific behaviour of precipitating (anti-serum) serum and of anti-fibrinogen serum, in that they had no action on the thrombocytes, definitely disposed of the theory that the platelet was a precipitate formed from the plasma proteins.

On the whole the evidence in favour of the thrombocyte being a product of altered blood plasma is not convincing and it is now almost universally accepted that the platelet is a constant preformed element of normal healthy blood. There is much to be said in support of this view.

In 1882, Bizzozero[43] actually saw the platelets and described their morphological characteristics as they appeared in the blood circulating in the mesenteric vessels of rabbits and guinea pigs and since then, his observations have been confirmed by others, notably by Eberth and Schimmelbusch.[84] Evidence that they are independent elements of the blood is also afforded by the

following findings:- They are present in the blood of all mammals in numbers which are constant within certain limits;[72,76] in health and disease their numbers fluctuate independently of the erythrocytes and leucocytes as shown by many of the graphs to be found in the appendix to this work; in health they are approximately uniform in size, shape, structure and staining reaction; also in view of the now well-known fact that platelets act as a specific antigen, the specific action of anti-platelet serum in producing a thrombocytopenia affords very strong evidence of their being separate elements of the blood.*

The case for the existence of the blood platelet is further strengthened if a survey is made of the blood cells of the lower animals. In birds, frogs, reptiles, other non-mammalian vertebrates and many invertebrates no platelets exist in the form met with in mammals, yet there are to be found nucleated cells - thrombocytes, spindle cells or explosive corpuscles - which have many characteristics, morphological and functional, in common with the mammalian blood platelet.** Their cytoplasm is hyaline and under abnormal conditions disintegrates with extreme rapidity, they adhere firmly to foreign bodies and agglutinate readily in shed and circulating blood and they are preserved by the fluids and greasy surfaces which also preserve mammalian platelets. In addition they participate in the formation of white thrombi and are intimately associated with the process of coagulation, and further, an anti-serum prepared against the bird thrombocyte produces a thrombocytopenia in much the same way as anti-platelet serum does in mammals.[133]

* References 33, 34, 64, 131, 138, 143, 144 & 156.
** References 2, 23, 43, 184, 185, 208, 209, 210, 212 & 213.

The fact that the thrombocyte in the lower animals is nucleated is not necessarily an argument against the existence of corresponding elements in man for it is well known that the human red corpuscle is non-nucleated while that of animals lower in the evolutionary scale is nucleated. A parallelism would thus appear to exist between the erythrocyte and the blood platelet, as the consensus of opinion declares that the mammalian platelet is without a nucleus. In this connection however, it should be mentioned that Bedson and Johnston[36] in studying the blood formation in the embryos of rabbits and guinea pigs could not produce any evidence supporting the view that the platelet in these animals had a nucleated precursor. Wright[123] thought that the platelet of lower animals was rather the homologue of the mammalian megakaryocyte from which, according to him, the platelet had its origin.

However the findings of these workers do not detract from the value of the indirect evidence afforded by the presence of these highly distinctive and easily discerned nucleated cells in the blood of lower animals as suggestive proof of the existence of a third morphological element in the circulating blood of mammals, namely, the blood platelet.

The question as to whether the blood platelet is a living element has given rise to a certain amount of speculation and research. It may be said at the outset that despite the work which has been done to elucidate this problem no conclusive evidence has been forthcoming. Achard and Aynaud[3] described certain movements and alteration in form which the platelet underwent in suitable preserving solutions when it was exposed to temperatures which were neither too high nor too low to kill it.

In addition to extremes of temperature they found that various protoplasmic poisons such as ether, chloroform, cocaine chloral-hydrate, quinine and potassium cyanide acted on and modified the form and motility. These observers never at any time noted true amoeboid movement and they never saw division or multiplication of platelets.

Further evidence of vital activity in blood platelets is suggested by the observation that, when suspended in plasma and preserving solutions at body temperatures, they decolorise dilute methylene blue solution, the colour reappearing however, when the suspension is shaken.[6] Under similar conditions the platelet can also absorb neutral red, the dye being taken into the interior of the element and not simply deposited on its surface.[8] These two actions are abolished by heating to 42 or 43 degrees C., cooling to freezing point, by the addition of sodium fluoride to the solution, and in the case of methylene blue, by quinine. Age and injury also render the thrombocytes ineffective. Achard and Aynaud thought that the motility, the ability to bring about alteration in form, and the properties of decolorisation and absorption shown by the platelets, all of which phenomena can be modified or abolished by agents which inhibit or destroy vital activity, argued in favour of the viability of these elements.

The above observations do not definitely establish the living nature of the platelet but they are highly suggestive. While that is so, and in spite of the fact that Warburg[215] produced some data to show that blood platelets respire oxygen, there is no very convincing proof of the presence of metabolic activity within these elements. Roskam[195] thought it necessary to find the respiratory quotient before the vitality of the platelet could be definitely established.

PLATELET MORPHOLOGY IN HEALTH AND DISEASE.

A well-known characteristic of the thrombocyte is the rapidity with which it loses its form and shape in shed blood. In order to keep it morphologically intact and to preserve it from immediate disintegration it is necessary to examine it in suspension in media such as the following:-

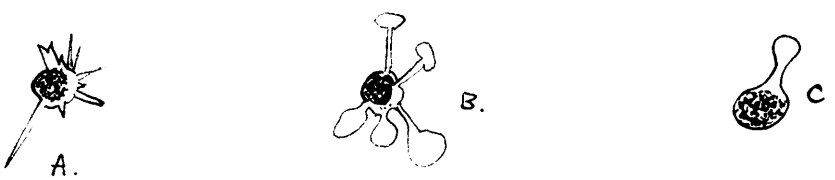
2% solution of sodium citrate made up in 0.29% solution of sodium chloride,

or, 2% to 5% solution of metaphosphate of soda,

or, 14% solution of magnesium sulphate.

In health the platelet varies somewhat in its size, stated by different authors to vary from 2 to 3 microns[72] or from 2 to 5 microns[87] in diameter. By the method of examination adopted in this work the average normal diameter was found to vary between 2 and 3 microns. Larger or smaller forms were very uncommon.

In wet preparations the thrombocyte is disc-like, spherical or oval in shape but at ordinary room temperatures the outline sometimes becomes irregular, the cytoplasm being prolonged into spike-shaped processes of differing lengths and numbers arranged in a radial manner around the platelet (fig. A).



Occasionally the free end of these processes becomes enlarged and spherical the platelet then being surrounded by knob-like or club-shaped projections. The appearance is that of a granular main body connected to these non-granular cytoplasmic masses by thin lines

of cytoplasm as, in such forms, it is common to find the granules congregated together in a dense mass, (figs B & C).

In dry preparations such bizarre forms are not commonly seen but in addition to the usual round, oval or slightly irregular disc-like forms some rather elongated platelets may be observed. Whether in wet or dry preparations however all these deviations in shape from the round, oval or slightly irregular forms may be regarded as artefacts.

A dry blood film stained with Leishman's stain shows the platelet to consist of a hyaline or very slightly basophilic cytoplasm in which are embedded numerous rather fine granules approximately equal in size and red or reddish violet in colour. When suspended in a suitable solution containing brilliant cresyl blue the cytoplasm is clear or it has a very faint bluish tinge and the granules stain a deep blue colour. The granules may be scattered uniformly throughout the cytoplasm or may be collected together in the centre, or at the periphery of the platelet. Wright[223] considered that these granules were peculiar only to the thrombocyte and the megakaryocyte.

As for the size of the platelet so also for the number of granules contained in it, each author, according to his methods, has a different standard. This is not surprising as even under normal conditions the number of granules varies within rather wide limits. Fegler[87] found, that in health, 60% to 70% of the thrombocytes were "rich" in granules while Reimann's[187] figures were 29% to 46%. from an examination of their findings however, it is apparent that, although the above percentages are so different, both authors were agreed that the larger the platelet the fewer were the granules it contained.

Usually the staining reaction of the cytoplasm is hyaline but in disease forms showing basophilia may be seen. In health however, basophilic platelets are rare.

The question as to whether the platelet has a nucleus is one which a number of observers have attempted to answer. Aynaud[22] thought that the thrombocyte contained nuclear substance in a diffuse state and Herwerden[107] satisfied himself that all grades of transition from small pyknotic to large pale nuclei could be observed although he was never able to distinguish mitotic division. The prevailing opinion* based on the most convincing work, favours the conception of the platelet as a non-nucleated element. Downey[76] stated that there was nothing in the staining reaction to show that the thrombocyte was related to the nucleus of erythrocytes or leucocytes. From observations made in the course of this work the nucleated appearance assumed by many thrombocytes appeared to be due to the aggregation of the granules within the cytoplasm to form a rather dense mass which was found most often near the periphery of the element. Nothing resembling a nuclear membrane was seen and mitosis was never observed.

At first the scope of the present work was confined to an investigation into the numerical variations of platelets in disease but after it had been in progress for some time, it was noticed in many cases that the size, granulation and staining reaction varied somewhat from the normal and it became a matter of interest to inquire into the significance of these changes. Very small or very large (giant) forms were observed and the number of granules in the thrombocytes was frequently found to be increased or diminished

* References 43, 72 & 76.

and, further, it was noticed that the cytoplasm in some cases became definitely basophil when stained with brilliant cresyl blue.

To carry out this inquiry some normal morphological standard was necessary. On reference to the literature it was found that very little work had been done on this subject and that, even where it had been attempted, there was no unanimity as to what constituted the normal in size and granulation.

In this work the standard size of the platelet was taken as varying between 2 and 3 microns. In the case of oval platelets the approximate size was calculated by taking the average of the greatest and smallest diameters. The same method was adopted in dealing with platelets in which the outline was irregular except in the cases where the irregularity was so gross that this could not be done. Such platelets were comparatively few and they were ignored.

Great difficulty was found in grouping the platelets according to the number of granules contained in the cytoplasm. Frequently the granules were congregated together to form a pyknotic mass but even where they were scattered it was impossible in many instances to count them. Thus in the absence of any recognised classification and in face of these difficulties an attempt was made to divide the platelets, in so far as their granular content was concerned, into the following rather arbitrary groups. (a) Those in which no granules were apparent, (b) those in which there was a marked diminution in the number of granules, (c) those in which, in spite of some variation in the number of granules, experience showed that the granulation present could be regarded as being within normal limits, and (d) those in which there was a very definite increase in the granular content. It is recognised that this classification is not

wholly satisfactory as it does not allow for those conditions in which the platelets included in group (c) may, on the whole, contain granules in numbers nearer to the lower or higher limit of the group thus suggesting slight diminution or slight increase in granulation as the case may be. Although lacking mathematical precision this method, used by the same individual provided a means by which daily observations on the granulation of platelets could be recorded and compared.

With regard to the staining reaction of the cytoplasm the normal hyaline platelets were distinguished from those which were definitely basophil.

The normal platelet may therefore be defined as a non-nucleated, round or oval disc-like body, with an average diameter varying between 2 and 3 microns, and with a hyaline cytoplasm containing numerous granules. In health the platelets are all of this type.

The following pages indicate the changes in the platelet picture in certain diseased conditions.*

Purpura hæmorrhagica. (Werlhof's disease, hereditary hæmorrhagic thrombasthenia, essential thrombopenia, essential thrombocytolytic purpura.) (Cases 1, 2 & 3.)

It is only within comparatively recent years that the blood platelet has been regarded as an element which plays an important part in the pathology of this disease. It is therefore natural that some attention has been paid to the morphology of the platelet in purpura hæmorrhagica, but it cannot be said that there is any unanimity of opinion with regard to the changes reported. The only point on which there seems to be some agreement is that varying numbers of large platelets appear in the blood.**

* Note. The details of each case discussed will be found in the tables on platelet morphology set out in the appendix.

** References 46, 124, 128 & 159.

With regard to the other changes Fegler[37,38] found that over 90% of the platelets were very granular and Rockwood and Sheard[99] by means of instantaneous microphotography described the thrombocytes in purpura hæmorrhagica as varying in size, shape and type of granulation from those found in a case of pernicious anæmia showing thrombocytopenia, the platelet granules in the former disease being very coarse. In his observations on the morphology of the platelets Glanzmann[100] described the presence of very large and very small forms, basophilia in varying degree, pyknosis of the granules, and variation in numbers, absence or diminution, rather than increase being the rule.

On the strength of some of these findings certain writers assumed that these morphological changes indicated defective platelets and were the outward expression of functional inefficiency. They have therefore been tempted to attribute to these apparently abnormal thrombocytes some part in the pathology of purpura hæmorrhagica.

In view of this the study of the morphology of the platelet in cases 1, 2 and 3 was of interest. Unfortunately in none of the three was a thrombocytopenia present at the time of the examination although other manifestations of the hæmorrhagic tendency were present, e.g., prolongation of bleeding time and spontaneous epistaxis.

Examination of the platelet picture on several occasions did not reveal any departure from the normal but on certain dates two of the three cases showed irregular distribution of the granules, some platelets showing diminution, and others increase in granulation. The granules however, did not differ, either in size or shape from those seen in health. The size and staining reaction of the thrombocytes were always normal.

Beyond noting at this stage that the findings in these three

cases do not agree with any of those cited above the relationship between platelet morphology and the pathology of purpura hæmorrhagica will not be discussed until the appearance of the thrombocyte in other diseases has been studied.

Static (mechanical) purpura. (Case 6.)

The structure of the platelet in this disease did not show any departure from that seen in health.

Acute myeloblastic leukæmia. (Case 10.)

Throughout the course of this patient's illness there was variation in the size of the thrombocytes, the smaller forms predominating for some time. The platelets showed irregular distribution of the granules, many of them in the early observations, being packed with granules. As the thrombocytopenia increased the granules became fewer in number, so much so, that the few forms observed during the period of very marked thrombocytopenia were almost agranular.

Chronic myeloid leukæmia. (Case 11.)

In this case large forms were present and, although the thrombocytes as a whole were frequently well filled with granules, some showed a decided increase in granulation. On one occasion however there was a marked increase in the number of less granular forms. Basophilia was rare. According to Stahl[204] the number of basophil forms in chronic myeloid leukæmia is rarer than would be expected from the nature of the disease.

Splenic anæmia. (Case 16.)

Although occasional basophilia and some variation in size, above and below the normal, were noted the feature of this case was the presence of a large number of platelets in which there was definite diminution in the amount of granulation.

Acholuric (hæmolytic) jaundice. (Case 18.)

When the patient was in hospital for the first time deficiency in granulation was sometimes a feature. For a few days after splenectomy (2nd admission) many large forms appeared in association with a rapid increase in the platelet count. At this time also the platelets became less granular and many of those present showed a basophil cytoplasm. After the numbers had reached their highest values and showed some tendency to diminish the platelet picture became normal in every respect. It was noted however that after being on holiday for over three weeks the patient had a few large granular and basophil forms in the circulation.

Malignant endocarditis. (Cases 19 & 20.)

Throughout the period of observation thrombocytopenia was a feature. Very small, normal and large platelets were present and there was an increase in the number of basophil forms. The granules were irregularly distributed and though a few thrombocytes were very granular a much greater proportion showed deficient granularity.

Pernicious anæmia. (Cases 23, 24 & 25.)

During the stage of thrombocytopenia there was a marked anisocytosis with however a preponderance of small forms. Many platelets were also deficient in granules and basophilia was not uncommon. With improvement in the condition of the patients the size became uniform, the amount of granulation increased and basophilia was not so frequent.

Anæmia secondary to hæmorrhage. (Cases 26 to 30 inclusive.)

In secondary anæmia certain observations have already been made by other writers. Fegler[87] observed that there was a tendency for the granular platelets to be diminished and Larrier[168] reported the presence of giant forms. In experimental anæmia, produced in

rabbits by bleeding, Degkwitz[72] also found that there was an increase in the number of large forms of platelets.

In the blood of the patients here investigated there was a definite anisocytosis with a tendency to increase in the number of large platelets. Basophilia was a feature and was of common occurrence during the period of rise in the platelet numbers. The distribution of the granules was very often irregular but usually there was an increase in those forms showing defective granulation. This did not seem to be related in any way to rise or fall in the thrombocyte values though on the whole it was usually a feature during the period of increase. All of the above findings were observed during the occurrence of hæmorrhage but in general they were most characteristic of the post-hæmorrhagic period.

Lobar pneumonia. (Cases 34, 35 & 36.)

In this disease Reimann[187] found that in the precritical period when thrombocytopenia was present, the average platelet was distinctly smaller and the cytoplasm more granular than in the later stages when thrombocytosis occurred.

A feature common to all three cases in the first few days of the illness was the increase in forms showing diminution in the number of granules. With improvement in the condition of the patients the granules became uniformly distributed although, in case 35, a certain amount of unequal granulation persisted throughout the whole period of observation. During the precritical stage in cases 34 and 35 the size varied, very large and very small forms being present. Basophilia was prominent before the crisis in case 34.

Acute rheumatism (rheumatic fever). (Cases 38 to 44 inclusive.)

In this disease an increase in the number of platelets sparsely filled with granules was the rule. This was more marked during the

acute stage of the illness, but nevertheless it was a prominent feature even in convalescence. Large and small forms were occasionally seen but on the whole the size was normal. Basophilia was uncommon.

Acute nephritis with hæmaturia. (Cases 47, 50, 52 & 53.)

Large and small forms were seen. There was also some basophilia and unequal distribution of the granules.

Diabetes mellitus. (Cases 56 to 61 inclusive.)

Nothing worthy of note was observed in the platelet picture in this disease except perhaps that the granules were not evenly distributed. Anisocytosis and basophilia were occasionally observed.

Chronic tuberculosis. (Cases 72 & 73.)

In tuberculous peritonitis with ascites Stahl[204] found isolated small basophil platelets. In the two cases examined frequent basophilia was the only deviation observed from the normal picture.

Hyperthyroidism. (Case 74.)

The platelet picture varied. Increase in size and some basophilia of the cytoplasm were occasionally noted.

In the following diseases a study of the morphology of the thrombocyte did not reveal any typical or characteristic changes:- Carcinoma, (Cases 62, 68 & 69.): Lymphosarcoma, (Case 67.): Jaundice, various causes, (Cases 64 & 65.): Pelvic sepsis, (Case 70.): and Pyæmia, (Case 71).

From the study of the morphology of the platelet in the foregoing diseases it will be seen that the thrombocyte picture was constantly changing, even within the short period of one or two days. It is very difficult therefore to draw any definite conclusions as to the significance of this constant change. However when a large series of observations is made and the platelet picture considered together with the platelet count and the state

of the patient it is possible to show that it conforms to certain broad general rules and gives some idea as to the influence exerted by the disease process on the thrombopoietic tissues.

When the platelets are diminished in number anisocytosis is common, the size varying from less than 1 micron to as much as 5 microns. On the whole there is an increase in the number of small forms (cases 10, 16, 23, 24 & 25). During the period of thrombocytosis the forms tend to be larger in size (cases 26 to 31 inclusive).

Diminution in the number of granules contained in the platelets is typically seen during the acute phase of an illness when associated with reduction in the number of thrombocytes (cases 10, 16, 19, 20, 23, 24, 25, 34, 35, 36 and 38 to 44 inclusive). This diminution may also be observed when the numbers are varying in the direction of an increase or are already high (cases 18, 26, 27, 29, 30, 31 and 38 to 44 inclusive). In convalescence the thrombocytes become more granular (cases 18, 23, 24, 25, 34, 35 & 36).

Basophilia is a notable feature when thrombocytopenia is present (cases 19, 20, 23, 24, 25 & 34), and also when the platelets are actively increasing in number (cases 18 & 26 to 30 inclusive).

In summing up it may be said that during a thrombocytopenic period or during a phase of marked reduction in the platelet values short of actual thrombocytopenia,* there is anisocytosis with a relative increase in the number of the smaller forms although a few very large forms may also be present. In addition there is a varying degree of basophilic staining of the cytoplasm together with irregular distribution in the granular content of the platelets. During a thrombocytosis or when the thrombocyte count is rapidly

* Note. Thrombocytopenia is regarded as being present when the platelets number 100,000 or less.

increasing the platelets tend to be larger and less granular. In the latter condition basophilia is a common feature.

It would thus appear that anisocytosis and unequal or diminished granulation appear in conditions in which there is diminution in the numbers and also in states where there is hurried production. If in addition, there is basophilia (basophilia being a sign of immaturity) it may be assumed, from the presence of these immature platelet forms in the circulation, that the thrombopoietic tissues are not producing mature thrombocytes as fast as they are being required. As would be expected these youthful forms are found in all thrombocytopenic states, and in the thrombocytosis which may follow hæmorrhage or splenectomy, or thrombocytopenia from any cause.

With regard to the morphology of the thrombocyte in purpura hæmorrhagica it will be apparent, from a consideration of these points, that all the thrombocyte types described by others as being peculiar to that disease, with the possible exception of the type with coarse granules, have been observed in other diseases particularly during the thrombocytopenic stage. It is likely that the presence of abnormal platelets is a feature of thrombocytopenia no matter how it is produced and is not peculiar to, or characteristic of, the thrombocytopenia of purpura hæmorrhagica.

As a corollary to this conclusion it follows that in purpura hæmorrhagica the structural and tinctorial abnormalities observed in the platelet by others do not afford good evidence that this element is functionally inefficient. The most that can be said for them is that these deviations from normal indicate immaturity. Similar abnormal forms are present in the blood in diseases which are not characterised by purpuric hæmorrhages and conversely, these

forms may be absent from the blood in conditions in which this hæmorrhagic tendency is present as shown by cases 2 and 3. The hæmorrhages characteristic of the disease are therefore not due to inherent defects in the blood platelets.

ORIGIN OF BLOOD PLATELETS.

Many theories have been advanced to explain the origin of the blood platelet and at one time or another, almost every cell belonging to, or derived from, the blood forming tissues has been suspected of giving birth to the thrombocyte. At the present time although the consensus of opinion favours the idea that it is derived from the megakaryocyte of the bone-marrow, yet it cannot be said that the problem is solved to the satisfaction of everybody.

It is of interest to recall that Hayem considered the blood platelet to be the precursor of the red corpuscle, a view which has long been discarded. Even up to the present times the platelet has been regarded as a precipitate of altered blood plasma. This matter has already been discussed and dismissed - see page 2. Certain evidence has also been forthcoming to demonstrate that the erythrocytes, by a process of budding or extrusion from their cytoplasm,[49] and the leucocytes, by fragmentation of their cytoplasm, gave rise to thrombocytes. Now if this were the case it is likely that the platelets would vary in number with numerical alterations in the red and white cells. In this connection the graphs of certain of the cases in the appendix are instructive. Some show that the thrombocyte curve may be roughly parallel with that of the erythrocytes, (cases 10, 19, 20, 24 & 25) or with that of the leucocytes, (cases 11, 14, 15, 16, 30, 37, 55 & 70). However when the curves are scrutinised carefully it will be seen that there is no very exact parallelism between those of the platelets and the red cells on the one hand and those of the platelets and the white cells on the other, and that the thrombocytes

may vary numerically quite irrespective of numerical change in the totals of the other formed elements of the blood. This independence is demonstrated very well in the graphs of cases 27, 28, 29, 34, 35, 36, 39 & 41. Thus there is good clinical evidence to show that the platelet is not directly related to either the erythrocytes or leucocytes and is unlikely to be derived from them.

There is also some experimental evidence in support of this view.* The anti-serum prepared against red cells acts only on these cells and does not harm the platelets. The same may be said of anti-white cell serum. If the blood platelets were derived from the erythrocyte or leucocyte it would be reasonable to expect that either one or other of these sera could produce thrombocytopenia. This has not been found to be the case and thrombocytopenia can be induced only by injecting, not anti-red or anti-white cell sera, but anti-platelet serum.*

Thus the specific action of anti-sera and the independent platelet reaction met with in disease make it very improbable that the thrombocyte has its origin by budding or extrusion from the cytoplasm of the erythrocytes, or by fragmentation from that of the leucocytes.

Although it has been shown that the platelet can react as an independent element in the blood stream yet it is of interest to note that Bedson and Johnston[36] could not obtain any data to support the idea that the thrombocyte was a preformed element having a nucleated precursor. Further these same observers on injecting anti-sera prepared against lymph glands and reticulo-endothelial system could find no proof that the thrombocyte derived its origin from these tissues.

* References 33, 34, 36, 64 & 138.

The only other theory which remains for discussion is that the platelet is derived from the megakaryocyte of the bone-marrow. This conception was first formulated by Wright[223] and his work has been confirmed and consolidated by others.[59,76] As already stated this theory is almost universally accepted as proven. Aschoff[17] considered the question settled beyond doubt.

Before going on to describe the mode of origin of the platelet according to this theory there are some points of interest to be noted regarding the megakaryocyte. In the embryo it is found in the liver, spleen and yolk-sac, while in the adult it is normally present only in the bone-marrow. It has been observed however in the lungs, spleen and blood stream in pathological states. In the bone-marrow it is present in all stages of development. The youngest form of the cell is non-granular and has a single nucleus which in the course of maturation becomes larger and more complex until ultimately several nuclei are formed.* The cytoplasm also increases in size and becomes full of very fine granules which Wright[223] and Downey[76] considered peculiar only to the megakaryocyte and the blood platelet. Thus the fully developed cell is very large and has a granular cytoplasm containing a number of nuclei. It is only in this adult state that the megakaryocyte can produce blood platelets.**

In his classical work Wright[223] demonstrated with the help of special staining methods that the blood platelets were portions of megakaryocytic cytoplasm detached and carried off into the blood stream. The separation took place by a process of pinching off, or segmentation, the line of cleavage being through a zone of hyaline cytoplasm. This cytoplasm was frequently prolonged into pseudopodia-

* References 60, 92, 160 & 199.
** References 36, 92 & 223.

like processes of varying sizes, shapes and numbers which projected into the blood channels through small openings in the vessel wall. Many of the granules seen in the megakaryocyte cytoplasm passed into the pseudopodia or collected into groups at the edge of the cell before segmentation and a pseudopodium might present the appearance of being composed of a chain of blood platelets united by the continuity of their ground substance which in turn was continuous with the hyaline cytoplasm of the mother cell.

In support of this conception of platelet origin Wright, and subsequently others, pointed out the parallelism which existed between the number of blood platelets in the circulation and the number of megakaryocytes in the bone-marrow. Both are increased in regenerative states following on hæmorrhage and toxæmia, in inflammatory states, in myelogenous leukæmia,[223] in Hodgkin's disease,* in experimental conditions following injections of anti-platelet serum[144] and anti-red cell serum[36] and following inoculation with diphtheria toxin.[80] Both are diminished in pernicious anæmia and lymphatic leukæmia,[223] in chronic benzol poisoning[202] in aleukia and aleukæmic leukæmia,[96,97] and after exposure to X-rays.[164] In favour of his hypothesis Wright also pointed out that platelets did not appear in the embryo before the appearance of megakaryocytes or their forerunners and that they were found only in mammals in which the megakaryocyte was present.

In the realm of experiment Firket[91] produced thrombocytopenia in rabbits by injecting saponin and then found that megakaryocytes appeared in the spleen. Within a few days there was an increase in the number of blood platelets. In a splenectomised rabbit he found

* References 59, 60, 204 & 223.

myeloid metaplasia in the liver, and in the lymphatic glands megakaryocytes were the sole myeloid elements present. This might result however from a general myeloid reaction and not necessarily be the response to a demand for blood platelets. Firket regarded his findings as supporting Wright's theory but he was doubtful if the platelet arose solely from the megakaryocyte.

More direct proof is provided by the observations of Sabin[99] who watched the clumping of the granules and fragmentation of the cytoplasm into typical platelets in megakaryocytes found in the circulation. Bedson and Johnston[36] examined megakaryocytes of the bone-marrow in a vital preparation and they too observed the accumulation of granules into little masses about the size of the platelet. The outline of the cell then became irregular and ragged and in some instances small platelet-like portions of the cytoplasm became attached to the periphery of the cell by a narrow stalk. Some hours later this became more marked and next day the cytoplasm of these cells had become almost completely fragmented into small, irregular, oval and granular masses lying free in the surrounding medium. This cycle of changes occurred in about 50% of the megakaryocytes examined. Commenting on these findings and those reported by Sabin, Bedson and Johnston thought that the megakaryocytes were undergoing degenerative changes rather than being in the active process of producing platelets. After injecting anti-platelet serum they saw no megakaryocytes in process of active platelet budding and later they noted that this serum produced an increase in the number of megakaryocytes in the bone-marrow. They also noted that red cell destruction brought about a similar regeneration of megakaryocytes. While this work may be considered as supporting Wright's theory, Bedson and Johnston concluded that the relationship between

megakaryocytic hyperplasia and increased platelet production was not clear. They however appeared to be satisfied that the platelet normally had its origin in the bone-marrow. In support of this conclusion they stated that anti-bone-marrow serum produced thrombocytopenia.

Less convincing evidence in support of Wright's conception is forthcoming from the work of Le Sourd and Pagniez[143,144] who, firm in the belief that the platelet was responsible for syneresis of the blood clot, found that the layer of megakaryocytes obtained from an emulsion made from the reacting marrow after injection of anti-platelet serum, brought about retraction of the clot. Thus because of the common retractile property existing between platelet and megakaryocyte they concluded that there was some close genetic relationship between the two elements.

McGowan[158] regarded the megakaryocyte as forming a reserve for the rapid production of hæmopoietic stem cells - hæmatoblasts - and he suggested that blood platelets might arise from the clippings and remnants formed by unequal division of these stem cells.

As an important point in Wright's theory is the similarity between the granules found in the megakaryocyte and in the blood platelet it may be of interest to mention briefly some of the views regarding their origin. One of these views is related to the debatable question as to whether or not the megakaryocyte has a phagocytic function. Red and white corpuscles as well as other cellular debris have been seen by some observers in the cytoplasm of the megakaryocyte and this has been regarded as a sign of phagocytic power. Woodcock[222] stated that the granules of the megakaryocyte represented the unassimilable materials of the process of ingestion. Others[36,93] however have never seen red cells

within the megakaryocyte and doubt if this cell has any phagocytic function. They have shown that such materials as washed red cells, lithium carmine, indian ink and trypan blue were not taken up by the megakaryocytes. The presence of leucocytes within the cytoplasm is therefore explained as being due to invasion of the megakaryocyte by the phagocytic leucocyte.

Downey[76] suggested that the granules characteristic of the megakaryocyte developed along with degenerative changes in the nucleus, and he further stated that the hyaline bodies which were constricted off from the cytoplasm of mononuclear cells and lymphocytes, especially in the rabbit, were in no way related to blood platelets, although smears showed them to contain an occasional azurophil granule. These azurophil granules were not, according to Downey, the same granules as are found in the blood platelet. This is of interest as some writers,[50,58] amongst whom may be numbered those who support Wright in his theory, have suggested that in times of need there may be a reversion to a vicarious type of blood platelet formation in which the large lymphocyte, the endothelial cells of the bone-marrow and the blood vessels,[66] the mononuclear and transitional cells of the bone-marrow, spleen and blood may take on the task of platelet production. This is not in agreement with the results obtained by injecting anti-lymph gland and anti-reticulo-endothelial sera as neither of these brings about reduction in the number of thrombocytes.[36]

From the foregoing considerations it will be evident that the platelet does not arise from the erythrocyte or leucocyte. There is very good presumptive evidence in favour of the hypothesis that the blood platelet has its origin from the cytoplasm of the megakaryocyte. While that is so it cannot be said that the problem is solved beyond question in view of the doubts which exist regarding the function of

the megakaryocyte. The fact that most of the evidence is based on morphological and tinctorial observations is unsatisfactory and as a result there is uncertainty on the part of some investigators who, while they guardedly support the megakaryocytic origin, do not seem to be convinced that it is the sole mechanism of platelet genesis.

After a consideration of all the evidence it would seem reasonable to conclude that, in the adult, the thrombocyte under normal conditions, has its independent origin in the bone-marrow and further, not unreasonable to assume that in times of stress the platelet may arise from other tissues which are potentially hæmopoietic.

DESTRUCTION OF BLOOD PLATELETS.

In health the spleen constantly contains a large number of thrombocytes and, with the possible exception of the bone-marrow, they are rarely to be found in any of the other organs of the body. In fact the spleen has been found to be rich in platelets when a thrombocytopenia was present in the circulating blood.[124,141] In specially stained preparations they may be seen in the splenic sinuses and their presence in the spleen may also be detected if a portion of that organ is teased out in a suitable medium and appropriately stained.[32,36] From a perusal of the literature it seems to be assumed that destruction of blood platelets takes place in the spleen and that the platelets are held up in the splenic sinuses preparatory to being destroyed. As proof of this destructive action it has been shown that there is an increase in the number of thrombocytes circulating in the blood after splenectomy in healthy experimental animals[32,36] and in the human subject when the organ is removed as a therapeutic measure in acholuric jaundice (case 18), splenic anæmia and purpura hæmorrhagica. The same phenomenon has also been reported on ligature of the splenic artery.[102] Further, it has been observed that the blood of the cubital vein and the splenic artery contains more thrombocytes than the blood of the splenic vein.[65,146]

It is very doubtful however if these observations can be taken as good evidence of the platelet destroying function of the spleen, as an increase in the platelet count follows other operative procedures, experimental and therapeutic.* Moreover, splenectomy

* References 24, 32, 35, 36 & 149.

is not always followed by a thrombocytosis.[47,203] It is also known that the spleen acts as a reservoir for red corpuscles[27,28] and it is a reasonable assumption that the thrombocytes observed in the spleen are not retained solely for destruction but simply for storage purposes. In this connection there is evidence to show that during acute asphyxia in dogs the platelets are mobilised, along with the other elements of the blood, a phenomenon which does not occur after these animals are splenectomised.[41] Further, after the administration of ephedrine[40] and adrenaline,[42] both substances which bring about splenic contraction, there is a rise in the number of circulating thrombocytes.

More convincing evidence in favour of the platelet destroying function of the spleen would be afforded by direct observation of intracellular destruction of these elements. Some workers* claim to have observed the presence of phagocytosed and degenerated thrombocytes within the endothelial cells of the spleen. Kaznelson,[124] who first practised splenectomy in purpura hæmorrhagica on the principle that there was excessive destruction of the platelets by the spleen, thought that the platelets were lysed rather than phagocytosed hence the name "essential thrombolytic purpura" which he gave to the disease. However in a note inserted in his paper he stated that he saw phagocytosis of thrombocytes in the spleen of one case of pernicious anæmia. On the other hand, Pardi,[170] even where he saw what resembled blood platelets contained within the cytoplasm of the phagocytic cells was not satisfied that this was good evidence of phagocytosis.

The difficulty in recognising phagocytosis of platelets must

* References 14, 65 & 201.

be great but the knowledge that the spleen contains many phagocytic cells which have the power to remove and destroy effete red cells makes it very probable that the platelets are also destroyed by them. The cells exercising this function belong to the reticulo-endothelial system which in man is in great part centred in the spleen and it is interesting to find that when the function of these cells is inhibited by "blocking"[32,127] after intravenous injection of suitable substances, e.g., trypan blue, there is an increase in the number of thrombocytes in the circulation. If splenectomy now be performed there is no further increase in the platelet count.[32] However the thrombocytosis following blockade of the reticulo-endothelial system is not sustained even when the injection is repeated and it would seem that the blockade, if it is the cause of the thrombocytosis, is not complete or only temporarily effective. It may be that some other tissue can take over the function of platelet destruction or that the substances when injected for the first time produce transient thrombopoietic activity.

NUMERICAL VARIATIONS OF PLATELETS IN HEALTH.

The adhesiveness of platelets for water "wettable" surfaces and the ease with which they disintegrate outside the body, make it very difficult to estimate the numbers in the circulation. This is reflected in the many methods which have been devised to count the thrombocytes. It is not surprising therefore that the normal figure of each method differs. Almost every method requires that the blood examined be diluted with some suitable solution and the ratio of platelets to red corpuscles found, the total number of thrombocytes then being estimated from the total number of erythrocytes which are counted in the usual way. Some methods require that the blood be drawn from a vein through suitably paraffined apparatus, others that the skin be punctured and the blood drawn directly into a red cell pipette containing diluting fluid, others again, that it be allowed to flow directly into the diluting fluid through which the puncture is made. The blood and fluid are then thoroughly mixed and the platelets counted against the reds in a counting chamber or on a glass slide under a cover slip which is ringed with vaseline.

The following table illustrates the differing normal standards:-

Average normal number of platelets per cu.mm.	Author(s).
216,000	Aynaud.[10]
250,000	Wright.*
262,000 (skin puncture)	Buckman & Hallisey.[51]
284,222 (venepuncture)	Buckman & Hallisey.[51]
Rarely less than 300,000	Gram.[112]
350,000	Thomsen.**
450,000	Pratt.*

* Cited by Osler & McCrae,[169]
** Cited by Reimann,[197]

Platelets per cu.mm. Normal limits.	Author(s).
150,000 to 300,000	Fonio.*
183,000 to 252,000	Aynaud.[20]
250,000 to 400,000	Cramer & Bannerman.[46]
263,000 to 360,000	Degkwitz.[72]

In view of these great variations and the uncertainty which existed as to what constituted the normal it was necessary to find the normal for the method of enumeration here adopted.***

As the result of counting the platelets in a number of healthy people it was found that the thrombocyte values varied not only with the individual but also in the same individual on different dates. The average of over 30 counts was 392,400 per cu.mm., and the total numbers ranged from 250,000 to 450,000 per cu.mm. From these figures and from those of other authors it is apparent that the platelet numbers fluctuate even in health within a wide range and it is evident that the fixing of a normal figure is at best only a rough guide to what constitutes the normal by the method of counting adopted. For the purposes of this work the average normal value has been arbitrarily fixed at 390,000 per cu.mm. On referring to the case notes and charts in the appendix it is advisable to remember that the platelet numbers may vary in health between 250,000 and 450,000 per cu.mm.

Very little is known regarding the causes which bring about such variation in health. Certain observations have however been made. Caccuri[62] reported a diminution in numbers after severe exercise. Degkwitz[72] found that there was a variation of 80,000 during the day, the numbers increasing towards the afternoon when the temperature was higher. Wittkower** noted that after a hot

* Cited by Osler & McCrae.[169]
** Cited by Leschke & Wittkower.[149]
*** Note. A full description of the method used, its value and limitations is given in the appendix.

bath of one hour's duration the platelets increased from 220,000 to nearly 300,000.

Considering the delicacy of the platelet's structure, the ease with which it can be made to disappear from the blood stream and the rapidity of its reappearance in certain conditions, the readiness with which it disintegrates outside the body and the way it adheres to injured vascular endothelium when the blood stream is slowed down or to foreign bodies introduced into the circulation it is likely that the life of the thrombocyte is short. In this connection Duke[77,80] found that by removing blood, deplateletising it by defibrination and then reinjecting it, the total number of platelets could be regenerated in dogs within three to five days and Möller[164] demonstrated that after guinea pigs had been exposed to the action of X-rays, which destroyed the megakaryocytes, the number of these cells fell two to three days before there was a corresponding diminution in the number of platelets. Even without these experiments and on clinical evidence alone it is very probable that the thrombocytes are produced and destroyed in very large numbers each day, the life of the platelet being of short duration, possibly only a few days.

It is not surprising therefore that the number of these elements in the blood should vary so greatly at short intervals even in health.

NUMERICAL VARIATIONS OF PLATELETS IN DISEASE.

Although the platelet count in health is not constant and the cause of the variation in numbers not always clear it is noteworthy that in disease the numerical changes may vary within much wider limits than in health. Further, these variations may occur in a constant and uniform manner and sometimes they may be correlated with certain phases of the illness. Before discussing the significance of these variations it is necessary to indicate the nature of the changes in the platelet count observed in the course of the following diseases.*

Purpura hæmorrhagica. (Werlhof's disease, hereditary hæmorrhagic thrombasthenia, essential thrombopenia, essential thrombocytolytic purpura.) (Cases 1, 2, 3 & 4.)

In 1887 Denys[74] pointed out that in purpura hæmorrhagica there was frequently a great diminution in the number of platelets. This observation has now been verified by many authors and it has become the custom to classify this disease under the heading of "thrombocytopenic purpura" as many think that diminution in the platelet numbers is the sole cause of the hæmorrhagic symptoms.

Although thrombocytopenia was observed only in one of the cases referred to in this group it is apparent from the histories and clinical findings that all four suffered from purpura hæmorrhagica, and it was of interest to find that in the presence of hæmorrhagic manifestations cases 2 and 3 showed very high platelet counts, varying from 300,000 to over 700,000 and 800,000 respectively. In case 1 the platelet numbers were as low as 140,000 and as high as

* Note. The details of each case will be found in the appendix.

525,000 but a marked thrombocytopenia* was never observed. Case 4, when first seen, had counts which varied from 100,000 to 264,000 but during a second period of observation a profound thrombocytopenia was present. Thus in purpura hæmorrhagica there may be periods of definite thrombocytopenia or diminution in the platelet numbers and at times a definite and spontaneous thrombocytosis. In other words purpura hæmorrhagica can exist without thrombocytopenia. Similar cases have recently been reported in the literature.[152,196]

Henoch-Schönlein (anaphylactoid) purpura. (Case 5)

It seems to be universally agreed that there is no thrombocytopenia in this type of purpuric disease. Although the platelet numbers in case 5 were slightly diminished yet the reduction was not low enough to be regarded as a thrombocytopenia.

Static (mechanical) purpura. (Case 6.)

In this case the thrombocytes varied between 243,000 and 440,000, that is, within healthy limits.

Scurvy. (Cases 7 & 8.)

In both cases the thrombocyte numbers varied greatly, case 8 showing the lowest and highest values, namely 110,000 and 400,000 respectively.

Hæmophilia. (Case 9.)

There was no diminution in the platelet numbers in this case. This is in agreement with the findings of other authors.**

Acute myeloblastic leukæmia. (Case 10.)

A reduction in the thrombocyte count has been noted in acute leukæmia by other authors.[32,204] This is in accordance with the findings in case 10 which were as follows:-

* Note. Thrombocytopenia is regarded as being present when the platelets number 100,000 or less.

** References, 116, 161 & 200.

Four weeks previously the patient had had a course of X-ray therapy and when he was first seen anæmia and leucopenia were present. At that time the platelets numbered 200,000 and they remained approximately at this level while the red corpuscles increased gradually and the white cells reached normal values. With further increase in the number of leucocytes there was a steady reduction in the number of thrombocytes until at the time of the last blood count no platelets were found after prolonged search. At this stage, as the result of X-ray treatment, the leucocytes had fallen from 103,000 to about 10,000. It is noteworthy that the platelet curve commenced to fall before the application of X-ray treatment. The diminution in the number of platelets was associated rather with the increase in the leucocyte count.

Chronic myeloid leukæmia. (Cases 11 & 12.)

In this disease the platelet count has been found by others to be normal or increased but never diminished.* As the result of the examination of these two cases it was found before treatment that case 11 had a high count and that in case 12 the thrombocytes were present in numbers just under the higher limit found in health.

Following X-ray treatment case 11 showed a reduction in the number of platelets, the leucocyte and thrombocyte curves being approximately parallel. With regard to case 12 however it is doubtful if the application of a single dose of X-ray therapy had any effect on the platelet count. The count was lower after irradiation but possibly this fall was due to some other cause as a similar reduction was frequently found when there was no exposure to Roentgen rays. It has to be noted however in this case that when

* References 72, 82, 112, 160 & 204.

the leucocytes were increasing in number there was a corresponding increase in the platelet count.

Diminution in the platelet count after X-ray treatment has been reported by Frank[97] and it has also been observed by others in the realm of experiment.[130, 134]

Polycythæmia vera. (Cases 13, 14 & 15.)

In none of these cases was there an increase in the number of platelets in the circulation before treatment, in fact, the numbers in case 13 were rather low.

Treatment with phenylhydrazine hydrochloride produced, in cases 14 and 15, a definite thrombocytosis and the counts in the latter case demonstrated how rapidly the platelets can vary in number - from 330,000 to over 1,200,000 and down again to about 500,000 all within the space of 48 hours.

Cases 13 and 15 received X-ray treatment but the effects produced differed. Case 13 responded well to treatment but the thrombocyte count did not seem to be influenced in any way. Case 15 did not improve with exposure to X-rays. In this case the platelets varied within wide limits being over 1,000,000 on one occasion. Ultimately they fell to below 100,000. On the whole the platelet curve tended to be lower towards the end of the course of treatment. If X-ray treatment had any effect on case 15 it seemed to stimulate, for a time at least, the production of platelets.

Splenic anæmia. (Cases 16 & 17.)

In this disease Rosenthal[190] did not find any characteristic variations in the thrombocyte count. In case 16 the platelets were always reduced in number. Case 17 is included to show that, two years after splenectomy, the thrombocytes were found to be well above average normal values.

Acholuric (hæmolytic) jaundice. (Case 18.)

Previous to splenectomy and during the period when the patient was in hospital for the first time the platelets varied between 200,000 and 400,000. Immediately following operation there was a fairly rapid increase in the count to over 1,000,000. The platelet numbers continued at a high level and 3½ months after operation the thrombocyte count was still high at nearly 700,000. Dyke[83] has reported the behaviour of the platelet counts after splenectomy in a similar case. From an examination of his figures the rise in the thrombocyte count was neither so rapid nor so well sustained as in case 18.

Malignant endocarditis. (Cases 19 & 20.)

In these two cases the platelets were diminished in number and in both there was a definite thrombocytopenia especially during the week or two before death.

Pernicious anæmia. (Cases 21 to 25 inclusive.)

In this disease diminution in the number of platelets has been reported by several authors.* In all the cases here investigated there was a reduction in the platelet count, and in three, cases 21, 24 and 25, there was a definite thrombocytopenia before treatment. After feeding the patients with liver, the thrombocytes increased in each case to about 400,000 with the exception of case 21 in which the platelet counts remained at a lower level. The platelet curve of case 23 showed a very quick response to the above treatment, the thrombocytes reaching a total of over 900,000 within two weeks. Thereafter there was a fall to within healthy limits.

Anæmia secondary to hæmorrhage from hæmorrhoids. (Cases 26 & 27)

There was no diminution in the number of thrombocytes but the

* References 65, 70, 72, 96 & 124.

platelet curve in each case differed. The variations in case 26 were slight but in case 27 the curve showed a steady increase to the very high value of 1,700,000 followed some days later by a fall to more normal numbers

Anæmia secondary to hæmorrhage from stomach and duodenum. (Cases 28, 29, 30 & 32.)

Cases 28, 29 and 30 were very similar in that all three suffered from duodenal ulceration and the hæmorrhage, as shown by the degree of anæmia, was rather copious. In each a platelet increase occurred. It commenced previous to, or immediately after, the cessation of the bleeding as indicated by the presence of melæna. After the curve had reached its height there was a drop to more normal values but in cases 28 and 29 there was a secondary rise and fall. With regard to case 30 the thrombocytosis was not so pronounced but it will be seen from the later platelet counts that the normal for this patient was probably low. The white cells were also reduced in this case so it is likely that the bone-marrow was less active than in the two other cases. Case 32 did not show any reaction after the hæmorrhage which was not however, the prominent feature of the illness.

Chronic gastric ulcer. (Case 33.)

Coincident with the general improvement in the condition of the patient there was an increase in the platelet count. Thereafter the platelet numbers remained more or less constant near the higher limit found in health.

Lobar pneumonia. (Cases 34, 35 & 36.)

Reimann[87] found in this disease that the number of platelets was diminished in the acute phase and increased in convalescence.

In general these three cases conformed to the above findings. In the first two the platelets were reduced in number until the

fifth day of the illness and then, before the crisis they commenced to increase. In the third however, the thrombocytes were very high on the fifth day and although there was a subsequent fall, the numbers were never much lower than 400,000. However after the crisis had passed a thrombocytosis occurred in this case also. In all three the platelets rose to values round about 1,000,000 and as convalescence advanced the curves fell to within healthy limits.

Acute rheumatism - Rheumatic fever. (Cases 37 to 45 inclusive.)

In this disease the results were not uniform, possibly because of the fact that the patients investigated had been ill for varying intervals before admission to hospital. Even so, certain interesting features were made out.

On the whole the platelet count tended to be high, only in case 37 did it ever reach to a value below 200,000 and that at a time when convalescence was well advanced. The curves of cases 41, 42 and 43 were noteworthy in that each showed evidence of a platelet reaction reaching to a value of at least 1,000,000. These cases were seen within ten days of the onset of the illness and it is possible that the higher counts noted at the commencement of the curves in cases 37, 39 and 40 represent the latter part of the reaction which may have occurred previous to admission to hospital. In the remaining cases, 38, 44 and 45 - the last being a case of rheumatic pericarditis and pleurisy - the thrombocytes did not show any noteworthy behaviour.

When a thrombocytosis occurred it did not seem to be related to convalescence, unless it heralded the onset of that condition, for it was present when the patient was acutely ill with pain and fever - cases 37, 39, 40 and 43 - as well as in convalescence - cases 41 and 42. Further, the increase was not influenced by age

or the presence of any particular manifestation of the disease, as for example, a cardiac lesion.

Acute nephritis. (Cases 47 to 53 inclusive.)

All the cases had hæmaturia.

The platelets always tended to be high in number rarely being lower than 300,000.* Case 50 showed a slight thrombocytosis but in cases 51, 52 and 53 it was a very prominent feature. In these cases it commenced during the presence of hæmaturia which may however, be present without giving rise to a thrombocytosis - case 47.

Chronic nephritis. (Cases 54 & 55.)

The platelets were always present in fairly large numbers. Both cases showed a marked platelet increase but case 54 demonstrated how quickly the platelet count can vary. The rapid fall from over 1,000,000 to just over 400,000 coincided with the appearance of pus in the urine for a period of two days. In both cases hæmaturia was present.

Diabetes mellitus. (Cases 56 to 61 inclusive.)

In this disease although the platelets varied between the moderately high value of 495,000 and the low value of 95,000 (case 56) it was found that on the average the platelet numbers were diminished and varied between 100,000 and 300,000. The administration of insulin did not appear to influence the platelet count.

Malignant disease. (Cases 32, 62, 63, 67, 68 & 69.)

The platelets in the several types of this disease investigated did not vary in any characteristic manner. On the whole there was a tendency for the numbers to be high. This finding is in agreement with those of Rud[147] who found the thrombocyte count to be high in

* Note. The low count of 193,880, recorded in case 48, was noted immediately previous to the onset of an epileptic fit.

cases of cancer of the cervix uteri.

Jaundice, various causes. (Cases 64, 65 & 66.)

The platelets were found to vary between 200,000 and 400,000.

Pelvic sepsis. (Case 70.)

The thrombocytes varied between 200,000 and 740,000. A marked increase was observed after the appearance of hæmaturia of two days duration. Apart from this increase the platelets tended to be diminished in number. The patient was never seen in convalescence.

Pyæmia. (Case 71.)

When this case was first seen the platelets were low and it was found that the numbers diminished progressively until death.

Chronic tuberculosis. (Cases 31, 72 & 73.)

There is a certain amount of evidence to show that the thrombocytes tend to be high in chronic forms of tuberculosis.[26,80] Cases 72 and 73 conformed to this tendency, the numbers varying between 400,000 and 800,000. Case 31 while in hospital developed acute tonsillitis which coincided with a marked diminution in the platelet count. As this acute infection subsided the platelet numbers varied but on the whole they gradually increased and settled at a level within normal limits.

Hyperthyroidism. (Case 74.)

The platelets varied between 200,000 and 400,000.

From a survey of the platelet counts in these diseases certain interesting facts emerge. Thus, the number of circulating platelets may vary with the disease and also in the same illness according to the stage, whether acute or convalescent. Furthermore, the behaviour of the thrombocytes also seems to depend on the reactive power of the individual bone-marrow, which in turn, can be influenced by

various agents such as X-rays, phenylhydrazine hydrochloride, liver and splenectomy.

The great variability in the thrombocyte numbers makes it difficult and of very doubtful value to classify the diseases according to the platelet count. However from the study of the foregoing cases it can be stated in a very general way that the platelets were diminished in the following diseases:- acute myeloblastic leukæmia, splenic anæmia, malignant endocarditis, pernicious anæmia (relapse), acute tonsillitis, lobar pneumonia (precritical phase), and pyæmia. They were normal or only slightly diminished in Henoch-Schönlein and static purpura, in scurvy, hæmophilia, acholuric jaundice, diabetes mellitus, certain hepatic diseases, pelvic sepsis and hyperthyroidism, while in chronic myeloid leukæmia, secondary anæmias, lobar pneumonia (convalescence), acute rheumatism, nephritis, malignant disease and chronic forms of tuberculosis the thrombocytes were normal or increased in number. In purpura hæmorrhagica and polycythæmia vera they were found in some cases to be diminished and in others to be increased. With regard to the diseases underlined it has not been possible to find any publications dealing with the platelet count in these conditions. Apart from these the observations made agree in a general way with those reported by others. The only unusual feature recorded is the high platelet count observed in cases of purpura hæmorrhagica.

CAUSE OF VARIATION IN THE PLATELET COUNT IN DISEASE.

The problem as to why there should be such a great variation in the number of circulating platelets is one which is difficult to explain in view of the uncertainty which exists regarding not only the origin, function, and destruction of these elements but also the pathology of some of the diseases investigated.

It has already been pointed out that the bulk of the evidence favours the idea that the thrombocyte is produced in the bone-marrow, probably by the megakaryocyte. This hypothesis is reasonable and when considered along with what is actually known of the pathology of the diseases investigated, some conclusions may be drawn as to the reason for these variations.

Thus in acute myeloblastic leukæmia the reduction in the number of thrombocytes and also the presence of anæmia would be explained by the fact that the hyperplasia of, and great activity in, the leucopoietic tissues of the bone-marrow would result in the crowding out of the platelet-forming cells as well as the erythroblastic tissue. This is illustrated in case 10 by the rapid increase in the number of immature white cells which coincided with the steady diminution in the thrombocyte count.

With regard to chronic myeloid leukæmia it is probable that the variations in the platelet count in individual patients will depend on the degree of activity in the leucopoietic and thrombopoietic tissues in each case. Thus the activity of both may be slightly or greatly increased (megakaryocytes are frequently found to be increased in the bone-marrow in this disease and they have also been observed in the circulating blood) or, although both are

active, the activity of white cell tissues may be relatively much greater than that of the platelet-forming tissues. It has already been pointed out that in acute leukæmia the hyperplasia and activity of the myeloid tissues may be such that the formation of platelets is interfered with and a thrombocytopenia result.

This difference in the degree of activity of each of the components of the formative tissues of the bone-marrow is well shown by the three cases of polycythæmia vera. In case 13 the red cell count was very high while the leucocyte and the platelet counts were low suggesting that erythropoiesis predominated in the bone-marrow. In case 14 the moderate erythrocytosis was associated with a slight leucocytosis and a very slight increase in the platelet count while case 15 illustrated the association of polycythæmia with a greater leucocytosis and a normal platelet count which was somewhat lower than that of the previous case. The two last cases illustrate a state of generalised activity in the bone-marrow, no one tissue reacting to the exclusion of the others.

With regard to the action of the spleen on the platelet count in leukæmia and polycythæmia it is conceivable that this organ might ultimately be unable to destroy the thrombocytes at the same rate as they are produced in the marrow and thus an increase in the number of circulating thrombocytes result. While this possibly occurs in some instances it is thought that alteration in productive activity rather than impairment of splenic function is by far the more important factor in bringing about change in the number of thrombocytes in the blood stream.

In pernicious anæmia the number of platelets is diminished. It is likely that the thrombocyte-forming tissues in common with the erythropoietic and leucopoietic tissues, are also influenced

by the pathological process responsible for this disease. Indeed there is some evidence to show that in pernicious anæmia the megakaryocytes of the bone-marrow are reduced in number.[223] The improvement in the condition of the patients brought about by liver treatment, is reflected as much by the increase in the number of platelets as by the increase in the number of red cells.

The inference that the bone-marrow in splenic anæmia, as illustrated by case 16, is inactive is justified by the presence of anæmia and leucopenia, and by the absence in the blood picture, of signs of regeneration on the part of the erythropoietic and leucopoietic tissues. It is likely also that the activity of the thrombopoietic tissues is diminished and in this way reduction in the thrombocyte count results. There was no evidence that in case 16 the spleen was hyperactive in destroying blood elements.

The diseases in which the greatest and most interesting variations in the platelet count were observed in this work now come up for consideration. They may be divided into two groups, the one characterised by hæmorrhage and the other by infection and toxæmia.

Diseases associated with hæmorrhage (except purpuric hæmorrhage). (Cases 26 to 30 inclusive, 32, 47 to 55 inclusive and case 70.)

The increase in the number of thrombocytes which occurs in secondary anæmias is fairly well known and has been recognised clinically for some time, especially in those cases where the anæmia has followed hæmorrhage. After rabbits had been bled Bunting[59] and Degkwitz[72] found that, following a temporary diminution in the platelet numbers, a thrombocytosis resulted. It is therefore not surprising that of the cases included in this group many - cases 27 to 30 inclusine, 50 to 55 inclusive and 70 - showed an

increase in the platelet count which could only be ascribed to the circumstance that blood had been lost. It has to be pointed out however that this phenomenon was not observed in every case but in case 26 the presence of large numbers of immature platelets suggested that the thrombopoietic tissues were active. In cases 32, 47 and 48 the hæmorrhage was slight and in cases 47, 48 and 49 the investigation was not carried out long enough to show whether a platelet reaction might follow. Indeed the counting of platelets in cases 47, 48 and 49 was, at that time, undertaken only to ascertain if by any chance the bleeding was related to the presence of a thrombocytopenia. This was found not to be the case as there was no diminution in the numbers when the bleeding took place.

It is therefore noteworthy that the platelet reaction was well marked in all the cases which were fully investigated, especially where much blood had been lost, and it must be assumed that the loss of blood was responsible for this augmentation in the numbers. The rise and fall in the platelet curve was observed to take place during the hæmorrhage or, more frequently, the increase commenced during the bleeding and reached its height after all sign of blood loss had disappeared. Sometimes the thrombocytosis was not observed until after the hæmorrhage had ceased.

The question arises as to whether this thrombocyte reaction is the result of an increased functional demand for platelets in view of the part these elements are said to play in hæmostasis, or whether it is merely a regenerative response on the part of the thrombopoietic tissues to make good the platelets lost in the bleeding. In light of the observation that where the bleeding was slight there may be no thrombocytosis and the fact that the peak of the increase frequently occurred when the hæmorrhage had ceased

and no platelets would be required for hæmostatic purposes it is likely that the platelet reaction is, in great part at least, a regenerative process and reflects the state of generalised activity occurring in the hæmopoietic tissues of the bone-marrow when a loss of blood has to be made good. This conclusion is all the more justified when, on consideration of cases 28 and 29, one tries to explain the secondary rise and fall in the platelet curves which occurred in the absence of hæmorrhage. In both cases the bone-marrow was in a reactive and unstable condition, as shown by the continued rise in the erythrocyte curve. In this connection it is interesting to note that increase in the number of megakaryocytes in the bone-marrow was found by Bedson and Johnston[36] to follow red cell destruction.

Diseases characterised by infection and toxæmia. (Cases 19, 20, 31,34 to 45 inclusive, 54 and 71.)

All the conditions considered under this heading gave some evidence of the presence of an acute infective process, and for the most part were distinguished by the behaviour of the platelet curves. These showed that, in the acute phase of the illness, there was a tendency for the platelets to become diminished and that, during convalescence, the thrombocytes tended to increase after which there was a gradual fall to within normal limits.

Isolated observations are to be found, mostly in foreign literature, regarding the variations in the thrombocyte counts in certain diseases. Thus in pneumonia,[187] diphtheria,[79] scarlet fever,[44,204] and the common cold[25] the thrombocytes have been found to be diminished in number in the acute stage of the illness and increased in convalescence. They have also been reported as reduced in influenza,*

* References 72, 125, 187 & 204.

hæmorrhagic small-pox, and typhus.[191,204]

The result of the investigations carried out on the diseases in this group is, with one exception, in general agreement with these findings. In malignant endocarditis (cases 19 and 20), and pyæmia (case 71) the platelets became progressively reduced until death supervened and in cases 31 and 54 the onset of tonsillitis and pyuria respectively produced a diminution in the thrombocyte counts. In two of the three cases of pneumonia (cases 34 and 35) the platelets were reduced to below 200,000 at some time during the acute period of the illness but in the third, case 36, they numbered over 1,000,000 on the fifth day of the illness and although the numbers were subsequently reduced for a few days, the diminution was only relative as the readings were never below the average number found in health. In all three cases however the thrombocytic increase occurred in convalescence.

Acute rheumatism proved to be the exception to the general rule. In this disease the platelets were never observed to be diminished when the patient was acutely ill - in fact the platelet numbers on the whole were high, and low readings were obtained only in one patient, case 37, and that at a time when convalescence was well advanced. Cases 37 and 39 to 43 inclusive showed evidence of a thrombocytosis which was most marked in the last three of these six cases. The time at which this platelet increase occurred in acute rheumatism differed from that observed in pneumonia in that it took place in some patients during the acute phase of the illness and in others during convalescence.

The almost consistent behaviour of the thrombocyte numbers which has been observed in the course of these infective illnesses, with the exception of rheumatic fever, suggests that the platelet

has an important function to perform and it is of interest to consider at this stage some of the experimental work and the conclusions derived therefrom which have some bearing on this subject.

Levaditi,[150] in 1901, noted in the course of other work, that cholera spirilla when injected into the circulation of vaccinated guinea-pigs sometimes became adherent to blood platelets. Some ten years later, Aynaud[21] observed that certain organisms brought about "in vitro" agglutination of thrombocytes. Neither of these observers however associated their findings with the elimination of organisms from the body and it is really from the work of Bull that most of the recent experimental work has its origin. Bull* in a series of publications in 1914 and 1915, reported that streptococci and pneumococci when introduced into the circulation of experimental animals rapidly disappeared from the blood unless they were extremely virulent. He further observed that typhoid bacilli and dysentery bacilli of the Flexner group were spontaneously agglutinated in the blood stream of the rabbit although in the case of the pneumococcus and the Shiga strain of dysentery bacillus agglutination occurred only when an anti-serum was injected into the circulation. In both cases the agglutinated organisms were rapidly removed and destroyed in the visceral capillaries. Any bacteria not so agglutinated remained in the blood stream and produced a septicæmia.

Delrez and Goværts**following up the work of Bull demonstrated that in the blood stream of the rabbit staphylococci and bacillus paratyphosus B adhered to the thrombocytes. This adhesion was associated with the disappearance of bacteria from the blood stream

* References 53 to 56 inclusive.
** References 73, 107 & 111.

and a diminution in the number of circulating thrombocytes. Two minutes after injection, mixed masses of platelets and organisms were found in the capillaries of the liver and spleen. This phenomenon was not observed when a virulent pneumococcus was injected into the rabbit. In the dog however the same virulent strain of pneumococcus united with the platelets and both disappeared from the circulation. Continuing the investigations Goværts[109] found that intravenous injection of washed blood platelets accelerated the elimination of typhoid bacilli from the blood of guinea pigs. He observed also that the red blood corpuscles of the sheep, after exposure to the action of rabbit plasma, were agglutinated "in vitro" by the platelets of the rabbit.[106] The same occurred in other animals when foreign red cells or particles of indian ink were injected into the circulation.[103,107]

All this work suggests that the thrombocyte plays an important role in maintaining the sterility of the blood stream by removing organisms and foreign substances to the deep viscera for ultimate destruction. Goværts* considered that adhesion of organisms to thrombocytes was comparable to the first steps in phagocytosis and he thought that it depended on the opsonic action of the plasma or serum on the bacteria, particles of indian ink and erythrocytes of animals of another species.

In addition to this important function of removing bacteria from the blood Popesco produced evidence to show that blood platelets took a more active part in protecting the organism against bacteria and their toxins. He demonstrated (a) that platelets from immunised and non-immunised animals prevented hæmolysis by

* References 104, 105, 107 & 110.

staphylolysin[179] (b) that well washed platelets from immunised rabbits when in contact with fresh serum brought about granular change in the cholera spirillum whereas this alteration was not produced by platelets from non-immunised animals,[180] (c) that the thrombocytes of a rabbit immunised against red cells of an animal of another species, for example, the sheep, produced hæmolysis when brought into contact with these red cells,[181] and (d) that platelets from a rabbit immunised against the cholera spirillum when injected into guinea pigs afforded some degree of immunity to these animals.[182] This same writer working with Combiesco[183] also demonstrated that the watery extract of platelets of a suitably immunised rabbit had a protective action against the cholera spirillum. A similar extract of platelets from non-immunused animals, although it afforded some slight protection, was not nearly so effective in its action. From this work it would seem that the platelet takes some part in keeping the body immune from infection.

The work of Goværts and Popesco thus suggests an explanation for the reduction in the thrombocyte numbers observed in acute infections. Diminution in the count would be due to the using up of platelets in removing and in destroying the infecting agents. In this connection it is interesting to note that absolute or relative diminution in the thrombocyte count occurred in cases 19, 20, 34, 35, 36 and 71. In cases 20 and 71 organisms were grown on blood culture, and in cases 19, 34, 35 and 36 the presence of organisms in the blood could be assumed with a reasonable degree of certainty. Further, when case 46 was given an intravenous injection of T.A.B. vaccine, the number of organisms injected being 100,000,000, it was found that the platelets in the capillary blood steadily diminished in number for twenty-five minutes after

the injection. Forty minutes later they had increased and within two hours they had regained their original level. All these observations are in keeping with the idea that the platelet is an important means whereby the organism is rendered immune from bacterial infection. Accordingly it would be reasonable to expect that where a thrombocytopenia existed there would be lowered resistance to infection. Certain writers take this view. Cramer, Drew and Mottram[67,68] considered that the increased susceptibility to infection which was found in rats when fed on a diet deficient in vitamin A, or exposed to the action of X-rays or radium, was due to the thrombocytopenia which resulted. They showed that sepsis occurred only when the platelets became diminished in number.

In spite of all the foregoing evidence the interpretation of the reduction in numbers as being due to a using up of thrombocytes in the elimination and destruction of bacteria is not free from objection. Although there may be no doubt that thrombocytes can adhere to organisms and other foreign bodies it is still not clear that this adhesion occurs to such an extent that the platelets are reduced in number and it certainly does not follow that this adhesion proves that the thrombocytes are really an important barrier against bacterial invasion. It has been shown that diminution in the number of thrombocytes did not occur in rheumatic fever and in case 36 - lobar pneumonia - although there was a relative diminution the numbers were never much below 400,000. It is recognised however that in acute rheumatism the presence of an infecting organism in the blood has not been established to the satisfaction of everyone and in the case of lobar pneumonia it is possible that the infecting agent was of a type that did not bring about adhesion of platelets to itself. Even so, these findings tend to cast some doubt

on the idea that the platelet is an active agent in maintaining the sterility of the blood stream, and that the presence of organisms in the blood brings about a reduction in the number of thrombocytes. Other observations which have been made justify this doubt.

It has been shown that in diphtheria[79], in which disease the causal organisms are not found in the blood, reduction occurs and the same result can be procured experimentally with diphtheria toxin[79] and the purpuric principle extracted from the pneumococcus.[123,198] Further it is not commonly the case that the thrombocytopenia met with in purpura hæmorrhagica and pernicious anæmia is associated with an increased susceptibility to infection. Furthermore it may be said, in contrast to the observations of Cramer and his co-workers, that Bedson and Zilva,[37,38] and Stammers[205] independently, were unable to produce a thrombocytopenia after feeding rats on a diet deficient in vitamin A. Some other explanation will therefore have to be found for the susceptibility to infection which occurs in the absence of vitamin A from the diet.

The best evidence that the platelet is not of any great importance as a barrier against infection is provided by the demonstration that bacteria can be eliminated from the blood in the absence of platelets. Goværts[108] himself discovered this on injecting bacillus typhosus into the guinea pig after producing a thrombocytopenia with anti-platelet serum. Delrez[73] and he also noted that when a rabbit suffering from pneumococcal septicæmia was inoculated with anti-pneumococcal serum the pneumococci were agglutinated to each other and disappeared from the circulation without any participation of the blood platelets. This was also observed to be the case by Bull and McKee[57] who showed that in immunised and non-immunised animals, whether deplateletised or not, agglutination of bacteria

depended on the amount of agglutinin the animal possessed and not on the presence of blood platelets. They also demonstrated that thrombocytes were not essential to the formation of bacterial clumps and that the presence of these elements in the agglomerations was merely an incidental phenomenon. Furthermore it was shown by Manwaring and Coe[155] that the capillary endothelium of the liver of an actively immunised rabbit fixed pneumococci when perfused with a quantity of Ringer's solution containing these organisms. This did not occur in the non-immunised liver except when immune serum was added to the perfusing fluid. It is apparent that other factors, humoral and cellular, are concerned in keeping the blood sterile and free from foreign bodies and it is likely that the sterility of the blood depends on the opsonising action of the blood plasma which brings about true agglutination of organisms between themselves and their adhesion not only to platelets but also to the phagocytes of the blood and to the cells of the reticulo-endothelial system.

The primary importance of the plasma in the phenomenon of elimination of foreign bodies is further emphasised by the demonstration by Roskam[195] that adhesion of opsonised foreign bodies to the platelets was independent of the life of these elements and was not due to a secretion liberated before death. He also found that despite a series of washings a pellicle of plasma adhered by adsorption to the surface of the thrombocytes so that the adhesion of opsonised organisms and other foreign bodies was not effected at the actual surface of the platelet but was due to the layer of surrounding plasma. Agglutination and adhesion are thus passive phenomena and not the result of any vital activity on the part of the thrombocyte. According to this view agglutination of bacteria is essentially a humoral function and the part played by the platelet

in removing organisms from the blood is accidental and is due to the "plasmatic atmosphere" which surrounds it.

While that is so, it should be mentioned that Popesco[181] in his experiments on the hæmolytic action of immunised platelets (page 51) could not attribute the hæmolysis to traces of hæmolysin which still adhered to the platelets. He found that the fluid in which the platelets were last washed did not have any hæmolytic power, and conversely, that normal platelets which had been in contact with hæmolytic serum and then washed in a similar manner did not possess any hæmolytic action.

Until the differing observations of Roskam and Popesco are satisfactorily explained the question as to whether or not the platelet is an active or passive agent in removing foreign bodies from the blood stream must remain open. In the meantime the more convincing evidence favours the idea that the blood plasma plays by far the greater role in combating microbic invasion of the blood stream and that the platelets have a minor and very unimportant part in the elimination of bacteria from the blood stream. Some cause other than the simple using up of platelets for the removal of organisms will therefore have to be found to explain the tendency to reduction in the platelet numbers in acute illnesses.

It is thought that in acute infections alteration in the platelet count is due to the presence within the body of a toxic agent. In the acute phase toxic disturbance would inhibit or otherwise modify the activity of the platelet-forming tissues and thus, according to the disease, the degree of toxæmia and possibly the duration of the infection there would be varying degrees of diminution in the thrombocyte count. In rheumatic fever and chronic forms of tuberculosis, cases 72 and 73, the toxic disturbance may not be

enough to produce a preliminary reduction in the platelet count; thus the numbers tend to be high. That the thrombocyte count depends to some extent on the degree of toxæmia is shown by the observation that although larger doses of tuberculin and diphtheria toxin poison, smaller doses irritate, the thrombopoietic tissues.[74]

With regard to the thrombocytosis which has been noted in the acute illnesses investigated it follows that it must be due to one of two causes. In the first place when it is preceded by reduction in the thrombocyte count and occurs just before or during convalescence it will be a reactive process due to subsidence of the infection and the removal of toxic inhibition of the platelet-forming tissues. On the other hand if it takes place when the patient is acutely ill as in rheumatic fever, cases 37, 39, 40 and 43, it is possible that it is evidence of stimulation of thrombopoiesis or that it is a reactive process indicating the approach of convalescence. It is unlikely that the thrombocytosis observed had anything to do with the establishment of a period of immunity to infection for it was observed to occur in case 33 in which there was no evidence of bacterial infection or toxæmia. When first admitted to the ward this patient was pale and ill-looking but with the improvement in her general health and the onset of a feeling of well-being a thrombocyte reaction resulted. It has been shown also that a similar rise in the platelet count occurs in the convalescence which follows surgical operations* and parturition[77] in the absence of sepsis.

According to this view the thrombocyte increase which so often occurs in convalescence merely reflects the state of bone-marrow activity and as such may be brought into line with the thrombocytosis noted in the hæmorrhagic group.

* References 32, 36, 71, 120 & 149.

THE CAUSE OF THROMBOCYTOPENIA IN PURPURA HæMORRHAGICA.

The frequent occurrence of thrombocytopenia in this disease has induced many authors to consider it the essential lesion and the one which explains all the symptoms characteristic of the illness. It has therefore become a matter of importance to find out how this great reduction in the thrombocyte count is brought about. Theoretically such a reduction could either be caused by diminished thrombopoietic activity or by increased activity in the platelet destroying tissue - the reticulo-endothelium - most of which is contained in the spleen. There are two theories each of which attempts to explain the cause of the diminished thrombocyte count in purpura hæmorrhagica.

The one attributes the thrombocytopenia to interference with platelet production due to selective toxic injury of the megakaryocytes in the bone-marrow. According to the adherents of this idea the myelotoxin arises in the spleen, therefore the good results which follow splenectomy are due to the removal of the source of the toxin.

Greater support has however, been given to the other theory the followers of which believe that the spleen is overactive in destroying platelets.[124] It has been shown that the blood platelets found in the thrombocytopenia of purpura hæmorrhagica are frequently very large thus suggesting regenerative activity in the marrow, rather than inhibition, an idea which is in turn supported by the finding that there is an increase in the number of megakaryocytes in the marrow. With regard to excessive destruction of platelets, supporters of this theory think that the presence of many platelets within the spleen, when contrasted with the thrombocytopenia of the blood, is evidence

of increased destruction of these elements and the fact that there is an immediate increase in platelet numbers after splenectomy is to them additional proof that the spleen is hyperactive in platelet destruction as it is unlikely, if the bone-marrow were injured by toxins, that the thrombocyte increase would be so sudden. They explain the cases in which there is a gradual return of the platelets, after splenectomy, to the former low level, and those cases in which removal of the spleen is not followed by an increase in the number of thrombocytes, by stating that other parts of the reticulo-endothelial system have taken over the function of the spleen, or that the whole of this system including those parts outwith the spleen, has been hyperactive from the beginning. It is known that vicarious hyperplasia of the reticulo-endothelial system may occur in splenectomised animals.[17] According to this view the operative results depend on the degree of hyperactivity of the reticulo-endothelial system outside the spleen.

If the reticulo-endothelium plays such an active part in the pathology of purpura hæmorrhagica it would be expected that examination of spleens removed from patients suffering from this disease would afford some evidence of increased destructive activity. The following is a brief summary of the more important appearances which have been noted.* The spleens varied in size, some were enlarged and others normal. The capsule and trabeculæ in some cases were thickened and the organ was soft and pulpy. The malphigian bodies were prominent, normal or under developed. The most constant of the changes reported was primary or secondary proliferation of the reticular cells in the sinuses and malphigian bodies. Some observers

* References 48,65, 99,124,128,166,167,201,203 & 207.

noted the presence of platelets or platelet-like substances within the endothelial cells, but others could not find, and others did not look for, any evidence of platelet destruction. Endothelial proliferation was found in a lymph gland removed at the time of splenectomy in a case of purpura hæmorrhagica by Sutherland and Williamson.[207]

With regard to the second theory it cannot be claimed that the evidence in favour of increased platelet destruction in the spleen is entirely satisfactory. The presence of more thrombocytes in this organ than are present in the blood is not sound proof of increased destruction for it is known that the spleen may act as a reservoir for platelets - see page 28. Again endothelial proliferation in the spleen might indicate that this organ was the source of some altered secretion which is introduced into the blood stream and upsets thrombopoiesis. Further, direct evidence of platelet destruction is not always found and what evidence there is is not very convincing. In addition, a very quick increase in the platelet numbers comparable to that occurring after splenectomy, for example in case 18, can occur where there has been toxic damage or toxic inhibition of the bone-marrow: rapid spontaneous increases are shown in many of the graphs in the appendix, notably that of case 35.

With regard to the idea that there is toxic interference with platelet production in the bone-marrow the work of Seeliger[201] is interesting. In a study of the spleen and the bone-marrow in essential thrombocytopenia he found that in about half of his cases the number of thrombocytes in the spleen was increased and he was of the opinion that in these cases there was destruction of defective platelets. In the remaining cases he got no evidence either of increase in the number of platelets contained in the spleen or of increased destruction

of these elements. In the bone-marrow of two cases there was no diminution in the number of megakaryocytes but Seeliger found that these giant cells showed signs of nuclear degeneration and were deficient in granules: indeed many were agranular.* This observer was of the opinion that the thrombocytopenia was due to toxic disturbance interfering with the normal functioning of the megakaryocytes.

Considering all the evidence it seems to be agreed that the platelet-forming cells are not diminished or absent. Even so it is not clear whether the thrombocytopenia of purpura hæmorrhagica is due to diminution in thrombopoietic activity or excessive platelet destruction in the spleen and there is room for doubt regarding the reliability of the evidence in favour of the latter view.

At this stage it is necessary to take a wider view of the subject. Reference to the four cases of purpura hæmorrhagica mentioned in this work will show that only in one, case 4, was a marked thrombocytopenia observed, and that on a previous occasion the platelets, though somewhat diminished, were not so low as to constitute a thrombocytopenia. In case 1 the thrombocytes were also diminished during the observations of 1928 but in 1929 they were rather above the average number found in health. The other two, cases 2 and 3, always showed high counts. During 1929 morphological examination of the platelets of cases 1, 2 and 3 did not give any clue, as would be suggested by the presence of immature forms, that the high counts in these cases were due to increased thrombopoietic activity in response to excessive platelet destruction. From the evidence afforded by the study of these cases it is apparent that

* Note. The material from one of Seeliger's cases was obtained by sternal puncture before splenectomy.

in purpura hæmorrhagica the platelets may vary numerically within wide limits. Thrombocytopenia may be present, or the platelets may be moderately diminished, normal or slightly increased in number in the presence of hæmorrhagic symptoms. Further, spontaneous increase in the count may occur without removing the spleen. Other writers have recently reported cases in which there was no reduction in the number of platelets* and Forster's[94] cases illustrate that in addition spontaneous numerical increase may follow thrombocytopenia.

It is very doubtful therefore if, in purpura hæmorrhagica, thrombocytopenia is the cause of the characteristic lesions. Rather it would seem that the platelet count varies independently of the hæmorrhages and that thrombocytopenia, although very commonly associated with bleeding in this disease, is merely a superimposed phenomenon of secondary importance. Tidy[214] is of the opinion that fall in the platelet numbers is secondary to damage of the capillary endothelium and loss by hæmorrhage. This hypothesis is not supported by the knowledge that in other diseases in which there is damage to, or alteration in the permeability of, the capillaries as in scurvy - cases 7 and 8 - and Henoch-Schönlein (anaphylactoid) purpura - case 5 - the platelets are not greatly diminished. With regard to the latter disease it has been found that in experimental anaphylaxis the transitory diminution in the number of thrombocytes is due to their agglutination and not to the demands made on them for protection of capillary walls.** It has already been pointed out that the presence of thrombocytes in increased numbers does not prevent prolonged hæmorrhage (cases 2 and 3). This would be unlikely if the platelets protected the capillary walls. Again there is no

* References 100, 152 & 196.
** References 10, 11 & 12.

apparent reason why thrombocytopenia or even diminution in the thrombocyte numbers should be present in this disease if the platelets are merely used up in protecting the capillary vessels seeing that the bone-marrow is active, or potentially active, as shown by the presence of megakaryocytes in normal or increased numbers and the frequent thrombocytosis which immediately follows splenectomy. Loss of platelets by hæmorrhage would not account for the thrombocytopenia as the platelets may be markedly reduced in some cases and yet the bleeding very slight. It is evident that some other factor is necessary to explain the thrombocytopenia which is frequently, but not always, present.

From the study of the four cases of purpura hæmorrhagica in this work it is thought that diminution in the platelet count so often found in this disease is a secondary or coincident phenomenon and not the essential cause of the illness. It has been shown that in diseases in which there is an undoubted toxæmia a reduction in the number of thrombocytes is a frequent occurrence and that a spontaneous increase follows when the toxic disturbance passes off. In all probability the variations in the thrombocyte count found in purpura hæmorrhagica are somewhat similar to those observed in toxæmic diseases. From the appearance of the megakaryocytes in the bone-marrow in purpura hæmorrhagica Seeliger[20] thought that there was toxic inhibition of thrombopoiesis. The "toxic" disturbance may not be of the same type as met with in acute infections and, considering the variations in the number of platelets, it may vary in intensity. Indeed the interference with normal thrombopoiesis may be due to some metabolic disturbance or to deficiency of some internal secretion. It is not altogether a new thing to have a thrombocytopenia produced by lack of some essential substance for,

in pernicious anæmia an increase occurs in the platelet count immediately liver is added to the diet - see page 66. According to this hypothesis the thrombocytopenia of purpura hæmorrhagica is due, not to excessive destruction but to interference with normal platelet formation.

OTHER FACTORS WHICH MODIFY THE PLATELET COUNT.

This group embraces those conditions in which variation in the number of circulating thrombocytes was brought about by (a) exposure to X-rays (b) by phenylhydrazine hydrochloride (c) by liver and (d) by splenectomy.

Influence of X-rays on the platelet count.

It is now well-known that leucopenia and anæmia can be produced when the ~~thrombopoietic~~ haemopoietic tissues are exposed to the action of deep X-rays. This knowledge has been made use of in the treatment of leukæmia and polycythæmia vera. Three cases of leukæmia, 10, 11, and 12, received this form of treatment and in all three leucopenia resulted. Similar therapeutic measures were adopted with two patients suffering from polycythæmia vera, cases 13 and 15, but only in the former was the desired result obtained, the red cells falling gradually from over 10,000,000 to about 4,260,000. In view of this action of X-rays on leucopoietic and erythropoietic tissues it was of interest to observe what influence irradiation would have on the blood platelet production as shown by the thrombocyte counts.

Frank[97] has reported cases of leukæmia in which, some time after exposure to this form of treatment, signs of purpura hæmorrhagica developed and on examination of the blood the thrombocytes were markedly reduced in number. Thrombocytopenia has also been produced in experimental animals after exposure to Roentgen rays. Lacassagne[130] and his co-workers exposed pregnant rabbits to the action of these rays and could not find any thrombocytes in the blood of the offspring and Möller,[164] after irradiating guinea pigs, produced a thrombocytopenia within 7 or 8 days.

The effect of radiation on cases 10, 11, 12, 13 and 15 varied. In acute leukæmia, case 10, the thrombocytopenia which was ultimately observed could not be attributed to the Roentgen rays as reduction in the platelet numbers seemed to be related to the increase in the white cells rather than to the X-ray treatment as the blood platelets were diminishing and the leucocytes increasing before X-ray treatment commenced. In chronic myeloid leukæmia the thrombocytes were diminished after irradiation in case 11 but not in case 12. The latter case had only one exposure and although the platelet count was somewhat lower after treatment it is doubtful if the diminution can be attributed to the X-rays, (see page 35). The results obtained in polycythæmia vera were also variable. In case 13, the platelet count did not seem to be influenced in any way. In case 15, the thrombocytes, after reaching a value of over 1,000,000 ultimately fell to below 100,000 and the impression was gained that in the beginning at least, the Roentgen rays stimulated the thrombopoietic tissues. In this case the polycythæmia was not influenced by the treatment.

In all these cases an erythema dose of deep X-ray therapy was given at each exposure but the total number of doses given varied in each case with the response to treatment.

From the results of these observations no very satisfactory conclusions emerge but it is apparent that, although the platelet numbers can be diminished by X-rays in the doses given, the effect varies with the patient and possibly with the disease, the thrombocyte count being more readily influenced in some cases than in others.

Influence of phenylhydrazine hydrochloride on the platelet count.

This drug has the power of destroying red blood corpuscles and it was used in the treatment of two patients, cases 14 and 15, both

of whom suffered from polycythæmia vera.[153] In each case the erythrocytes were reduced in number but the presence of reticulocytes and polychromasia showed that an active process of red cell regeneration was going on side by side with destruction. This together with the leucocytosis and increase in the number of platelets, pointed to the fact that the bone-marrow in both cases was very active. This generalised hæmopoietic activity was probably a response to the demand for red cells to replace those destroyed by the phenylhydrazine although it is difficult to exclude the possibility that the blood-forming tissues were not directly stimulated, in view of the knowledge that certain drugs, phenylhydrazine being one of them, can call forth a neutrophil polymorphonuclear leucocytosis. The increase in the platelet numbers may therefore be due to direct stimulation of the thrombocyte-forming tissues but it is much more likely that the thrombocytosis in these two cases is similar to that which is present after severe hæmorrhage and is merely an expression of generalised hæmopoietic activity. Attention has already been drawn to the finding of Bedson and Johnston[36] that an increase in the number of megakaryocytes occurred in the bone-marrow in presence of red cell destruction.

Influence of liver on the platelet count.

Impressed with the earlier work of Whipple Hopper and Robscheit[221] who found that liver was very efficient in promoting complete blood regeneration, Minot and Murphy[163] were the first to treat pernicious anæmia with that substance. Its beneficial action in that disease is now well-known and as five cases of pernicious anæmia admitted to the wards showed a diminution in the number of platelets the opportunity was taken to observe what influence liver treatment exerted on the thrombocyte count.

In all cases the blood platelets increased although in case 21 the count remained low. However most of the observations on this patient were carried out during the time he was reporting as an out-patient and it was not possible to be sure that liver was taken regularly. In the remaining four cases the thrombocyte counts increased to within normal figures while the patients were still in hospital. Cases 22 and 24 were known to have had pernicious anæmia for many years and it will be seen that the response in these cases was very gradual. The response in case 25 was however more rapid. In these three cases the counts never reached beyond 400,000 but in case 23 the curve was unusual in that it showed a very rapid rise to the high value of over 900,000 and then a gradual return to the 400,000 level. The two cases in which the more rapid response was observed were not of very long standing and it was noticeable that in these cases also there was an increase in all three formed elements of the blood - erythrocytes, leucocytes and thrombocytes.

It is apparent therefore that in pernicious anæmia treatment with liver produces an increase in the number of circulating thrombocytes. The platelet-forming tissues therefore participate in the general improvement in hæmopoietic activity produced by liver. It is not understood whether the liver supplies the marrow with some substance necessary for normal blood cell production, or whether it neutralises the action of some substance which is inhibiting or modifying this function.

Influence of splenectomy on the platelet count.

It has been stated in previous pages that the spleen destroys effete blood platelets, a function which it exercises in virtue of its association with the reticulo-endothelial system most of which,

in the human being, is contained in the spleen. Thus when splenectomy is performed an increase in the number of circulating platelets should result. This was found to be so in case 18, the numbers being maintained at a high level. Three and a half months after operation the count was nearly 700,000. This finding supports the conclusion that the spleen removes and destroys blood platelets, the numbers remaining high until some other tissue takes over the function of the spleen. It must be remembered however that after other operative procedures an increase in the platelet count occurs* so that the thrombocytosis following on splenectomy may be due in part to the operative interference. The increased platelet count due to surgical operation however does not become evident until about the sixth day after operation and normal numbers are reached within about three weeks. It may be concluded therefore that the behaviour of the thrombocytes after splenectomy in case 18 was due to the removal of the spleen and not simply to the surgical measures involved.

It is of interest to note that the platelet counts of case 17, two years after splenectomy, showed the thrombocytes to vary between 490,000 and 590,000. These numbers are perhaps somewhat high yet when compared with the higher values shown after splenectomy by case 18 they are in keeping with the idea that some tissue may have assumed the role of the spleen in regulating the number of platelets in the blood. Vicarious hyperplasia of the reticulo-endothelial tissue has been found in splenectomised animals by Pearce and Austin.[171]

* References 32, 36, 71, 120 & 149.

BLOOD PLATELETS AND COAGULATION.

The absence of general agreement as to the mechanism of coagulation of shed blood makes it somewhat difficult to discuss the relationship of the platelet to this process. In addition to this difficulty doubt exists in the minds of many people as to the part, if any, played by the thrombocyte in this very complex phenomenon. However a number of observers attribute to the platelet an important function in coagulation.

Hayem[43] and Bizzozero[43] thought that the blood platelets initiated the clotting process as they found that fibrin was formed only where thrombocytes had accumulated, for example, at the nodes in the fibrin network. The thrombocytes of frogs' blood have been observed, in the process of coagulation, to undergo agglutination and rapid disintegration[184] and they have been found also where strands of fibrin cross each other.[209] Moreover in certain crustacæ, the "explosive corpuscles" which are regarded as the homologues of the thrombocytes of the frog and the platelets of man, disrupt on coming into contact with clean foreign surfaces and then become the centres of coagulation.[208]
It has been said that a similar platelet cytolysis occurs when human blood is shed and thus spontaneous coagulation is inaugurated.[211,212]
This concept is supported by the observations of Tait and Burke[210] who watched the changes taking place in platelets contained in the plasma from which red corpuscles and white cells had been removed. Under dark field illumination they noted that the blood platelets first tended to agglutinate. The individual thrombocytes then gradually expanded until they suddenly disintegrated. When this occurred globules were liberated and projected into the surrounding

medium and in their trail they left a strand of fibrin. The fibrin was most dense where cytolysis had been most abundant. Tait and Burke regarded the globular material as thrombin. Wright and Minot[224] also thought that agglutination and fusion of blood platelets in shed blood was intimately associated with the early stages of coagulation.

Other workers also regarded the platelet as the source of a coagulating principle which was liberated on lysis of the element. Howell[118] and others[29,121] believed it to contain prothrombin and thromboplastin. Morawitz[165] thought it contained thrombogen and thrombokinase, while Bordet[45] regarded the blood platelet as one of the sources of cytozyme.

The importance of lysis of the platelet in setting in motion the clotting process seems to be substantiated by the well known fact that coagulation occurs only in the presence of free calcium. Calcium chloride has been found to produce lysis of platelets and it has been thought that under normal conditions calcium acts on the platelet and inaugurates clotting. It is noteworthy that many of the substances which preserve the morphological characteristics of the platelet also inhibit coagulation. Many of them fix calcium.* On the other hand it has been shown that platelet extracts reinforce and accelerate clotting**

The view that the thrombocyte is of primary importance in coagulation receives further support from the study of the clotting process as it occurs in plasma from which thrombocytes have been removed. It has been found that deplateletised mammalian blood clots but slowly[118,210] and Burke and Tait[61] considered that wholly deplateletised blood would not clot spontaneously on glass. Oxalated plasma, after filtration through a Berkefeld filter, is deplateletised and clotting

* Note. Pickering[172] does not think that a general correspondence exists between anti-coagulants and substances which preserve platelets.

** References 45, 69 & 126.

fails to occur on the addition of calcium chloride.[64] In the same way frog's plasma also remains fluid after filtration.[212] Similarly lymph and hydrocele fluid are platelet free and these coagulate only very slowly, if at all. They do not clot spontaneously and the process can be initiated and hastened by the addition of platelet extracts. The larger the number of platelets or the greater the quantity of the extract added the more rapid is coagulation and the richer the coagulum in fibrin.[45]

From all these experiments and observations it would seem that the thrombocyte is essential not only for the initiation of coagulation but also for the acceleration of the process.

It cannot be said that this conception is accepted by all as a number of observers deny to the platelet such an important function as the initiation of the clotting process in extravasated blood. They consider that the plasma and not the platelet is the primary factor on which coagulation depends. Denys,[74] in a case of purpura hæmorrhagica showing thrombocytopenia, found that the fibrin network was laid down without the presence of blood platelets. Achard and Aynaud observed that agglutination of blood platelets occurred independently of coagulation[1] and they found that the thrombocytes could remain isolated and independent of the fibrin network.[9] They thought that the modifications occurring in the platelets were secondary to the process of clotting and induced by the coagulating agents. Further, they did not observe any constant relationship between the integrity or alteration of the platelet on the one hand and the coagulability or incoagulability of the blood on the other.[4] Moreover, platelets can be preserved on oiled or paraffined surfaces, when the first stage of clotting - the formation of a reversible gel - has occurred.* From these observations it

* Burker, cited by Pickering.[172]

would appear that coagulation is initiated and fibrin laid down without the aid of blood platelets.

Certain work has also been done on the clotting of blood in the absence of blood platelets. After a thrombocytopenia had been produced by the injection of gelatine into the circulation it was found that the blood coagulated and retracted rapidly in the absence of thrombocytes[7]. Conversely, in incoagulable peptone blood, even after the thrombocytes had returned to the circulation the blood remained incoagulable.[5,176] The action of nucleic acid is similar to that of peptone as it exercises its anti-coagulating power in the presence or absence of platelets.[176]

The validity of the filtration experiments has been called in question on the grounds that although the platelets have been removed the plasma has also been modified. It has been pointed out that the filter holds back for a time not only suspended elements but also various proteins in colloidal solution in the plasma, in such a way that the earlier portions of the filtrate do not clot while the later portions coagulate readily.[101] Even as early as 1878 Hayem[113] found that filtered plasma clotted but the process took longer to complete.

It is apparent from these experiments that the plasma may be modified so as to inhibit coagulation thus suggesting that it is the plasma and not the platelet which is the important factor in coagulation.

It will therefore be seen that the position of the platelet in the process of coagulation is not definitely settled and that there is controversy as to whether the plasma or the platelet is of primary importance in this phenomenon. However it would seem that disintegration of platelets is not necessary for the inception of clotting and that coagulation of blood is due rather to alteration

in the stability of the colloidal equilibrium of the plasma. Pickering and Reeves[177] found that, although the thrombocyte-free plasma of birds coagulated slowly, it contained all the essentials necessary for coagulation. It appears however that platelets and their extracts can accelerate coagulation of deplateletised plasma or platelet-free fluids. This acceleration can also be produced by the addition of some tissue extracts and serum both of which probably act in virtue of platelet substance which they contain. In this connection it is difficult to exclude the possibility that the acceleration is due to the presence, in the extracts, of traces of the original plasma from which the platelets or their substances were obtained. It has been shown that it is difficult to get rid of such plasma as it is adsorbed to the platelet surface.[89,195] While that is so it is probable that platelets and their extracts hasten coagulation. Under this assumption platelets are not responsible for the commencement of coagulation and play only a secondary part in the process. They would however exercise an important influence on hæmostasis in that they would accelerate clotting. If this conclusion is justified it would receive support from the result of clinical investigation into the relationship between the duration of clotting time and the number of platelets in the circulation at the time of bleeding.

This relationship is not a subject to which a great deal of attention has been paid but a few references are available and from them it is apparent that the question is still unsettled. Roskam[191] produced an experimental thrombocytopenia in dogs and found that the clotting time remained more or less constant although the platelet count varied from over 400,000 to about 33,500. In certain diseases associated with splenomegaly showing thrombocytopenia

Rosenthal[170] did not find any change in the clotting time. Other authors* as the result of clinical investigation did not find any relationship between the number of platelets in the circulation and the coagulation time. On the other hand Evans[85] and others[74,198] were inclined to favour the idea that duration of clotting time varied with the number of thrombocytes in the blood and they published data to show that there was some slight correspondence, which however they did not wish to stress, between prolongation of coagulation time and thrombocytopenia on the one hand and diminished coagulation time and increase in the number of platelets on the other. In influenza with hæmorrhagic manifestations, delay in the clotting time has been attributed to reduction in the number of blood platelets.[125] In the acute phase of lobar pneumonia some authors found the coagulation time to be shortened[15] and others found it to be prolonged.[75,162] Let it be said here that in none of the three cases of lobar pneumonia investigated in this work did the coagulation time vary in any constant fashion either with the phase of the illness or with alteration in the number of circulating platelets.

These observations serve to illustrate the diversity of opinion on this subject. The clinical evidence afforded by investigation of the cases in the appendix, favoured the conclusion that alteration in the duration of clotting time did not depend on the number of platelets in the circulation at the time of bleeding. In practically every case the two varied independently of each other. In the same patient, case 10, the coagulation time was 1'45" when the platelets numbered 1,970 and 2' when the number was 194,035 or, as in case 36, when the clotting time was constant at 1'45" the thrombocyte count

* References 70, 74, 113 & 202.

on separate days was 377,585 and 1,007,770.

Where prolongation of coagulation time was present it was found not to depend on changes in the platelet count but rather on the presence of hæmophilia (case 9) or jaundice (cases 18, 62 & 65), but even where the latter was present delay in clotting was not a constant feature (cases 63, 64 & 66).

In hæmophilia the delay in coagulation has been ascribed to qualitative change in the hæmophilic blood platelet. Addis[13] showed that there was a defect in the prothrombin which revealed itself in the longer time this substance required to change into thrombin. Minot and Lee[161] working on the assumption that the platelet was the source of prothrombin, thought that the hæmophilic thrombocyte was defective, in that it failed to give up prothrombin readily. They demonstrated that platelets when isolated from normal blood and transferred to hæmophilic blood shortened the coagulation time although hæmophilic platelets when added to hæmophilic blood shortened the coagulation time only very slightly. Doubt has been thrown on the value of this work by Roskam[195] and Feissly[89] both of whom have shown that washed platelets are active only because of the plasma which is adsorbed to their surface. It is difficult to obtain platelet substance free from adsorbed plasma even after repeated washings. Thus it appears that the defect in the coagulability of the blood in hæmophilia is present in all probability in the plasma itself and not in the platelets. This is also the view of Pickering and Gladstone[173,174] who submit that the delay in clotting in hæmophilia is due to the persistence in adult life of an embryonic state of the plasma in which there is an excess of stable protective colloid.

From a consideration of the experimental work it must be concluded that the blood platelet takes some part in the process

of coagulation. If the results of "in vitro" experiments are accurate indications it is probable that the thrombocyte functions to hasten this process. Beyond this no further statement can be made. From the evidence afforded by the clinical data it is apparent that the number of thrombocytes in the circulation is no guide to the rapidity with which clotting occurs when blood is shed. On this account it is very doubtful if the platelet factor in the clotting process is of more than secondary importance. Coagulation of extravasated blood is a very complex phenomenon and the clinical data obtained in this work seem to strengthen the idea that coagulation depends primarily on the state of the colloidal equilibrium of the plasma.

BLOOD PLATELETS AND THROMBOSIS.

It is well known that the white thrombus is composed of blood platelets. Bizzozero[43] watched the formation of the thrombus in the mesenteric vessels of the frog by the gradual accumulation of platelets when the vessel wall was pressed upon or cauterised, and Eberth and Schimmelbusch[84] showed that when the blood flow was slowed down the platelets passed into the periphery of the stream and, if the vessel wall was damaged, they adhered to the injured surface. It is equally well recognised that when spontaneous thrombosis occurs the first step in the process is the formation of the white thrombus by adhesion of masses of platelets to the vessel wall. This thrombus can only be formed in the flowing blood stream and it is only when the lumen of the vessel becomes closed in the neighbourhood of the white thrombus that the column of blood becomes stationary and then rapidly undergoes coagulation to form the red portion of the thrombus.

Since the white thrombus is made up of blood platelets it is of considerable importance to understand what relationship the number of thrombocytes circulating in the blood, bears to the occurrence of thrombosis. Rosenthal[190] pointed out the coincidence between thrombosis and an increased platelet count in certain cases showing Banti's syndrome, and he mentioned one such case in which, after excision of the spleen, the platelets rose to over 1,000,000 and thrombosis supervened. After this there was a diminution in the number of platelets. Dawburn, Earlam and Evans[71] showed that the clinical tendency to thrombosis and pulmonary embolism commonly occurred during the period of platelet increase which followed surgical operations and parturition. In thrombocytopenic purpura Leschke and

Wittkower[149] noted that in three of their patients a rise in the number of thrombocytes preceded thrombosis.

Although it must be recognised that the blood platelet plays a very important role in thrombosis it should be borne in mind that increase in the platelet count alone is not sufficient to bring about this phenomenon. Reference to the cases in the appendix will demonstrate that many of the cases showed a rise in the thrombocyte count to numbers varying between 800,000 and 1,700,000 and yet thrombosis did not result. The diseases in which this rise occurred included leukæmia, gastric and duodenal ulcer with and without hæmorrhage, lobar pneumonia, acute rheumatism, nephritis and malignant disease, in none of which is thrombosis a common feature. Thrombosis is however a frequent complication of polycythæmia vera and it occasionally occurs after the operation of splenectomy. It was not observed in either of the two cases of splenectomy (cases 17 & 18) mentioned in the appendix. In polycythæmia vera, although a thrombocytosis occurred in both cases, 14 and 15, it was only in case 14 that thrombosis occurred. This could not be attributed directly to the phenylhydrazine as in case 14, there was a history of thrombosis and hæmatemesis.[153]

It can only be concluded therefore that increase in the number of circulating thrombocytes is not sufficient to induce thrombosis but is only one of several variable factors, for example, slowing of the blood stream, damage to the endothelial lining of the vessel wall, alteration in the coagulability of the blood plasma and possibly changes in the agglutinability of the blood platelets. The relative importance of each of these factors is difficult to assess.

BLOOD PLATELETS AND CLOT RETRACTION.

When blood from a healthy person is collected into a test-tube, capillary tube or open dish and kept at body or laboratory temperature, it coagulates, the coagulum being equal in volume to the amount of blood contained in the vessel. Within one hour the clot commences to shrink from the side of the containing vessel and within the period of a few hours this shrinkage has progressed to such a degree that the clot floats freely in the serum which has been extruded from the coagulum in the process of contraction. This phenomenon of shrinkage or contraction of the clot, with extrusion of the serum, is known as syneresis or retraction.

Many authors have shown, and it is accepted by most, that syneresis depends on the presence of thrombocytes in the blood and it has been stated that the amount of retraction and extrusion of serum is directly proportional to the number of platelets present.*

Hayem[115] observed that in purpura hæmorrhagica the phenomenon of retraction of the blood clot was absent. This observation has now been so extensively confirmed that asyneresis has come to be regarded as an important sign of that disease. It has been occasionally noted however in pernicious anæmia, aplastic anæmia, and in certain types of Banti's disease;[130] all conditions in which thrombocytopenia is not uncommon. In these diseases it is frequently found that when the number of circulating platelets falls below 100,000 the clot formed is soft and jelly-like and there is scarcely any retraction or expulsion of serum.

* References 18, 78 & 115.

Further clinical support for the idea that the amount of retraction depends on the number of platelets in the blood is afforded by the observation that after the spleen has been removed in the treatment of purpura hæmorrhagica and Banti's disease, retraction of the clot becomes progressively increased coincident with the rise in the thrombocyte count which habitually follows this operation.*

In the realm of experiment it has been shown that after sedimentation and filtration of plasma retraction occurred only in proportion to the number of platelets present.[115] It has been observed also that when well-washed rabbit blood platelets were added to cell-free oxalated plasma retraction occurred on recalcification and that the larger the number of platelets added the greater was the amount of retraction.[136] The same has been found when hydrocele fluid and cell-free paraffined plasma were substituted for oxalated plasma.[147] "In vivo" experiments have also shown an intimate relationship existing between the thrombocyte and retraction.[137,139] It has been demonstrated that blood from an animal deplateletised by injection of antiplatelet serum lost its power of retraction on coagulation until blood platelets had reappeared in the circulation[131,134] and similarly that the platelet-free incoagulable blood of experimental anaphylaxis failed to retract when coagulation was induced.[135]

The importance of the thrombocyte in syneresis of the clot is further emphasised by the knowledge that agents which modify or destroy platelets can influence syneresis. This phenomenon can be retarded or suppressed by crushing or drying the platelets,[147] by heating them to between 50° and 58° Centigrade,[136] by cooling them to

* References 47, 85, 86, 99 & 124.

4° Centigrade,[16] or by exposing them to the action of anti-platelet serum,[137,139] sulphuric acid, chloroform, ether, saponin and bile, to distilled water and sodium fluoride[16] and to quinine and chlorcalcium.[149] Ageing of the platelets also modifies clot retraction.[16,140]

The foregoing observations taken collectively form a mass of evidence strongly in favour of the hypothesis that retraction of the blood clot and extrusion of serum is a function of the thrombocyte and that it depends to some extent on the life* of this element. Indeed Le Sourd and Pagniez[142] were so convinced that syneresis depended on the blood platelets that they used it as a guide to detect the presence of these elements within an organ. They found that extracts of the bone-marrow and spleen had the power, analagous to that of an emulsion of platelets, of bringing about retraction of recalcified oxalated plasma. As the retractive property of the bone-marrow seemed to be due to the presence of the megakaryocytes these writers favoured Wright's view of the megakaryocytic origin of the blood platelet.[143,144] They regarded the retractile power of splenic extract as being due to the constant presence of platelets within that organ and as no extract of any other organ of the body except the bone-marrow would bring about retraction, even after the spleen had been removed, these investigators concluded that a very close and peculiar relationship existed between the blood platelet and the spleen.[142]

Certain workers turned their attention to the problem of finding out how the thrombocyte exercised its retractile function. Frank[95] thought that, in the process of coagulation, shrinkage of

* Note. Leschke and Wittkower[141] found that when platelets were exposed to the action of potassium cyanide or were deprived of oxygen syneresis occurred. This suggests that retraction does not depend on the viability of the platelet.

Table, compiled from selected cases, to show that the degree of syneresis is not dependent on the number of platelets present in the blood.

Number of platelets.	Retraction.			
	Nil.	"Poor" *	"Fair" **	"Good" ***
0 to 10,000	(4)(10)	(21)		
10,000 to 20,000	(4)(10)			
20,000 to 40,000	(4)(10)	(10)	(10)(20)	
40,000 to 60,000	(10)		(25)	
60,000 to 80,000	(19)	(10)(24)	(19)	(24)
80,000 to 100,000	(19)	(10)(16)(19)	(10)(20)(24)(25)	
100,000 to 120,000	(19)	(19)	(20)(24)(25)	(16)
120,000 to 140,000	(19)	(16)	(1)(20)(21)(31)	(19)
140,000 to 160,000	(4)(19)	(16)(19)(34)	(21)	
160,000 to 180,000		(31)(34)	(24)(35)	(18)(21)
180,000 to 200,000			(21)(34)	
200,000 to 300,000		(34)	(24)(25)(31)(35)	(23)
300,000 to 500,000	(35)(36)	(36)	(34)	(1)(2)(25)(35)
500,000 to 1,000,000			(35)(36)	(1)(2)(3)(23)(34)(35)
Over 1,000,000	(36)		(35)	(36)

The numbers in brackets are the case numbers.

the little groups of platelets set in the knots of the fibrin network brought about retraction. On the other hand Le Sourd and Pagniez[134] found that the retractile property of the platelets was destroyed by heating and they concluded therefore that syneresis was due to some"ferment" action of the platelets. Glanzmann[100] favoured this idea and he called the ferment, "retractozyme". In connection with the possible ferment action of the platelet it should be noted that Roskam[192] failed to find evidence of any proteolytic or lipolytic ferments in the blood platelets of the rabbit or dog.

In spite of the many ingenious experiments and the support afforded by the bulk of clinical evidence, certain observations have been made which require explanation, otherwise reasonable doubt arises as to whether the platelets are responsible for clot retraction. Reference to the appendix will show that in most of the cases syneresis of the clot was not proportional to the number of platelets in the blood. It will be seen in many instances that with the same number of platelets the amount of retraction varied, and conversely, that the same degree of syneresis was present when the thrombocyte counts were at widely different levels. These differences are evident not only in the same case but also when different cases are compared - see table on the page opposite. This table was compiled from selected cases and it shows that syneresis was present but "poor" when the platelets were below 10,000 (case 21) and that it was "fair" at thrombocyte values between 20,000 and 40,000 (cases 16 & 20). At these values, according to prevailing opinion, retraction should be absent. In the literature I have been able to find two references reporting the presence of retraction when the platelets numbered 28,000 in one case[124] and just below 50,000 in the other.[44] Conversely, in some of the other cases retraction was absent when

the platelets were between 140,000 and 160,000 (cases 4 & 19), between 300,000 and 500,000 (cases 35 & 36), and at the high value of 1,000,000 (case 36). In addition to this the degree of syneresis was "poor" at counts varying between 200,000 and 500,000 (cases 34 & 36). At these figures clot retraction is usually well marked. Even so other writers have noted that retraction was absent and the serum not extruded from the clot when the platelets were present in numbers varying from 120,000 to over 400,000.* Myers[167] observed that in closed tubes of blood, sent for agglutination tests and Wassermann reaction from cases in which there could not have been essential purpura, there was non-retraction of the clot in 40%. Kaznelson[124] however on examining many hundreds of samples of blood always found that retraction occurred at room temperature if blood platelets were present in high numbers provided the blood was held in U tubes, one millimeter in diameter. When it was contained in ordinary tubes there was sometimes no retraction even when the platelets were present in large numbers. It is possible that difference in technic may account for some of the contradictory findings and more especially will this be so in view of the observations of Howell,[119] and Pickering and Hewitt[175] regarding the modifications produced in syneresis by adhesion, see pages 87 & 88. In this connection it was noticed that samples of blood from cases 50 and 51, when contained in an ordinary test-tube, failed to retract and expel serum within 24 and 21 hours respectively after they had been withdrawn. However when the blood was gently loosened from the sides of the tube syneresis occurred very quickly. It must be remembered that adhesion may interfere with syneresis. For the purpose of the investigations carried out in this work,

* References 63, 100 & 219.

with the exception of a very few cases, blood was drawn into clean capillary tubes which had been previously flamed until they were red hot. In order to avoid the fallacy of non-retraction due to adhesion the precaution was always taken to let the end of the capillary tube fall smartly on a glass slab in order to loosen the clot if this had not occurred. This procedure was not always necessary but in these cases in which asyneresis was noted, even after the clot was separated from the walls of the tube no retraction followed.

From these clinical findings it will be seen that, contrary to common belief, syneresis of the clot may be present when the platelets are greatly diminished and that it may be absent even when the thrombocytes number over 1,000,000. It is therefore doubtful if the platelet is really the important factor in producing retraction. It may be that its retractile property is modified in disease in such a way that it is hyperactive in the cases in which retraction occurs in spite of low numbers, or diminished in those in which syneresis is absent and the thrombocyte values high. This however is improbable as it is unlikely that in the same disease the platelets would be changed or their functions modified to cause retraction in one case and not in another (cases 19 & 20), or that, in the same patient syneresis would be absent at higher numbers and present at lower (case 19). Also in pernicious anæmia irretractility is the rule when the numbers are diminished but quite the opposite was observed in cases 21 and 25. Again in purpura hæmorrhagica retraction is commonly absent. Glanzmann[100] produced evidence to show that in this disease the platelets had lost their retractile power. This however does not explain why syneresis should be absent when the platelets number 143,750 (case 4) and "fair" at 137,250 (case 1).

The fact that in the precritical stage of lobar pneumonia (cases 34, 35 & 36) retraction was absent or diminished when the thrombocyte count was not, or only slightly reduced, must be of some significance. Although it is possible that there is some toxic damage to the platelets it is more likely that the disturbance is situated in the blood plasma especially when one considers that in the acute phase of this disease the fibrinogen content of the plasma is greatly increased.[220] There are certain experimental findings which favour the idea that the blood plasma is an important factor in retraction.

Achard and Aynaud[7,11] found that pleural exudate, which contains no blood platelets, coagulated and retracted and that these two processes also rapidly occurred in blood after a complete thrombocytopenia had been produced by injecting gelatine, electrargol, gum or lecithin into the circulation. It has also been demonstrated that, during the period of disappearance of the platelets from the blood after intravascular injection of peptone or thymus nucleic acid, the clot retracted.[175] Additional evidence that the thrombocyte-free plasma can retract is afforded by the work of Roskam[193,194] who showed that the clot resulting from coagulation in a "floating drop" of platelet-free plasma contracted spontaneously and gave rise to a considerable quantity of serum, removal of which favoured syneresis.

Even from the work of Le Sourd and Pagniez[140] evidence is forthcoming to suggest that other factors might be necessary to bring about retraction of the clot. On adding small quantities of acid - hydrochloric acid, sulphuric acid or acetic acid - they found that oxalated plasma containing platelets, when left for 24 to 48 hours or when heated to 45° or 46° Centigrade in order to make it irretractile, contracted. The acid did not act directly on, or fix itself to, the platelets but it had to be present in the plasma

before retraction occurred, as blood platelets from acidified plasma when added to limpid oxalated plasma did not bring about retraction. When the H ion concentration of the blood was altered by the addition of calcium other writers found that the irretractile clot of purpura retracted although it was also found that retraction was absent, not only in the absence of calcium, but also in the presence of excess of that substance.* All these observations suggest that the plasma is an important factor in the phenomenon of retraction and that it can be so modified that normal syneresis is altered.

More direct proof of the importance of the plasmatic factor in syneresis has been furnished by Howell[119] who confirmed the work of Stubel that when clotting of the blood occurred the fibrin was deposited as separate needles or crystals which were formed by an aggregation of fibrinogen particles. He extended this work and found that syneresis of the clot was connected directly with the fibrin needles. By increasing the alkalinity of blood he discovered that the fibrinogen, instead of forming a crystalline gel, could be modified to give a structureless gel which was soft and transparent and showed no tendency to retract or express serum. Howell also pointed out that contraction was a phenomenon exhibited by many gels, for example, gelatine, agar-agar, casein and even the structureless gel of crab's blood. He found that cell-free oxalated plasma or solutions of pure fibrinogen showed the property of retraction to a marked degree on the addition of thrombin and he suggested that the blood platelets were connected indirectly with syneresis in that they might be a source of thrombin.

With regard to adhesion of the clot Howell pointed out that

* Cited by Leschke and Wittkower.[149]

adhesion to the walls of the containing vessel inhibited retraction which however appeared when the clot was gently loosened from the sides of the containing vessel. Pickering and Hewitt[175] also discovered that the amount of surface exposed to the forces of adhesion played a part in the retraction of the gels formed after the recalcification of oxalate and citrate plasmas. They were of the opinion that the presence of platelets was not necessary for the occurrence of syneresis, that adhesion was a primary factor in the disappearance of normal contractility of blood clots and that the latter might be modified by changes in viscosity of the blood. They were however impressed with the findings of other authors who considered the presence of blood platelets essential for clot retraction and they put forward the idea that absence of platelets might be a contributary factor in the disappearance of normal contractility of the clot because, in the absence of platelets, the viscosity and adhesiveness of the blood was altered.

It is therefore apparent from a review of all the work on the subject of retraction of the blood clot, that the thrombocyte is not the all-important factor in bringing about this phenomenon. In all likelihood syneresis depends on the state of the plasma particularly with regard to the properties of its fibrin content which can be so altered or modified that different types of gel may be formed in the process of clotting. The thrombocyte hastens coagulation and as retraction may be regarded as the last act in the completion of clotting it would be reasonable to expect that the platelet extended its influence into this phase of the coagulative process. The constancy with which the addition of uninjured and physiologically active thrombocytes to coagulable fluids increases the degree of retraction, and the clinical evidence which demonstrates

the association between diminution or increase in syneresis with diminution or increase in the number of thrombocytes respectively cannot be disregarded. It can only be concluded therefore that the platelet takes some part in bringing about clot retraction. When present in the blood under normal conditions it will bring about an increase in the amount of retraction but in disease, for example, lobar pneumonia, modifications in the plasma will produce changes in the degree of syneresis which however will vary with the extent to which the plasma is altered or modified. Thus in the acute phase of lobar pneumonia the alteration in retractility is not due to the diminution in the number of platelets - they are not reduced to any great extent - but to changes occurring in the fibrinogen content of the blood plasma.

According to this view syneresis of the clot depends on (a) the blood plasma and (b) the blood platelets. Of these the former is the more important and as it is a very complex and unstable substance it is probable that the varying results obtained on investigation of some of the cases in this work were due to alteration in the retractile property of the plasma rather than to alteration in the retractile function of the platelet. In retraction of the clot the thrombocyte is of secondary importance and serves to augment the retractile property of the plasma.

BLOOD PLATELETS AND CAPILLARY HæMORRHAGE.

The capillaries of the body make up an organ for the interchange of substances between the blood and the tissues. Although the calibre of these vessels varies in a passive way with variations in the arterial blood pressure yet the capillary walls have a tone of their own and may show contractions and relaxations independent of the corresponding reactions of the arterial walls. According to Krogh[129] alteration in the capillary diameter is effected by contractile cells - the Rouget cells - which are placed at irregular intervals along the capillary vessels and encircle the wall by means of prolongations of their cell body protoplasm. These Rouget cells form the muscular coat of the capillaries and they are arranged in the form of a wide-meshed network which leaves the greater part of the endothelial surface uncovered and adapted for the passage of substances between the blood and tissues. Aschoff[17] however is unwilling to admit the contractile function of the Rouget cells and apparently there is doubt in the minds of others as to the function of these cells.[151] Aschoff claims that they belong to the reticulo-endothelial system.

The exact functional relationship which exists between platelets and capillaries is unknown but it is widely believed that one of the functions of the platelets is to close potential spaces in the capillary wall and thus prevent the passage of blood into the surrounding tissues. It has been stated that the tendency to spontaneous capillary hæmorrhage exists in proportion to the number of thrombocytes in the circulation. In support of this statement certain clinical and experimental data have been recorded.

Duke[78] was the first to point out that where this tendency to spontaneous capillary hæmorrhage existed, notably in purpura hæmorrhagica, the duration of the blood flow from a freshly punctured wound was prolonged although coagulation time was normal. The duration of bleeding from such a wound he called "Bleeding time". Normally it varies from ½ to 3 minutes. Duke showed that prolongation of bleeding time was associated with diminution in the number of platelets circulating in the blood and he found that a marked thrombocytopenia was always accompanied by hæmorrhage. Clinical evidence of this relationship has been found not only in purpura hæmorrhagica but also in acute leukæmia and pernicious anæmia (cases 10, 21, 24 and 25 of this work) and in aplastic anæmia, diphtheria, hæmorrhagic small-pox and benzol poisoning.* In experimental work with diphtheria toxin and benzol Duke also found that prolongation of bleeding time and the onset of hæmorrhage coincided with thrombocytopenia and the same has been found by others in work with anti-platelet serum** and irradiation with X-rays.[130,164] In other purpuric conditions in which the platelet count was normal or slightly increased the bleeding time was found by Duke to be within normal limits. In common with many other authors* Duke considered that, in order to stop capillary hæmorrhage, platelets were necessary in view of their property of adhering to the edges of injured endothelium and initiating the formation of a thrombus which closed the wound and prevented hæmorrhage.

From the clinical and experimental evidence which has accumulated it must be admitted that a very close connection exists between thrombocytopenia, tendency to spontaneous capillary hæmorrhage and prolongation of bleeding time. Nevertheless from investigation of

* References 70, 78, 79, 94, 95, 112 & 124.
** References 128, 131, 132 & 134.

some of the cases detailed in this work certain observations have been made which throw doubt on the usually accepted explanation that paucity of circulating platelets is responsible for the spontaneous hæmorrhages and increased bleeding time met with in purpura hæmorrhagica pernicious anæmia, aplastic anæmia, acute leukæmia and certain infectious diseases.

In the first place thrombocytopenia may be present, (cases 19 & 20) or the platelets may be diminished to values around 100,000 (case 16) and yet no increase in the bleeding time or no spontaneous hæmorrhage result.*** In case 10 also thrombocytopenia was present for about ten days before any increase in the bleeding time was noted. The presence of thrombocytopenia and the absence of hæmorrhage has also been noted by other writers in various conditions.*

Secondly, spontaneous capillary hæmorrhage and prolongation of bleeding time may exist in the presence of thrombocytes in the following numbers:-

140,000	(Cases 1 & 4.)
750,000	(Case 2.)
800,000	(Case 62.)
825,000	(Case 3.)

Similar findings have also been ~~made~~ reported by a few observers especially in some cases of jaundice, chronic liver disease** and pregnancy.[218] In these conditions however the clotting process is frequently delayed and although increase in coagulation time is not commonly associated with prolongation of bleeding time it is possible that when they occur together delay in coagulation is a factor in altering the duration of bleeding time. In cases 25 and 62 both were increased

* References 44, 167, ~~203~~ [203] & 219.
** References 63, 166, 203 & 217.
*** Note. The hæmorrhages which developed in case 19 were due to emboli and it is likely that a similar cause will explain the hæmaturia in case 20.

together. However it is noteworthy that in cases 1, 2, 3 and 4 the coagulation time was normal. These four were cases of purpura hæmorrhagica yet there was no thrombocytopenia. Roskam,[196] and Little and Ayres[152] have recently reported similar cases in which spontaneous hæmorrhage and increased bleeding time were both associated with normal platelet counts.

Thirdly, bleeding time may vary within wide limits not only throughout the course of purpura hæmorrhagica (cases 1 & 4) but also in other conditions, for example, acute leukæmia (case 10), when the blood platelets are constantly diminished. This may also be observed when a comparison is made between different individuals. Not only so but in the same person at the same time the duration of bleeding time may vary with the site of puncture even when corresponding parts of the body are compared under similar conditions. The fact that duration of bleeding time varies with the site of puncture in the same patient at the same time is illustrated by many of the cases in this work, for example, cases 1, 2, 4, 10, 21, 25 and 62.

These observations, namely, normal bleeding time and absence of hæmorrhage in the presence of thrombocytopenia, prolongation of bleeding time and the presence of capillary hæmorrhage when the platelets are normal or increased in number, and variation in the bleeding time with change in the site of puncture are not in keeping with the idea that thrombocytopenia is the cause of prolonged hæmorrhage from capillary vessels. They suggest that factors, other than diminution in the number of blood platelets, are concerned in controlling the duration of hæmorrhage. Two possible factors exist, namely, alteration in the coagulability of the plasma or, alteration in the walls of the capillary vessels.

Roskam[196] showed that when a moderate or intense thrombocytopenia

was associated with delay in coagulation the duration of bleeding time was slightly increased. The experiments of Duke[77] on the rate of regeneration of blood platelets also showed in effect that when the fibrinogen content of the plasma was diminished at the same time as the number of blood platelets a marked tendency to hæmorrhage existed. However alteration in the coagulability of the blood plasma is not all-important in bringing about change in the duration of bleeding time, for although increase in the coagulation time may be associated with increase in bleeding time in the presence of thrombocytosis (case 62) or thrombocytopenia (case 25) it is more frequently found without a corresponding increase in bleeding time (cases 9, 18, 63 & 65). Further, coagulation time may be normal and the bleeding time increased (cases 1, 2, 3, 4, 10, 21 & 24).

Far more important are the results of the following experiments. In the earlier work with anti-platelet serum, benzol, diphtheria toxin and X-rays it was difficult to exclude the possibility that in addition to producing a thrombocytopenia, the endothelium of the capillary vessels was also damaged. More recently it has been demonstrated that, after intravenous injection of gelatine, a very marked reduction in the number of blood platelets occurred in the dog, and, although there was a slight increase in the duration of bleeding time the great prolongation met with in purpura hæmorrhagica was never obtained.[195] Even more striking is the work of Bedson[34] who injected agar serum into the vascular system of rabbits and found that the platelet count could be considerably reduced without the occurrence of hæmorrhage. If however the endothelium of the capillary vessels was damaged by injecting anti-red cell serum then purpuric hæmorrhages, resembling those produced by anti-platelet serum, appeared. Wittkower* also, by means of X-rays, produced a profound

* Cited by Leschke and Wittkower.[149]

thrombocytopenia in guinea pigs and found that no hæmorrhage resulted even when the platelets numbered only 19,700. These experimental results confirm the clinical observations that thrombocytopenia may exist without the appearance of hæmorrhage or without any increase in the duration of bleeding time.

On the other hand there does not seem to be any experimental work to show that prolongation of bleeding time may exist when the blood platelets are present in increased numbers as shown by cases 2, 3 and 62. However, Pulvertaft[186] has shown that without any diminution in the platelet count the clinical picture of purpura fulminans may be simulated when streptococcal toxin is injected into rabbits the lesion being due to damage to the capillary endothelium. In these experiments the bleeding time was not estimated.

From a consideration of all the clinical and experimental evidence it is very doubtful if the thrombocyte plays the part assigned to it by Duke and others.* It is also questionable if the thrombocytopenia which is frequently found in purpura hæmorrhagica, pernicious anæmia and acute leukæmia is the cause of the hæmorrhagic symptoms and the prolongation of bleeding time. The coagulation time is usually normal in these diseases therefore it is unlikely that the plasma is at fault. It can only be concluded therefore that the lesion exists in the walls of the capillary vessels. This conclusion is the natural outcome of the knowledge that bleeding time may be prolonged when the thrombocytes are normal or increased in number and that thrombocytopenia may exist without any increase in the bleeding time or the appearance of spontaneous hæmorrhage. It is further justified by the knowledge that the duration of

* References 70, 78, 79, 94, 95, 112 & 124.

bleeding time varies with the site of puncture. The variations which have been observed can only be explained on the basis that the capillaries are able to modify bleeding time. It is obvious that the time taken to close the puncture wound will depend on the integrity of the capillary wall. It is also obvious that the amount of bleeding will vary according to the state of contraction and relaxation of the capillaries as determined by the temperature of the skin and the surrounding atmosphere and possibly to some extent on the arterial blood pressure. It has been shown experimentally that bleeding time can be modified by adrenalin, pituitrin, amyl nitrite and emetine all of which act through the medium of the capillaries.[216] The active process of capillary contraction is, in health, the normal mode of reaction to injury. In the presence of this mechanism it is difficult to understand why platelets should be necessary to "plug" potential spaces. Moreover when contraction does occur it is likely that "plasma skimming" takes place with the result that plasma only has access to the wounded capillary vessels, the red and white cells, and probably the platelets being excluded. Eberth and Schimmelbusch[84] were struck by the fact that even when a vessel was pierced by a needle the platelets did not adhere to the injured wall unless the speed of the blood stream was diminished.

In disease however, the capillary endothelium may be so weakened or damaged, by toxins or nutritive disturbance, that this reaction to injury is modified. When the distribution of many of the skin eruptions in disease is considered it is quite reasonable to expect that the degree of capillary weakness or damage would vary throughout the body with the result that other conditions being equal, the duration of bleeding time would vary with the site of puncture. Such variations would be unlikely if bleeding time depended on the

number of platelets in the circulation.

It is conceivable also that according to the nature of the disease the type of capillary abnormality will be different and thus give rise to different purpuric manifestations. Thus there is the type in which bleeding takes place into a macule, papule, blister or the lesion of an exanthematous rash, the type met with in scurvy or frankly toxic states or that which gives rise to the hæmorrhagic manifestations peculiar to purpura hæmorrhagica, pernicious anæmia and acute leukæmia. With regard to purpura hæmorrhagica Leschke* noted that capillary contraction was delayed, absent or diminished in intensity. However he drew attention to the findings of Von Bermuth* who observed normal capillary response in this disease. The technic of these two observers was different, so also was the site of puncture and it has already been pointed out how the latter might influence the results obtained. Further evidence of capillary damage is furnished by Leschke and Wittkower[141] who in all their cases of purpura hæmorrhagica found endothelial cells in the blood taken from the ear. These workers regarded the presence of endothelial cells in the circulation as a sign of increased vulnerability of the capillary walls.

A test which is regarded by many authors as indicating capillary weakness is the "capillary resistance test" of Hess[116] (the "brassard sign" of Roskam[146] and the "tourniquet test" of other authors). To carry out this test the circulation of an arm is constricted and, where capillary weakness exists, it is claimed that petechiæ or larger skin hæmorrhages appear after the constriction is removed. This test is frequently positive in thrombocytopenic conditions

* Cited by Leschke and Wittkower.[141]

and Frank[96] graded the hæmorrhages according to the number of blood platelets in the circulation, the petechial hæmorrhages appearing and becoming more marked as the thrombocytes diminished progressively below the value of 75,000. In cases 21 and 25 no skin hæmorrhages were observed when the platelets numbered 14,000 and 45,000 respectively but in case 25 petechiæ were observed when the platelets numbered 115,000. Other writers obtained negative results when the platelets were low* for example, at 6,000,[116] and positive results when the thrombocytes were present in normal numbers.[116,96] The result of the test is therefore not dependent on the number of blood platelets. Even so, its reliability as a guide to capillary weakness is doubtful as it may be negative in the presence of extensive petechial hæmorrhage into the skin, (case 4 and Clopton[63]). The test is therefore more of interest than of practical value although a positive test would certainly indicate vascular abnormality. In all four cases of purpura hæmorrhagica investigated in this work it was negative but in case 10 (acute leukæmia) and case 25 (pernicious anæmia) a positive result was obtained on certain dates.

It is evident that the problem of the cause of the spontaneous hæmorrhages and increased bleeding time in thrombocytopenic conditions is one of great complexity. In the diseases in which diminution in the number of thrombocytes is a feature, alteration in the coagulability of the plasma does not commonly occur; therefore the cause of the hæmorrhage must be ascribed either to the thrombocytopenia or to the vascular abnormality. In the present state of knowledge the functional relationship which exists between the capillaries and platelets is not understood but the constancy with which

* References 47, 94 & 116.

diminution in the platelet numbers is associated with bleeding makes it difficult to exclude altogether the possibility that thrombocytopenia is in part responsible for hæmorrhage. However in view of the evidence, clinical and experimental, that bleeding time may be prolonged when the platelets are normal or increased in number, or that it may vary within normal limits in the presence of thrombocytopenia it must be concluded that the all-important factor in controlling capillary hæmorrhage is not the number of blood platelets but the ability of the capillary vessels to contract. It is thought that the thrombocytopenia so often associated with purpuric hæmorrhage is merely a coincident phenomenon, see page 62. According to this view purpura hæmorrhagica is due to some defect in the capillary walls.

BLOOD PLATELETS AND ANAPHYLACTIC PHENOMENA.

During the investigations carried out in this work the opportunity of studying the behaviour of the blood platelets in active anaphylaxis did not present itself but as some authors regard the platelet as the cause of certain of the phenomena of anaphylactic shock a summary of the work associating the thrombocyte with anaphylactic and anaphylactoid states will therefore be given. It may be said at the outset that most of the work is more of speculative interest than of practical value.

Achard and Aynaud* found that when a foreign protein, for example peptone, was injected into the circulation the platelets, after agglutination, collected in the capillaries of the liver. At the same time there was a transitory thrombocytopenia. In sensitised anaphylactic dogs they observed that the tendency to agglutinate was much increased. Lee and Vincent[135] noted also that on producing experimental anaphylaxis a diminution occurred in the number of circulating thrombocytes.

This agglutination of platelets has been thought to cause the severe symptoms of the anaphylactic state. Pesci** believed that agglutination of thrombocytes in the capillaries of the brain brought about intravascular thrombosis and flocculation of the plasma colloids. Pardi[170] could not find any morphological evidence of agglutinated or even isolated platelets in the brains of guinea pigs killed by anaphylaxis but he found large numbers in the arterial and venous vessels and the larger capillaries of the liver,

* References 10, 11 & 12.
** Cited by Klecki and Pelczar.[126]

lungs and spleen and he suggested that the presence of thrombotic masses of platelets in these viscera would be responsible for the phenomena of anaphylaxis.

On the other hand it has been supposed that these phenomena were due to toxic substances liberated on the destruction of platelets.* In this connection it was shown that the powerful constricting action of serum on a ring of artery isolated from the sheep[122] was due to substances liberated from platelets[206] and that aqueous extracts of blood platelets from the rabbit and the horse, but not the dog, brought about constriction of an isolated arterial ring from the dog.[148,195] However, contrary to what would have been expected from these findings, serum from rabbit plasma rich in platelets, when injected into the circulation of the rabbit, produced a marked fall in blood pressure, the fall being in proportion to the number of thrombocytes contained in the plasma.[145] A similar hypotensive effect resulted when aqueous extract of rabbit platelets was injected intravenously into the rabbit or dog.[146,195] However it was found that extracts of the platelets of man and the dog did not influence the blood pressure of rabbits or dogs.[146,195]

It will be seen therefore that although platelet substances have a vaso-constricting property yet when injected into the circulation they produce a fall in blood pressure. Klecki and Pelczar[126] attempted to correlate these contradictory results by postulating the liberation of two substances having different actions but Roskam,[195] as the result of ingenious reasoning from certain experimental observations, concluded that the aqueous extract of rabbit platelets acted like histamine in that it

* Zeller, Fruend. Cited by Klecki & Pelczar.[126]

increased the tone of arteries and probably veins while at the same time it exercised a marked dilator effect on the capillary vessels. With regard to the difference in action between the extract of rabbit platelets and that of the platelets of man and the dog Roskam suggested that the same double action occurred but that an equilibrium was established between the vaso-constrictor and vaso-dilator actions so that blood pressure was not altered. He thought that the liberation of substances from the platelets of man, dog and rabbit determined the fall in blood pressure met with in anaphylactic shock. In the case of the human being and the dog he thought that the action was localised to the capillaries of the viscera in which the platelets were agglutinated. Roskam admitted however that his theory was hardly justified from the results of his experiments as there was no reason to suppose that the aqueous extract of blood platelets was similar in composition to any substance liberated by the living platelets. He pointed out that if the active substance present in the aqueous extract of the platelet was histamine or a "histamine-like" body then it would be likely that the platelet contained it in common with many other cells of the body so that any effect the platelet might produce would not be specific. However apart from this criticism, it had already been shown by Achard and Aynaud that the agglutinated thrombocytes could be recovered unaltered by perfusion of the liver[5]. Moreover within half-an-hour after anaphylaxis had been induced there was a progressive increase in the platelet numbers in the circulation so that within one hour the count was once more normal[7]. Neither of these happenings would occur if the platelets were destroyed. In addition, Zunz and Goværts[225,226] found that all the phenomena of anaphylaxis could be produced in sensitised guinea pigs in the

absence of platelets from the circulation and Klecki and Pelczar[126] showed that an increase in the platelet count, obtained by injecting platelets into the rabbit, did not influence the course of anaphylactic shock. They also injected into sensitised animals decomposed platelets in order to produce an excess of platelet substance in the circulation and found that only some of the phenomena of anaphylactic shock followed, whereas many other phenomena, not observed in that state, resulted.

In face of this evidence it must be concluded that neither brisk agglutination nor destruction of blood platelets with liberation of toxic substances produces anaphylaxis. It is likely that agglutination of thrombocytes, rather than being the cause of the anaphylactic symptoms, is merely one of the manifestations of the state of anaphylaxis.

SUMMARY AND CONCLUSIONS.

The blood platelet is present in human blood as a definite morphological element.

When examined in a suitable preserving solution containing brilliant cresyl blue the blood platelet in health is seen to be a non-nucleated round or oval disc-like body having an average diameter varying between 2 and 3 microns, and a hyaline cytoplasm containing numerous blue coloured granules.

In certain diseases the size, granulation and staining reaction of the blood platelets vary from the normal. When the thrombocytes are markedly reduced in number there is anisocytosis with a relative increase in the number of the smaller forms although a few very large forms may be present. In addition there is a varying degree of basophilic staining of the cytoplasm with irregular distribution in the granular content of the platelets. During a thrombocytosis or, when the thrombocyte count is rapidly increasing, the platelets tend to be larger and less granular. In the period of rapid increase basophilia is common. Basophilia of the platelet cytoplasm indicates immaturity.

The abnormalities in size, granulation and staining reaction of the platelets described by others as peculiar to purpura hæmorrhagica have been found in the blood in other pathological states. The hæmorrhages characteristic of purpura hæmorrhagica are not due to inherent defects in the blood platelets as shown by change in the morphological features.

The blood platelet does not have its origin from erythrocytes or leucocytes. It has its independent origin in the bone-marrow

probably from the megakaryocyte.

Effete platelets are destroyed in the spleen by the cells of the reticulo-endothelial system.

In health the number of platelets in the blood of man varies between 250,000 and 450,000 per cu.mm. The average number present is about 390,000 per cu.mm.

In disease the platelet count varies within much wider limits. It is diminished in acute myeloblastic leukæmia, splenic anæmia, malignant endocarditis, pernicious anæmia(relapse), acute tonsillitis, lobar pneumonia(precritical phase) and pyæmia. The count is normal or only slightly diminished in Henoch-Schönlein and static purpura, in scurvy, hæmophilia, acholuric jaundice, diabetes mellitus, pelvic sepsis and hyperthyroidism, while in chronic myeloid leukæmia, secondary anæmias, lobar pneumonia (convalescence), acute rheumatism, nephritis, malignant disease and chronic forms of tuberculosis the platelet numbers are normal or increased. In purpura hæmorrhagica and polycythæmia vera the counts may be diminished or increased.

In acute myeloblastic leukæmia, chronic myeloid leukæmia and polycythæmia vera the platelet count depends on the degree of activity in, and hyperplasia of, the leucopoietic or erythropoietic tissues. In pernicious anæmia and splenic anæmia the platelet-forming tissue is affected in common with the other hæmopoietic tissues.

Loss of blood gives rise to a thrombocytosis. This increase in the platelet count is a regenerative process and reflects the state of generalised activity in the hæmopoietic tissues.

The platelet count is reduced in the acute phase of some illnesses and increased in convalescence. No reduction in the count was observed to occur in the acute phase of rheumatic fever.

The diminution in the platelet numbers found in acute infections is due to toxic action on the platelet-forming tissues, and the thrombocytosis of convalescence is a sign of increased hæmopoietic activity.

Thrombocytopenia, when it occurs in purpura hæmorrhagica, is due to "toxic" inhibition of normal platelet genesis and not to excessive destruction of platelets.

The effect of X-rays on the platelet count varies with the patient, the disease and the dosage given.

Phenylhydrazine hydrochloride produces a thrombocytosis which is merely an expression of generalised hæmopoietic activity.

When patients suffering from pernicious anæmia are fed with liver the thrombocytes become increased in number.

Splenectomy is followed by an increase in the platelet count.

The number of thrombocytes in the circulation is no guide to the rapidity with which coagulation occurs. Clotting of blood depends primarily on the plasma and the influence of the platelet is only of secondary importance.

Increase in the number of platelets in the circulation does not induce thrombosis.

Retraction of the clot is not proportional to the number of platelets in the blood. It depends on (a) the blood plasma and (b) the blood platelets. Of these two factors the former is the more important.

Thrombocytopenia may be present in the absence of spontaneous capillary hæmorrhage or prolongation of bleeding time. Spontaneous capillary hæmorrhage and prolongation of bleeding time may exist in the presence of thrombocytes in increased numbers. Bleeding time varies within wide limits when the platelets are constantly diminished. It also varies with the site of puncture.

The capillary resistance test (positive result) does not depend on the number of blood platelets in the circulation.

The most important factor in controlling spontaneous capillary hæmorrhage or duration of bleeding time is not the blood platelet but the ability of the vessel wall to contract. The hæmorrhages characteristic of purpura hæmorrhagica are due to defect in the capillary walls.

The blood platelets are not responsible for the phenomena observed in anaphylactic shock.

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* Note. The number in parenthesis denotes the volume and the number which follows signifies the page.

THE BLOOD PLATELET.

A clinical study and review of the literature.

APPENDIX.

CONTENTS of APPENDIX.

A. Technic.

I. Platelet morphology.

All the observations were made on platelets obtained and stained according to the method described under "Enumeration of platelets." The measurements were made with eyepiece and stage micrometers. All the observations were made under oil immersion(objective 1/12 inch, eyepiece No. 4).

As a rule a hundred platelets were examined and the size, granulation and staining reaction of each recorded. The totals obtained were then tabulated in percentages. In those cases in which a marked thrombocytopenia existed as many platelets as could be found within a period of approximately 30 minutes were investigated. In case 10, on 30th Oct. and 2nd Nov. the total number counted on each of these dates was only two.

II. Enumeration of platelets.

The method used in this work aims at estimating the number of blood platelets in the capillary blood.

The following solution and apparatus were used.

(a) Platelet diluting fluid. 2% solution of sodium citrate made up in 0.29% solution of sodium chloride. Before use the fluid was heated to boiling point, filtered and cooled.

(b) Platinum wire loop, 1/8 inch in diameter, coated with clean hard paraffin.

(c) Straight Hagedorn needle.

(d) Clean blood slide on which a drop of a saturated solution of brilliant cresyl blue in absolute alcohol was first placed. The alcohol was then allowed to evaporate and a thin film of precipitated stain was thus deposited on the slide.

(e) Clean No. 1 cover slip, 7/8 inch square.

The skin over the pulp of a finger was cleansed with absolute alcohol and allowed to dry. A drop of diluting fluid was then placed on the skin and the skin sharply punctured through the drop. The outflowing blood was allowed to pass directly into the diluting fluid. No pressure was used to make the blood flow freely. Care was taken to ensure that the blood was diluted in such a way that not more than 60 red corpuscles were present in any one microscopic field. In practice the number of erythrocytes present was usually in the neighbourhood of 40 per field. The blood and diluting fluid were thoroughly mixed together by means of the paraffined loop and a loopful of the mixture transferred to the centre of the film of precipitated brilliant cresyl blue on the blood slide. It was then covered with the coverslip and ringed

with vaseline. The amount of diluted blood transferred to the slide was such that the fluid spread out in a capillary layer between slide and coverslip. Two preparations were made and both were laid aside for at least 30 minutes at laboratory temperature to allow the blood elements to settle. During this period the number of red and white cells in the blood were enumerated in the usual way.

By this method the thrombocytes were not unduly damaged and their morphological features were easily made out. The platelet granules stained blue.

All the counting was done under oil immersion (objective 1/12 inch, eyepiece No. 4). For counting purposes the microscopic field was divided into quadrants. This was conveniently done by cutting out two cardboard rings of suitable size and gumming them together after two fine hairs stretched at right angles to each other had been placed between them. The whole arrangement was then inserted into the eyepiece.

Any preparation in which agglutination of platelets had occurred was discarded. The ratio of platelets to erythrocytes was determined in a series of successive fields, a total of at least 1,000 red cells being counted in each of <u>two</u> preparations. The average number of thrombocytes per 1,000 erythrocytes was then determined from the results obtained from each preparation and from the previously calculated number of red cells the number of platelets per cubic millimeter was obtained.

Apart from the difficulty due to irregularity in platelet distribution possible sources of error are provided by the

fallacies inherent in counting the erythrocytes. Thus in some of the cases the red cell count varied from day to day because of alteration in the fluidity of the blood and in the state of the capillary blood vessels. To overcome this difficulty the erythrocyte count was always repeated if the numbers obtained by the first count were unexpectedly higher or lower than the numbers obtained in the count immediately preceding. Although the number of platelets is shown as an exact figure it is recognised that the calculated results are only approximately correct and that there must be a fairly large margin of error, possibly as large as 10%. However the method of enumeration adopted is simple and it can be used for repeated clinical examinations without distressing the patient. Further it is as accurate as the best of the other methods, some of which were tried, and the results obtained have a certain comparative value as indicating daily variations in the number of circulating platelets. The opportunity arose of testing its accuracy by comparison with the number of platelets present in venous blood. As a therapeutic measure venepuncture was carried out on case 15 the blood being drawn off through a wide bore needle lined with hard paraffin. During the procedure a few drops of blood were caught in a paraffin cell which contained diluting fluid. This venous blood was found to contain 33 platelets per 1,000 red cells while capillary blood taken at the same time contained 31 thrombocytes per 1,000 erythrocytes. These results were taken as an indication that the method adopted for counting the platelets was reasonably accurate.

(Note. In case 4 the ratio of platelets to erythrocytes was counted on a dry blood film stained with Leishman's stain.)

III. Coagulation time.

The method used in this work was that described by Gibbs.[98] It consisted essentially in measureing the time taken by a drop of shed blood, obtained by puncture of the skin, to coagulate while it was kept moving to and fro on a loop of platinum wire. The end point was definite and it was reached when the drop of blood ceased to move on the platinum loop. The whole apparatus was constructed so that the blood could be kept in a humid atmosphere at any fixed temperature. In this work the coagulation time was estimated at a temperature which varied between 37 and 40 degrees Centigrade. According to Gibbs the normal coagulation time at this temperature falls between 92 and 103 seconds. It has been my experience that these figures are rather low as it was found on many occasions that the coagulation time was as high as 150 seconds in patients whose blood, when examined by other methods, clotted within normal time limits. This observation casts doubt on the accuracy of Gibbs' method. It may be objected that the blood used has been in contact with tissue juice and that it is difficult to control the ~~proportion to~~ amount of tissue fluid in any one drop of blood even where the greatest care is taken to avoid congestion in the capillary vessels of the skin when the puncture is made. Because of this difficulty the results obtained by Gibbs' method are not so reliable as those obtained by using blood which has been taken from a vein with only a minimum of contact with the tissue fluids.

Although the method is open to a certain amount of criticism

it has the merit of being simple of application and it can be used to make daily estimations of coagulation time without great inconvenience to the patient. In the hands of the same individual the possibility of error is reduced to a minimum and the margin of error constant so that a series of observations has a comparative value.

In this work the coagulation time of blood was regarded as prolonged or increased if it exceeded 150 seconds.

(Note. In cases 4 and 5 the coagulation time was found by collecting blood in a test-tube and noting the interval which elapsed until it clotted as shown by the fact that inversion of the test-tube failed to dislodge the clot formed at the bottom of the tube. The normal by this method varies from 5 to 7 minutes.)

IV. Clot retraction.

Clean capillary tubes, 4 or 5 inches long, were flamed until they were red hot and then allowed to cool. Blood obtained by needle puncture of the skin was drawn into the capillary tube until it was half full. After ensuring that the blood occupied the middle two fourths of the tube it was set aside for 20 to 24 hours.(Sometimes the ends of the tube were sealed off in a Bunsen flame.) At the end of that time the amount of retraction and extrusion of serum was noted as being "nil", "poor", "fair" or "good". In order to avoid the fallacy of asyneresis due to adhesion of the plasma to the walls of the tube care was taken in those cases in which retraction was "nil" or "poor" to tap each end of the capillary tube smartly on a glass slab in order to loosen the clot. The tube was then laid aside for further inspection to find out if loosening the clot had made any difference to the amount of retraction.

(Note. In cases 50 and 51 certain observations on syneresis of the clot were made on blood which had been allowed to coagulate in test-tubes.)

V. Bleeding time.

After the usual aseptic precautions the skin was punctured with a sharp Hagedorn needle to a depth of 3 to 4 millimeters and the blood which flowed from the wound wiped away every 15 to 30 seconds by means of a piece of filter paper. Care was taken not to touch the edges of the wound. The time which elapsed between the commencement and cessation of the bleeding was noted as bleeding time. The site usually chosen for the puncture was the lobe of the ear. Occasionally the pulp of the thumb was used.

VI. Capillary resistance test.

The armlet of a mercurial sphygmomanometer was applied to the arm or leg in the usual way and the pressure raised to a point mid-way between systolic and diastolic blood pressure. The pressure was maintained for a period of five minutes after which the apparatus was removed and a search made for petechial hæmorrhages.

B. Key to signs and abbreviations used in the case tables.

Bleeding time.

RE Lobe of right ear.
LE Lobe of left ear.
BE Lobes of both ears.
RT Pulp of right thumb.

Clot retraction.

* "Poor" retraction.
* * "Fair" retraction.
*** "Good" retraction.

Platelet morphology.

(a) Size.

"Small" Platelets less then 2 microns in average diameter.
"Normal" Platelets between 2 and 3 microns in average diameter.
"Large" Platelets more than 3 microns in average diameter.

(b) Granulation.

0 Complete absence of granules.
\+ Marked diminution in the number of granules.
\+ \+ Normal number of granules.
\+\+\+ Definite increase in the number of granules.

C. Index to case notes.

D. Case notes and charts.

Ward No. 9. Journal No. 88, page 12. Case No. 1.

Patient. D. C., Male.
Age. 17 years.
Occupation. Message boy.

Diagnosis. Purpura hæmorrhagica.

Clinical notes. On 14th July, when the patient was admitted to hospital he was bleeding profusely from the gums. This hæmorrhage had been going on for 3 or 4 months. Apparently the bleeding was of spontaneous onset coming on at frequent intervals and lasting for a few hours or a whole day. During the week previous to admission the hæmorrhage had been constant and profuse so that the patient became pale and weak. He was small for his age and was said to bleed readily on the slightest injury. The spleen was not enlarged, the blood picture was not characteristic and the Wassermann reaction was negative.

Patient was one of a family of seven children all of whom were alive. Three of the family had never suffered from this tendency to hæmorrhage but of the others, Hendry, aged 19, was said to have"outgrown" this tendency from which he had suffered in earlier life. The remaining two, Margaret aged 15, and Mary, aged 12, were subject to epistaxes. In addition Margaret bruised very easily and frequently suffered from spontaneous hæmorrhage from the gums. (See cases 2 & 3)

The father and mother of the patient were healthy and neither gave a history of spontaneous bleeding. There was no history of the hæmorrhagic tendency in the mother's family but on the father's side a brother, i.e., an uncle of the patient was said to have hæmophilia which had been transmitted to him through his mother.

After admission to the ward a small transfusion was given. The bleeding from the gums eventually stopped and the patient was dismissed from hospital feeling very well. He reported at the ward from time to time. There has been no return of the bleeding and he has remained in good health.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1928						
Jul.17	3,050,000	6,000	137,250	6' RE 9'30"LE 3' LT	Normal	* *
" 19	-	-	-	7'10"RE 6' LE	Normal	-
" 21	-	-	144,900	2' RE 21'15"LE	-	-
" 25	3,210,000	-	142,845	9'30"LE		
1929						
Jun.30	5,020,000	8,950	524,590	1'30"RT 1'30"RE	3'	***
Jul. 7	4,950,000	5,850	463,225	2'30"RE 3' RT	2'30"	***
Oct.13	5,070,000	4,700	471,510	2'30"BE	2'30"	***
Nov.11	5,030,000	8,000	500,485	2'30"BE 2' RT	2'	***

(over)

Platelet morphology.

Date.	Size.			Granulation.				Staining.	
	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Jun.30	-	100	-	-	-	100	-	100	-
Jul. 7	-	100	-	-	-	100	-	100	-
Oct.13	-	100	-	-	4	96	-	100	-
Nov.17	-	100	-	-	-	100	-	100	-

Summary. During the period of hæmorrhage in 1928 the blood platelets were diminished in number but there was no marked thrombocytopenia. The number of thrombocytes present has been noted in other cases with no hæmorrhagic diathesis. On the occasions on which the patient subsequently reported the platelets were always present in numbers above average normal values.

While in hospital the bleeding time was definitely increased even although there was no thrombocytopenia. The duration of bleeding time varied with the site of puncture. Transfusion did not shorten it as on the following day - 21st July, 1928 - the bleeding time was longer than ever.

Coagulation time was normal.

Retraction of the clot was always present.

The capillary resistance test was negative.

During 1929 the platelets were normal in size, granulation and staining reaction.

Out-Patient. Case No. 2.

Patient. M. C., Female.
Age. 15 years.
Occupation. Packer.

Diagnosis. Purpura hæmorrhagica.

Clinical notes. Since childhood this patient suffered from recurring epistaxes and bleeding from the gums. She was always easily bruised. She had a cardiac lesion and was said to have been a "blue baby".

She is a sister of cases 1 and 3.

On the 30th June 1929 there were large bruises on the left arm and she was bleeding badly from the gums. Apparently the hæmorrhage in each case was spontaneous as there was no history of injury.

On August 1st a tooth was extracted and the patient bled for 84 hours.

She had rather profuse epistaxes on 29th Nov., 2nd Dec. and 5th Dec.

The spleen was never enlarged and the capillary resistance test was always negative. The blood picture was normal.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929				7' RT		
Jun.30	5,020,000	6,500	504,510	2'30" RE	2'45"	***
Jul. 7	5,320,000	11,350	335,160	4' RE	2'	***
				4' LT		
Nov.10	4,540,000	6,200	751,370	20+' RE	2'	* *
Dec. 8	4,300,000	8,750	492,350	15+' RE	2'	* *

Platelet morphology.

	Size.			Granulation.				Staining.	
Date.	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Jun.30	5	95	-	-	-	96	4	100	-
Jul. 7	-	100	-	-	4	94	2	100	-
Nov.10	-	100	-	-	11	89	-	100	-
Dec. 8	-	100	-	-	-	100	-	100	-

Summary. The platelet numbers were always high.

Bleeding time was always prolonged. This was most striking on 10th Nov. when it was more than 20 minutes, the platelets at that time numbering more than 700,000. The duration of bleeding time varied with the site of puncture.

Coagulation time was normal.

Syneresis of the clot was present.

The capillary resistance test was negative.

There was some tendency towards irregular distribution of the granules. A few small forms were also noted.

Out-Patient. Case No. 3.

Patient. Mary C.
Age. 12 years.
Occupation. At school.

Diagnosis. Purpura hæmorrhagica.

Clinical notes. This patient is a sister of cases 1 & 2. She suffered from epistaxes only. The spleen was not enlarged and the blood picture was normal. The capillary resistance test was always negative. On the 5th Dec. 1929 she had a spontaneous epistaxis.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Jun.26	4,350,000	12,800	582,900	1'30"RE	1'45"	***
Jul. 7	4,170,000	10,050	502,485	2'RE&RT	2'30"	***
Nov.11	4,230,000	9,400	824,850	46+' RE	2'30"	* *
Dec. 8	4,080,000	4,300	632,400	15+' RE	2'30"	***

Platelet morphology.

	Size.			Granulation.				Staining.	
Date.	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Jun.26	-	100	-	-	-	100	-	100	-
Jul. 7	-	100	-	-	-	100	-	100	-
Nov.11	-	100	-	-	19	81	-	100	-
Dec. 8	-	100	-	-	-	100	-	100	-

Summary. The platelet numbers were always high.
Great increase in bleeding time was associated with the two highest thrombocyte counts.
Coagulation time was not increased.
Syneresis of the clot was always present.
The capillary resistance was negative.
Beyond the presence of some forms poor in granules on 11th Nov., when the numbers were highest, the platelets showed no unusual morphological alterations.

Ward No. 9. Journal 66, page 258. Case No. 4.

Patient. J. V., Male.
Age. 10 years.
Occupation. At school.

Diagnosis. Purpura hæmorrhagica.

Clinical notes. From the age of 7 this patient was never free from "spots" over his body. These "spots" appeared in crops and it frequently happened that fresh ones appeared before the previous"ppots" had disappeared. Epistaxis occurred for the first time at the age of 8 and since then the patient bled from the nose every three weeks. There was never any hæmorrhage from the mouth or bowel and there was no history of arthritis or abdominal pain. The patient's maternal grandmother was said to have bruised readily. Otherwise there was no familial history suggesting the hæmorrhagic diathesis.

On admission to the ward petechial spots of size varying from a pin-head to a split-pea and of variable colour were scattered over the arms, trunk and legs. Bruising was noted over the left shoulder, left upper arm, right superior iliac spine and dorsum of the right foot. The spleen was not enlarged and the blood picture showed a polymorphonuclear leucocytosis. The capillary resistance test was negative. The purpuric eruption disappeared with rest in bed. Patient developed mumps and was discharged from hospital on 4th Dec.1925.

Results of investigation of the blood.

Date.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1925				
Nov.12	143,750	9' RE	Normal	Nil
" 20	100,000	-	-	-
" 24	264,062	-	-	-

Summary. Although the platelet numbers tended to be low yet there was no profound thrombopenia.
Bleeding time was slightly prolonged.
Coagulation time was normal.
Retraction of the clot was absent when the platelets numbered 143,750
The capillary resistance was negative.

Re-admission September 1928.

Clinical notes. Since leaving hospital in 1925 patient was never without a purpuric rash or bruising of the skin. Apart from a few epistaxes he had no other hæmorrhages.

On 18th Sept. while in hospital bleeding from the gums was observed. With rest in bed the petechial rash and bruising disappeared.

The patient reported on the 10th Nov. 1928 and once again a petechial rash covered the skin.

(over)

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1928						
Sep.13	4,560,000	13,000	13,680	-	-	nil
" 18	4,560,000	-	27,360	25+' RE 7' LE	-	nil
" 21	5,740,000	10,600	11,480	-	-	nil
" 26	6,231,000	8,200	6,230	-	-	nil
Oct. 1	-	-	-	-	Normal	-
" 5	4,650,000	-	18,600	7'30"RE 4' LE	-	-
Nov.10	4,510,000	-	13,530	-	-	-

Summary. On the occasion of the re-admission a marked thrombocytopenia was observed yet the hæmorrhagic symptoms of the disease were not so profound as might be expected.
Bleeding time was prolonged and it varied with the site of puncture.
Coagulation time was normal.
Retraction of the clot was absent.

Note. The platelet counts in this case were done on dry blood films.

Ward No. 8. Journal No. 83, page 16. Case No. 5.

Patient. I. L., Female.
Age. 15 years.
Occupation. At school.

Diagnosis. Henoch-Schönlein purpura.(Anaphylactoid purpura.)

Clinical notes. Patient complained of purpuric spots on the arms and legs of 4 weeks duration. At the beginning of the illness she had an epistaxis followed by sickness, vomiting and epigastric pain. Some time later she had pain in the knee, elbow and wrist joints which did not disappear until admission to hospital. When first seen the spots on the legs had faded but reddish papules, shotty to the feel and about the size of a lentil, were present on the extensor aspects of the arms. The papules did not disappear on pressure and after a week they became purplish and finally disappeared.

There was no cutaneous reaction to vegetables, meat, fish, intestinal organisms and fruit. The capillary resistance was negative.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1928						
Mar.14	3,140,000	8,832	210,000	-	-	-
" 16	-	-	285,000	2' BE	Normal	***

Summary. Although the platelet numbers were slightly below average normal values there was no thrombocytopenia.
Bleeding time and coagulation time were not prolonged.
Retraction of the clot was "good".
Capillary resistance test was negative.

Dispensary case. Case No., 6.

Patient. J. McF., Male.

Age. 34 years.
Occupation. Unemployed.

Diagnosis. Static (Mechanic) purpura.

Clinical Notes. Immediately after an attack of pneumonia in 1919 blood stained "spots and splashes" appeared on the legs. The eruption passed off but since then patient has had similar attacks at varying intervals. They always came on after hard work or after he had been standing for a long time. The rash never appeared on the trunk or arms and it was never associated with abdominal pain. Apart from occasional bleeding from hæmorrhoids there was no history of spontaneous hæmorrhage.

Patient was first seen at the Dispensary on 19th April, 1929. At that time he complained of a purpuric eruption on the lower legs of one day's duration. The purpuric patches varied in size from that of a lentil up to that of a halfpenny and they were scattered irregularly over the lower leg up to the level of the knee joint. The joints were not swollen and there were no varicose veins. The capillary resistance applied to the arms and legs was negative. Three days later the rash had faded. Except for the rash the patient was quite well. There was no possibility of scurvy and in view of the negative result of the capillary resistance test the purpuric eruption was not regerded as artefact.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Apr.22	5,540,000	9,200	295,000	1' RE	-	-
" 29	5,580,000	11,600	318,060	1' 8"RE	2'	***
May 6	5,520,000	9,200	297,540	1'30"RE	2'30"	-
" 20	5,440,000	10,800	440,640	1' RE	2'	*
June 3	5,540,000	7,750	243,760	1' RE	2'	* *
" 24	5,440,000	5,650	427,040	1' RE	1'50"	***
Jul.15	5,250,000	7,850	257,250	-	-	-

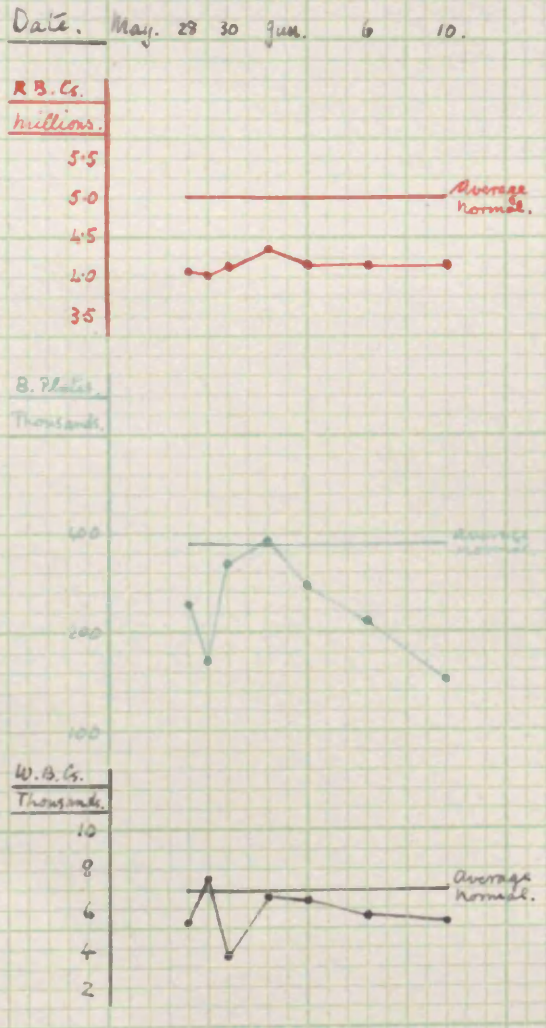
Platelet Morphology.

	Size.			Granulation.				Staining.	
Date.	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929									
Jun.24	-	99	1	-	-	100	-	99	1
Jul.15	-	100	-	-	-	100	-	100	-

Summary. Thrombocytopenia was never observed.
Bleeding time and Coagulation time were always normal.
Clot retraction was always present.
Capillary resistance test was negative.
The platelets stained well. One basophil form was noted.
Granularity and size were normal.

Case No. 7.

Patient. P. C.



Ward No. 9. Journal No. 93, page 162. Case No. 7

Patient. P. C., Male.
Age. 69 years
Occupation. Miner.

Diagnosis. Scurvy.

Clinical notes. Patient had been living on a vegetable-free diet. On admission there was swelling of the left knee-joint and an extensive ecchymosis involving the left leg and thigh. Petechial spots in the neighbourhood of the hair follicles were also noted on the outer aspects of both thighs. The patient made an uninterrupted and rapid recovery.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
May 28	4,030,000	5,150	265,980	1' RE	1'45"	* *
" 29	4,000,000	7,650	172,000	-	-	-
" 30	4,130,000	3,900	342,790	-	-	-
Jun. 1	4,390,000	6,700	399,490	-	-	-
" 3	4,215,000	6,350	295,050	1' RE	2'	-
" 6	4,200,000	5,620	233,100	-	-	-
" 10	4,210,000	5,150	153,665	1'15"RE	2'	-

Summary. The platelet counts tended to be somewhat below average normal values.
Bleeding time was not prolonged and the coagulation time was within normal limits.
Syneresis on one occasion was "fair".
The capillary resistance test on 28th May was negative.

Ward No. 9. Journal No.,86, page 86 Case No. 8.

Patient. R. B., Male.
Age. 66 years.
Occupation. Night watchman.

Diagnosis. Scurvy.

Clinical notes. Patient had not been receiving sufficient food and his diet had seldom contained vegetables. On admission he was anæmic and the legs were oedematous. Purpuric patches were scattered over the lower limbs and petechiæ were noted in the neighbourhood of the hair follicles. The gums were soft, swollen and painful. Platelet counts were made only during the first six days after admission.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1928						
May 26	-	-	145,000	2' RE	normal	***
" 27	-	-	111,050	-	-	-
Jun. 1	2,280,000	2,600	400,000	2' RE 1' LE	normal	* *

Summary. On 26th and 27th May the platelets were diminished but within six days they had increased to normal figures.
Bleeding time and coagulation time were not prolonged.
Syneresis of the clot was present.
The capillary resistance test was negative.

Ward No. 9. Journal No. 87, page 30. Case No. 9.

Patient. J. M., Male.
Age. 23 years.
Occupation. Miner.

Diagnosis. Hæmophilia.

Clinical notes. Since childhood patient had suffered from spontaneous hæmorrhages from the nose and the mouth. He also bruised very easily. On admission he was bleeding from the nose and gums. The knee and elbow joints were swollen and painful and the skin over them was discoloured. During his stay in hospital blood was effused into the joints on four occasions.

The coagulation time of venous and capillary blood was always prolonged.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1928						
Mar.20	4,390,000	7,800	418,095	1'30"RT 3' RE	22' *	***
Apr.16	-	-	365,800	1'45"RE	4'15"	-

Summary. The platelets were not diminished in number and the bleeding time, although varying with the site of puncture, was not prolonged.

Coagulation time of venous and capillary blood was greatly prolonged. (The observation marked * in the table was made on venous blood.)

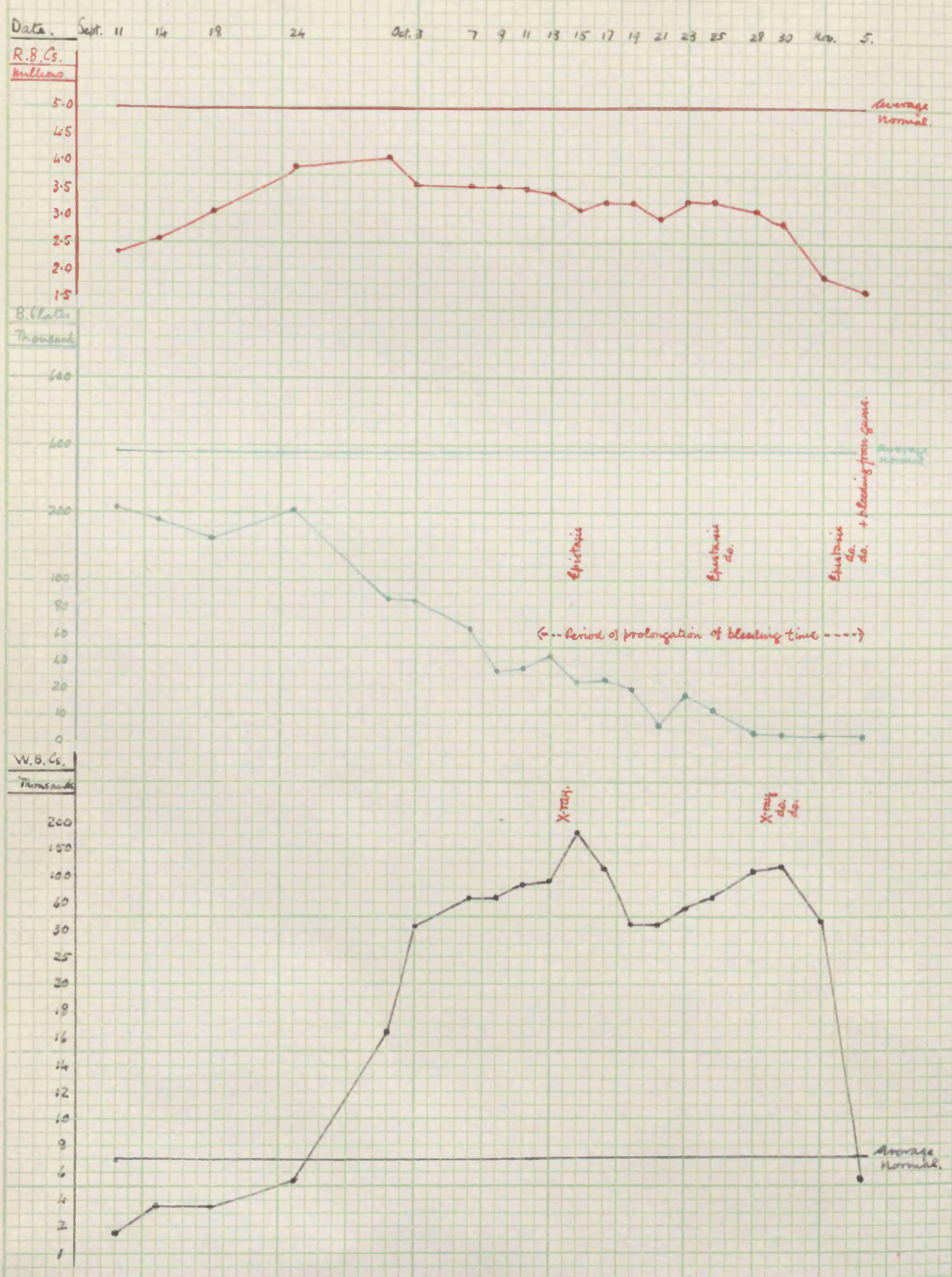
Retraction of the clot was "good".

The capillary resistance test on the above dates was negative.

Some large platelets were observed.

Case No. 10.

Patient. J. D.



Ward No. 9. Journal No. 93, page 532. Case No. 10.

Patient. J. D., Male.
Age. 11 years.
Occupation. At school.

Diagnosis. Acute myeloblastic leukæmia.

Clinical notes. Patient was admitted to the ward on 2nd August, 1929, suffering from epistaxis and bleeding from the lips and gums. He was pale, the spleen was very large and lymph glands were palpable in the neck, axillæ and groins. The blood count showed red cells to number 1,510,000 and white cells 33,687. After exposing the spleen, femora and right humerus to a course of deep X-ray therapy the reds numbered 840,000 and the whites 8,200 on 11th August. Next day 500 c.cs blood were transfused. The leucocytes however continued to diminish so that on the 20th August only 1,700 were counted. About this time bleeding from the nose, gums and alimentary canal occurred. On 22nd August the patient received a transfusion of 300 c.cs blood. By the 24th the leucocytes numbered 900. Thereafter the red and white cells increased so that on the 11th Sept. - when the platelet counts commenced - the red count was 2,280,000 and the white count 1,650. The prevailing white cell was the myeloblast.

When the observations on the platelet numbers commenced the patient was feeling comparatively well. However the leucocytes continued to increase in number so that by the 14th Oct. the count was over 100,000. X-ray therapy was tried again (the abdomen and femora being exposed) with the result that the leucocytes fell to about 30,000. However they rapidly increased and spontaneous hæmorrhage from nose and gums became a feature of the illness(see chart). A third course of X-ray treatment was given on 29th, 30th and 31st Oct. with the result that there was a marked fall in the white cell count with however no alteration in the amount of hæmorrhage. Patient was taken home on 5th Nov. and he died there 5 days later.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Sep.11	2,280,000	1,650	207,480	-	-	-
" 14	2,570,000	3,450	194,035	2'30"RE	2'	-
" 18	3,120,000	3,250	163,750	-	-	-
" 24	3,890,000	7,100	210,060	-	-	-
Oct. 1	4,010,000	16,500	86,215	2' RE	2'	* *
" 3	3,500,000	36,700	85,750	2' BE	2'	*
" 7	3,540,000	65,600	61,950	2' BE	-	*
" 9	3,530,000	61,950	32,005	2'30"BE	-	*
" 11	3,510,000	80,100	33,345	2' BE	-	nil
" 13	3,320,000	96,400	41,500	6' RE 3' LE	-	nil
" 15	3,090,000	177,700	21,630	2' BE	1'45"	* *
" 17	3,270,000	115,500	24,525	-	-	nil
" 19	3,280,000	35,700	19,680	13' RE 2' LE	-	nil
" 21	2,920,000	47,250	5,840	7' RE 6' LE	-	nil

(over)

Case No. 10.(continued)

Results of investigation of the blood.(continued)

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Oct.23	3,250,000	57,650	17,375	7' RE 15+' LE	-	nil
" 25	3,270,000	67,300	11,445	30+' BE	2'45"	nil
" 28	3,020,000	103,300	4,530	-	-	nil
" 30	2,760,000	122,000	2,760	20+' BE	3'30"	nil
Nov. 2	1,970,000	40,100	1,970	9+' LE	1'45"	nil
" 5	1,670,000	9,750	nil	-	-	-

Platelet morphology.

	Size.			Granulation.				Staining.	
Date.	Small.	Normal.	Large.	0	-	- -	---	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Sep.11	-	98	2	-	12	88	-	100	-
" 14	-	100	-	-	2	83	15	98	2
" 18	-	100	-	-	4	82	14	100	-
" 24	-	100	-	-	-	89	11	100	-
Oct. 1	7	93	-	-	19	79	2	100	-
" 3	6	94	-	-	40	56	4	100	-
" 7	6	94	-	-	61	39	-	100	-
" 9	-	100	-	-	24	71	5	100	-
" 11	31	69	-	-	70	30	-	100	-
" 13	-	96	4	-	84	16	-	100	-
" 15	-	100	-	-	7	93	-	100	-
" 17	-	100	-	-	79	21	-	100	-
" 19	-	100	-	-	100	-	-	100	-
" 21	-	100	-	-	-	100	-	100	-
" 23	-	100	-	-	37	63	-	100	-
" 25	-	100	-	-	100	-	-	100	-
" 28	-	100	-	-	67	33	-	100	-
" 30	-	100	-	-	100	-	-	100	-
Nov. 2	-	100	-	-	100	-	-	100	-

Summary. With increase in the leucocyte count there was a steady diminution in the number of platelets so that on 5th Nov. no platelets were observed after a prolonged search. X-ray therapy did not have any effect on the number of thrombocytes.

This case is of interest in that a fairly profound thrombocytopenia existed for about 10 days before there was any increase in the bleeding time or the appearance of spontaneous hæmorrhage. Thereafter the duration of bleeding time varied according to the site. It also varied from the same site on different dates. On 15th Oct. the platelets numbered 21,000 and bleeding time from each ear was only 2 minutes.

Coagulation time did not vary with alteration in the number of platelets.

(over)

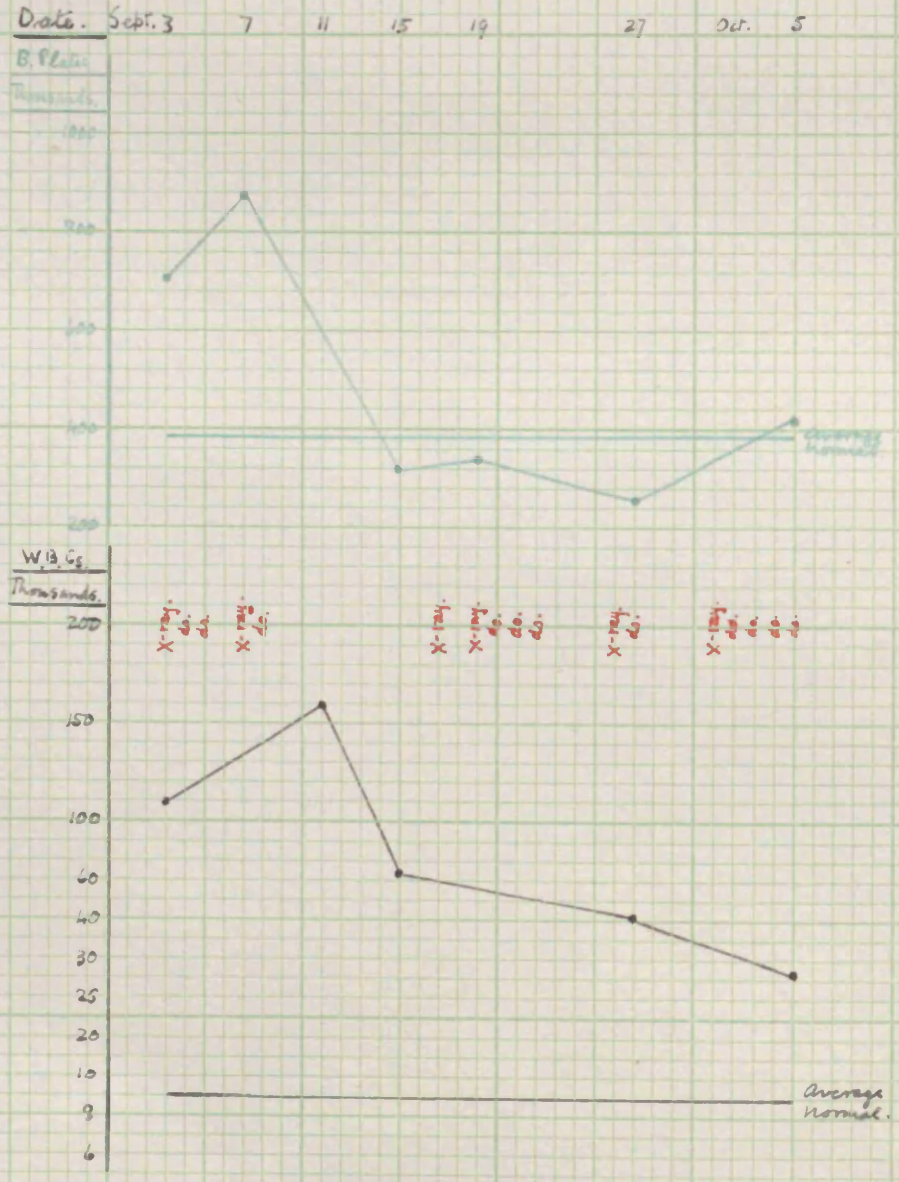
Summary. (contd) In a general way retraction of the clot diminished as the thrombocytopenia increased until it was completely absent. It was noted however that on 15th Oct. syneresis was "fair" when the thrombocytes numbered 21,630.

The capillary resistance test produced petechiæ on both arms on 12th, 15th, 19th and 25th Oct. No petechiæ were however produced on the left leg even after apparent effective stasis had been established.

Throughout the period of investigation there was a preponderance of platelets deficient in granules. This feature became more marked as the thrombocytopenia increased. Basophilia was noted only on one occasion at the commencement of the investigations. The size of the thrombocytes varied but on four days there was an increase in the number of small forms. As the thrombocytopenia increased large basophil forms did not appear in the blood.

Case No. 11.
Patient. E. L.

Graph No. 1. (1928)



Ward No. 8. Journal No. 88, page 70. Case No. 11.

Patient. E. L., Female.
Age. 29 years.
Occupation. At home.

Diagnosis. Chronic myeloid leukæmia.

Clinical notes. Patient was in hospital on two occasions. When she was first admitted on 30th August, 1928 the spleen was very large and the leucocytes numbered 124,000. Myeloblasts and myelocytes were present in the blood. After treatment with deep X-ray therapy on various dates the number of white cells was reduced to the neighbourhood of 20,000 when she was dismissed on 9th Oct, 1928. (X-ray exposures were given over the scapulæ, femora, knees, vertebræ and abdomen)

On 2nd Sept., 1929 she was readmitted as the leucocytes numbered 248,000. She was again treated with deep X-ray therapy so that when she was dismissed on 12th Oct., 1929 the white count was 3,600. (The whole abdomen was exposed to the action of X-rays on each occasion.)

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1928						
Sep. 3	3,770,000	110,000	716,300	-	-	-
" 9	-	-	878,410	-	-	-
" 15	3,410,000	67,400	317,130	-	-	-
" 19	-	-	323,950	-	-	-
" 27	3,500,000	43,600	252,000	-	-	-
Oct. 5	4,200,000	28,100	420,000	-	-	-
1929						
Sep. 2	3,400,000	248,000	-	-	-	-
" 6	-	160,000	-	-	-	-
" 7	-	138,000	-	-	-	-
" 9	-	105,000	-	-	-	-
" 11	3,610,000	53,320	741,855	-	-	* *
" 14	3,970,000	21,700	698,720	-	-	-
" 18	3,570,000	20,000	371,280	1'30"RE	2'15"	-
" 24	4,360,000	10,900	556,440	-	-	-
Oct. 2	3,870,000	5,650	261,205	-	-	-
" 8	3,980,000	3,600	157,210	1'30"RE	2'	-

Platelet morphology.

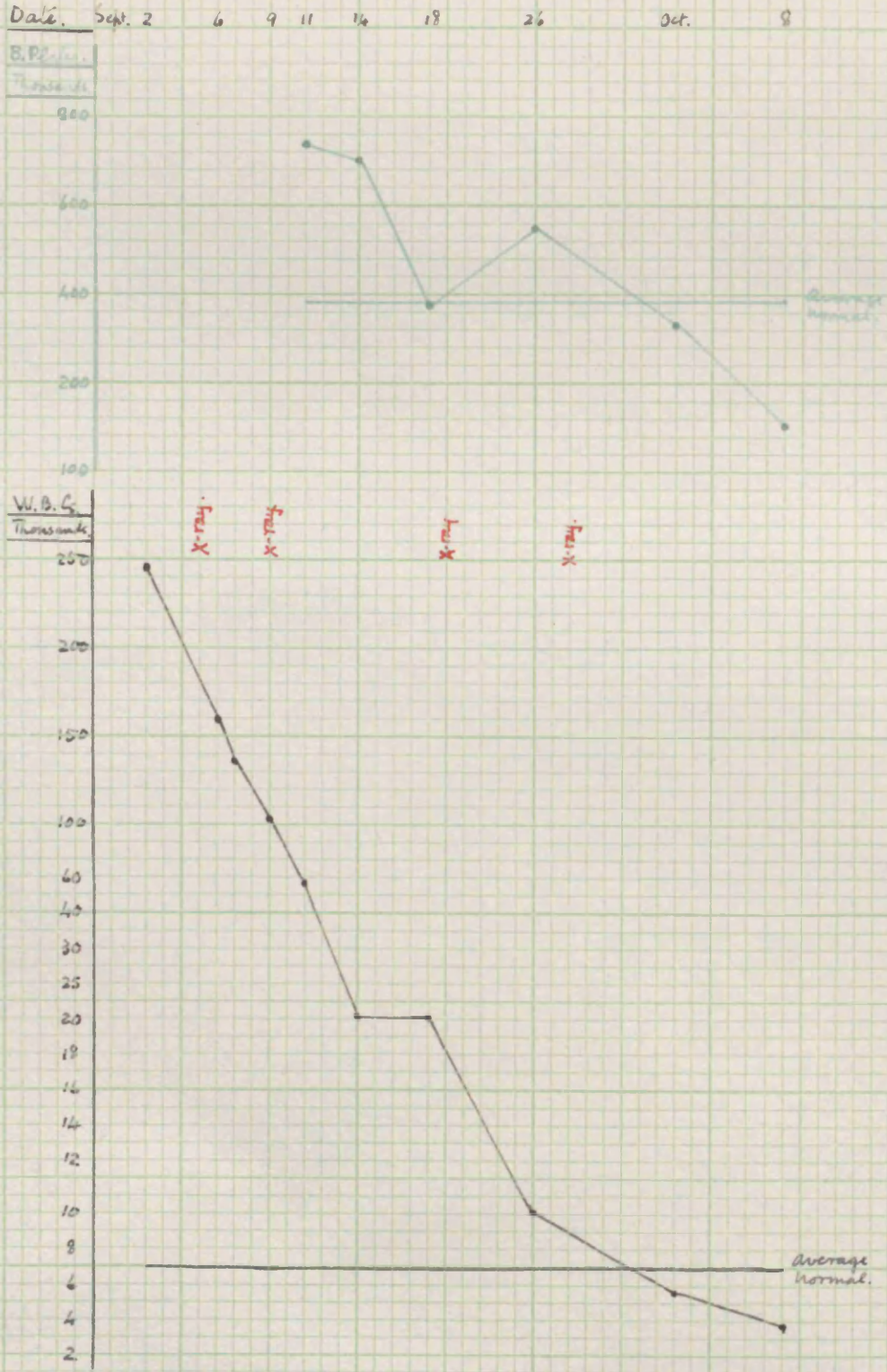
Date.	Size.			Granulation.				Staining.	
	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Sep. 11	-	100	-	-	67	33	-	100	-
" 14	-	98	2	-	-	100	-	100	-
" 18	-	98	2	-	-	77	23	100	-
" 24	-	100	-	-	-	88	12	100	-
Oct. 2	-	99	1	-	1	89	10	97	3
" 8	-	100	-	-	4	96	-	100	-

(over)

Case No. 11.

Patient. E. L.

Graph No. 2. (1929).

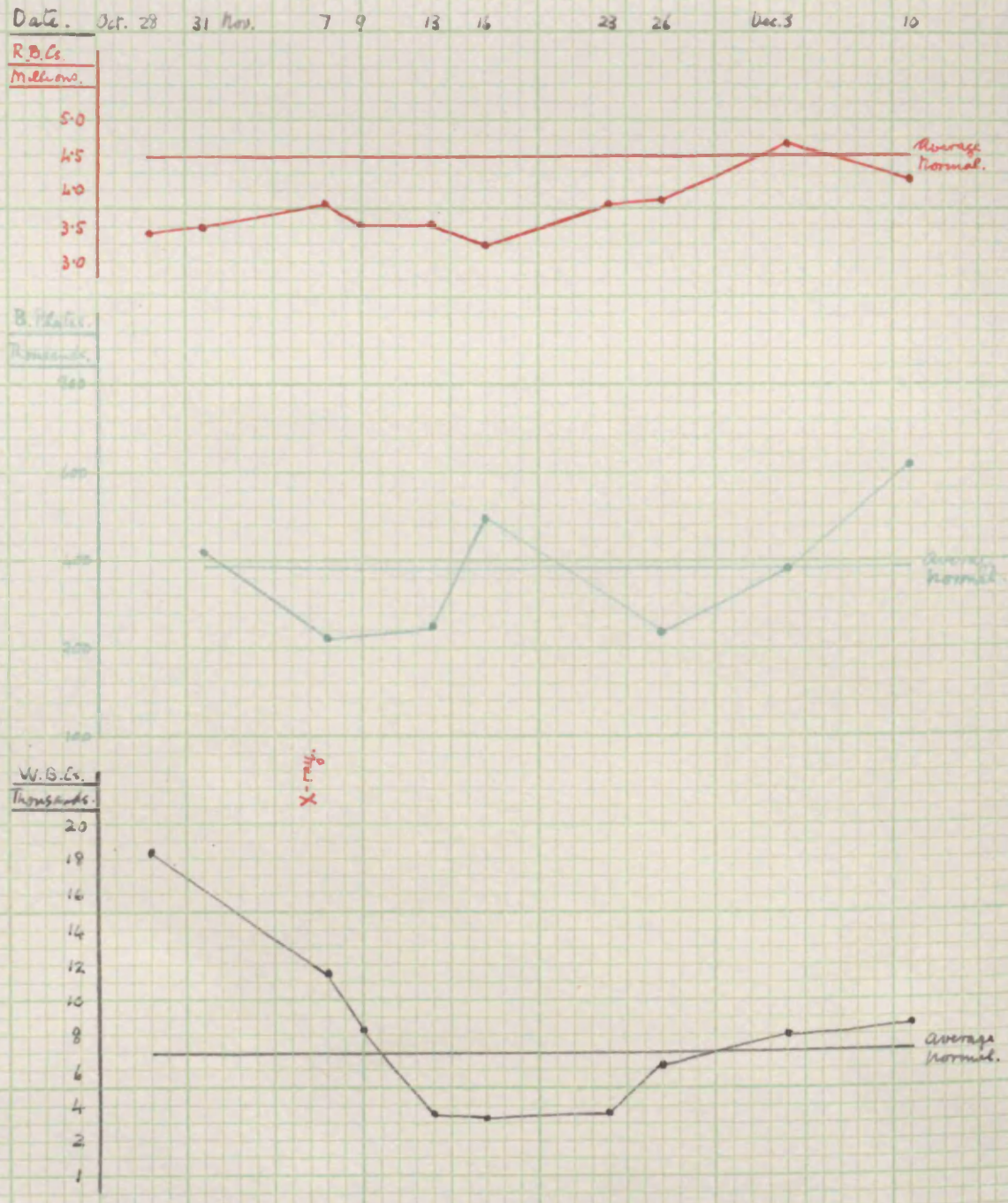


Summary. Following X-ray treatment reduction in the number of leucocytes was accompanied by a diminution in the platelet count. The fall in each case was however only approximately parallel as the diminution in the number of white cells was steady whereas that of the thrombocytes showed an occasional rise.

During the period of the patient's second stay in hospital it was observed that when the numbers were highest a large percentage of the platelets were not well granulated. As the thrombocyte count diminished very granular forms made their appearance in the blood and basophilia was noted on 2nd Oct. Large forms were noted occasionally.

Case No. 12.

Patient. M. M.



Ward No. 8. Journal No. 89, page 328. Case No. 12.

Patient. M. M., Female.
Age. 46 years.
Occupation. At home.

Diagnosis. Chronic myeloid leukæmia.

Clinical notes. When the patient was admitted to hospital the spleen was enlarged and the leucocytes numbered 18,600. The blood picture was typical of chronic myeloid leukæmia. On 6th Nov. deep X-ray therapy was applied over the spleen. The white cell count diminished almost immediately but it was evident some time before dismissal that the leucocytes were increasing.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.
1928			
Oct. 28	3,450,000	18,600	-
" 31	3,500,000	-	420,000
Nov. 7	3,820,000	11,600	225,380
" 13	3,510,000	3,500	252,720
" 16	3,200,000	3,200	496,000
" 23	3,760,000	3,700	-
" 26	3,880,000	6,133	240,560
Dec. 3	4,715,000	8,000	377,200
" 10	4,120,000	8,800	626,240

Summary. The thrombocytes were found to have diminished in number after irradiation but it is possible that this fall is mere coincidence and due to some other cause as a similar reduction has been noted frequently without exposure to Röengten rays. Indeed an almost identical fall is seen when the platelet counts of 16th and 26th Nov. are compared. Towards the end of the observations the platelets increased at the same time as the leucocytes. Even so, the behaviour of the two curves was not parallel.

Before treatment the number of thrombocytes in the blood was normal.

Private patient. Case No.13.

Patient. I. D. M., Male.
Age. 39 years.
Occupation. Minister.

Diagnosis. Polycythæmia vera.

Clinical notes. Patient received doses of deep X-ray therapy on the following dates.

1928
Nov. 19th, 20th, 21st and 22nd.
Dec. 6th, 13th, 20th and 27th.
1929
Jan. 3rd.
Feb. 7th and 14th.

After an interval of about a month from the date of the first exposure there was a steady diminution in the number of red cells until a level of just over 4,000,000 was reached. Previous to the treatment the patient never had a leucocytosis but during irradiation a leucopenia occurred. The appearance and general health of the patient improved as the red cell count diminished and on the date of the last count he was fit and well.

(The knees, thighs, spleen, hip, scapulæ and vertebræ were exposed to the action of X-rays on various occasions as indicated above.)

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1928						
Mar.21	8,175,000	5,625	-	-	-	-
Apr.16	9,520,000	5,000	142,800	2' RE	-	-
Nov. 5	10,770,000	4,400	216,770	1'45"RE	-	-
" 22	10,560,000	4,400	237,600	1'40"RE	-	-
Dec. 6	10,650,000	5,000	202,350	1'30"RE	-	-
" 13	10,780,000	4,000	174,870	1'30"RE	-	-
" 20	8,920,000	-	182,860	-	-	-
" 27	8,640,000	-	-	-	-	-
1929						
Jan. 3	8,570,000	3,800	265,670	2' RE	1'45"	-
Feb. 7	7,730,000	3,600	208,710	2' RE	-	-
" 14	7,150,000	4,800	239,525	1'45"RE	2'15"	-
" 21	6,200,000	4,400	201,500	1'30"RE	2'	-
Mar. 4	5,720,000	2,200	291,720	2' RE	-	-
" 18	4,600,000	3,440	170,200	1'30"RE	2'	-
Apr. 8	4,430,000	2,400	168,340	1'30"RE	2'	-
May 6	4,480,000	3,050	161,280	1'30"RE	2'	-
Jun. 6	4,260,000	2,800	129,930	1'30"RE	2'	*
Oct. 7	4,430,000	4,900	245,865	1'40"RE	2'	***
Dec.23	4,880,000	3,250	244,000	1'30"RE	2'	***

(over)

Summary. The platelet numbers always tended to be low. In view of the variation in the thrombocyte counts recorded before and during the course of treatment it is doubtful if the low readings noted from the 18th March to 10th June are the result of treatment. It is noteworthy however that this period of diminution in the platelet count coincided with reduced bone-marrow activity as reflected by the number of red and white cells.

Bleeding time and coagulation time did not vary with alteration in the platelet numbers.

Retraction of the clot on the occasions on which it was observed was present. It was "poor" on 10th June 1929 when the platelet count was only 130,000.

Beyond the observation on 6th May 1929 that some large platelets were seen no morphological changes were recorded.

Case No. 14.
Patient. T. H.

Ward No. 9. Journal No. 86, page 230. Case No. 14.

Patient. T. H., Male.
Age. 74 years.
Occupation. Artist.

Diagnosis. Polycythæmia vera.

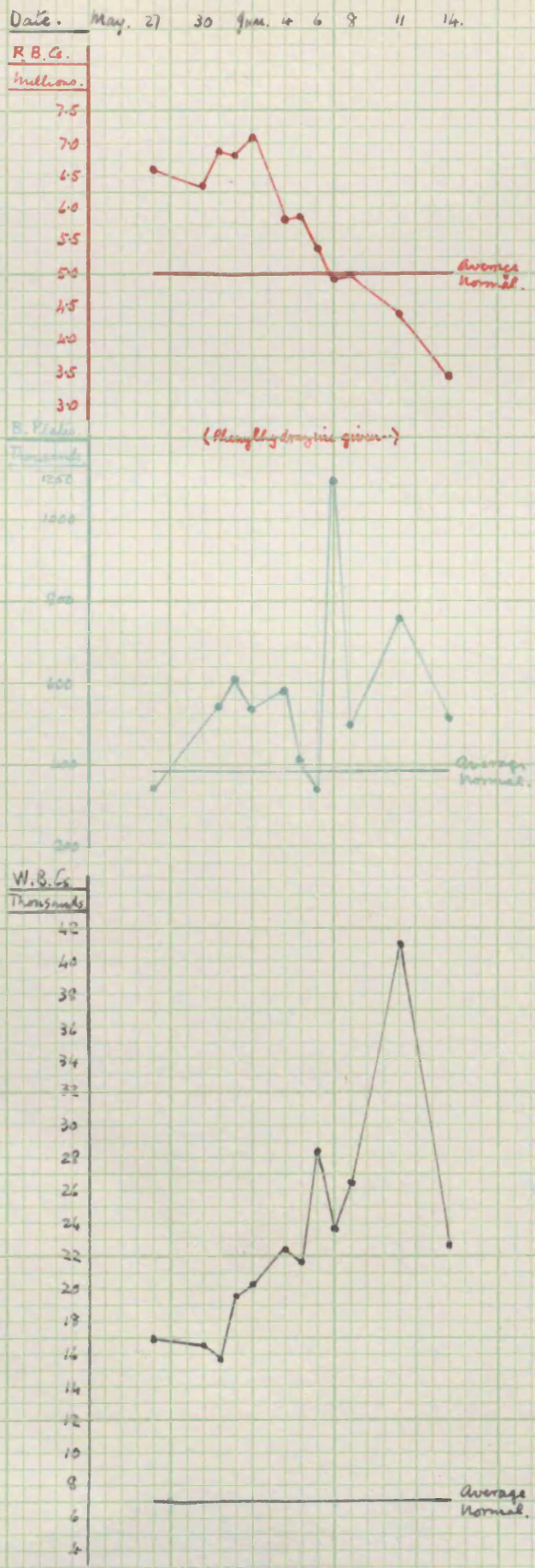
Clinical notes. On admission patient had an enlarged spleen and a red cell count of 7, 690,000. He was treated with varying doses of phenylhydrazine hydrochloride between 11th June and 2nd July, 1928. By that date the red cells had fallen to 4,390,000 but they continued to diminish in number for a further period of one week. On 7th July patient developed a phlebitis in the right great saphenous vein. Previous to treatment he had a history of hæmatemesis and phlebitis of the veins of the leg.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.
1928			
Jun. 12	7,690,000	9,800	421,740
" 15	7,980,000	10,600	478,800
" 21	7,660,000	9,000	689,400
" 28	6,170,000	14,000	820,610
Jul. 2	4,340,000	16,400	988,200
" 20	3,620,000	6,800	217,200

Summary. Under treatment with phenylhydrazine hydrochloride the platelets increased in number until they had reached to almost 1,000,000 five days before the onset of the phlebitis. Thirteen days later the thrombocytes numbered only 217,000.

Case No. 15. Patient. R. G. Graph No. 1 (1928).



Ward No. 9. Journal 86, page 122. Case No. 15.

Patient. R. G., Male.
Age. 48 years.
Occupation. Engineer.

Diagnosis. Polycythæmia vera.

(1) Clinical notes. This patient has suffered from polycythæmia vera since 1922. When admitted on 25th May 1928 he was treated with phenylhydrazine hydrochloride administered by mouth. The treatment commenced on 30th May and finished on 11th June. As a result the red cells were reduced to 3,500,000 and the leucocytes increased.

(1) Results of investigation of the blood.
(Graph No. 1.)

Date.	Red cells.	White cells.	Platelets.
1928			
Mar. 7	6,030,000	18,400	-
May 12	6,500,000	15,000	-
" 27	6,640,000	17,000	332,000
" 30	6,440,000	16,600	-
" 31	6,980,000	15,900	547,400
Jun. 1	6,910,000	19,600	604,000
" 2	7,140,000	20,400	530,000
" 4	5,730,000	22,400	573,000
" 5	5,760,000	21,800	403,200
" 6	5,490,000	28,400	334,890
" 7	4,950,000	23,600	1,291,950
" 8	5,030,000	26,700	503,000
" 11	4,475,000	41,000	769,700
" 14	3,480,000	22,600	518,520

Summary. The blood platelets underwent extraordinary variations and on one occasion rose from 330,000 to over 1,200,000 within one day and during the next day fell to 500,000. The platelets behaved independently of the red and white cells yet it seemed that the production of all three elements was stimulated.

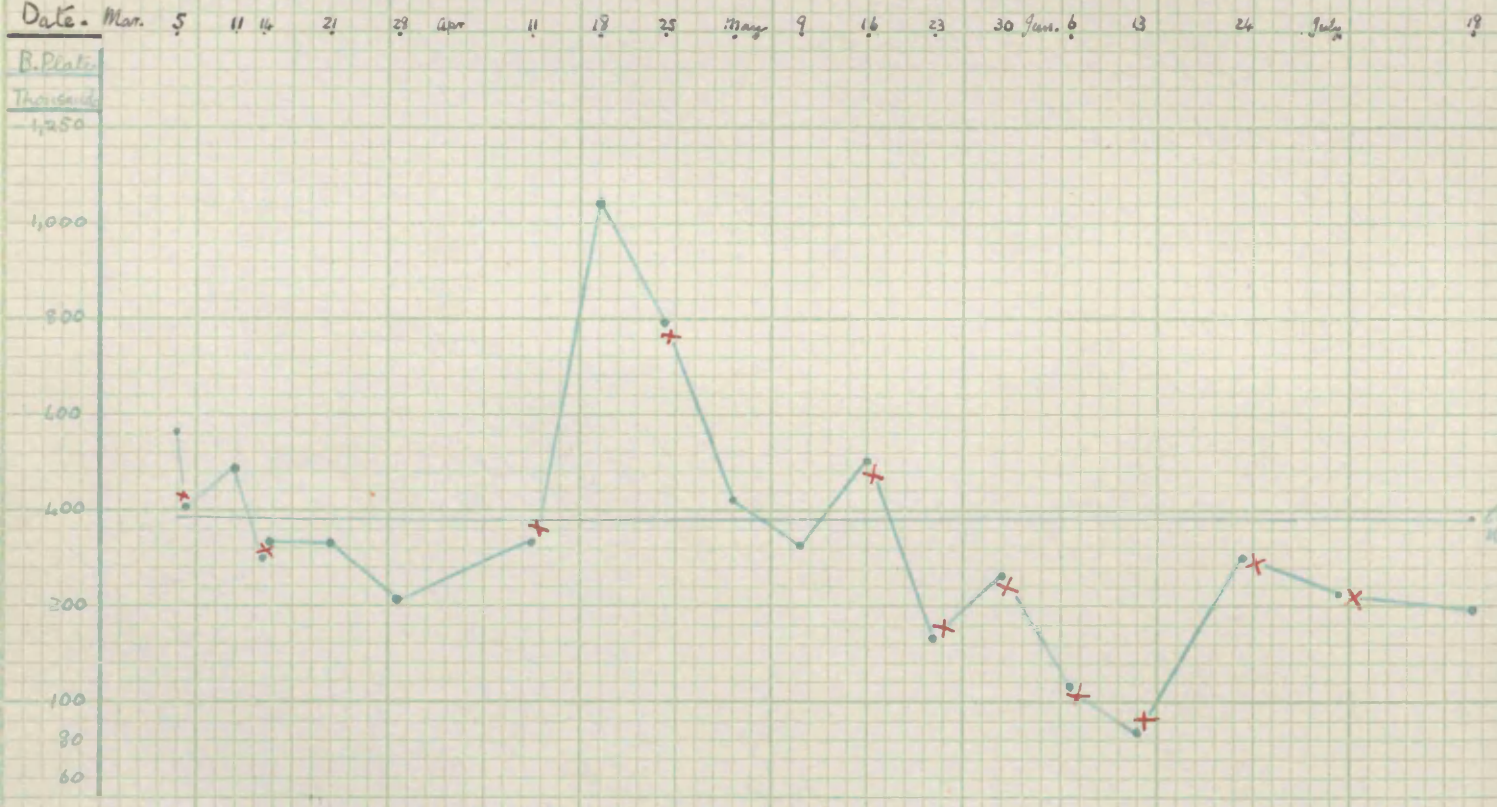
(2) Clinical notes. The patient eventually became tired of treatment with phenylhydrazine hydrochloride and it was then resolved to treat him as an out-door patient with deep X-ray therapy. As a rule blood counts were made immediately before each exposure. Irradiation in this case failed to bring about any permanent reduction in the erythrocytes and eventually it was abandoned. (The parts exposed to the action of X-rays were the scapulæ, vertebræ, hip and knee joints and the spleen.)

(over)

Case No. 15.

Patient. R. G.

Graph No. 2 (1929).



X = application of deep X-ray therapy.

(2) Results of investigation of the blood.
(Graph No. 2)

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Mar. 3	-	-	573,720	-	-	-
" 6	-	-	409,800	-	-	-
" 11	7,060,000	22,000	494,200	1' RE	1' 6"	* *
" 14	5,540,000	18,000	315,780 *	-	-	-
"			342,480**			
" 21	5,760,000	15,600	339,840	-	-	-
" 28	5,040,000	8,400	211,680	normal	normal	* *
Apr.11	6,040,000	5,900	338,240	-	-	-
" 18	6,770,000	6,600	1,068,660	-	-	-
" 25	7,750,000	9,400	798,250	1' RE	3'	-
May 2	6,380,000	10,800	420,680	2' RE	2'45"	*
" 9	6,650,000	11,600	332,500	-	-	-
" 16	7,850,000	8,600	510,250	-	-	-
" 23	8,630,000	5,950	163,970	1' RE	2'	* *
" 30	8,470,000	7,450	271,040	-	-	-
Jun. 6	8,225,000	7,750	119,262	1'30"RE	1'30"	* *
" 13	7,830,000	6,400	82,215	1'30"RE	2'15"	* *
" 24	8,360,000	6,150	305,140	-	-	-
Jul. 7	7,630,000	6,950	225,085	-	2'30"	-
" 18	8,670,000	4,600	199,410	-	-	-
Sep.16	10,000,000	9,000	535,800	-	-	* *

Summary. During the course of treatment the platelets underwent great numerical alterations which were apparently independent of any influence due to the X-ray treatment. The platelets were found to be increased after the exposure on four occasions, in fact, after irradiation on 11th April the platelets trebled their numbers within three days. On other occasions the numbers were usually diminished. The impression was gained that at the commencement of the treatment the thrombocyte producing tissues were stimulated.

Note. The sign * in the platelet column denotes the count before treatment.
The sign ** denotes the count immediately after treatment.

Case No. 16.

Patient. Mrs P.

Ward No. 8. Journal No. 71, page 126. Case No. 16.

Patient. Mrs P.
Age. 28 years.
Occupation. At home.

Diagnosis. Splenic anæmia.

Clinical notes. When patient was admitted to the ward she was pale and the spleen was very large. The following is a typical differential count:-

Neutrophil polymorphs	73%
Eosinophil "	1%
Lymphocytes	25%
Myelocytes	1%

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Dec.17	1,910,000	3,460	92,535	2'10"BE	2'15"	*
" 18	1,850,000	4,510	149,850	1'45"RE	-	*
" 20	1,830,000	4,150	150,975	-	2'10"	*
" 23	2,170,000	5,950	121,520	-	-	***
" 26	2,130,000	6,200	202,358	-	-	-
" 28	2,340,000	9,750	215,080	-	-	-
" 30	2,370,000	6,450	188,415	-	2'	-
1930						
Jan. 2	2,300,000	5,750	220,800	-	-	-
" 4	2,500,000	5,300	132,500	2' RE	-	*
" 6	2,800,000	5,900	109,200	2' RE	1'55"	-
" 8	2,780,000	4,850	176,530	2' RE	-	***
" 10	2,940,000	4,300	179,340	2'30"RE	2'	-

Platelet morphology.

	Size.			Granulation.				Staining.	
Date.	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Dec.17	6	94	-	-	7	93	-	100	-
" 18	-	97	3	-	3	97	-	97	3
" 20	-	100	-	-	-	100	-	100	-
" 23	4	96	-	-	1	99	-	100	-
" 26	-	100	-	-	-	100	-	100	-
" 28	-	100	-	-	14	86	-	100	-
" 30	-	100	-	-	18	82	-	100	-
1930									
Jan. 2	-	100	-	-	7	93	-	100	-
" 4	-	100	-	-	19	81	-	100	-
" 6	-	100	-	-	-	100	-	100	-
" 8	1	99	-	-	8	92	-	94	6
" 10	-	100	-	-	-	100	-	100	-
" 13	-	100	-	-	7	93	-	100	-
" 16	-	100	-	-	-	100	-	100	-
" 22	-	100	-	-	1	99	-	100	-

(over)

Summary. The platelet numbers varied but the count was always low. In the earlier observations the platelets increased along with increase in the red and white cells. Subsequently the behaviour of each of the three curves was different.

Bleeding time was never prolonged in spite of the fact that the thrombocytes on occasion were in the neighbourhood of the 100,000 level.

Coagulation time did not vary with alteration in the number of platelets.

Retraction of the clot varied in amount but the variations did not depend on the thrombocyte count.

Anisocytosis of platelets was observed. Deficiency in granulation was a feature especially when the platelet values were increased. Basophilia was noted on two occasions.

Ward No. 9. Journal No. 74, page 281. Case No.17.

Patient. A. D., Male.
Age. 21 years.
Occupation. Steelworker.

Diagnosis. Splenic anæmia.

Clinical notes. This patient had suffered from splenic anæmia and splenectomy had been performed on 9th June, 1927. The result of the operation was good and the patient was now in perfect health. There was no history of post-operative thrombosis.

Results of investigation of the blood.

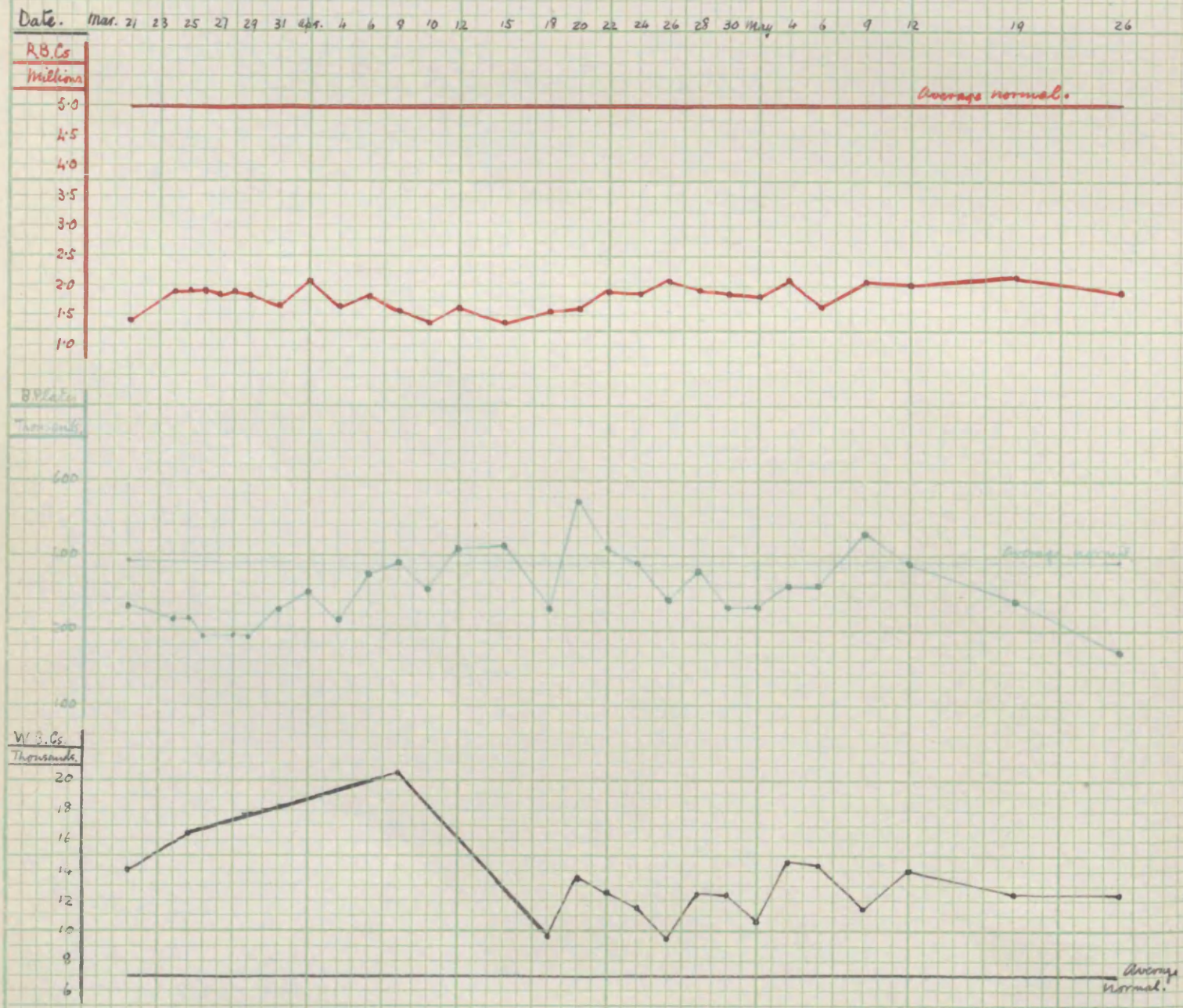
Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Jun.17	5,110,000	7,950	592,760	1'15"RE	1'45"	-
Jul.17	4,800,000	8,150	489,600	-	-	***

Summary. The platelets were present in numbers above normal average values.
Bleeding time and coagulation time were normal and retraction of the clot was "good".
The platelets were of normal size and well granulated. The cytoplasm was hyaline in staining reaction.

Case No. 18.

Patient. J. C.

Graph, 1st admission.



Ward No. 9. Journal No.92, page 146. Case No. 18.

Patient. J. C., Male.
Age. 35 years.
Occupation. Craneman.

Diagnosis. Acholuric jaundice.

Clinical notes. Patient was in the ward on two occasions. He had a profound degree of anæmia, the skin was lemon yellow in colour and the fragility of the red cells was increased. On the occasion of the first admission the splenic area was not increased but when he was re-admitted about seven months later the spleen was palpable. On 11th Dec.1929 the spleen was removed and thereafter the patient made a rapid recovery. He was dismissed from hospital on 7th Jan. 1930 and reported on two occasions.

Results of investigation of the blood.
(1st admission)

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Mar.21	1,490,000	14,000	280,120	-	-	-
" 24	1,855,000	-	244,860	-	-	-
" 25	1,930,000	16,600	243,180	-	-	***
" 26	1,930,000	-	194,930	-	4'	-
" 27	1,830,000	-	161,040	-	-	-
" 28	1,900,000	-	199,000	-	-	-
" 29	1,770,000	-	182,310	-	-	-
" 31	1,630,000	-	252,650	-	-	-
Apr. 2	2,160,000	-	304,560	-	-	-
" 4	1,640,000	-	239,600	-	-	-
" 6	1,860,000	21,600	360,840	-	15+'	-
" 8	1,590,000	-	391,140	-	-	-
" 10	1,290,000	-	312,180	-	-	-
" 12	1,612,000	-	434,016	-	-	-
" 15	1,320,000	-	435,600	-	-	-
" 18	1,520,000	9,600	256,880	-	-	-
" 20	1,580,000	13,400	562,600	-	-	-
" 22	1,900,000	12,466	414,200	2'15"RE	5'	-
" 24	1,870,000	11,600	379,610	-	-	-
" 26	2,060,000	9,400	284,280	1' RE	3'	-
" 28	1,970,000	12,400	364,450	-	4'	-
" 30	1,900,000	12,200	264,100	-	4'45"	-
May 2	1,780,000	10,600	267,000	1' RE	4'	-
" 4	2,170,000	14,800	329,840	-	-	-
" 6	1,650,000	14,400	320,100	1' RE	3'	-
" 9	2,100,000	11,500	472,500	-	-	-
" 12	2,000,000	14,000	376,000	1' RE	2'	-
" 19	2,210,000	12,600	287,300	-	-	-
" 26	1,900,000	12,300	172,900	1'15"RE	3'45"	***

(over)

Case No. 18.

Patient. J. C.

Graph. 2nd admission.

Results of investigation of the blood.
(2nd admission)

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Dec,11	2,410,000	17,450	175,930	-	-	-
" 12	2,320,000	23,000	266,800	-	-	-
" 13	2,150,000	17,550	390,225	-	-	***
" 14	1,870,000	13,550	287,045	-	-	-
" 15	2,340,000	15,300	553,410	-	1'40"	-
" 17	2,560,000	14,800	567,040	-	-	-
" 18	2,460,000	15,200	847,470	-	-	-
" 19	2,360,000	17,300	985,300	-	1'55"	-
" 20	2,540,000	18,600	626,110	-	-	-
" 21	2,700,000	34,300	950,400	-	-	-
" 23	2,780,000	26,500	963,270	-	-	-
" 24	2,730,000	22,850	834,015	-	-	-
" 25	2,810,000	17,350	1,159,125	-	-	-
" 26	2,890,000	18,650	1,034,612	1'30"RE	-	-
" 27	2,880,000	20,300	940,320	1'45"RE	-	-
" 28	2,910,000	19,550	964,665	1'45"RE	1'10"	-
" 30	3,160,000	21,850	873,740	-	-	-
" 31	2,900,000	13,900	904,800	-	-	-
1930						
Jan. 2	3,140,000	12,850	946,710	-	-	-
" 4	3,280,000	11,200	838,040	2'30"RE	1'30"	***
" 6	3,310,000	14,700	810,950	1'50"RE	-	***
" 31	4,190,000	12,250	747,915	-	-	-
Mar.28	4,180,000	19,450	693,880	-	-	-

Platelet morphology.(2nd admission)

	Size.			Granulation.				Staining.	
Date.	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil
1929	%	%	%	%	%	%	%	%	%
Dec.11	-	100	-	-	-	100	-	100	-
" 12	-	93	7	-	1	99	-	100	-
" 13	-	95	5	-	-	100	-	95	5
" 14	-	88	12	-	-	100	-	94	6
" 15	-	99	1	-	-	100	-	100	-
" 17	-	100	-	-	56	44	-	90	10
" 18	-	100	-	-	15	85	-	100	-
" 19	-	100	-	-	-	100	-	98	2
" 20	-	100	-	-	4	96	-	100	-
" 21	12	84	4	-	12	84	4	100	-
" 23	-	98	2	-	-	100	-	88	12
" 24	-	100	-	-	11	79	10	100	-
" 25	-	100	-	-	-	100	-	100	-
" 26	-	99	1	-	-	100	-	92	8
" 27	-	100	-	-	-	100	-	100	-
" 28	-	88	12	-	-	100	-	100	-
" 30	-	100	-	-	-	100	-	100	-
" 31	-	100	-	-	-	100	-	100	-
1930									
Jan. 2	-	100	-	-	-	100	-	100	-
" 4	-	100	-	-	-	100	-	100	-
" 6	-	100	-	-	-	100	-	100	-
" 31	-	98	2	-	-	97	3	99	1

(over)

Summary. The platelet numbers varied greatly during the period of 1st admission. There was nothing characteristic in the shape of the curve. After splenectomy there was a fairly rapid increase in the count to over 1,000,000. The numbers continued at a high level and 3½ months after operation the thrombocyte count was nearly 700,000.

Bleeding time was never prolonged.

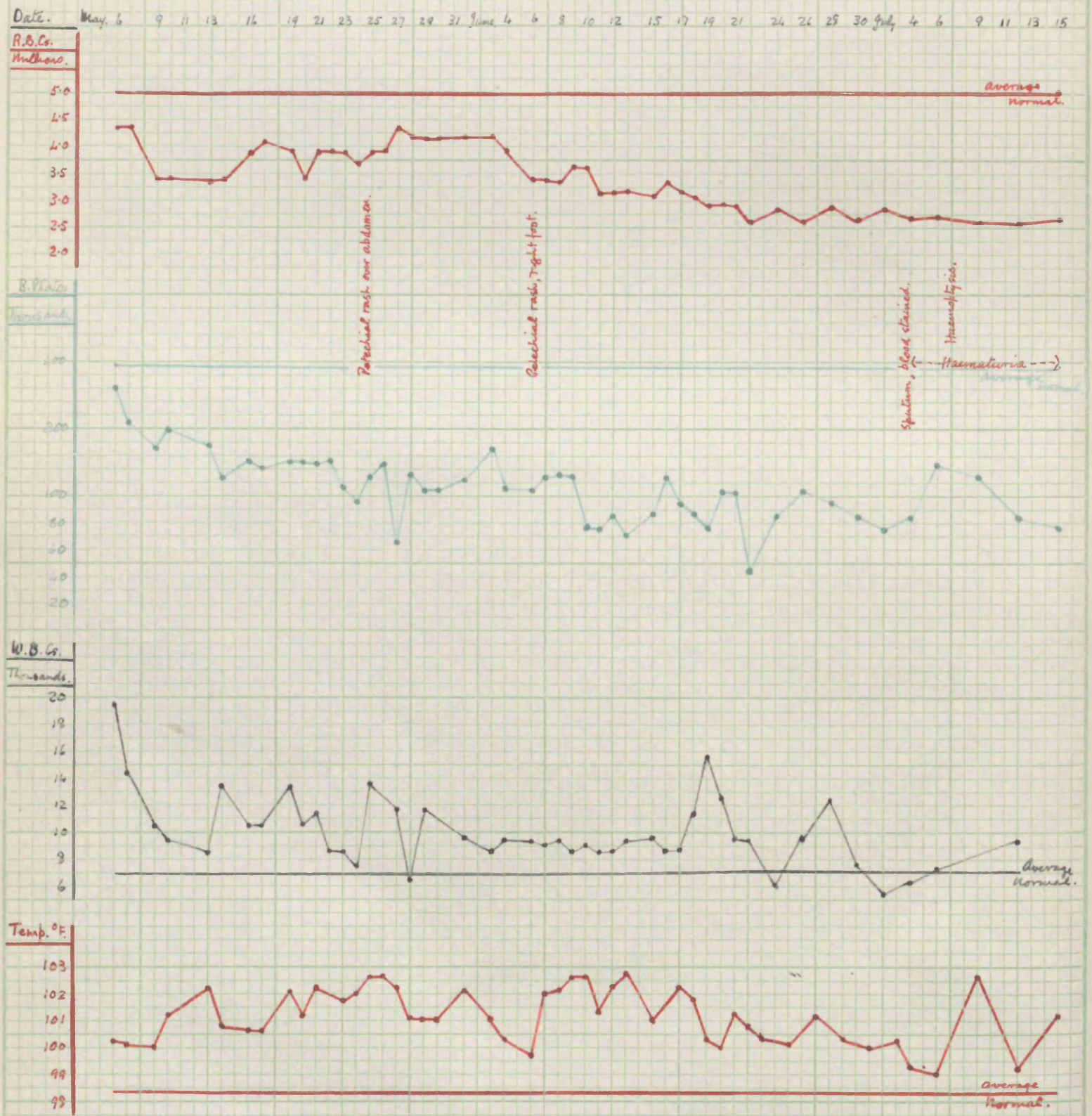
Coagulation time was increased during the 1st admission when jaundice was present. After splenectomy the icterus disappeared and the coagulation time remained normal.

Syneresis of the clot was always "good".

During the period of first admission deficiency in granulation was sometimes a feature. For a few days after splenectomy many large platelets appeared i.e. during the increase in the platelet numbers. At this time also the thrombocytes became less granular and many showed basophilia of the cytoplasm. After the numbers had reached their highest values and showed some tendency to diminish the platelet picture became normal. On 31st Jan., after the patient had been on holiday, a few large granular and basophil forms were present in the blood.

Case No. 19.

Patient. D. D.



Ward No. 9. Journal No. 92, page 392. Case No. 19.

Patient. D. D., Male.
Age. 25 years.
Occupation. Grocer.

Diagnosis. Malignant endocarditis.

Clinical notes. Some 9½ years previously patient had been in the ward suffering from acute rheumatism, pericarditis and pneumonia. During the period of the present illness blood culture was negative on three occasions. Patient died on 19th July and post-mortem examination confirmed the diagnosis. On 4th July hæmaturia and blood stained sputum were observed and both continued until death when they were found to be due to emboli.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
May 6	4,390,000	19,200	320,470	1'30"RE	2'30"	-
" 7	4,310,000	14,400	228,430	1'30"RE	2'	-
" 9	3,450,000	10,200	169,050	1'45"RE	1'45"	-
" 10	3,460,000	9,200	200,680	1'45"RE	2'15"	* *
" 13	3,370,000	8,600	178,610	2' RE	1'30"	-
" 14	3,400,000	13,200	125,800	-	-	-
" 16	3,770,000	10,800	158,340	-	-	-
" 17	4,030,000	10,600	140,650	-	-	-
" 19	3,900,000	13,400	152,100	-	-	-
" 20	3,480,000	10,650	149,640	2' RE	2'15"	nil
" 21	3,880,000	11,400	147,440	-	-	*
" 22	3,890,000	8,600	159,490	-	-	-
" 23	3,800,000	8,500	117,800	1'30"RE	2'	-
" 24	3,720,000	7,200	96,200	1' RE	2'	-
" 25	3,840,000	13,700	138,240	-	-	-
" 26	3,985,000	-	147,445	-	-	-
" 27	4,315,000	11,700	62,700	1' RE	1'45"	* *
" 28	4,210,000	6,500	134,720	1' RE	1'45"	-
" 29	4,110,000	11,750	106,860	-	-	-
" 30	4,160,000	-	108,160	-	-	-
Jun. 1	4,200,000	9,600	126,000	1' RE	2'	-
" 3	4,240,000	8,750	173,840	1' RE	2'	-
" 4	3,950,000	9,550	116,525	1' RE	2'	*
" 6	3,340,000	9,150	113,560	-	-	*
" 7	3,330,000	9,000	128,205	-	-	***
" 8	3,280,000	9,400	136,120	1' RE	2'	nil
" 9	3,410,000	8,450	129,580	1' RE	-	-
" 10	3,380,000	9,000	79,430	1' RE	2'	nil
" 11	3,100,000	8,250	74,400	-	-	nil
" 12	3,200,000	8,450	86,400	1'30"RE	2'	*
" 13	3,270,000	9,050	70,305	-	-	-

(over)

Results of investigation of the blood.

Date. 1929	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
Jun. 15	3,050,000	9,650	86,925	-	-	-
" 16	3,330,000	8,700	133,200	-	-	nil
" 17	3,210,000	8,950	93,090	1'30"RE	2'45"	-
" 18	3,030,000	11,250	89,385	-	-	nil
" 19	2,870,000	15,850	77,490	-	-	-
" 20	2,955,000	12,500	103,425	-	-	*
" 21	2,870,000	9,900	101,885	-	-	-
" 22	2,530,000	9,400	45,540	2' RE	-	-
" 24	2,780,000	6,000	84,790	-	-	-
" 26	2,530,000	9,400	111,320	1'30"RE	2'45"	nil
" 28	2,820,000	12,100	93,060	2'30"RE	-	nil
" 30	2,620,000	7,800	81,220	2' RE	2'	-
Jul. 2	2,825,000	5,400	74,862	-	-	-
" 4	2,700,000	6,100	86,400	-	-	-
" 6	2,750,000	7,200	148,500	1'45"RE	2'	-
" 9	2,590,000	18,500	125,615	-	-	nil
" 12	2,510,000	9,200	81,575	2' RE	2'30"	-
" 15	2,600,000	-	75,400	-	-	-

Platelet Morphology.

Date. 1929	Size. Small. %	Normal. %	Large. %	Granulation. 0 %	+ %	+ + %	+++ %	Staining. Hyaline. %	Basophil. %
Jun. 21	-	100	-	-	15	83	2	97	3
" 22	-	100	-	-	3	97	-	96	4
" 24	3	93	4	1	13	86	-	93	7
" 26	-	99	1	-	4	94	2	100	-
" 28	-	100	-	-	5	88	7	100	-
" 30	-	97	3	-	65	35	-	93	7
Jul. 2	-	99	1	-	-	99	1	99	1
" 4	-	100	-	-	-	59	41	100	-
" 6	13	85	2	-	39	61	-	100	-
" 9	-	100	-	-	14	86	-	95	5
" 15	-	97	3	-	19	81	-	98	2

Summary. The platelets showed remarkable variations in numbers. As the patient became progressively worse a definite thrombocytopenia set in.

Bleeding time was not increased even when the platelets varied between 45,000 and 100,000.

Coagulation time was never prolonged and its duration did not depend on the number of platelets present.

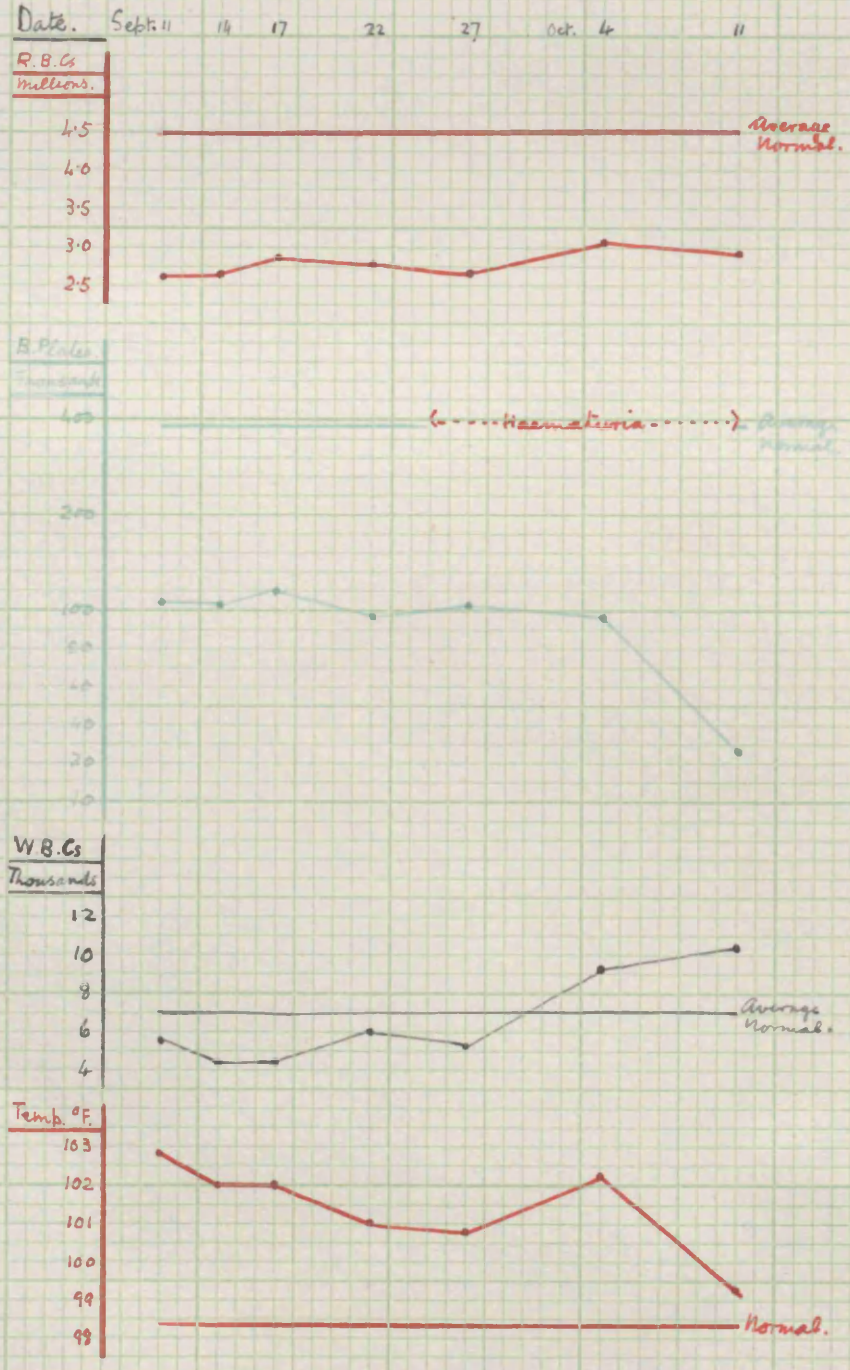
Syneresis of the clot was generally "poor"or absent and the amount of retraction could not be taken as a guide to the number of platelets present. Retraction was absent on one occasion when the thrombocytes numbered 149,640.

(over)

Summary. During the whole period of investigation there was marked anisocytosis, very large and very small platelets being present. The distribution of the granules was uneven many of the thrombocytes being deficient in granules while a goodly number were highly granular. The sparsely granular forms, on the whole, became more numerous in the two weeks before death. Basophilia was a prominent feature particularly in the later stages of the illness.

Case No. 20.

Patient. A. L.



Ward No. 8. Journal No. 93, page 228. Case No. 20.

Patient. A. L., Female.
Age. 24 years.
Occupation. Machinist.

Diagnosis. Malignant endocarditis.

Clinical notes. Patient gave a history of rheumatism. The heart was enlarged, the sounds were poor and a soft systolic murmur was audible. The spleen was enlarged. A short chained streptococcus was grown on blood culture. Hæmaturia was observed on 25th Sept. and it persisted until the end of the observations.

Results of investigation of the blood.

Date. 1929	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
Sep.11	2,660,000	5,800	106,400	2' RE	2'	* *
" 14	2,680,000	4,500	103,180	2'30"RE	2'15"	-
" 17	2,850,000	4,350	122,550	-	-	* *
" 22	2,780,000	6,150	97,300	1'55"RE	-	* *
" 27	2,640,000	5,950	105,600	2'15"RE	2'	-
Oct. 4	3,040,000	9,150	94,240	2'30"RE	-	* *
" 11	2,980,000	11,400	29,800	2' RE	-	* *

Platelet Morphology.

	Size.			Granulation.				Staining.	
Date.	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Sep.11	-	97	3	-	-	100	-	97	3
" 14	-	97	3	-	3	90	7	100	-
" 17	4	95	1	-	61	38	1	100	-
" 22	4	93	3	-	-	96	4	97	3
" 27	-	100	-	-	89	11	-	100	-
Oct. 4	1	99	-	-	13	86	1	100	-
" 11	14	81	5	-	14	86	-	95	5

Summary. Thrombocytopenia was present and even when the platelets numbered 29,800 there was no increase in the bleeding time. The hæmaturia noted was probably of embolic origin.

Coagulation time was never prolonged.

Clot retraction was always present even in the presence of a marked thrombocytopenia.

The platelet picture showed an increase in the very small and very large forms and although a few very granular elements were noted there was a general increase in the less granular forms. Basophilia was noted on occasion.

Ward No. 9. Journal No. 85, page 214. Case No. 21.

Patient. G. C., Male.
Age. 51 years.
Occupation. Riveter.

Diagnosis. Pernicious anæmia.

Clinical notes. On admission the patient was anæmic, the skin was lemon-yellow in colour, the mucous membranes pale and the spleen enlarged. The bilirubin content of the blood serum was increased and no free hydrochloric acid was present on gastric analysis. The blood picture was that of pernicious anæmia. On 22nd and 23rd May 1928 there was spontaneous bleeding from the gums. Liver treatment was commenced on the 24th May and on 25th May he was transfused. After this the patient progressed slowly but steadily. After dismissal he reported from time to time. He has also continued to take liver daily in his diet.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1928						
May 23	-	-	14,140	5' LE 11' RE 3' RT	-	-
" 24	930,000	4,370	7,840	13' RE 4'30" LE 2' LT	2'	*
Jun, 1	1,310,000	3,200	110,000	3' BE	-	-
" 5	1,900,000	4,000	126,000	3' BE	-	-
1929						
Apr,23	4,260,000	5,200	178,920	1'30" BE	2'	***
May 8	4,370,000	6,000	183,540	1'30" RE	2'	* *
Jun.12	4,270,000	5,300	140,720	1'30" RE	2'	-
Jul.10	3,870,000	3,750	135,450	1'30" RE	1'30"	* *
Sept.11	3,620,000	4,850	126,700	1'45" RE	1'30"	* *

Platelet Morphology.

Date.	Size.			Granulation.				Staining.	
	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Jul.10	-	97	3	-	1	99	-	97	3
Sept.11	-	100	-	-	-	99	1	100	-

Summary. This case illustrates in a general way the relationship between spontaneous hæmorrhage, prolongation of bleeding time and thrombocytopenia. With improvement in the condition of the patient the platelet numbers increased but they have always remained low.

(over)

Summary. The duration of bleeding time varied with the site of puncture and it was not so prolonged as might be expected from the very marked degree of thrombocytopenia.

Coagulation time did not depend on the number of platelets.

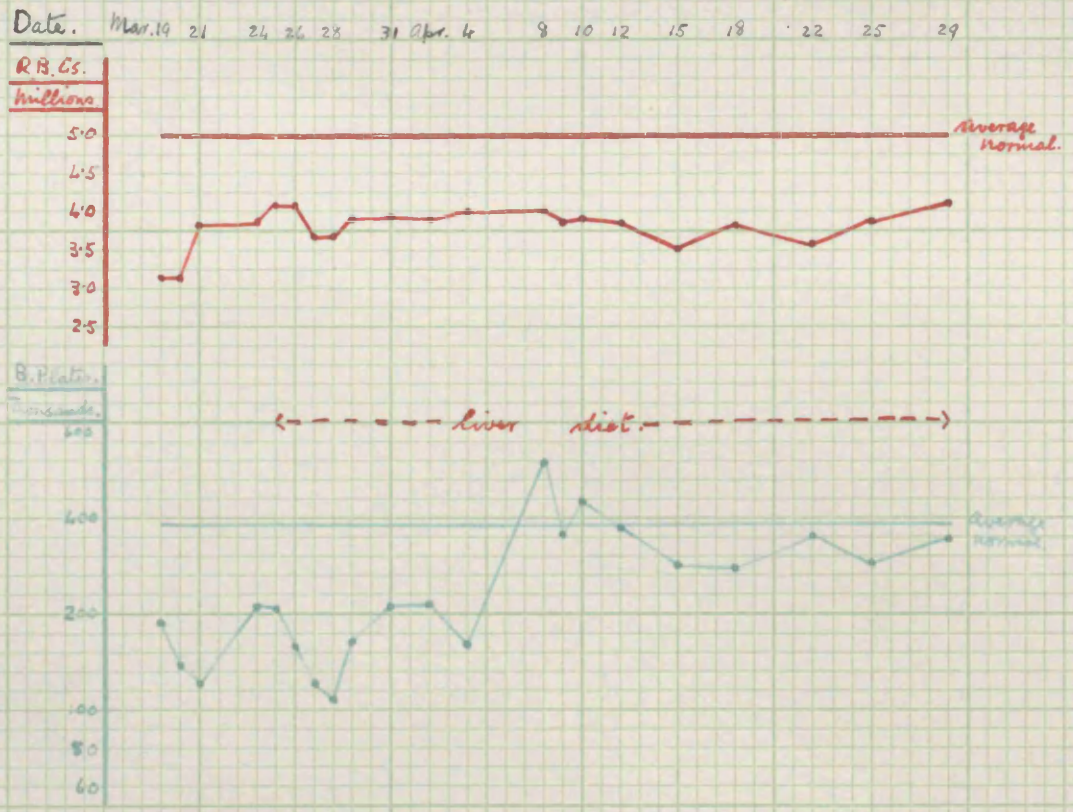
Retraction of the clot although "poor" was present when the platelets were below 10,000 in number.

Capillary resistance test was negative on 23rd May and 5th June, 1928.

On 10th July 1929 3% of the thrombocytes were large and showed basophilia. There was some irregularity in the distribution of the granules.

Case No. 22.

Patient. J. B.



Ward No. 9. Journal No. 92, page 90. Case No. 22.

Patient. J. B., Male.
Age. 58 years.
Occupation. Labourer.

Diagnosis. Pernicious anæmia.

Clinical notes. Patient had been in the ward on previous occasions when the diagnosis of pernicious anæmia was made. In the present instance he complained of symptoms suggestive of sub-acute combined degeneration of the cord. Liver treatment commenced on 25th March 1929.

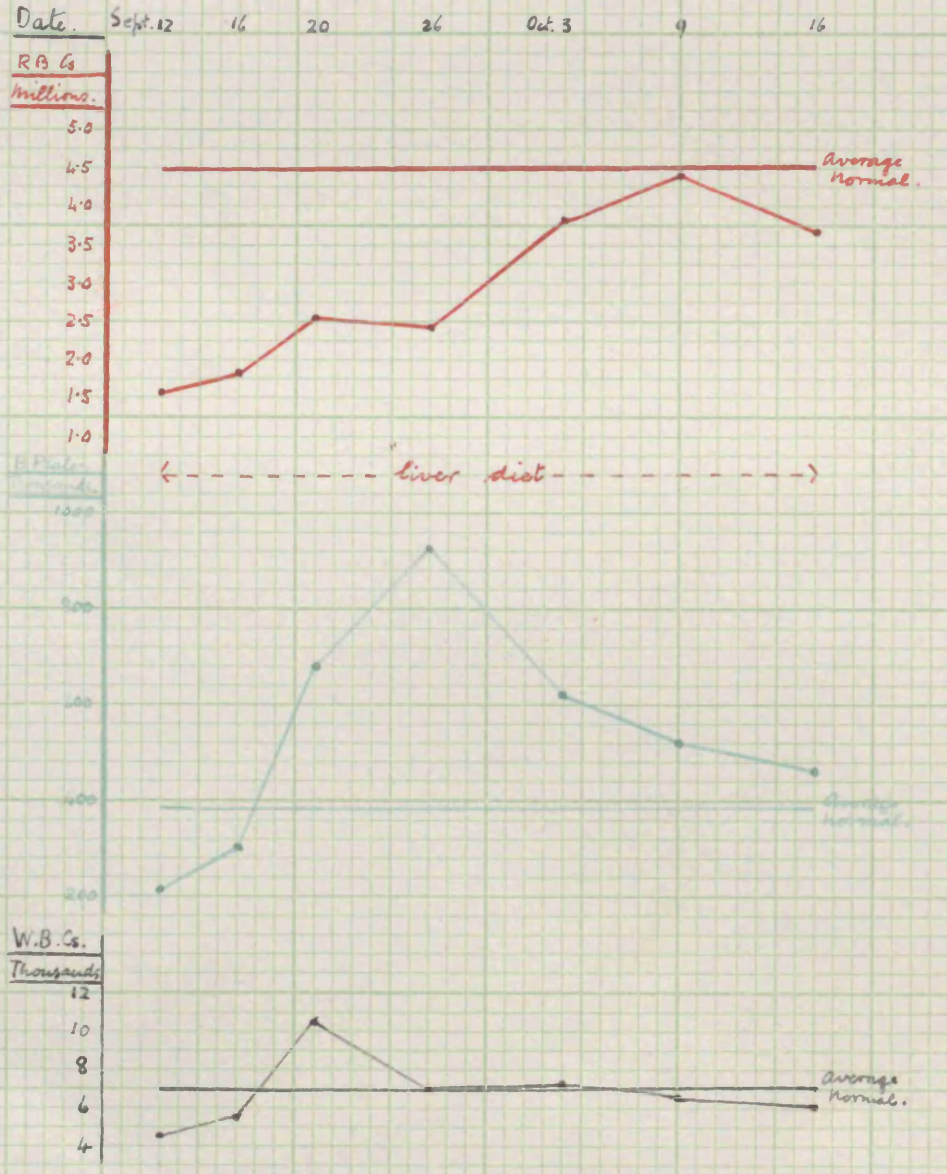
Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Mar. 19	3,210,000	-	182,970	-	-	-
" 20	3,210,000	-	144,450	-	-	-
" 21	3,780,000	-	128,520	-	-	-
" 24	4,040,000	-	214,120	-	-	-
" 25	3,830,000	-	218,310	1'30" RE	2'	-
" 26	4,040,000	-	161,160	1' RE	1'50"	-
" 27	3,730,000	-	134,280	-	-	-
" 28	3,730,000	-	111,900	1' RE	-	-
" 29	3,910,000	-	179,860	-	2'15"	-
" 31	3,980,000	-	210,940	1'15" RE	-	-
Apr. 2	3,980,000	-	222,880	-	-	-
" 4	4,010,000	-	168,420	-	2'	-
" 8	4,010,000	-	525,310	2' RE	-	-
" 9	3,840,000	-	357,120	-	-	-
" 10	3,930,000	-	436,230	-	2'	-
" 12	3,840,000	-	376,320	1'30" RE	-	-
" 15	3,500,000	-	290,500	-	-	-
" 18	3,760,000	9,000	270,720	-	-	-
" 22	3,550,000	9,200	362,100	1' RE	2'	-
" 25	3,890,000	10,200	307,310	-	1'30"	-
" 29	4,120,000	8,600	358,440	-	1'45"	-

Summary. At first the platelet count was comparatively low and there was no definite rise in the numbers until some two weeks after liver treatment had commenced. Thereafter the number of thrombocytes remained at a much higher level than formerly.
Bleeding time and coagulation time did not vary with alteration in the platelet numbers.

Case 23

Patient. Mrs L.



Ward No. 8. Journal No. 93, page 412. Case No. 23.

Patient. Mrs L., Female.
Age. 59 years.
Occupation. Housewife.

Diagnosis. Pernicious anæmia.

Clinical notes. Patient was anæmic and the blood picture was megalocytic. No free hydrochloric acid was present in the gastric juice. Liver treatment was commenced on the 12th Sept. and thereafter the patient improved steadily.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Sep.12	1,500,000	4,800	207,000	1'30"RE	2'	***
" 16	1,760,000	5,500	312,400	-	-	-
" 20	2,600,000	10,400	682,500	1'45"RE	2'	***
" 26	2,400,000	7,000	940,800	-	-	***
Oct. 3	3,570,000	7,100	614,040	1'15"RE	1'55"	-
" 9	4,290,000	6,950	523,380	-	-	***
" 16	3,690,000	6,350	466,785	1' RE	2'	-

Platelet Morphology.

	Size.			Granulation.				Staining.	
Date.	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Sep.12	11	88	1	-	96	4	-	99	1
" 16	-	100	-	-	22	78	-	100	-
" 20	-	100	-	-	7	93	-	100	-
" 26	-	100	-	-	-	98	2	100	-
Oct. 3	-	99	1	-	-	100	-	100	-
" 9	-	100	-	-	9	91	-	100	-
" 16	-	100	-	-	3	97	-	100	-

Summary. Under treatment the platelets increased rapidly up to a value of over 900,000. Thereafter there was a gradual fall to the average value of health. There was no parallelism between the red cell, white cell and platelet curves.

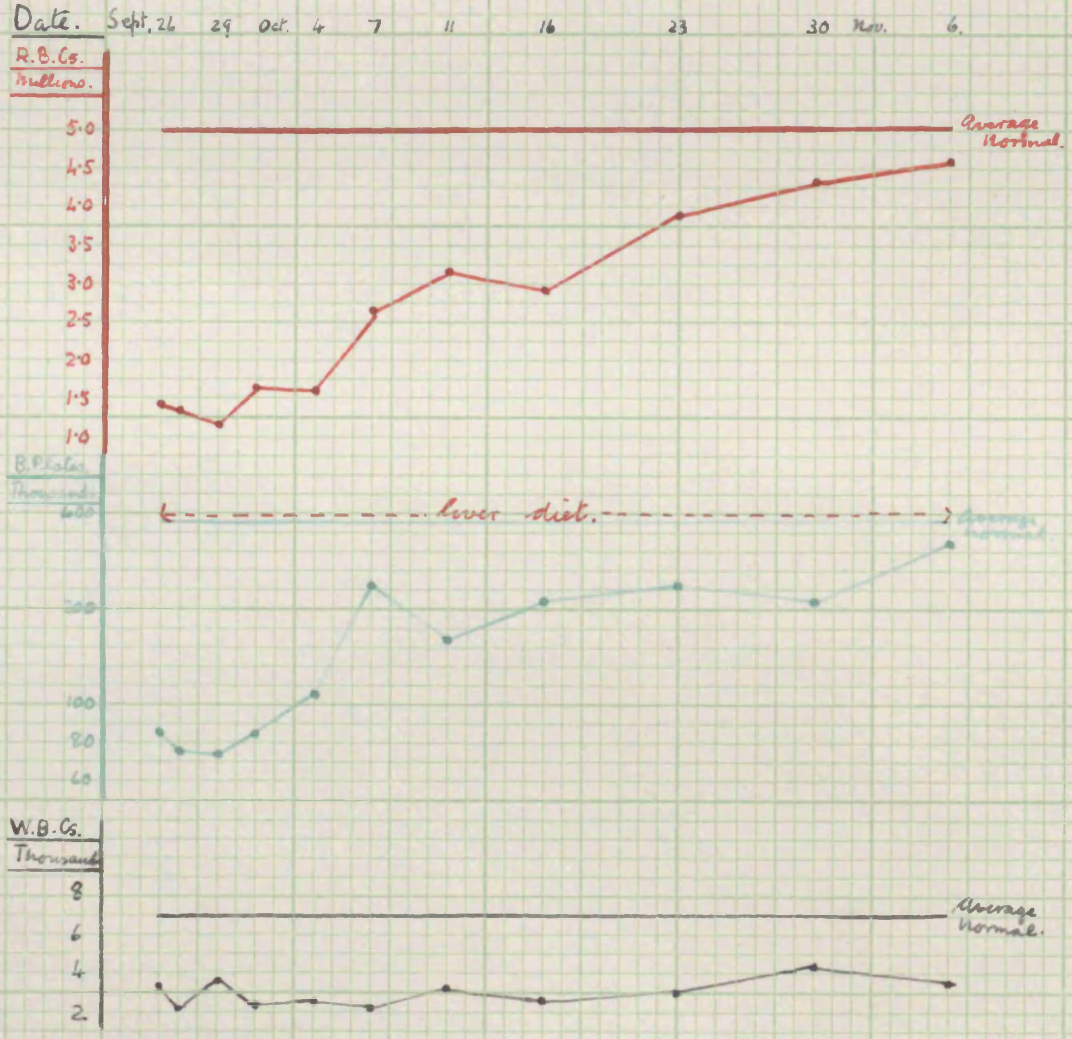
Bleeding time and coagulation time did not vary with the number of platelets.

Retraction was always "good".

To begin with one basophil form was noted and there was anisocytosis of platelets with a tendency to increase in the small forms. At first the granulation was poor but as the patient progressed more normal granulation was the rule.

Case No. 24.

Patient. W. P.



Ward No. 9. Journal No. 20, page 425. Case No. 24.

Patient. W. P., Male.
Age. 60 years.
Occupation. Engineer.

Diagnosis. Pernicious anæmia.

Clinical notes. Patient was in the ward suffering from pernicious anæmia in 1916. He was readmitted on 22nd Sept. 1929 when he was treated with cooked liver and dilute hydrochloric acid. Treatment commenced on 26th Sept. and the patient made steady progress.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Sept 26	1,420,000	3,100	80,940	4'30"RE 6'30"LE	2'	* *
" 27	1,290,000	2,350	76,755	5' BE	2'	***
" 29	1,220,000	3,950	73,810	4' BE	1'30"	*
Oct. 1	1,680,000	2,450	80,640	4' BE	1'45"	* *
" 4	1,570,000	2,800	111,470	3' BE	-	* *
" 7	2,610,000	2,350	224,460	3'30"BE	-	* *
" 11	3,210,000	3,250	162,105	2' BE	1'50"	* *
" 16	2,960,000	2,800	207,200	-	-	-
" 23	3,970,000	3,000	250,110	-	-	* *
" 30	4,270,000	4,250	209,230	2' RE	2'	-
Nov. 6	4,540,000	3,750	340,500	-	-	-

Platelet Morphology.

Date.	Size.			Granulation.				Staining.	
	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Sep. 26	-	96	4	1	42	57	-	96	4
" 27	-	100	-	-	25	74	1	79	21
" 29	5	92	3	-	41	55	4	100	-
Oct. 1	4	96	-	-	17	83	-	100	-
" 4	11	89	-	-	31	69	-	99	1
" 7	-	100	-	-	3	97	-	100	-
" 11	-	99	1	-	1	98	1	99	1
" 16	-	100	-	-	1	98	1	100	-
" 23	-	100	-	-	9	91	-	100	-
" 30	-	100	-	-	6	94	-	100	-
Nov. 6	-	100	-	-	3	97	-	100	-

Summary. There was a steady increase in the platelet numbers from below 80,000 to just above 200,000 at which level the numbers remained until the last observation recorded when the count reached 340,000. There was some degree of similarity between the red cell and platelet curves.

(over)

Summary (contd). During the period of thrombocytopenia there was slight prolongation of the bleeding time and even when the platelets numbered over 200,000 on the 7th Oct., bleeding time tended to be longer than normal. There was however a definite shortening of the bleeding time with the increase in the number of platelets. It has to be noted that on 26th Sept. duration of bleeding time varied with the site of puncture.

Coagulation time did not correspond with the number of thrombocytes in the circulation.

Retraction of the clot was always present. It was noted that during the period of thrombocytopenia it was "poor" "fair" or "good" on different occasions.

During the thrombocytopenic stage there was great variation in size many of the platelets being very small. A smaller proportion were large. The distribution of granules was irregular but on the whole there was an increase in the less granular forms. With improvement in the condition of the patient the platelets became more granular. Basophilia was a prominent feature in the early observations but it disappeared as convalescence advanced.

Case No. 25.

Patient. E. McG.

Ward No. 8. Journal No. 94, page 192. Case No. 25.

Patient. E. McG., Female.
Age. 31 years.
Occupation. At home.

Diagnosis. Pernicious anæmia.

Clinical notes. The blood picture in this case was characteristic of pernicious anæmia. The patient improved under treatment with liver and dilute hydrochloric acid. The treatment commenced on 28th Oct.,1929.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Oct.19	1,350,000	4,800	67,500	-	-	-
" 22	1,480,000	2,900	45,880	4' BE	5' +	* *
" 23	1,530,000	3,050	115,515	8' BE	17' +	* *
" 25	1,360,000	2,950	88,400	5' RE 14' LE	3'30"	* *
" 28	1,685,000	3,100	92,400	-	-	-
" 31	1,810,000	4,100	217,200	2'30"BE	1'50"	* *
Nov. 4	1,840,000	9,350	278,640	2' BE	-	-
" 9	2,560,000	5,750	405,760	2'30"BE	2'	***
" 15	3,070,000	5,600	446,685	2'15"BE	1'45"	-
" 22	3,360,000	5,950	446,880	1'45"BE	1'45"	-
" 29	3,180,000	6,300	440,430	2' BE	2'	***

Platelet Morphology.

	Size.			Granulation.				Staining.	
Date.	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Oct.19	14	86	-	-	40	60	-	100	-
" 22	4	96	-	-	68	32	-	100	-
" 23	32	76	1	-	40	60	-	98	2
" 25	16	83	1	-	22	78	-	98	2
" 28	43	57	-	-	46	54	-	100	-
" 31	10	90	-	3	68	29	-	100	-
Nov. 4	-	92	8	-	35	65	-	100	-
" 9	-	100	-	-	6	94	-	100	-
" 15	6	93	1	-	22	78	-	99	1
" 22	-	100	-	-	10	90	-	100	-
" 29	-	100	-	-	44	56	-	99	1

(over)

Summary. The platelet count increased steadily with the improvement in the condition of the patient and was within normal limits by the 9th Nov., where it remained during the next twenty days of observation. The rate of increase in the number of platelets was much quicker than that of the red cells.

The bleeding time was prolonged when the platelet count was low but the duration did not seem to depend on the number of thrombocytes. On one occasion bleeding time varied with the site of puncture. On 22nd, 23rd and 25th Oct. bleeding into the puncture wounds was noticed and on the last two dates the capillary resistance test when applied to the right arm produced a few petechiæ. On the other hand the capillary resistance test was negative on 22nd Oct. when the platelets numbered 45,880.

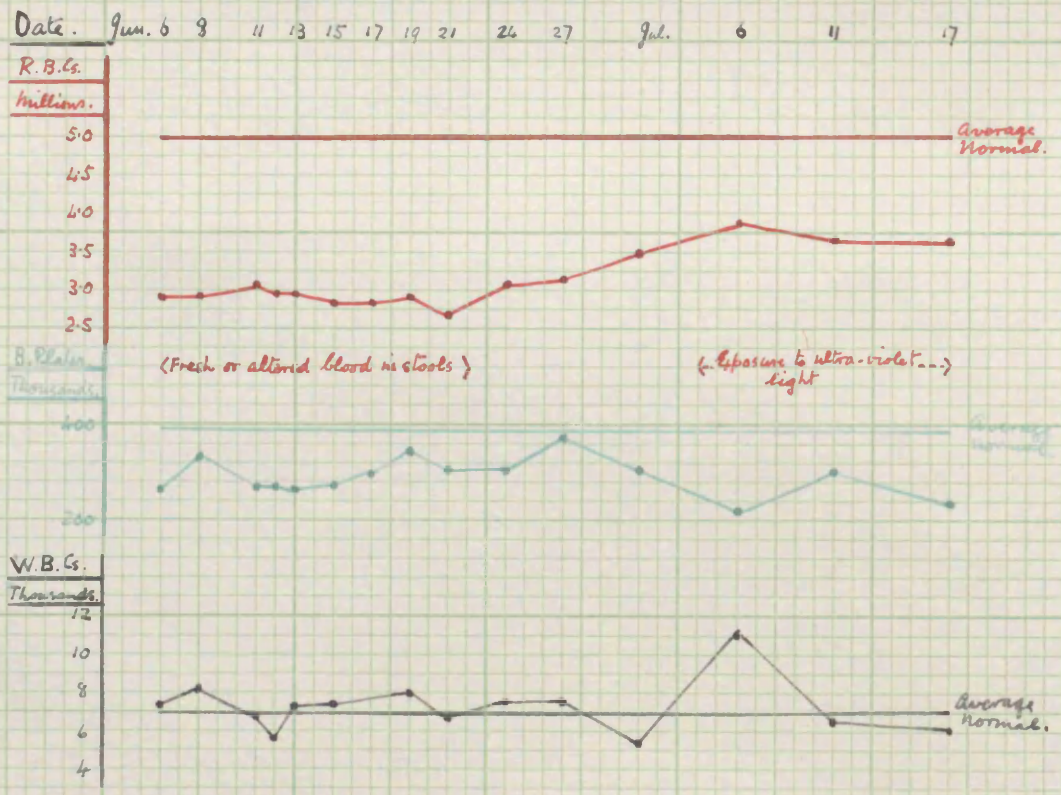
The coagulation time was also increased when the thrombocytopenia was present but here again its duration did not depend on the number of platelets in the circulation.

Retraction of the clot with extrusion of the serum was quite definite even when the platelet count was as low as 45,880. It was noted however that syneresis was increased when the thrombocytes numbered over 400,000.

When thrombocytopenia was a feature many of the platelets were small and less granular than normal. As the platelets increased in number the percentage of small forms diminished but, although the tendency was for the thrombocytes to become more granular a rather large number of sparsely granular forms persisted. Basophilia was noted on four occasions.

Case No. 26.

Patient. J. M.



Ward No. 9. Journal No. 59, page 296. Case No. 26.

Patient. J. M., Male.
Age. 45 years.
Occupation. Blacksmith.

Diagnosis. Secondary anæmia, hæmorrhoids.

Clinical notes. Patient had steadily lost blood from hæmorrhoids for a period of over six months before admission. While in hospital the hæmorrhoids were injected.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Jun. 6	2,900,000	7,300	274,050	-	-	***
" 9	2,950,000	8,050	348,100	1'30" RE	1'45"	-
" 11	3,010,000	6,900	276,920	-	-	-
" 12	2,930,000	5,900	281,280	-	-	-
" 13	2,946,000	7,100	276,871	-	-	***
" 15	2,850,000	7,450	296,400	-	-	-
" 17	2,790,000	-	315,270	1' RE	2'15"	-
" 19	2,900,000	8,000	353,800	-	-	-
" 21	2,740,000	6,900	309,620	-	-	-
" 24	3,130,000	7,850	305,175	-	-	-
" 27	3,230,000	7,600	384,370	1' RE	1'15"	-
Jul. 1	3,500,000	5,050	318,500	1' RE	1'45"	***
" 6	3,810,000	11,000	222,885	-	-	-
" 11	3,670,000	6,500	301,950	-	-	-
" 17	3,610,000	6,150	234,650	-	-	-

Platelet Morphology.

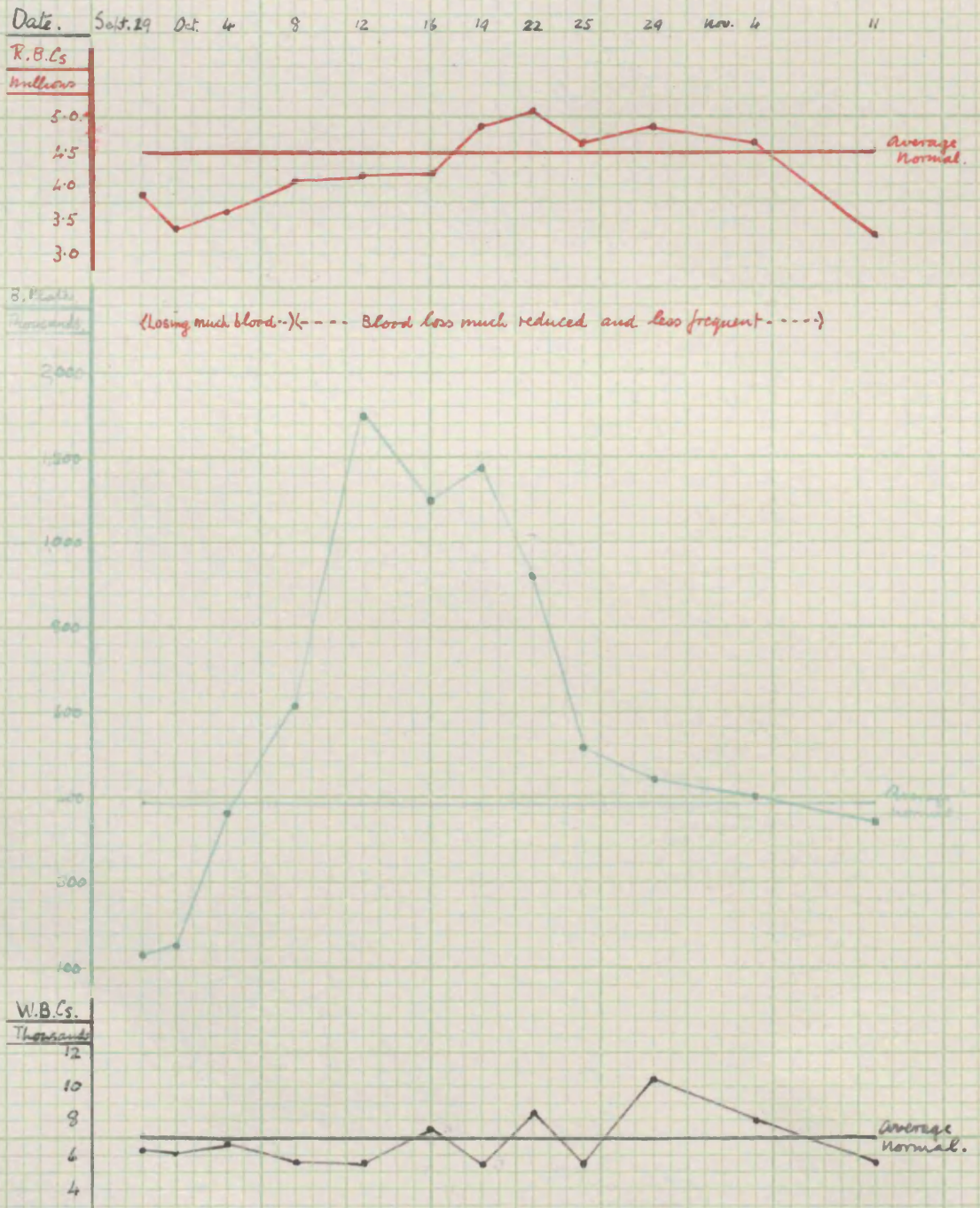
Date.	Size.			Granulation.				Staining.	
	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Jun. 21	-	96	4	-	2	96	2	96	4
" 24	-	99	1	-	13	81	6	97	3
" 27	-	99	1	-	-	100	-	100	-
Jul. 1	5	91	4	-	-	98	2	99	1
" 6	-	99	1	-	-	100	-	99	1
" 11	-	99	1	-	7	89	4	100	-
" 17	-	99	1	-	-	100	-	98	2

(over)

Summary. The number of platelets varied between 220,000 and 380,000 and the curve did not have any characteristic form.
Bleeding time and coagulation time did not show any relationship to variation in the platelet numbers.
Retraction of the clot was "good".
This case showed a marked platelet anisocytosis with a preponderance of large basophilic forms. The granules were unevenly distributed a few thrombocytes being deficient in granules while an approximately similar number contained an increased quantity of granules. The anisocytosis and basophilia were most marked during or immediately after the period of bleeding.

Case No. 27.

Patient. Mrs D.



Ward No. 8. Journal No. 94, page 82. Case No. 27.

Patient. Mrs D., Female.
Age. 57 years.
Occupation. At home.

Diagnosis. Secondary anæmia, hæmorrhoids. Chronic nephritis.

Clinical notes. In this case there was a history of hæmorrhoidal bleeding, off and on, for 37 years. For the first 9 days after admission abundant fresh blood was present in the stools. Under treatment the number of red blood cells increased rapidly. On 22nd Oct. slight hæmorrhage returned and persisted until 4th Nov. During the stay in hospital the general health of the patient was much improved.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929				3' LE		
Sep.29	3,870,000	6,500	116,100	4' RE	1'15"	* *
Oct. 1	3,290,000	6,100	123,375	2' BE	-	* *
" 4	3,580,000	6,950	372,320	-	-	* *
" 8	4,030,000	5,900	620,620	2' RE	1'30"	-
" 12	4,070,000	5,800	1,746,630	-	-	-
" 16	4,100,000	7,800	1,244,350	1'50"RE	1'30"	-
" 19	4,880,000	5,400	1,452,000	1'45"RE	2'	***
" 22	5,150,000	8,350	921,850	-	-	-
" 25	4,540,000	5,550	522,100	1'30"RE	1'50"	* *
" 29	4,880,000	10,700	448,960	-	-	-
Nov. 4	4,570,000	8,000	409,015	2' RE	2'	-
" 11	3,750,000	5,050	348,750	-	-	* *

Platelet Morphology.

	Size.			Granulation.				Staining.	
Date.	Small.	Normal.	Large.	0	+	+ +	+++	Hyalin.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Sep.29	3	96	1	-	3	97	-	100	-
Oct. 1	-	97	3	-	9	81	10	100	-
" 4	9	89	2	-	12	88	-	100	-
" 8	-	100	-	-	-	100	-	99	1
" 12	-	98	2	-	28	72	-	93	7
" 16	-	100	-	-	-	100	-	100	-
" 19	-	100	-	-	-	100	-	100	-
" 22	-	100	-	-	-	100	-	100	-
" 25	-	100	-	-	-	100	-	100	-
" 29	-	99	1	-	-	100	-	87	13
Nov. 4	-	100	-	-	13	87	-	100	-
" 11	-	100	-	-	27	73	-	100	-

(over)

Summary. The number of platelets rose rapidly from a relatively low value to over 1,700,000 within 12 days during which there was much hæmorrhoidal bleeding. This period of platelet increase persisted for about 10 days when the number of thrombocytes gradually diminished to about average normal values. During this period of diminution the amount of bleeding was very much reduced.

Bleeding time was slightly increased on 29th Sept. when the platelets numbered 116,000 but thereafter it diminished with the increase in the platelets. The duration of bleeding time did not however depend on the number of thrombocytes.

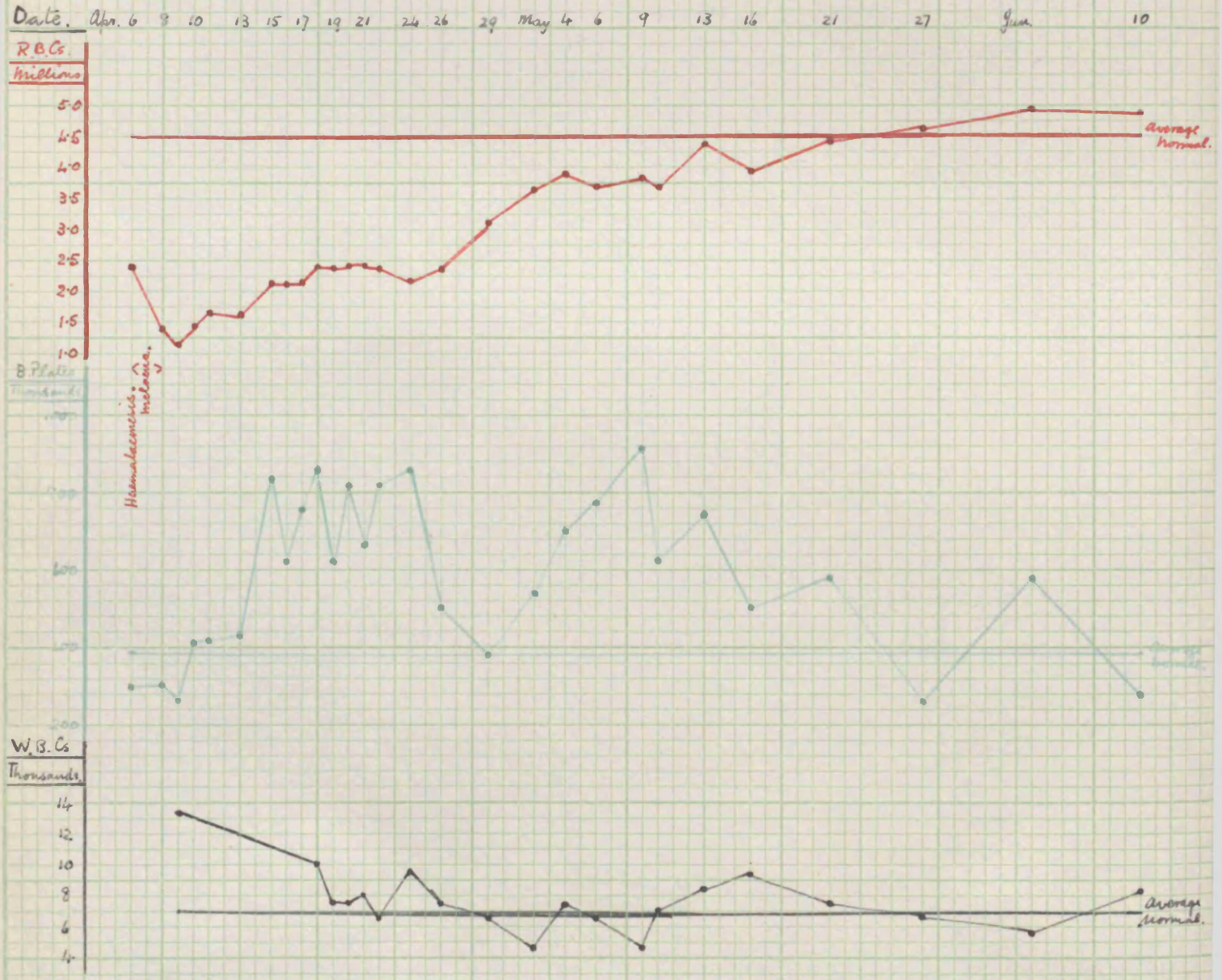
There was no relationship between coagulation time and the number of platelets.

Clot retraction was always present even when the thrombocyte values were somewhat low.

Throughout the period of observation there was some variation in the size ofthe platelets. In the early stages very small and very large forms were noted but gradually they became more uniform in size. During the whole period there was an increase in the less granular forms but on 1st Oct. 10% of the forms were highly granular. In the course of the investigation basophil forms were noted. On the 29th Oct., when the numbers were more or less constant, they numbered 13%.

Case No. 28.

Patient. A. M.



Ward No. 8. Journal No. 92, page 62. Case No. 28.

Patient. A. M., Female.
Age. 31 years.
Occupation. Pit-head worker.

Diagnosis. Hæmatæmesis, ? duodenal ulcer.

Clinical notes. There was a previous history of slight indigestion. Patient had vomited blood for about 24 hours before she was first seen on 6th April. Melæna was noted up until the 8th April. Thereafter there was no further bleeding and the patient made an uninterrupted recovery.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Apr. 6	2,440,000	-	295,240	2' RE	2'15"	-
" 8	1,430,000	-	306,650	-	-	-
" 9	1,140,000	13,200	268,900	1'55"RE	-	-
" 10	1,440,000	-	404,640	-	-	-
" 11	1,710,000	-	403,560	2' RE	-	-
" 13	1,520,000	-	434,720	-	-	-
" 15	2,140,000	-	830,320	1'45"RE	-	-
" 16	2,070,000	-	608,580	-	-	-
" 17	2,130,000	-	764,670	2' RE	-	-
" 18	2,460,000	10,000	851,160	-	-	-
" 19	2,350,000	7,800	620,400	-	-	-
" 20	2,440,000	7,800	822,280	-	-	-
" 21	2,440,000	8,000	683,200	-	-	-
" 22	2,400,000	6,600	811,200	-	1'30"	-
" 24	2,190,000	9,900	860,670	1'15"RE	-	-
" 26	2,340,000	7,200	567,640	1' RE	1'30"	-
" 29	3,100,000	6,600	381,300	-	1'45"	-
May 2	3,660,000	4,800	541,680	1' RE	3'	-
" 4	3,850,000	7,600	710,250	-	-	-
" 6	3,710,000	6,600	793,940	1' RE	1'30"	-
" 9	3,770,000	4,800	923,650	-	-	-
" 10	3,710,000	7,000	615,860	1' RE	1'45"	***
" 13	4,370,000	8,200	760,000	1' RE	2'	-
" 16	3,990,000	9,400	501,740	-	-	-
" 21	4,480,000	7,450	577,920	-	-	***
" 27	4,560,000	6,350	250,800	1' RE	1'45"	-
Jun. 3	4,970,000	5,800	561,610	45"RE	1'45"	-
" 10	4,940,000	8,150	284,050	-	-	-

Summary. Immediately after the hæmorrhage had ceased there was a rise in the platelet numbers to well above average normal values. This increase continued at a varying height for about nine days when there was a fairly sharp fall to normal. However a second but more gradual increase occurred to over 900,000. This was followed by a steady but interrupted fall.

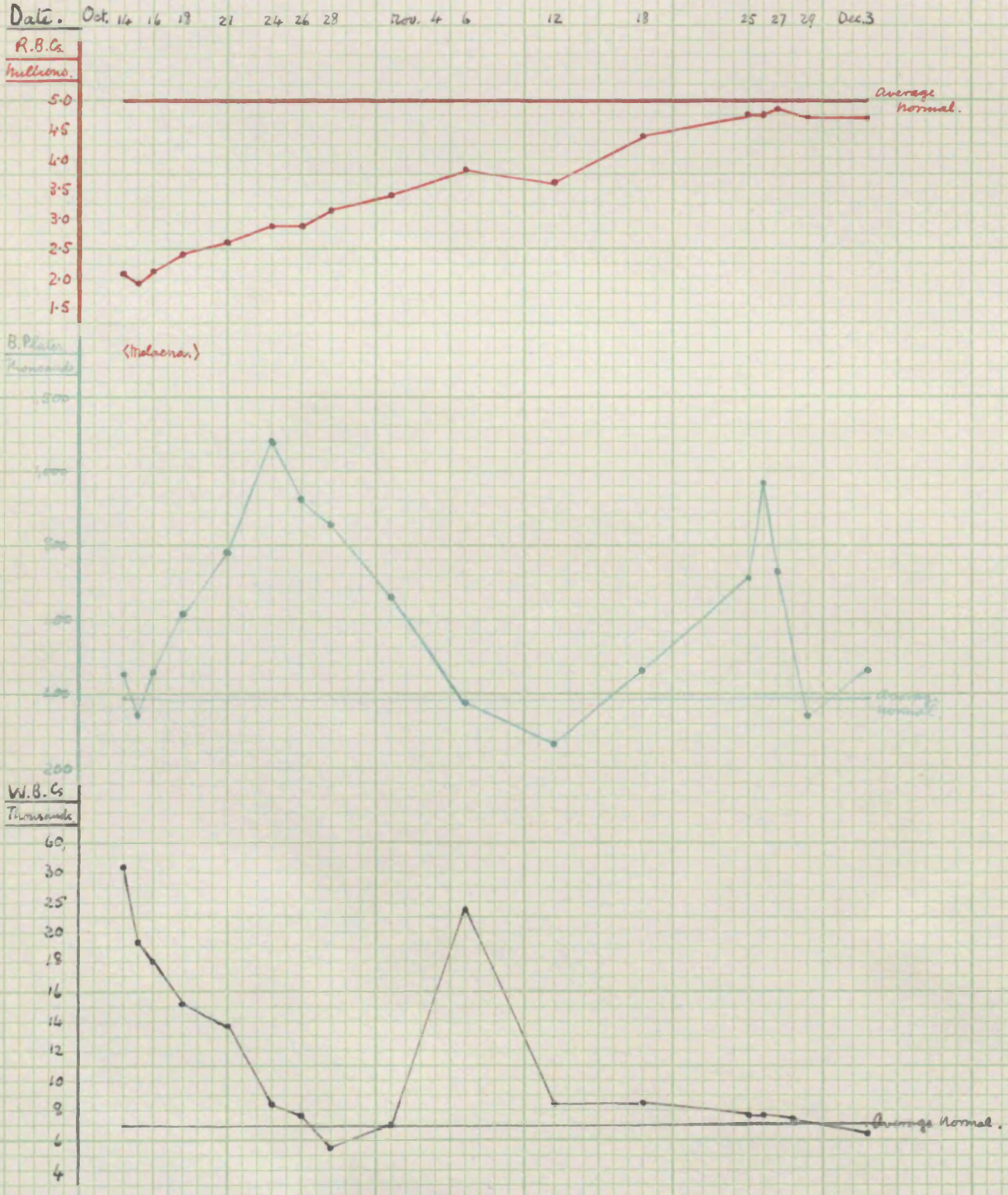
The duration of bleeding time and coagulation time varied independently of the platelet numbers.

Syneresis of the clot was "good" on two occasions.

Throughout the whole period many large platelet forms with basophil cytoplasm were observed.

Case No. 29.

Patient. R. McE.



Ward No. 9. Journal No. 94, page 358. Case No. 29.

Patient. R. McE., Male.
Age. 43 years.
Occupation. Motor fitter.

Diagnosis. Hæmatæmesis, duodenal ulcer.

Clinical notes. Patient had indigestion for a week and had vomited blood for three days previous to admission on 12th Oct. Blood was present in the vomitus on 13th Oct. and melæna or fresh blood were noted in the stools until the 19th Oct.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Oct.14	2,020,000	29,250	450,460	1'30"BE	1'45"	***
" 15	1,930,000	19,200	336,785	-	-	-
" 16	2,180,000	18,050	455,620	1'45"BE	-	-
" 18	2,400,000	15,200	624,000	-	-	-
" 21	2,540,000	13,900	796,290	-	-	-
" 24	2,880,000	8,100	1,200,9600	1'40"RE	1'30"	-
" 26	2,850,000	7,650	929,100	-	-	-
" 28	3,210,000	5,600	865,095	-	-	***
Nov. 1	3,470,000	7,000	655,830	2' RE	-	-
" 6	3,800,000	23,500	372,400	-	-	-
" 12	3,560,000	8,400	272,340	-	1'45"	-
" 18	4,330,000	8,500	478,465	-	-	-
" 25	4,740,000	7,700	720,000	-	-	-
" 26	4,750,000	7,900	973,750	-	-	-
" 27	4,800,000	-	729,600	-	-	-
" 29	4,670,000	7,750	336,260	-	-	-
Dec. 3	4,710,000	6,500	452,160	-	-	-

Platelet Morphology.

Date.	Size.			Granulation.				Staining.	
	Small.	Normal.	Large.	0	-	- -	---	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Oct.14	-	99	1	-	-	100	-	99	1
" 15	-	100	-	-	-	100	-	100	-
" 16	-	100	-	-	12	88	-	100	-
" 18	-	99	1	-	8	92	-	100	-
" 21	-	99	1	-	-	100	-	98	2
" 24	-	100	-	-	-	100	-	100	-
" 26	-	100	-	-	-	100	-	100	-
" 28	-	98	2	-	-	100	-	100	-
Nov. 1	-	98	2	-	-	100	-	98	2
" 6	-	99	1	-	4	96	-	98	2
" 12	-	100	-	-	4	96	-	100	-
" 18	-	100	-	-	-	100	-	100	-
" 25	-	100	-	-	11	89	-	100	-
" 26	-	100	-	-	6	85	9	100	-
" 27	-	96	4	-	-	100	-	94	6
" 29	-	95	5	-	-	95	5	100	-
Dec. 3	-	99	1	-	-	100	-	99	1

(over)

Summary. When the patient was still losing blood the platelets commenced to increase in number so that five days after the bleeding had apparently stopped they had reached to over one million. Thereafter they steadily diminished to below normal only to rise and fall again in the later stages of the patient's convalescence. The curves show that the thrombocytes react independently of the red and white corpuscles.

There was no relationship between the duration of bleeding time and the number of platelets in the circulation.

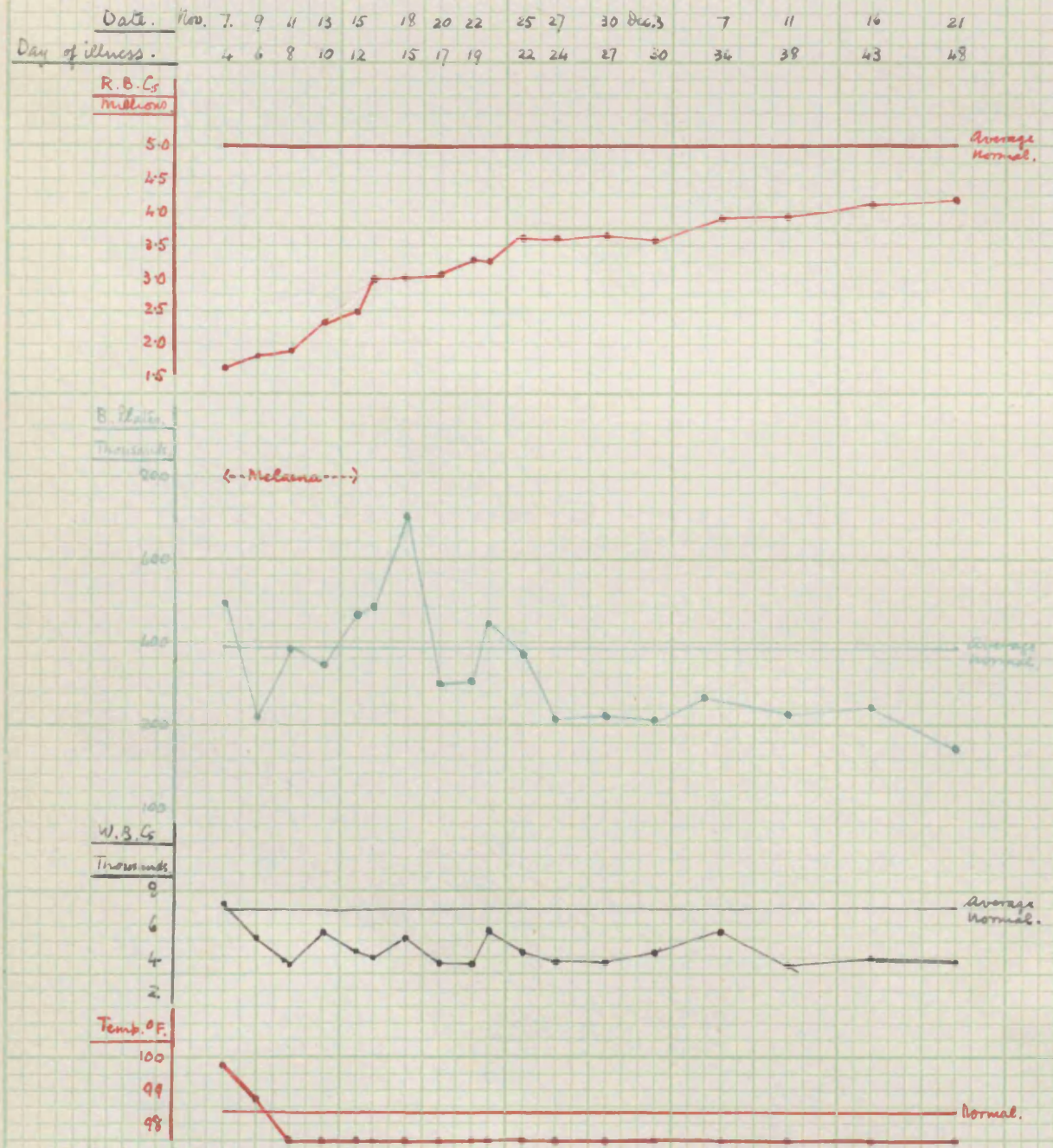
In this case coagulation time was shortened when the platelets were at their highest value.

Retraction of the clot with extrusion of the serum was "good" on two occasions.

Throughout the period of investigation there was a tendency towards increase in size of the platelets. This was associated with an increase in the number of basophil forms. On the whole the thrombocytes were always granular but occasionally a fair percentage were deficient in granules especially during the periods of increase in the total platelet numbers.

Case No. 30.

Patient. J. C.



Ward No. 9. Journal No. 95, page 12. Case No. 30.

Patient. J. C., Male.
Age. 41 years.
Occupation. Slater.

Diagnosis. Hæmatæmesis, duodenal ulcer.

Clinical notes. Patient had hæmatæmesis and melæna for 3 days before admission. Melæna continued for 12 days after admission. The patient's progress to health was uninterrupted. The leucocyte count was consistently low throughout.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Nov. 7	1,660,000	7,100	496,340	1'20"RE	1'40"	* *
" 9	1,830,000	5,300	222,345	-	-	-
" 11	1,920,000	3,700	396,480	1'35"RE	-	-
" 13	2,320,000	5,700	351,280	-	1'45"	-
" 15	2,510,000	4,350	475,645	-	-	* *
" 16	3,060,000	4,000	485,010	1'40"RE	-	-
" 18	3,030,000	5,200	708,505	-	1'30"	-
" 20	3,120,000	3,750	293,280	-	-	-
" 22	3,320,000	3,750	318,720	2' RE	-	***
" 23	3,280,000	5,850	447,720	-	-	-
" 25	3,660,000	4,350	367,830	-	-	-
" 27	3,660,000	3,600	204,960	1'50"RE	-	-
" 30	3,700,000	3,950	227,550	-	-	***
Dec. 3	3,510,000	4,400	210,600	-	-	-
" 7	3,950,000	5,450	275,625	1'50"RE	2'	-
" 11	3,940,000	3,750	228,520	-	-	-
" 16	4,150,000	4,050	249,000	-	-	***
" 21	4,210,000	3,950	172,610	1'45"RE	-	-

Platelet Morphology.

	Size.			Granulation.				Staining.	
Date.	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Nov. 7	7	93	-	-	-	100	-	99	1
" 9	-	100	-	-	36	64	-	100	-
" 11	-	100	-	-	2	98	-	100	-
" 13	-	99	1	-	-	100	-	99	1
" 15	-	100	-	-	4	96	-	100	-
" 16	-	100	-	-	7	93	-	100	-
" 18	-	100	-	-	-	100	-	90	10
" 20	-	100	-	-	-	98	2	100	-
" 22	-	100	-	-	-	100	-	100	-
" 23	-	98	2	-	-	100	-	100	-
" 25	-	100	-	-	-	100	-	100	-
" 27	-	100	-	-	-	100	-	100	-
" 30	-	99	1	-	-	100	-	100	-
Dec. 3	-	99	1	-	-	100	-	98	2
" 7	-	100	-	-	-	100	-	100	-
" 11	-	100	-	-	-	100	-	100	-
" 16	-	100	-	-	-	100	-	100	-
" 21	-	100	-	-	-	100	-	99	1

(over)

Summary. The platelet count was never high but it reached its highest point just after the melæna ceased. Thereafter it tended to be rather low. In this respect there is some agreement between the platelet and the white cell curves.

The duration of bleeding time, although it was always within healthy limits was slightly longer during the period when the patient was definitely improving than during the period of hæmorrhage.

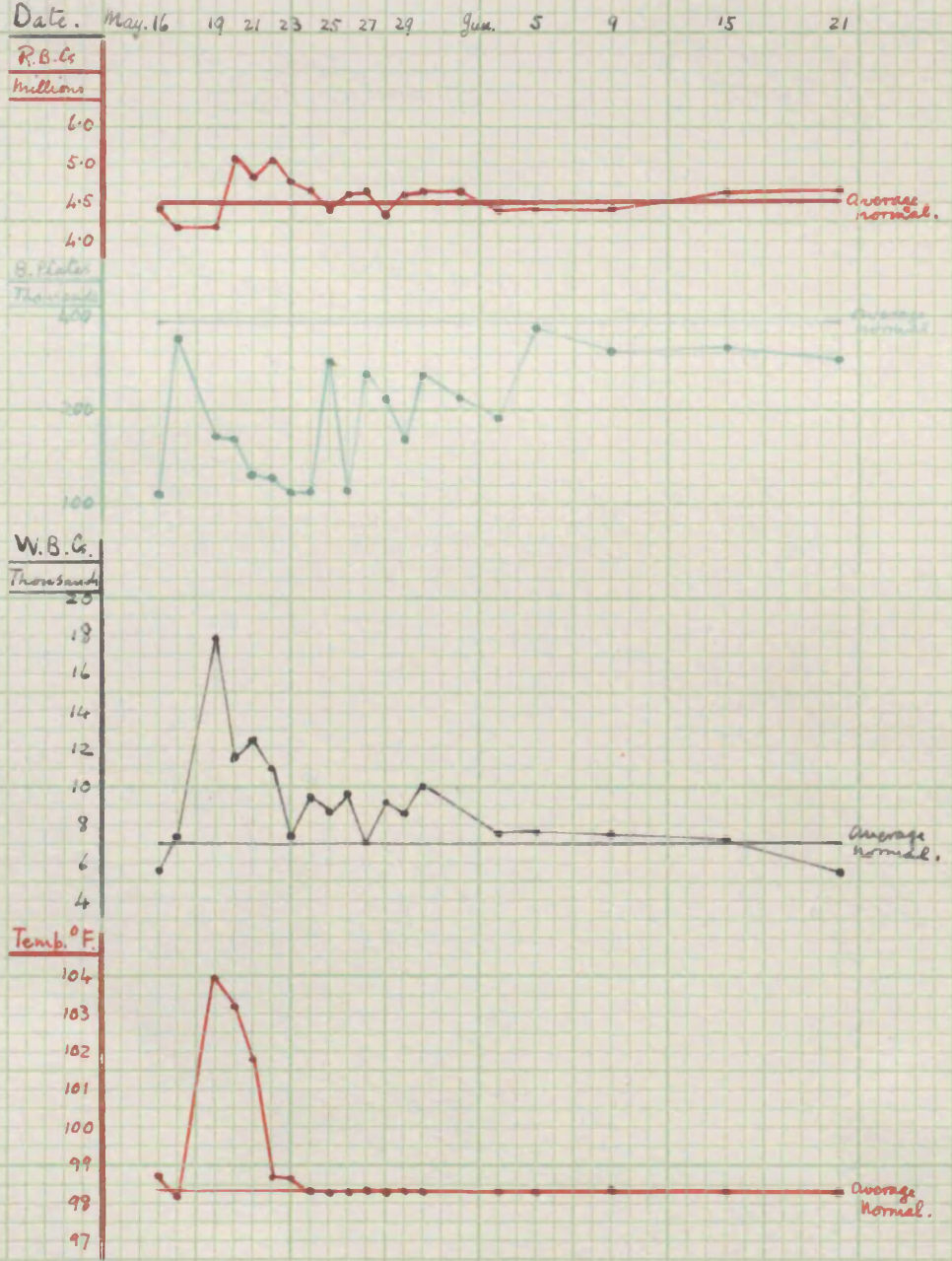
Coagulation was not in any way related to the number of platelets in the circulation.

Clot retraction was always present.

A few large platelets were noted throughout the period of observation. There was a preponderance of basophil forms - about 10% - on the 18th Nov. during the period of platelet increase. In this stage also the thrombocytes were less granular than normal.

Case No. 31.

Patient. Mrs M. M.



Ward No. 8. Journal No. 92, page 300. Case No. 31.

Patient. Mrs M. M., Female.
Age. 23 years.
Occupation. At home.

Diagnosis. Abdominal tuberculosis - hæmatæmesis and melæna.
Acute tonsillitis.

Clinical notes. In February, 1927, when in the surgical wards, this patient was found to have miliary tubercles all over the omentum, uterus and Fallopian tubes.

She was admitted to Ward 8 on 15th May, 1929, with a history of recent hæmatæmesis and melæna. Neither of these was ever noted in the Ward and she did not have a profound degree of anæmia. This case is of interest however as on 19th May she developed a follicular tonsillitis which did not clear up until 3 or 4 days later. Thereafter her general health steadily improved. Examination of the lungs was negative and X-ray examination of the stomach did not reveal the presence of gastric or duodenal ulcer.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
May 16	4,350,000	5,870	106,570	-	-	-
" 17	4,220,000	7,400	360,720	-	-	-
" 19	4,280,000	18,000	179,760	-	-	-
" 20	5,320,000	11,600	170,240	1' RE	1'45"	*
" 21	4,810,000	12,700	134,680	1' RE	2'	* *
" 22	5,160,000	11,000	129,000	-	-	-
" 23	4,740,000	7,350	118,500	1'30"RE	2'	-
" 24	4,620,000	9,350	115,500	-	-	-
" 25	4,450,000	8,650	308,150	-	-	-
" 26	4,570,000	9,750	118,820	-	-	-
" 27	4,675,000	7,000	280,500	-	-	* *
" 28	4,380,000	9,200	227,760	1' RE	1'15"	-
" 29	4,560,000	8,600	168,720	-	-	-
" 30	4,610,000	10,000	281,210	-	-	-
Jun. 1	4,530,000	-	233,680	-	-	-
" 3	4,390,000	7,400	197,550	30"RE	2'	-
" 5	4,400,000	7,900	374,000	1' RE	2'15"	-
" 9	4,420,000	7,600	322,660	1' RE	1'45"	-
" 15	4,610,000	7,100	329,615	1' RE	1'45"	-
" 21	4,690,000	5,900	314,230	-	-	-

Summary. During the period of the acute tonsillitis there was a fall in the number of platelets. After the acute illness had passed off the numbers varied somewhat but eventually the platelets increased and remained at approximately a constant level. The leucocyte curve in its variations somewhat resembled the thrombocyte curve.

(over)

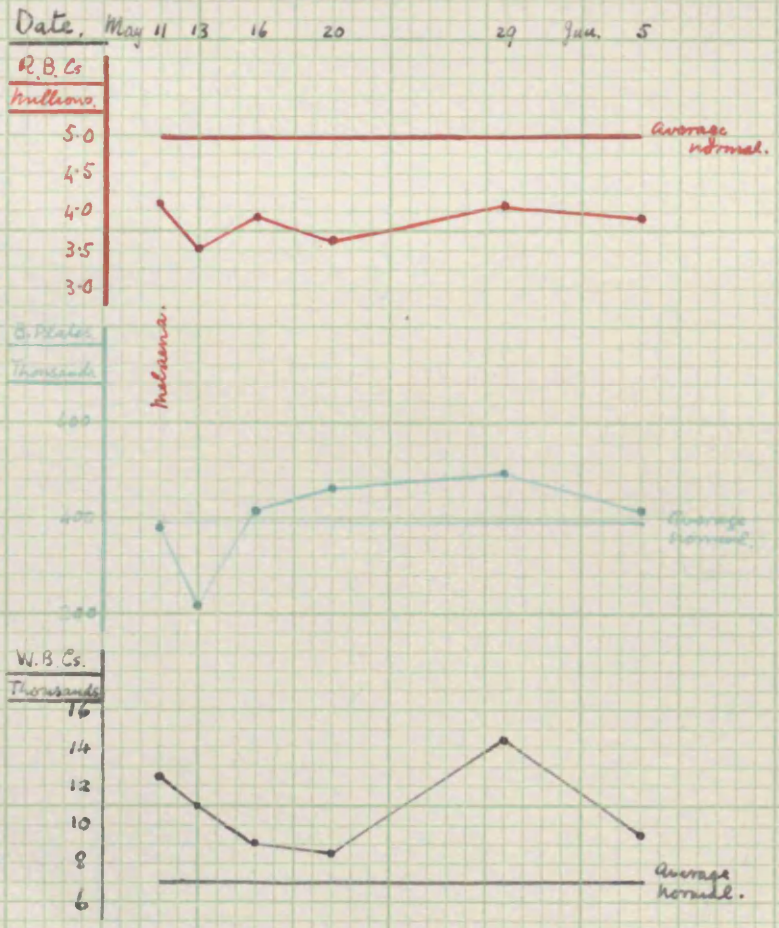
Summary. (contd) Bleeding time and coagulation time did not vary in any constant fashion with alteration in the number of platelets.

Syneresis of the clot was present but the amount of retraction did not depend on the number of thrombocytes present.

During the period of the acute illness the platelets were small and not well stained. Between 25th and 28th May, when the platelets were varying somewhat many larger and more granular forms were present. From the 29th onwards the platelets were rather small and showed irregular distribution of the granules.

Case No. 32.

Patient. D. R.



Ward No.9. Journal No. 93, page 30. Case No.32.

Patient. D. R., Male.
Age. 60 years.
Occupation. Unemployed.

Diagnosis. Gastric carcinoma - hæmatæmesis and melæna.

Clinical notes. This patient was admitted with a history of a recent hæmatæmesis. No blood was vomited after admission but melæna was present for two days - the 10th and 11th May.

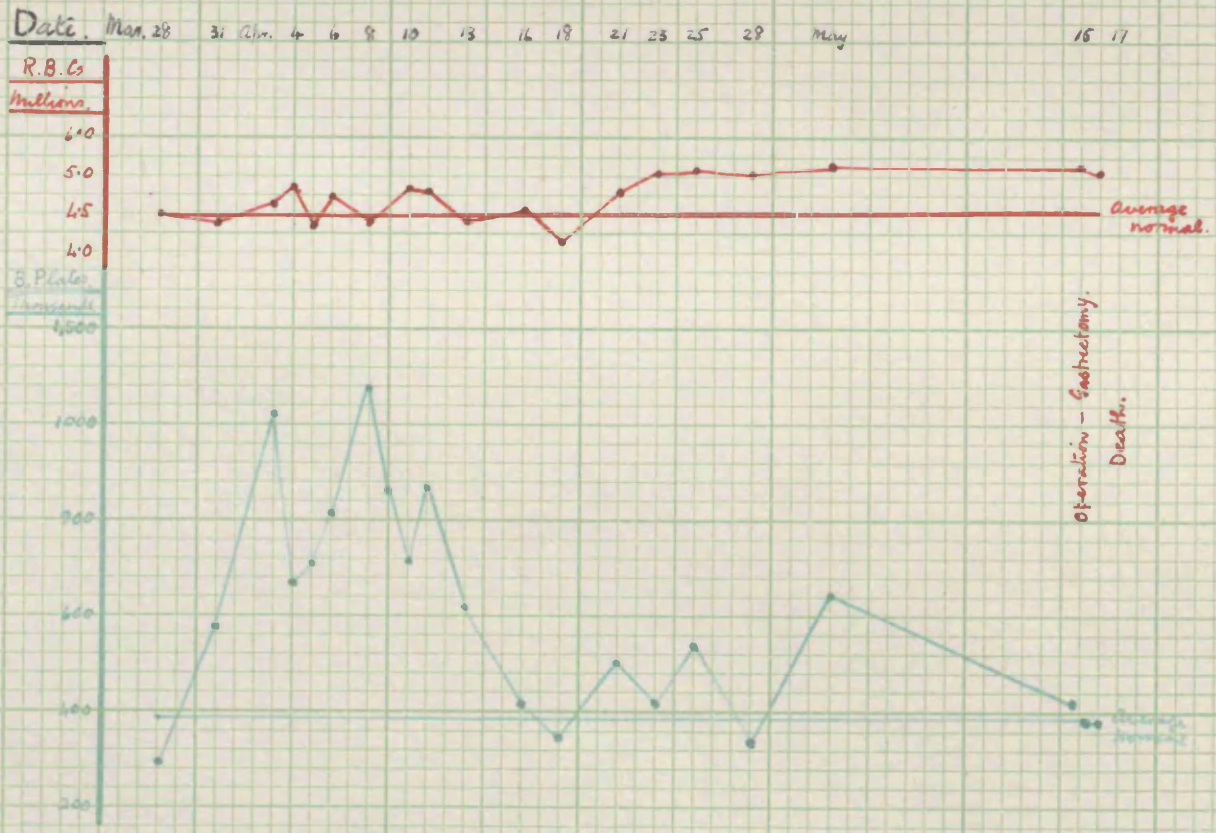
Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
May 11	4,080,000	12,600	379,440	1' RE	1'45"	-
" 13	3,590,000	11,000	204,630	1' RE	1'30"	-
" 16	3,950,000	9,000	402,900	-	-	-
" 20	3,660,000	8,400	461,160	1' RE	1'45"	* *
" 29	4,050,000	15,600	494,100	-	-	-
Jun. 5	3,840,000	9,300	405,120	1' RE	1'30"	-

Summary. With the exception of the reading on the 13th May the platelet numbers did not vary much from normal average values.
The duration of bleeding time and coagulation time did not depend on the number of blood platelets present in the circulation.
On one occasion syneresis of the clot was "fair".

Case No. 33.

Patient. Mrs E. D.



Ward No. 8. Journal No. 91, page 362. Case No. 33.

Patient. Mrs E. D., Female.
Age. 26 years.
Occupation. At home.

Diagnosis. Chronic gastric ulcer - secondary anæmia.

Clinical notes. Patient was in the Ward for 17 days before the platelet count was first investigated. She had a very low colour index, about 0.5. While in the Ward her general condition improved steadily. She was operated on in the surgical wards on 15th May when it was found that the ulcer had perforated and was burrowing into the pancreas. Gastrectomy was performed. The patient died two days later.

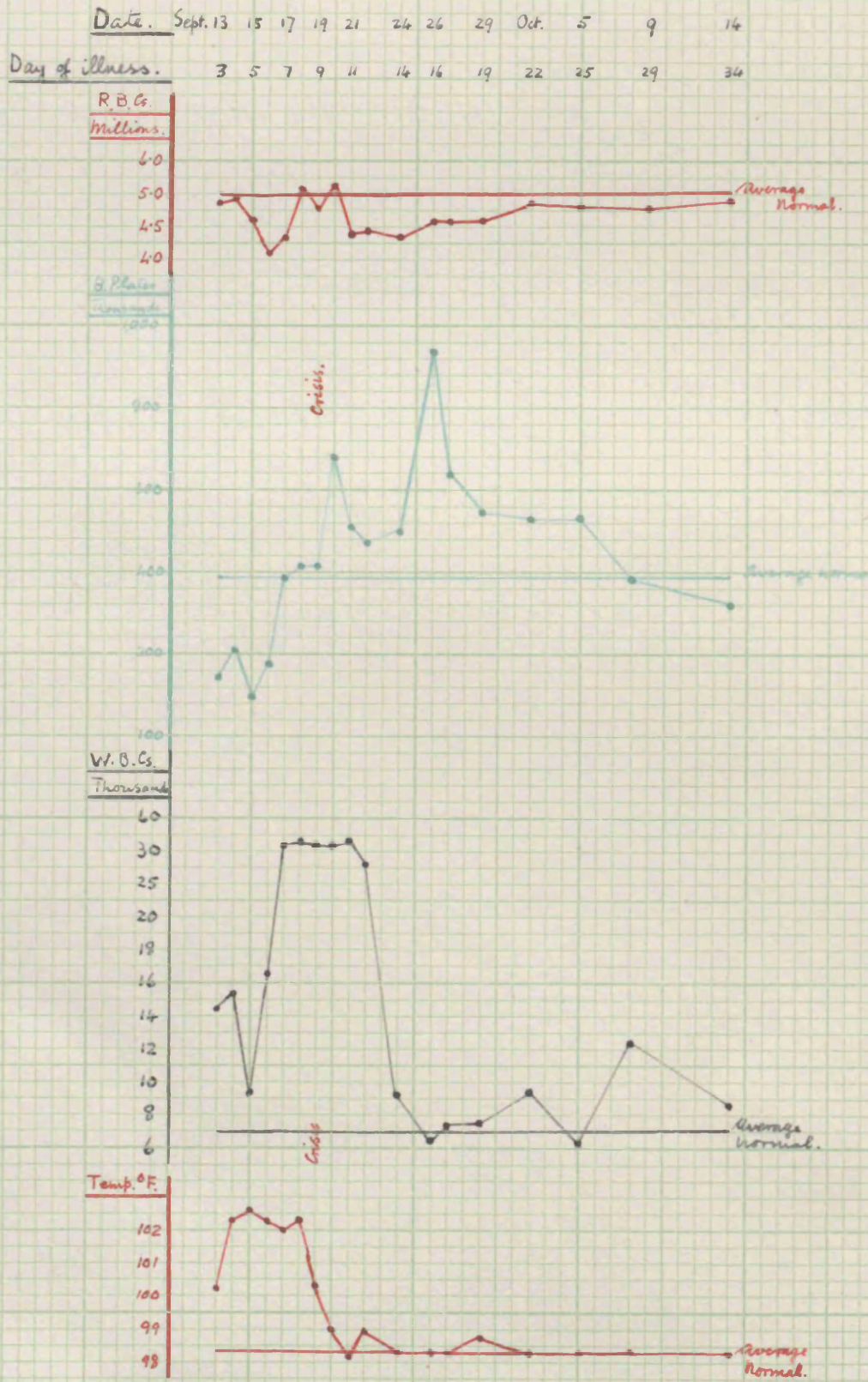
Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Mar. 28	4,500,000	-	297,000	-	-	-
" 31	4,360,000	-	584,240	-	-	-
Apr. 3	4,630,000	-	1,069,530	-	-	-
" 4	4,930,000	-	685,270	-	-	-
" 5	4,390,000	-	711,180	-	-	-
" 6	4,750,000	-	807,500	-	-	-
" 8	4,440,000	-	1,206,560	-	-	-
" 9	-	-	848,040	-	-	-
" 10	4,900,000	-	715,000	-	-	-
" 11	4,800,000	-	883,200	-	-	-
" 13	4,390,000	-	610,210	-	-	-
" 16	4,560,000	-	419,520	-	-	-
" 18	4,190,000	7,600	364,530	-	-	-
" 21	4,780,000	6,200	506,680	-	-	-
" 23	5,140,000	7,600	411,200	-	-	-
" 25	5,150,000	9,000	530,000	-	2'	-
" 28	5,120,000	11,000	348,160	-	2'	-
May 2	5,280,000	9,000	644,100	1' RE	2'30"	-
" 15	5,390,000	-	415,030	Before operation.		
	5,390,000	26,200	398,860	After operation - afternoon.		
" 16	5,170,000	21,400	398,090	-	-	-

Summary. The observations commenced at the beginning of platelet increase during which on two occasions the thrombocytes numbered over 1,000,000. Thereafter there was a fall to a more settled state round about normal values. The increase in the platelet values occurred in the early part of the period of improvement in the general condition of the patient.

Case No. 34.

Patient. G. C.



Ward No. 9. Journal No. 94, page 148. Case No. 34.

Patient. G. C., Male.
Age. 18 years.
Occupation. Apprentice painter.

Diagnosis. Lobar pneumonia.

Clinical notes. Patient was first investigated on the third day of illness. The crisis occurred on the 9th day and thereafter he made an uncomplicated recovery.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Sep.13	4,850,000	14,500	179,450	1' RE	2'	*
" 14	4,920,000	15,650	201,720	-	1'20"	*
" 15	4,590,000	9,200	144,585	1' RE	1'30"	*
" 16	4,120,000	16,750	189,520	-	-	* *
" 17	4,300,000	40,350	393,450	1'15"RE	2'	* *
" 18	5,130,000	42,900	413,530	-	1'50"	* *
" 19	4,720,000	37,300	420,080	1'10"RE	-	-
" 20	5,230,000	35,200	679,900	-	1'50"	-
" 21	4,870,000	39,100	550,050	-	-	-
" 22	4,960,000	27,450	473,680	2' RE	1'50"	* *
" 24	4,320,000	9,400	522,720	-	1'30"	-
" 26	4,600,000	6,300	943,000	-	1'30"	***
" 27	4,520,000	7,100	635,060	-	-	-
" 29	4,520,000	7,350	553,700	1'50"RE	1'45"	-
Oct. 2	4,870,000	9,550	530,830	-	1'30"	***
" 5	4,790,000	6,250	536,480	-	-	-
" 9	4,770,000	12,550	376,370	-	-	-
" 14	4,890,000	8,500	322,740	2' RE	-	-

Platelet Morphology.

Date.	Size.			Granulation.				Staining.	
	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Sep.13	-	98	2	-	47	53	-	100	-
" 14	-	97	3	-	-	93	7	89	11
" 15	3	95	2	-	3	89	8	94	6
" 16	-	100	-	-	5	74	21	100	-
" 17	3	92	5	-	17	65	18	89	11
" 18	-	100	-	-	17	83	-	100	-
" 19	-	100	-	-	10	62	28	100	-
" 20	-	100	-	-	14	86	-	100	-
" 21	-	100	-	-	-	95	5	100	-
" 22	-	100	-	-	3	94	3	100	-
" 24	-	100	-	-	8	70	22	100	-
" 26	-	100	-	-	9	91	-	100	-
" 27	-	100	-	-	25	75	-	100	-
" 29	-	100	-	-	-	100	-	100	-
Oct. 2	-	99	1	-	1	96	3	100	-
" 5	-	100	-	-	2	94	4	98	2
" 9	-	100	-	-	7	93	-	100	-
" 14	-	97	3	-	-	97	3	100	-

(over)

Summary. In the early period of the acute phase the platelets were reduced in number but just before the onset of the crisis they commenced to increase. In this case the platelet reaction was not sustained yet it was quite definite and with advance in convalescence there was a gradual diminution in total numbers. The platelet curve behaved altogether differently from that of the white cells.

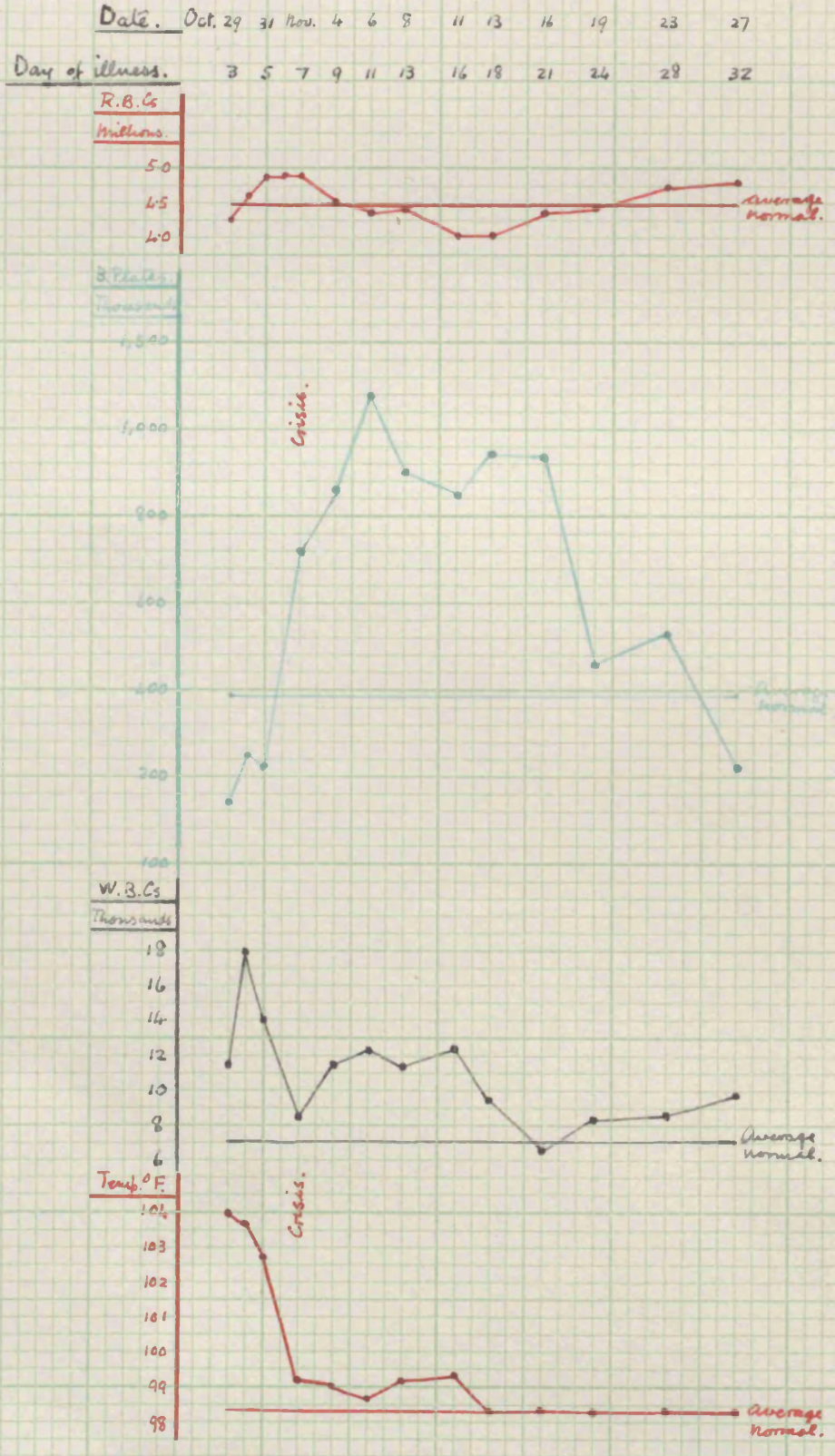
Bleeding time and coagulation time did not vary in any regular manner with alteration in the platelet numbers.

Retraction of the clot was "poor" in the early stage of the acute phase, "fair" in the few days before the crisis and "good" in convalescence.

To begin with there was an anisocytosis some of the thrombocytes being very large. This was particularly the case previous to the crisis and it was associated with a marked basophilia. The platelet picture became more normal with improvement in the condition of the patient although some irregularity in the distribution of the granules was always present.

Case No. 35.

Patient. N. F.



Ward No. 8. Journal No. 96, page 262. Case No. 35.

Patient. N. F., Female.
Age. 26 years.
Occupation. Burrough's operator.

Diagnosis. Lobar pneumonia.

Clinical notes. The blood of this patient was first investigated on the third day of illness. The crisis occurred on the 7th day and thereafter the patient progressed steadily to health.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Oct.29	4,270,000	11,750	175,670	2'15"RE	1'50"	* *
" 30	4,630,000	18,100	245,390	-	2'	* *
" 31	4,790,000	14,100	361,645	1'50"RE	2'	nil
Nov. 1	-	-	-	-	-	*
" 2	4,860,000	8,400	748,440	-	2'	* *
" 4	4,490,000	11,900	855,345	-	2'	* *
" 6	4,350,000	12,150	1,197,550	1'45"RE	-	* *
" 8	4,400,000	11,550	893,200	-	-	-
" 11	3,990,000	12,350	839,895	1'30"RE	-	***
" 13	3,910,000	9,200	944,265	-	2'	-
" 16	4,280,000	6,600	939,460	-	-	-
" 19	4,340,000	8,150	468,720	2' RE	-	***
" 23	4,730,000	8,300	539,220	-	-	-
" 27	4,750,000	10,000	228,000	-	-	-

Platelet Morphology.

	Size.			Granulation.				Staining.	
Date.	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Oct.29	8	91	1	-	11	89	-	100	-
" 30	-	100	-	-	9	91	-	100	-
" 31	-	99	1	-	9	91	-	99	1
Nov. 2	-	100	-	-	-	100	-	100	-
" 4	19	80	1	-	-	100	-	100	-
" 6	-	99	1	-	-	100	-	100	-
" 8	-	100	-	-	-	100	-	100	-
" 11	-	100	-	-	-	100	-	100	-
" 13	-	100	-	-	-	100	-	100	-
" 16	-	100	-	-	-	100	-	100	-
" 19	-	100	-	-	-	100	-	100	-
" 23	-	100	-	-	-	100	-	100	-
" 27	-	100	-	-	-	100	-	100	-

(over)

Summary. Previous to the crisis the platelet count was low. Even so, it was noted that before the crisis the platelet numbers had increased. The rise was rapid and steady and the increased count persisted for about 14 days. The numbers then fell to within normal limits. The platelet curve behaved independently of that of the white cells.

Bleeding time was not related in any to the number of platelets.

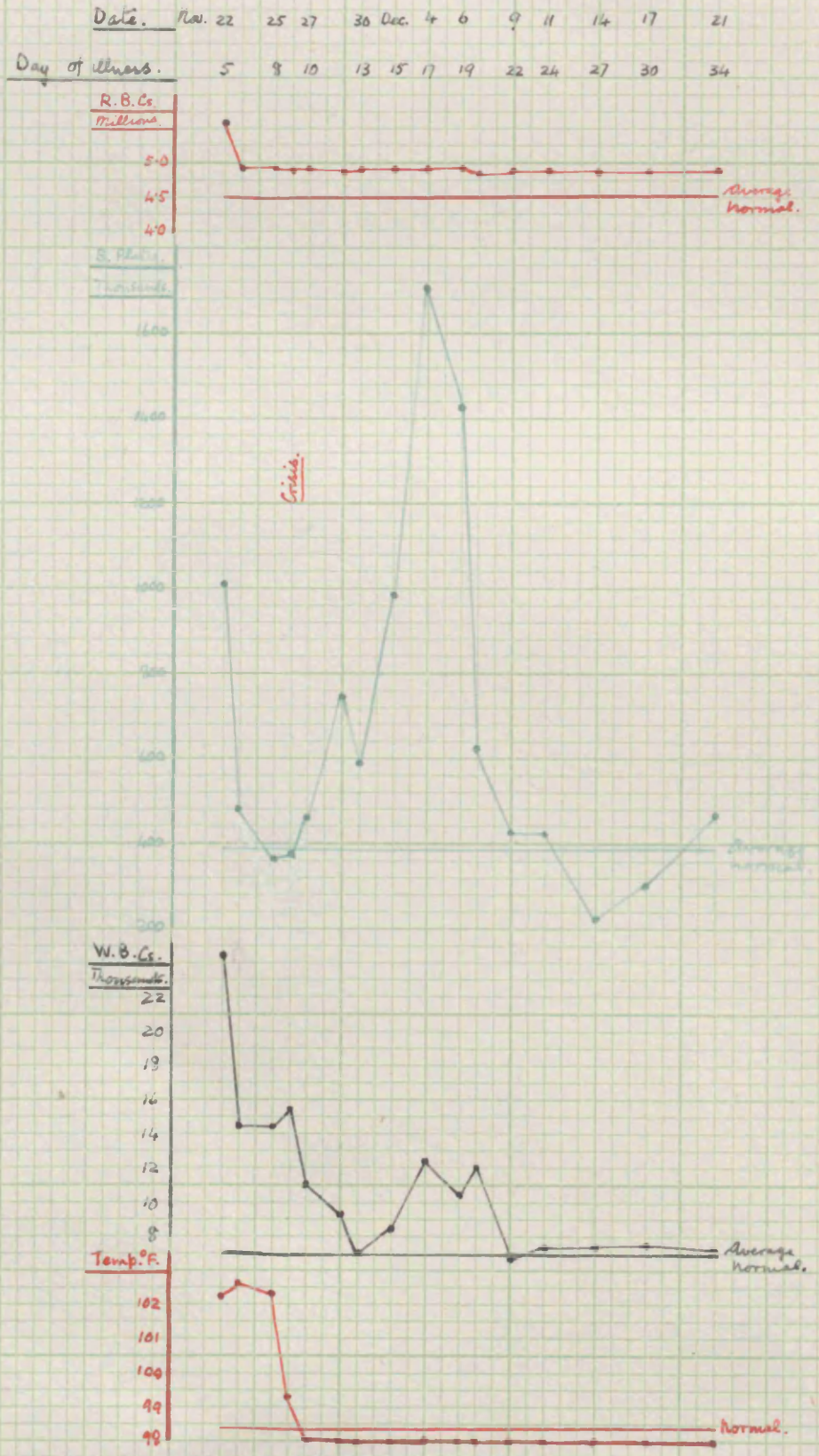
Coagulation time was more or less constant throughout the acute and convalescent periods.

Clot retraction was absent on the 5th day of illness. On the 6th day it was "poor". Syneresis improved with improvement in the condition of the patient.

In the acute stages of the illness there was some anisocytosis with an increase in the small and less granular forms. After the crisis and during convalescence the size and number of contained granules increased. Basophilia was noted on the 5th day of illness only.

Case No. 36.

Patient. I. O.



Ward No. 8. Journal No. 94, page 372. Case No. 36.

Patient. I. O., Female.
Age. 10 years.
Occupation. At school.

Diagnosis. Lobar pneumonia.

Clinical notes. The crisis occurred on the 9th day of the illness. Thereafter the patient made a steady recovery.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Nov.22	5,630,000	24,650	1,007,770	1'30"RE	1'45"	nil
" 23	4,820,000	14,600	482,000	-	2'	nil
" 25	4,840,000	14,300	367,840	1'30"RE	2'	nil
" 26	4,810,000	15,500	377,585	-	1'45"	*
" 27	4,820,000	10,800	448,240	1'45"RE	-	*
" 29	4,800,000	9,400	748,800	-	1'30"	* *
" 30	4,880,000	7,150	590,480	-	-	* *
Dec. 2	4,890,000	8,750	992,670	1'15"RE	1'45"	* *
" 4	4,930,000	12,350	1,705,780	-	-	***
" 6	4,910,000	10,400	1,433,720	-	1'15"	***
" 7	4,710,000	12,000	638,205	2' RE	-	-
" 9	4,820,000	6,800	421,750	-	1'55"	-
" 11	4,840,000	7,850	418,660	-	-	-
" 14	4,770,000	7,450	217,035	-	-	-
" 17	4,810,000	7,950	307,840	-	-	-
" 21	4,820,000	7,150	472,360	-	-	-

Platelet Morphology.

	Size.			Granulation.				Staining.	
Date.	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Nov.22	-	100	-	-	-	100	-	100	-
" 23	-	100	-	-	10	90	-	100	-
" 25	-	100	-	-	5	95	-	100	-
" 26	-	100	-	-	19	81	-	100	-
" 27	-	100	-	-	-	100	-	100	-
" 29	-	100	-	-	-	100	-	100	-
" 30	-	100	-	-	-	100	-	100	-
Dec. 2	-	99	1	-	-	100	-	100	-
" 4	-	100	-	-	-	100	-	100	-
" 6	-	100	-	-	-	100	-	100	-
" 7	-	100	-	-	-	100	-	100	-
" 9	-	100	-	-	-	100	-	100	-
" 11	-	100	-	-	-	100	-	100	-
" 14	-	100	-	-	-	100	-	100	-
" 17	-	100	-	-	-	100	-	100	-
" 21	-	100	-	-	-	100	-	100	-

(over)

Summary. On the 5th day of illness the platelets numbered over 1,000,000. Then they diminished rapidly until the crisis occurred on the 9th day. Thereafter they steadily increased in number until the 8th day of convalescence when they dropped to a rather low value within 4 days. The thrombocytes reacted independently of the red and white cells.

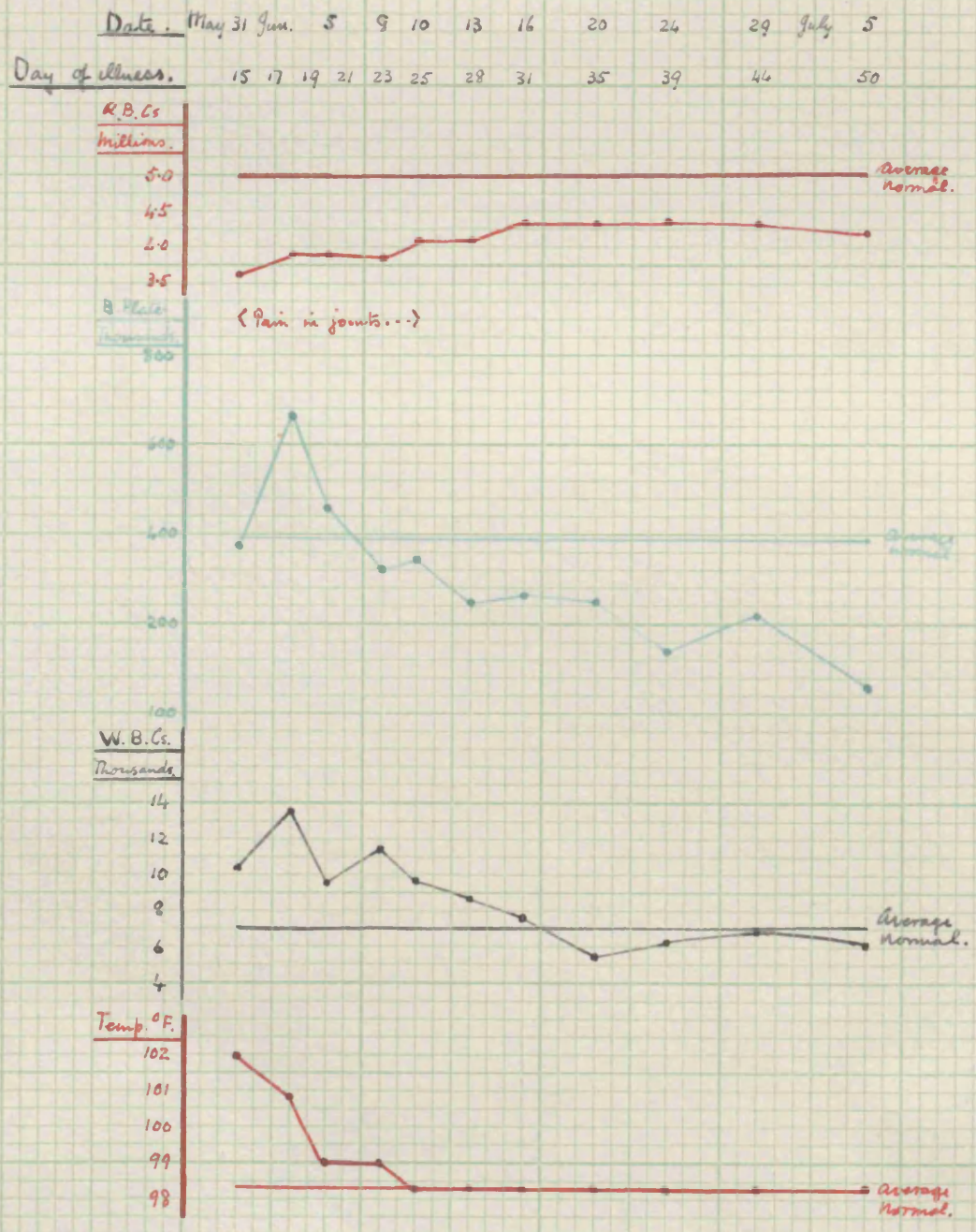
The duration of bleeding time bore no relation to the number of blood platelets and the same may be said for coagulation time.

Retraction of the clot was absent during the acute phase of the illness and returned gradually in convalescence. It was found that there was no syneresis even in the presence of a platelet count of over 300,000. The same was noted when the thrombocytes numbered 1,000,000.

In the acute phase of the illness many of the platelets were poor in granules. The staining was always hyaline and the size more or less constant.

Case No. 37.

Patient. A. D.



Ward No. 9. Journal No. 93, page 184. Case No. 37.

Patient. A. D., Male.
Age. 37 years.
Occupation. Labourer.

Diagnosis. Acute rheumatism. (Rheumatic fever.)

Clinical notes. Patient was ill with pain and stiffness in the joints for 15 days previous to the first platelet count. The pain disappeared and the temperature subsided within ten days of admission to hospital and thereafter patient improved slowly.

Results of investigation of the blood.

Date. 1929	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
May 31	3,680,000	10,250	371,680	-	-	* *
Jun. 3	3,960,000	13,350	681,120	1'30" RE	2'30"	-
" 5	3,950,000	9,300	432,525	-	2'45"	-
" 8	3,880,000	11,400	316,220	1' RE	1'45"	-
" 10	4,160,000	9,800	351,526	1' RE	2'	-
" 13	4,105,000	8,700	242,195	-	-	-
" 16	4,350,000	7,700	263,175	1' RE	2'15"	-
" 20	4,280,000	5,350	231,120	-	-	-
" 24	4,310,000	6.100	161,625	1'30" RE	2'30"	-
" 29	4,260,000	7,000	221,520	1'30" RE	2'	-
Jul. 5	3,710,000	6,000	126,140	-	-	-

Summary. The platelet curve was highest in the early stage of the period of observation when the pain was still present and the temperature rather high. Before the fever had subsided and the pain had disappeared the platelet numbers commenced to fall steadily as the patient improved. The lowest count was recorded on the day previous to dismissal from hospital.

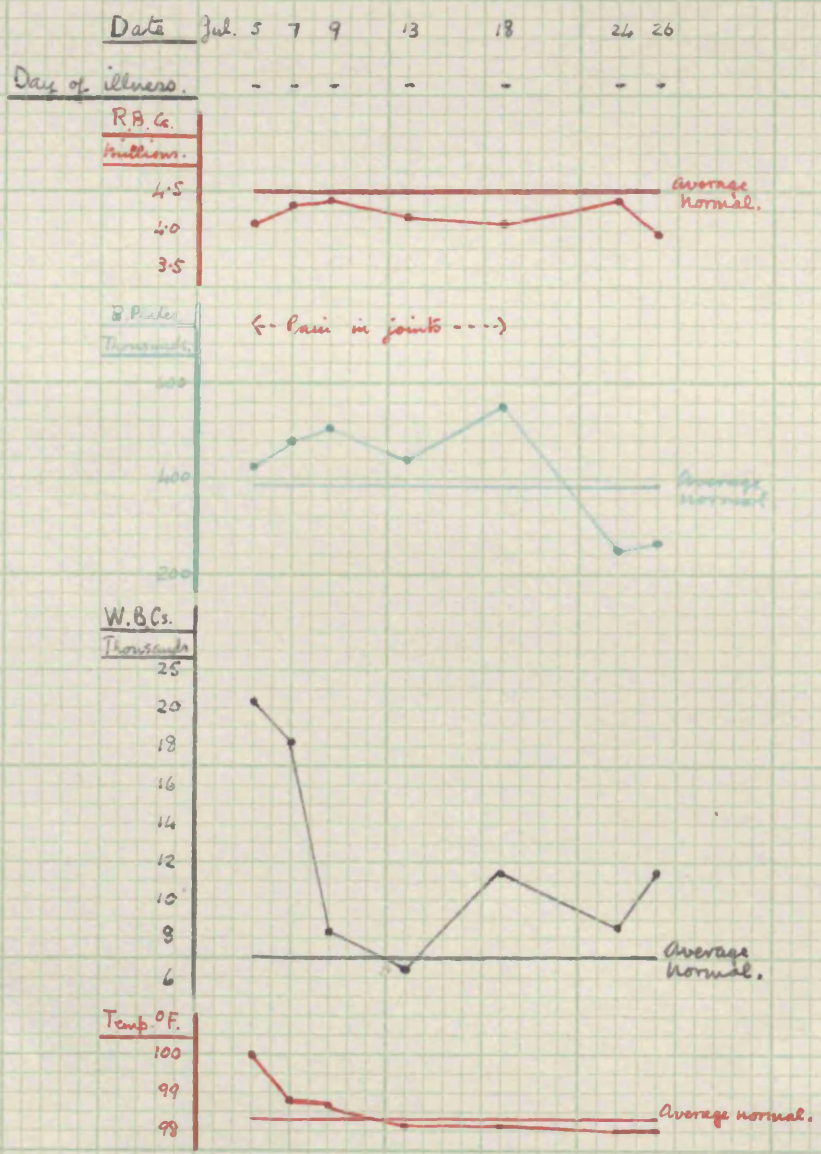
There was some similarity between the shape of the leucocyte curve and that of the thrombocytes.

Bleeding time and coagulation time did not vary with differences in the thrombocyte count.

Retraction of the clot was "fair" on one occasion.

Case No. 38.

Patient. J. G.



Ward No. 8. Journal No. 93, page 90. Case No. 38.

Patient. J. G., Female.
Age. 24 years.
Occupation. Domestic servant.

Diagnosis. Acute rheumatism. (Rheumatic fever.)

Clinical notes. Patient complained of pain in the joints until the 18th July although the temperature had subsided one week previously. She made a good recovery.

Results of investigation of the blood.

Date. 1929	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
Jul. 5	4,030,000	20,950	427,180	1'30"RE	2'15"	* *
" 7	4,290,000	18,000	497,640	-	-	-
" 9	4,430,000	8,100	505,020	1'30"RE	2'10"	* *
" 13	4,200,000	6,650	430,500	-	-	-
" 18	4,160,000	11,700	551,200	1'30"RE	-	* *
" 24	4,460,000	8,850	263,140	-	-	-
" 26	4,200,000	11,700	281,400	1'45"RE	1'45"	* *

Platelet Morphology.

Date. 1929	Size. Small. %	Normal. %	Large. %	Granulation. 0 %	+ %	+ + %	+++ %	Staining. Hyaline. %	Basophil. %
Jul. 5	-	100	-	-	100	-	-	100	-
" 7	-	99	1	-	-	100	-	100	-
" 9	-	99	1	-	-	100	-	99	1
" 13	-	99	1	-	-	100	-	100	-
" 18	-	100	-	-	20	80	-	100	-
" 24	-	99	1	-	29	63	8	100	-
" 26	-	100	-	-	-	99	1	100	-

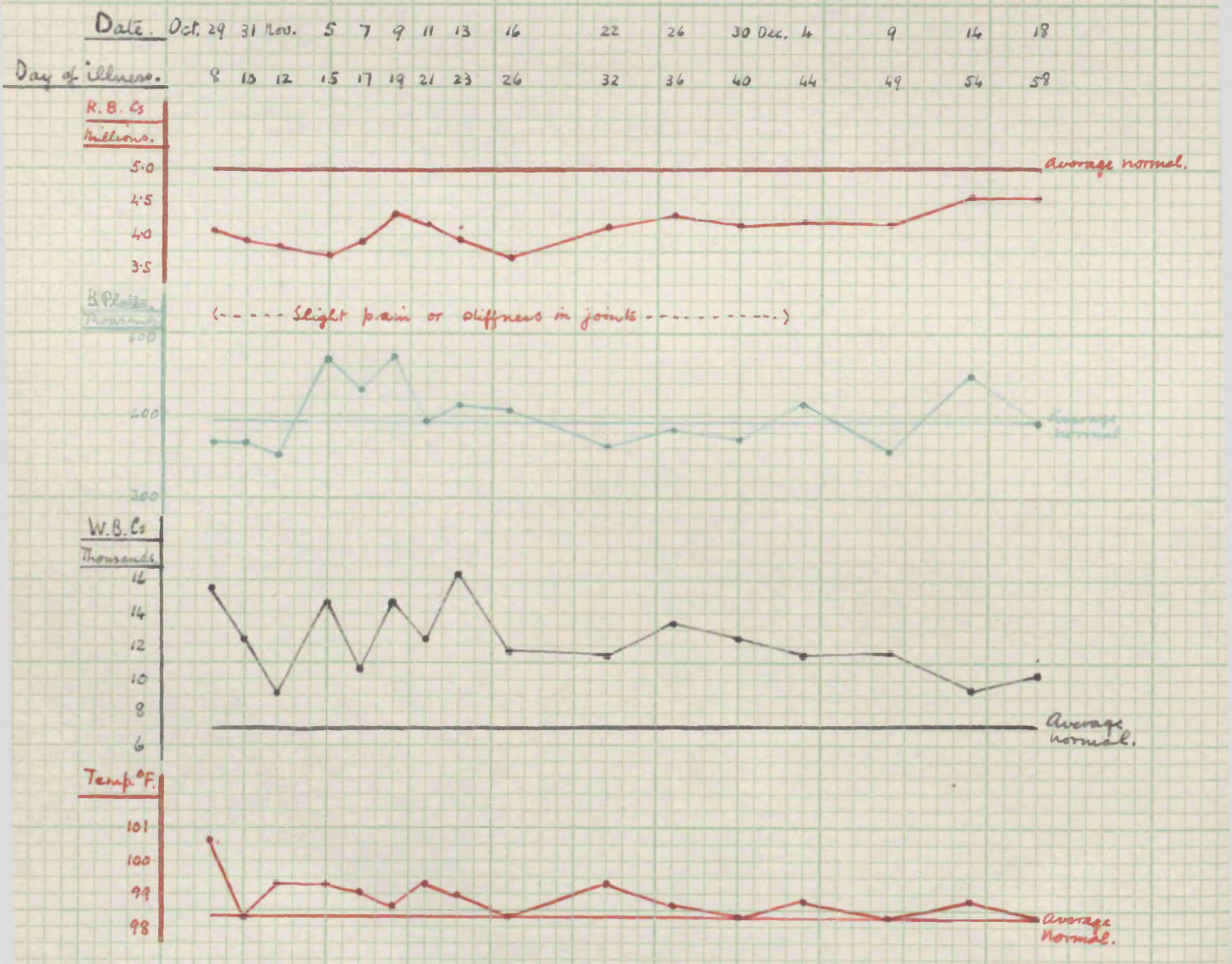
Summary. While pain was present the platelets were just above average normal numbers. Thereafter there was a fall to almost half these figures.

Bleeding time and coagulation time did not depend on the number of circulating platelets.

Retraction of the clot was always present.

The occasional presence of a large platelet indicated that on the whole the thrombocytes tended to be increased in size. When the first observation was made all the platelets were deficient in granules but with improvement in the condition of the patient the forms became more granular although some irregularity in the distribution of the granules was noted even in convalescence. On the 26th July however the platelets showed normal granulation. One basophil form was noted.

Case No. 39.
Patient. A. W.



Ward No. 9. Journal No. 94, page 438. Case No. 39.

Patient. A. W., Male.
Age. 13 years.
Occupation. At school.

Diagnosis. Acute rheumatism. (Rheumatic fever.)

Clinical notes. Patient had arthritic pain for 8 days before the observations commenced. He did not react satisfactorily to treatment. Pain persisted off and on for about 5 weeks, the pulse was always fast and there was a continued slight rise in the temperature.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Oct.29	4,020,000	15,650	333,660	2' RE	1'30"	* *
" 31	3,940,000	12,440	330,960	-	-	-
Nov. 2	3,790,000	9,150	303,200	2'10"RE	-	-
" 5	3,740,000	14,950	551,650	-	1'45"	-
" 7	3,900,000	10,750	464,100	-	-	-
" 9	4,390,000	14,950	557,466	2' RE	-	-
" 11	4,150,000	12,200	352,825	-	-	* *
" 13	3,920,000	16,400	435,120	-	-	-
" 16	3,660,000	11,750	409,920	1'50"RE	1'40"	-
" 22	4,240,000	11,550	326,480	-	-	-
" 26	4,290,000	13,350	368,940	-	-	-
" 30	4,180,000	12,550	541,510	1'45"RE	-	-
Dec. 4	4,210,000	11,450	439,945	-	-	* *
" 9	4,200,000	11,800	312,900	2' RE	-	-
" 14	4,570,000	9,150	500,415	-	1'30"	-
" 18	4,510,000	10,100	387,860	-	-	***

Platelet Morphology.

	Size.			Granulation.				Staining.	
Date.	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Oct.29	-	100	-	6	86	8	-	100	-
" 31	-	100	-	-	11	78	11	100	-
Nov. 2	-	100	-	-	-	100	-	97	3
" 5	-	100	-	-	13	87	-	100	-
" 7	-	100	-	-	-	100	-	100	-
" 9	-	100	-	-	4	96	-	100	-
" 11	-	100	-	-	37	63	-	100	-
" 13	-	100	-	-	-	100	-	100	-
" 16	-	100	-	-	5	95	-	100	-
" 22	-	100	-	-	-	100	-	100	-
" 26	-	100	-	-	7	93	-	100	-
" 30	-	100	-	-	4	96	-	100	-
Dec. 4	-	100	-	-	-	100	-	100	-
" 9	-	100	-	-	-	100	-	100	-
" 14	-	100	-	-	-	100	-	100	-
" 18	-	100	-	-	-	100	-	100	-

(over)

Summary. There was a slight platelet reaction between the 14th and the 19th days of illness. Between these two dates pain and fever were both present. A leucocytosis was present throughout. Apart from the slight reaction the thrombocyte curve could be regarded as varying within normal limits.

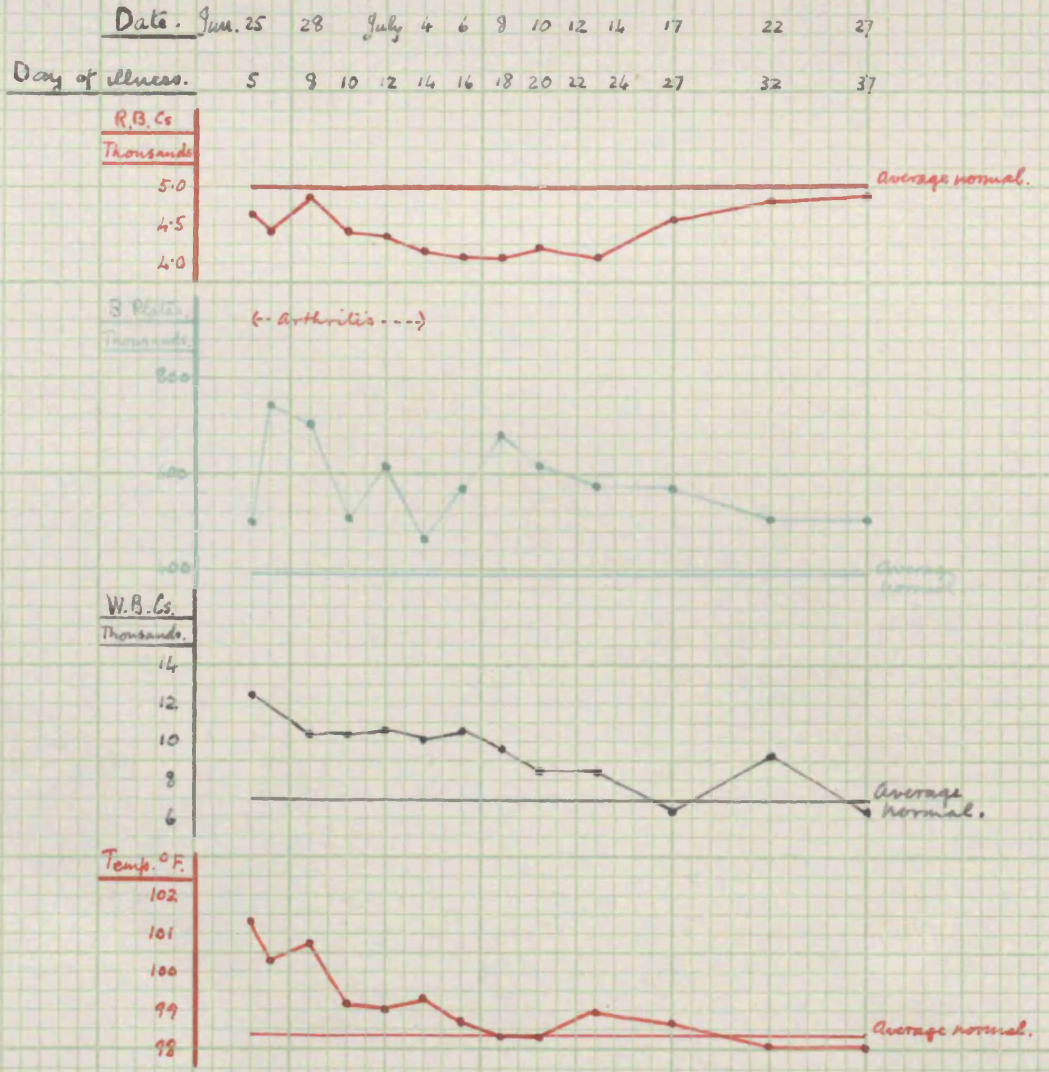
Bleeding time and coagulation time were not related in any way to the number of platelets.

Clot retraction was always present.

The size of the platelets was normal throughout. Deficiency in the number of granules was noted up to the 40th day of illness but it was very marked on the first observation when about 6% of the forms did not contain any granules at all. Thereafter the thrombocytes steadily became more granular. Basophilia was noted only on one occasion.

Case No. 40.

Patient. R. M.



Ward No. 9. Journal No. 93, page 262. Case No. 40.

Patient. R. M., Male.
Age. 21 years.
Occupation. Cinema operator.

Diagnosis. Acute rheumatism. (Rheumatic fever.)

Clinical notes. Patient complained of painful swelling of the knees and ankles for a period of four days before the investigation of the blood commenced. The pain disappeared 9 days afterwards.

Results of investigation of the blood.

Date. 1929	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
Jun.25	4,710,000	12,750	506,325	-	-	***
" 26	4,460,000	-	767,120	1' RE	2'	-
" 28	4,910,000	16,500	716,500	-	-	***
" 30	4,460,000	10,250	510,670	1' RE	2'	-
Jul. 2	4,360,000	10,700	608,220	-	-	-
" 4	4,210,000	10,000	465,205	-	-	-
" 6	4,190,000	10,500	576,125	1'10"RE	2'15"	-
" 8	4,130,000	9,700	697,970	-	-	-
" 10	4,250,000	8,350	601,375	-	-	-
" 13	4,080,000	8,100	583,440	55"RE	2'	-
" 17	4,570,000	6,250	582,675	-	-	-
" 22	4,800,000	9,350	501,600	-	-	***
" 27	4,850,000	6,450	514,100	-	-	-

Platelet Morphology.

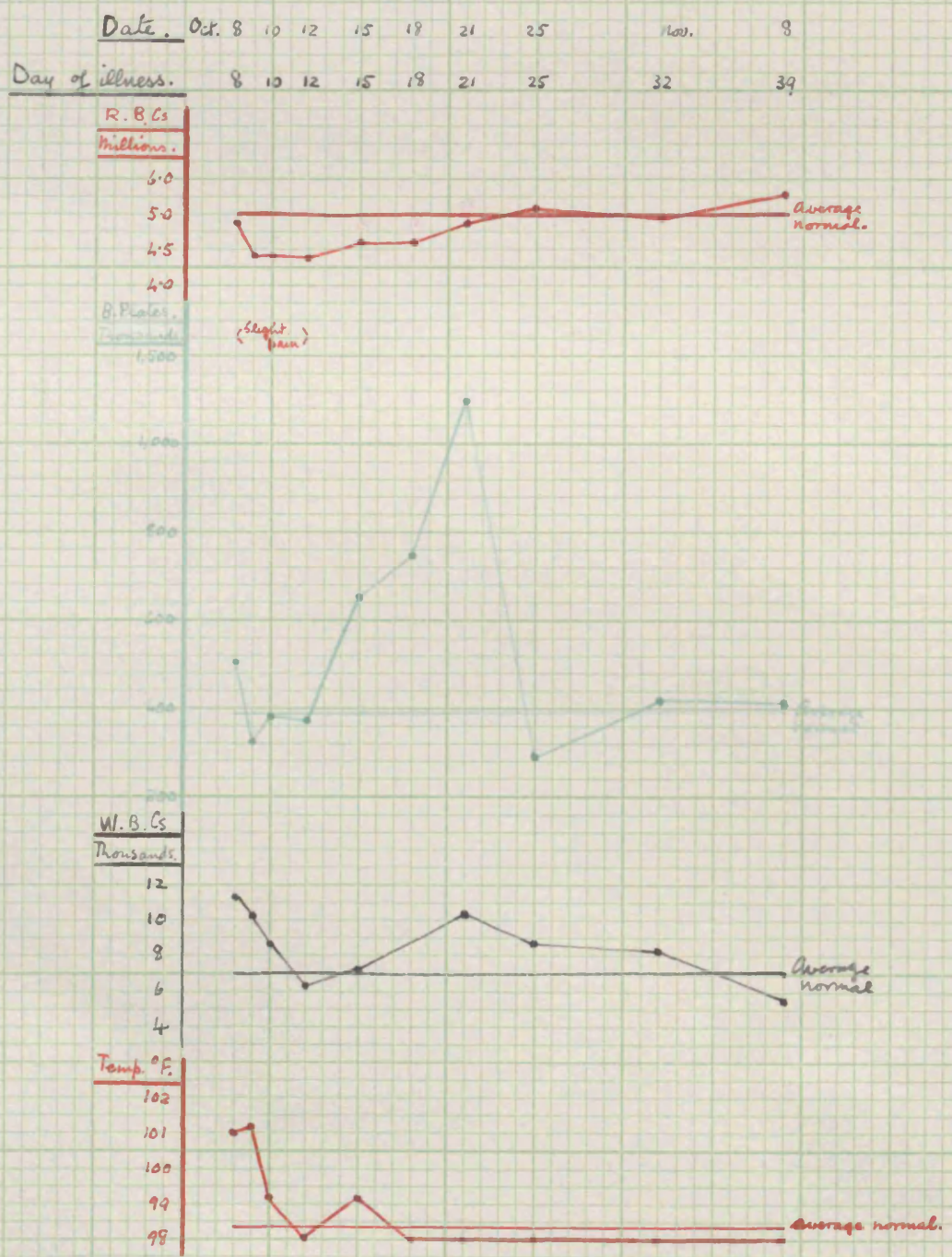
	Size.			Granulation.				Staining.	
Date. 1929	Small. %	Normal. %	Large. %	0 %	+ %	+ + %	+++ %	Hyaline. %	Basophil. %
Jun.25	-	100	-	-	-	100	-	100	-
" 26	-	99	1	-	-	100	-	100	-
" 28	-	100	-	-	-	100	-	100	-
" 30	-	100	-	-	100	-	-	100	-
Jul. 2	-	100	-	-	24	76	-	99	1
" 4	-	100	-	-	19	81	-	100	-
" 6	-	100	-	-	100	-	-	100	-
" 8	-	100	-	-	8	92	-	100	-
" 10	-	100	-	-	37	63	-	100	-
" 13	28	72	-	-	89	11	-	100	-
" 17	-	100	-	-	-	100	-	100	-
" 22	-	99	1	-	-	100	-	100	-
" 27	-	100	-	-	16	84	-	100	-

(over)

Summary. The platelet count was always above normal average values. The higher counts were noted early in the illness. The red and white cell and platelet curves behaved independently of each other.
Bleeding time and coagulation time did not vary with variation in the number of platelets.
Retraction of the clot was always "good".
Some variation in the size of platelets was present. Large forms were occasionally noted and on one occasion - 13th July - 28% were small. The thrombocytes were frequently deficient in granules especially when the patient was improving. Only one basophil form was ever noted.

Case No. 41.

Patient. F. O.



Ward.No. 9. Journal No. 94, page 324. Case No. 41.

Patient. F. O., Male.
Age. 14 years.
Occupation. At school.

Diagnosis. Acute rheumatism. (Rheumatic fever.)

Clinical notes. Patient had been ill for about 8 weeks before admission to the ward. Within a few days the arthritic pain disappeared and with fall in temperature definite and steady improvement set in.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Oct. 8	4,800,000	11,050	508,800	1'45"RE	1'50"	***
" 9	4,480,000	10,300	336,000	-	-	-
" 10	4,470,000	8,900	393,360	2' RE	2'	-
" 12	4,380,000	6,900	378,870	-	-	-
" 15	4,660,000	7,050	647,740	1'50"RE	2'	***
" 18	4,678,000	-	764,853	-	-	-
" 21	4,870,000	10,150	1,251,590	1'30"RE	1'30"	-
" 25	5,090,000	8,900	290,130	-	-	***
Nov. 1	4,910,000	8,100	427,170	-	-	-
" 8	5,650,000	5,850	412,450	2' RE	1'45"	***

Platelet Morphology.

	Size.			Granulation.				Staining.	
Date.	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Oct. 8	6	94	-	-	13	87	-	100	-
" 9	-	100	-	-	7	89	4	100	-
" 10	11	89	-	-	56	44	-	100	-
" 12	-	100	-	-	42	58	-	100	-
" 15	4	96	-	-	4	96	-	100	-
" 18	-	100	-	-	19	81	-	100	-
" 21	-	100	-	-	-	100	-	100	-
" 25	-	100	-	-	56	44	-	100	-
Nov. 1	5	95	-	-	16	84	-	100	-
" 8	-	100	-	-	4	96	-	100	-

(over)

Summary. With the disappearance of the pain and fall in the temperature there was a steady rise in the platelet curve until the 21st day of illness. Thereafter the platelet numbers fell below normal.

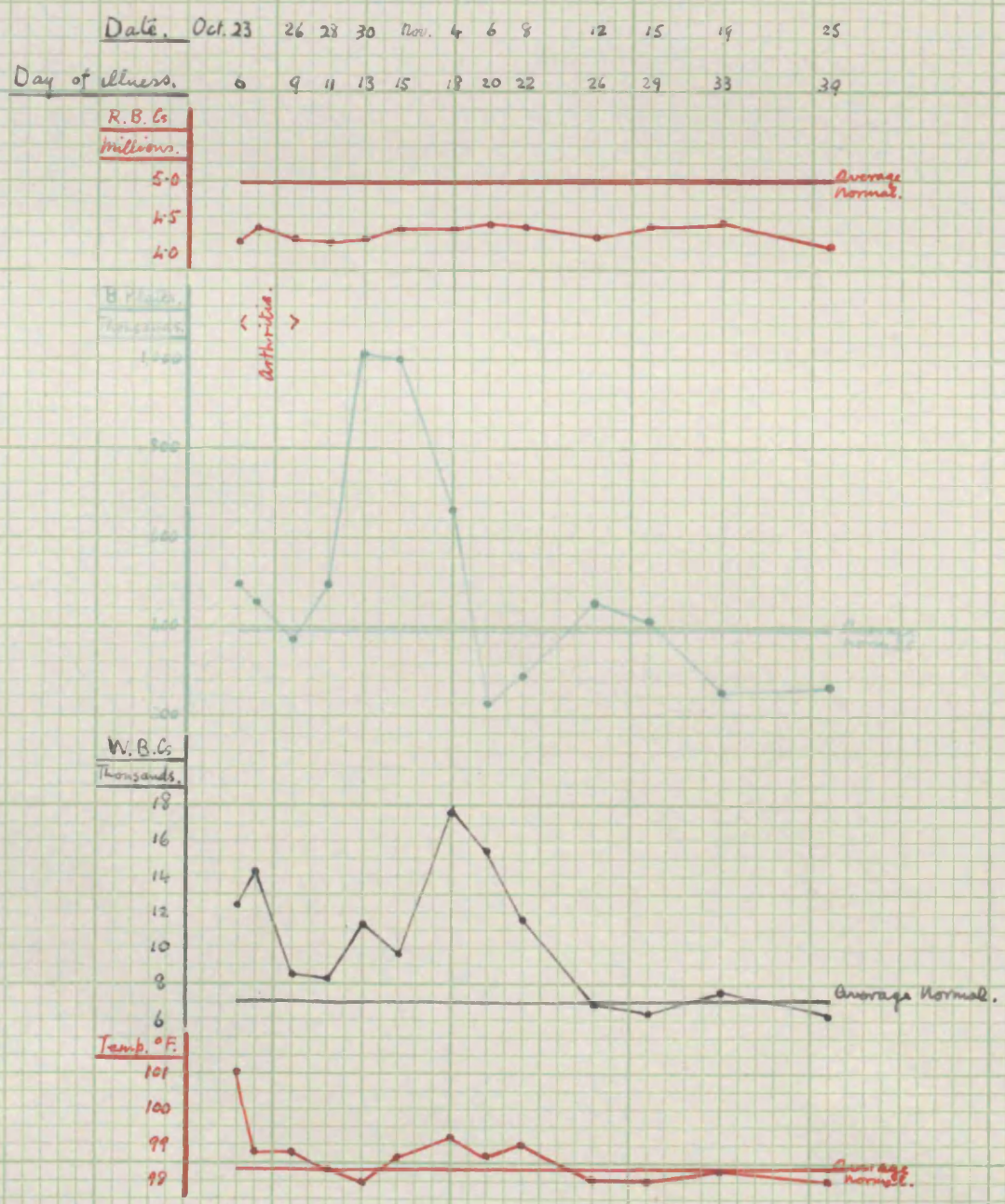
Bleeding time and coagulation time did not depend on the number of circulating platelets.

Retraction of the clot was always "good".

Frequently a number of small forms were present and and, with the exception of one day early in the period of observation when 4% very granular forms were counted, the platelets were constantly deficient in granules. The cytoplasm was always hyaline.

Case No. 42.

Patient. D. McD.



Ward No. 9. Journal No. 94, page 408. Case No.42 .

Patient. D. McD., Male.
Age. 54 years.
Occupation. Blacksmith.

Diagnosis. Acute rheumatism. (Rheumatic fever.)

Clinical notes. Patient complained of pain in the joints for 6 days before the first platelet count was made. The pain disappeared within 3 days but the temperature did not settle for about 19 days. The patient made an uncomplicated recovery.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time,	Clot retraction.
1929						
Oct.23	4,190,000	12,550	492,325	1' RE	2'	* *
" 24	4,290,000	14,400	456,885	-	-	-
" 26	4,210,000	8,700	374,690	1'30"RE	2'	-
" 28	4,160,000	8,250	495,040	-	-	-
" 30	4,210,000	11,400	1,008,295	-	1'45"	***
Nov. 1	4,290,000	9,750	999,570	1' RE	-	-
" 4	4,270,000	17,050	683,200	-	-	-
" 6	4,420,000	15,050	240,890	-	2'	-
" 8	4,360,000	11,600	294,200	-	-	***
" 12	4,240,000	7,100	447,230	1'45"RE	-	-
" 15	4,330,000	6,450	402,690	-	2'	-
" 19	4,480,000	7,750	257,500	-	-	***
" 25	4,080,000	6,100	281,520	1'45"RE	-	-

Platelet Morphology.

	Size.			Granulation.				Staining.	
Date.	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Oct.23	-	100	-	-	-	100	-	100	-
" 24	-	100	-	-	53	47	-	100	-
" 26	-	100	-	-	12	88	-	100	-
" 28	-	100	-	-	-	100	-	100	-
" 30	-	100	-	-	-	100	-	100	-
Nov. 1	13	86	1	-	5	95	-	100	-
" 4	-	100	-	-	-	100	-	100	-
" 6	-	100	-	-	10	90	-	100	-
" 8	-	100	-	-	10	90	-	100	-
" 12	-	100	-	-	-	100	-	100	-
" 15	-	100	-	-	3	97	-	100	-
" 19	-	100	-	-	-	100	-	100	-
" 23	-	100	-	-	-	100	-	100	-

(over)

Summary. With the disappearance of the pain there was a definite rise in the platelet numbers for a period of 8 days. Thereafter the numbers were always below average normal values. Although the pain had disappeared there was still some febrile disturbance during the period of the platelet reaction and there was also an associated rise in the leucocyte count.

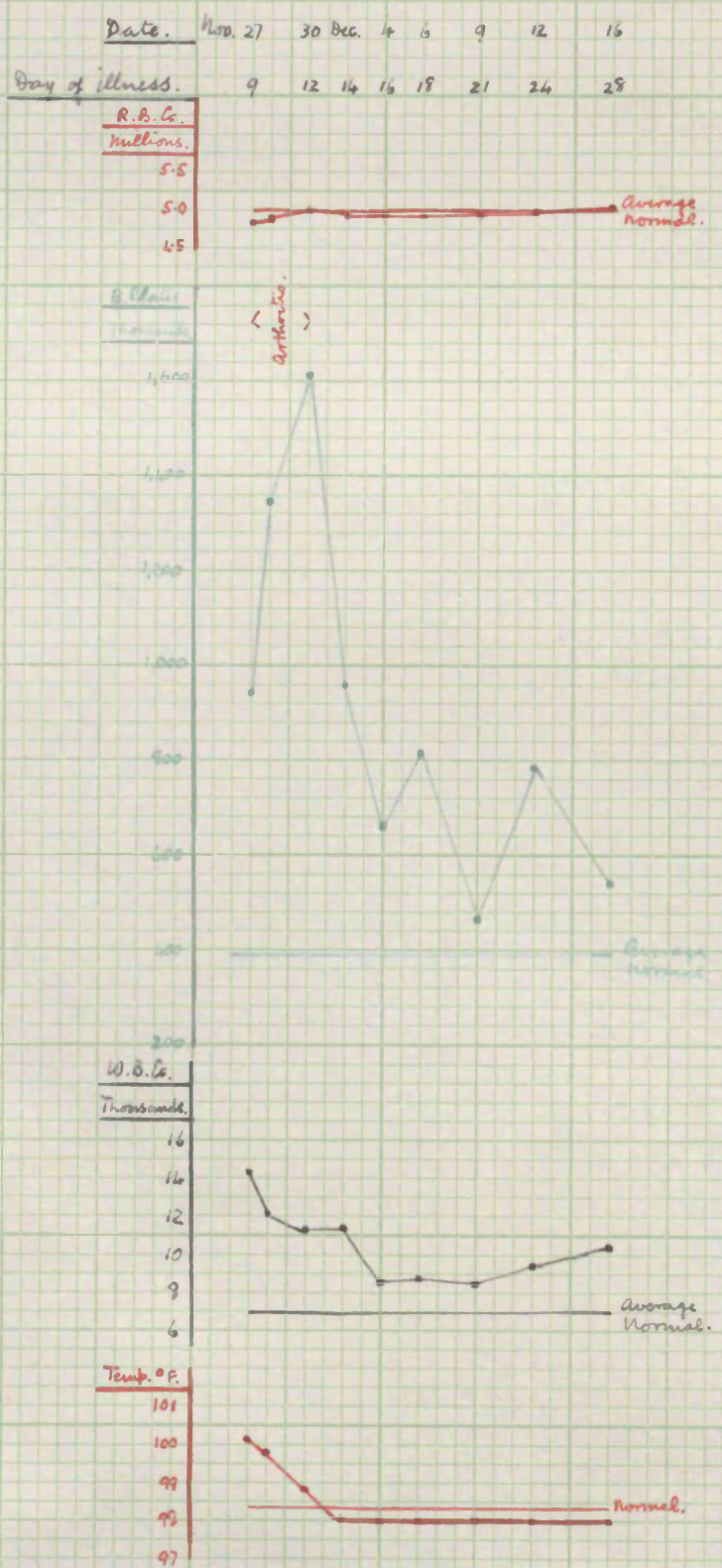
The duration of both bleeding and coagulation time did not depend on the number of platelets.

Retraction of the clot was always present.

Except for one occasion when the thrombocyte numbers were high the size of the platelets was always within normal limits. Early in the observations there was an increase in the number of less granular forms but as the patient improved there was a tendency for the number of granular thrombocytes to increase. The cytoplasm was always hyaline.

Case No. 43.

Patient. D. T.



Ward No. 9. Journal No. 95, page 114. Case No.43 .

Patient. D. T., Male.
Age. 19 years.
Occupation. Machineman.

Diagnosis. Acute rheumatism. (Rheumatic fever.)

Clinical notes. Patient was admitted on the 8th day of illness. The arthritic pain disappeared in a few days and the patient made a rapid recovery.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Nov.27	4,780,000	14,350	946,640	1'30"RE	-	* *
" 28	4,850,000	12,000	1,358,000	1'20"RE	-	***
" 30	5,010,000	11,350	1,618,530	1'45"RE	1'15"	***
Dec. 2	4,860,000	11,200	959,850	-	-	-
" 4	4,990,000	8,800	668,660	1'45"RE	-	-
" 6	4,910,000	8,950	805,995	-	1'30"	-
" 9	4,920,000	8,600	489,540	1'30"RE	-	***
" 12	5,000,000	9,400	787,500	-	-	-
" 16	5,050,000	10,200	542,400	-	-	-
" 19	4,910,000	9,900	473,815	-	-	-

Platelet Morphology.

	Size.			Granulation.				Staining.	
Date.	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Nov.27	-	100	-	-	23	77	-	100	-
" 28	-	100	-	-	-	100	-	100	-
" 30	-	100	-	-	40	60	-	100	-
Dec. 2	-	100	-	-	-	100	-	100	-
" 4	-	100	-	-	-	100	-	100	-
" 6	-	100	-	-	-	100	-	100	-
" 9	-	100	-	-	-	100	-	100	-
" 12	-	100	-	-	6	90	4	100	-
" 16	-	100	-	-	11	89	-	100	-
" 19	-	100	-	-	4	96	-	100	-

Summary. The platelet count was very high in the earlier observations but with fall in the temperature and improvement in the condition of the patient the number of thrombocytes fell somewhat but continued at varying values above normal. There was no relationship between the curves of the red and white cells and the platelets.

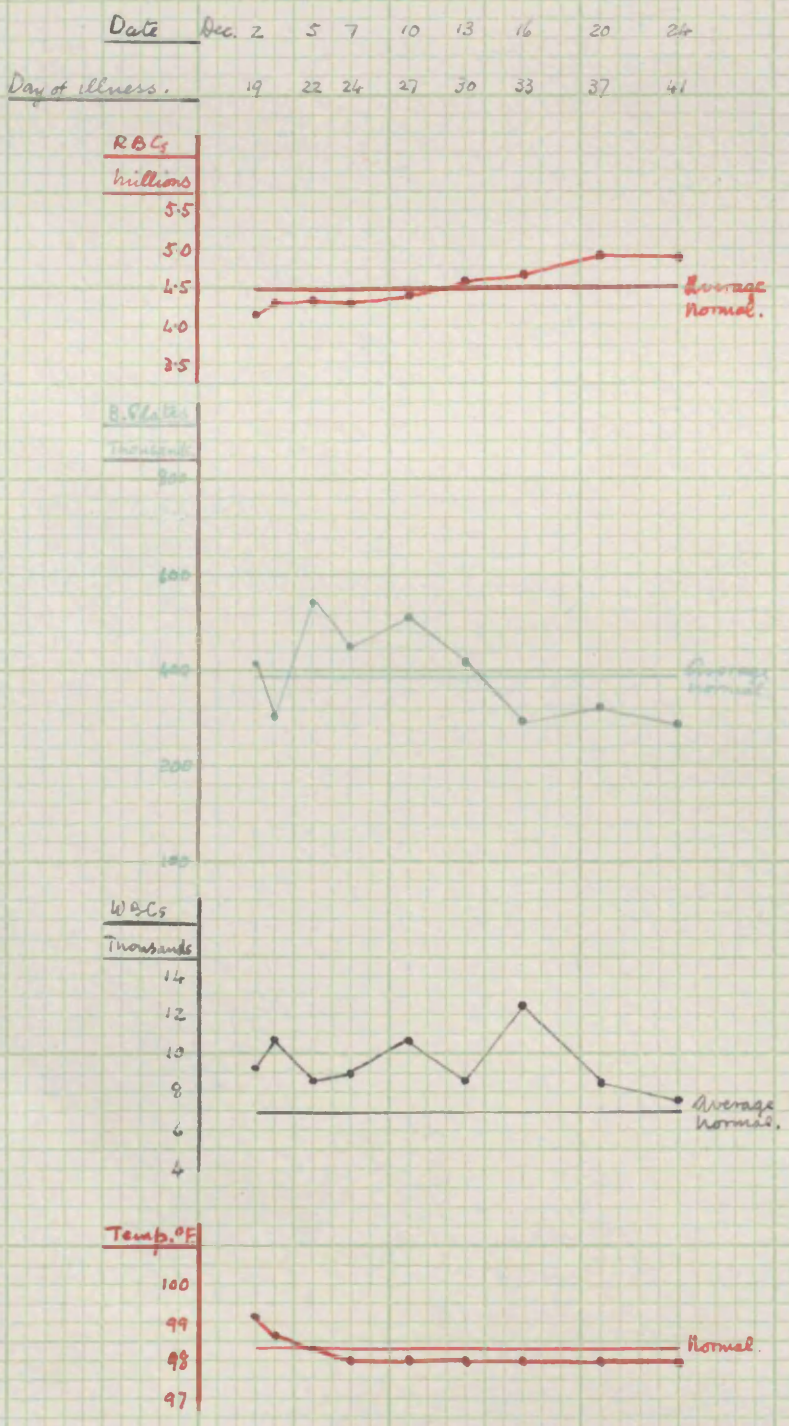
The duration of bleeding time and coagulation time did not depend on the number of thrombocytes present in the blood.

Retraction of the clot was always "good".

The platelets were regular in size throughout and became more granular as the patient improved. However towards the end of the period of observation less granular forms appeared. Variation in granulation was not necessarily associated with increased numbers. The staining reaction was always hyaline.

Case No. 44.

Patient. E. H.



Ward No. 8. Journal No. 94, page 422. Case No. 44.

Patient. E. H., Female.
Age. 26 years.
Occupation. Paper worker.

Diagnosis. Acute rheumatism. (Rheumatic fever.)

Clinical notes. The observations on the blood of this patient commenced about the 19th day of illness. By the 21st day the pain and fever disappeared.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Dec. 2	4,240,000	9,050	407,640	2' RE	1'45"	* *
" 3	4,260,000	10,750	298,200	2' RE	-	-
" 5	4,310,000	8,600	540,905	1'30" RE	1'45"	-
" 7	4,280,000	9,000	440,840	-	-	***
" 10	4,390,000	10,700	518,020	-	-	-
" 13	4,510,000	8,550	408,155	2' RE	2' 5"	-
" 16	4,740,000	12,500	282,030	-	-	-
" 20	4,950,000	8,150	326,620	-	-	-
" 24	4,890,000	7,550	283,620	-	-	-

Platelet Morphology.

Date.	Size.			Granulation.				Staining.	
	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Dec. 2	-	100	-	-	-	100	-	100	-
" 3	-	100	-	-	15	85	-	100	-
" 5	-	100	-	-	-	100	-	100	-
" 7	-	100	-	-	-	100	-	100	-
" 10	-	100	-	-	-	100	-	100	-
" 13	-	100	-	-	-	100	-	100	-
" 16	-	100	-	-	-	100	-	100	-
" 20	-	100	-	-	-	100	-	100	-
" 24	-	100	-	-	-	100	-	100	-

Summary. The platelet count was at its highest for some days after the temperature became sub-normal. Thereafter it continued at a lower level. The platelet curve behave independently of the red and white cell curves.

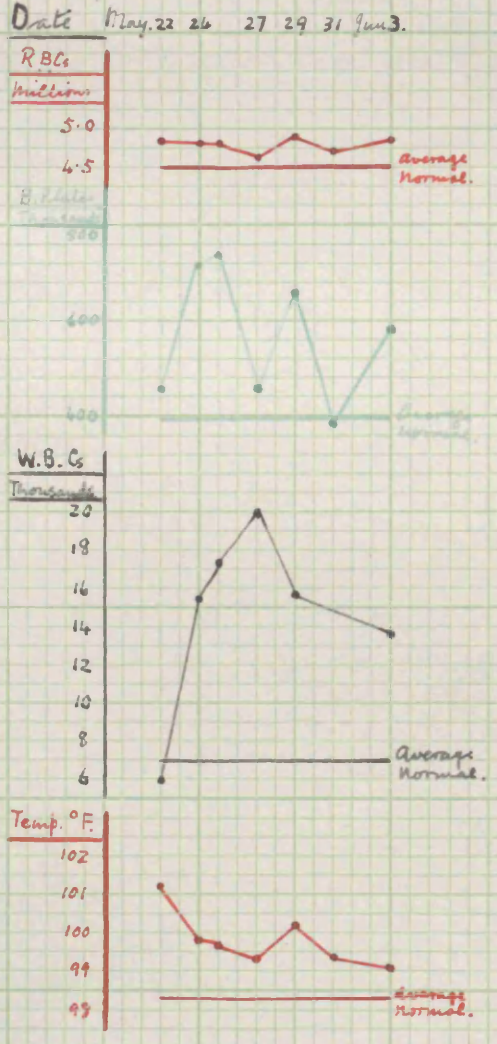
Bleeding time and coagulation time were not related to the number of platelets in the circulation.

Retraction of the clot was always present.

The platelets were of normal size throughout the period of observation and, except for one occasion, they were always well granulated. The cytoplasm was always hyaline.

Case No. 45.

Patient. C. D.



Ward No. 8. Journal No. 92, page 326. Case No. 45.

Patient. C. D., Female.
Age. 16 years.
Occupation. Maid.

Diagnosis. Rheumatic pericarditis and pleurisy.

Clinical notes. While in hospital patient was always acutely ill. She died on 6th June.

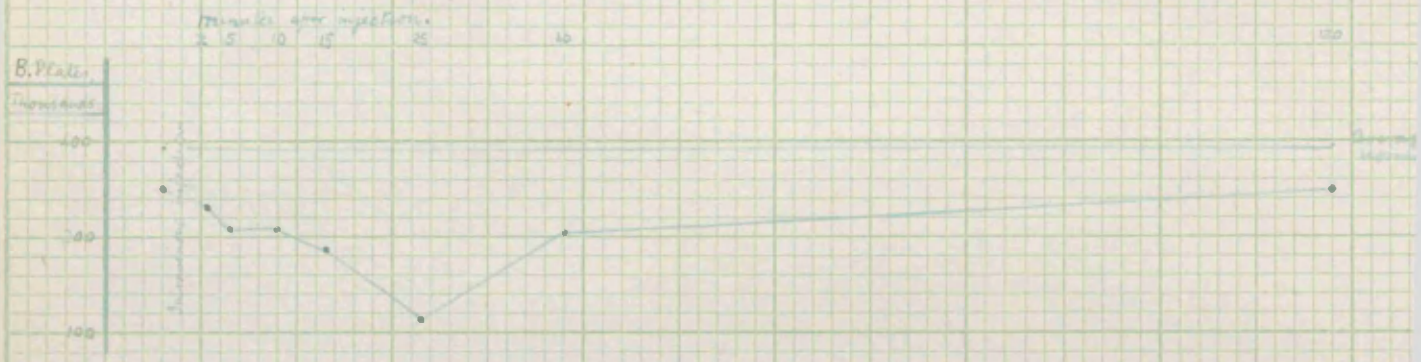
Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
May 22	4,840,000	6,000	454,960	55"RE	1'50"	***
" 24	4,810,000	15,650	711,880	-	-	-
" 25	4,810,000	17,100	731,120	-	-	-
" 27	4,660,000	20,000	466,000	1' RE	2'	***
" 29	4,900,000	15,600	666,400	-	-	-
" 31	4,700,000	-	427,700	-	-	-
June 3	4,850,000	13,600	596,550	1' RE	2'	-

Summary. The platelet count varied from day to day but on the whole it was high.
Bleeding time and coagulation time did not bear any relationship to differences in the platelet count.
Retraction of the clot was "good".
Towards the end of the period of observation the platelets did not stain well.

Case No. 46.

Patient. Mrs F.



Ward No. 8. Journal No. 92, page 276. Case No. 46.

Patient. Mrs F., Female.
Age. 40 years.
Occupation. At home.

Diagnosis. Rheumatoid arthritis.

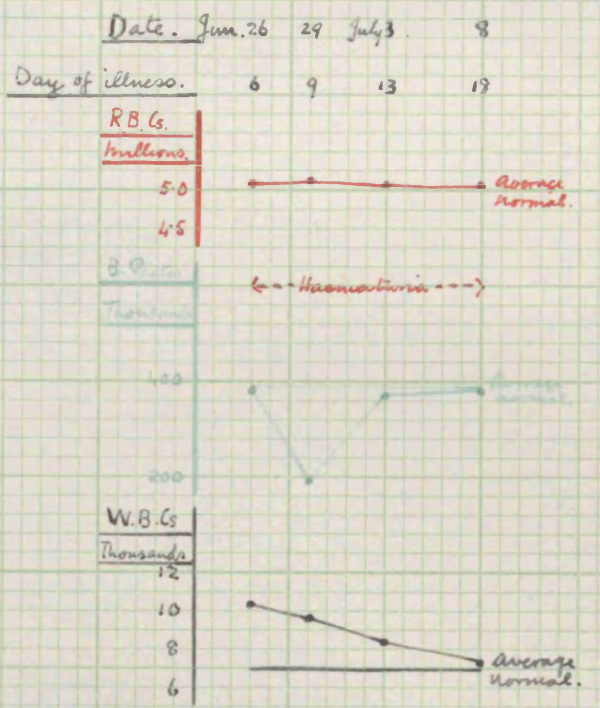
Clinical notes. As a therapeutic measure this patient was given protein shock. A dose of T.A.B. vaccine containing 100,000,000 organisms was injected intravenously on 9th July, 1929. The following is a note of the platelet counts immediately before, and at varying intervals after, the injection.

Before injection			.....	315,330	Platelets.
2½	minutes	after	"	274,200	"
5	"	"	"	210,220	"
10	"	"	"	210,220	"
15	"	"	"	187,370	"
25	"	"	"	118,820	"
40	"	"	"	201,080	"
120	"	"	"	297,050	"

Summary. There was a steady fall in the number of platelets contained in the capillary blood until 25 minutes after the injection. Thereafter the thrombocytes increased to nearly their original figures within 120 minutes.

Case No. 47.

Patient. J. S.



Ward No. 9. Journal No. 93, page 272. Case No.47 .

Patient. J. S., Male.
Age. 44 years.
Occupation. Labourer.

Diagnosis. Acute nephritis.

Clinical notes. During the period of observation a trace of blood was always present in the urine. Patient was subject to epileptic seizures.

Results of investigation of the blood.

Date. 1929	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
Jun.26	5,070,000	10,550	397,995	1'30"RE	1'30"	* *
" 29	5,240,000	9,800	193,880	1'30"RE	1'45"	-
Jul. 3	5,130,000	8,300	384,750	-	-	-
" 8	5,050,000	7,200	393,900	-	-	-

Platelet Morphology.

Date.	Size.			Granulation.				Staining.	
	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Jun.26	-	98	2	-	12	87	1	100	-
" 29	-	99	1	-	-	100	-	98	2
Jul. 3	-	100	-	-	-	100	-	99	1
" 8	-	99	1	-	-	99	1	100	-

Summary. With the exception of the second observation which was made immediately before an epileptic fit, the platelet count was more or less constant and varied independently of the red and white cells.

Bleeding time or coagulation time did not vary with alteration in the platelet count.

Retraction of the clot on one occasion was "fair".

Occasionally a large platelet was noted. On 26th June 12% of the forms were deficient in granules.

Basophilia was observed on two separate dates.

Ward No.9. Journal No. 93, page 40. Case No. 48.

Patient. R. S., Male.
Age. 24 years.
Occupation. Joiner.

Diagnosis. Acute nephritis.

Clinical notes. Patient had been ill for a fortnight before admission on the 10th May. On the 11th May the urine contained blood but on the 13th and 19th of that month the urine was free from blood.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
May 11	4,750,000	12,000	380,750	1' RE	2'30"	***
" 13	4,700,000	11,600	308,000	1' RE	2'30"	-
" 19	4,930,000	8,000	320,450	-	-	-

Summary. The platelet numbers remained constant within normal limits. There was no platelet reaction after the cessation of hæmorrhage.
Bleeding time and coagulation time showed nothing of note.
Syneresis of the clot was "good".

Ward No. 9, Journal No. 91, page 78. Case No. 49.

Patient. J. D., Male.
Age. 45 years.
Occupation. Carter.

Diagnosis. Acute nephritis.

Clinical notes. This case was in the ward for two months previous to the first platelet count. During this time blood was constantly present in the urine. The thrombocytes were counted to discover if the continued hæmorrhage was due to thrombycytopenia.

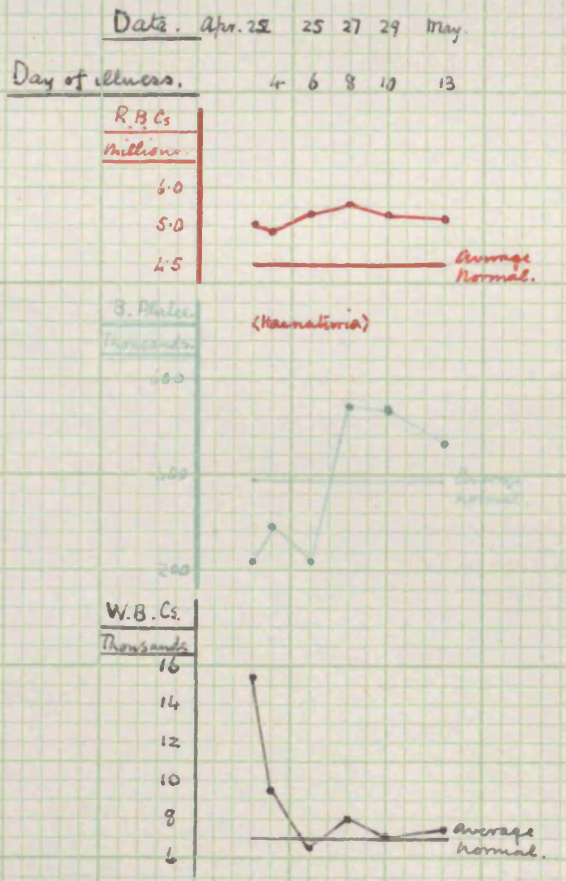
Results of investigation of the blood.

Date.	Red cells.	Platelets.	Bleeding time.	Coagulation time.
1929 Mar.26	4,660,000	312,220	1' RE	2'15"
" 29	4,290,000	386,100	-	-

Summary. The platelets were present in normal numbers. Bleeding time or coagulation time did not show anything worthy of note.

Case No. 50.

Patient. R. D.



Ward No. 8. Journal No. 92, page 194. Case No. 50.

Patient. R. D., Female.
Age. 40 years.
Occupation. At home.

Diagnosis. Acute nephritis.

Clinical notes. Patient was ill for three days before the observations commenced. The hæmaturia diminished gradually so that by the 28th April it had disappeared.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Apr. 22	5,000,000	15,400	220,000	2' RE	1'45"	Note.
" 23	4,950,000	9,600	297,000	-	-	-
" 25	5,470,000	6,800	224,270	1'50" RE	1'45"	-
" 27	5,590,000	8,400	547,820	-	1'45"	-
" 29	5,390,000	7,400	544,390	-	1'45"	-
May 2	5,260,000	7,400	478,660	2' RE	2'	-

Note. In this case the blood was collected in a test-tube. No retraction of the clot or extrusion of the serum was noted after 24 hours. However, when this irretractile clot was gently loosened from the sides of the test-tube rapid syneresis occurred.

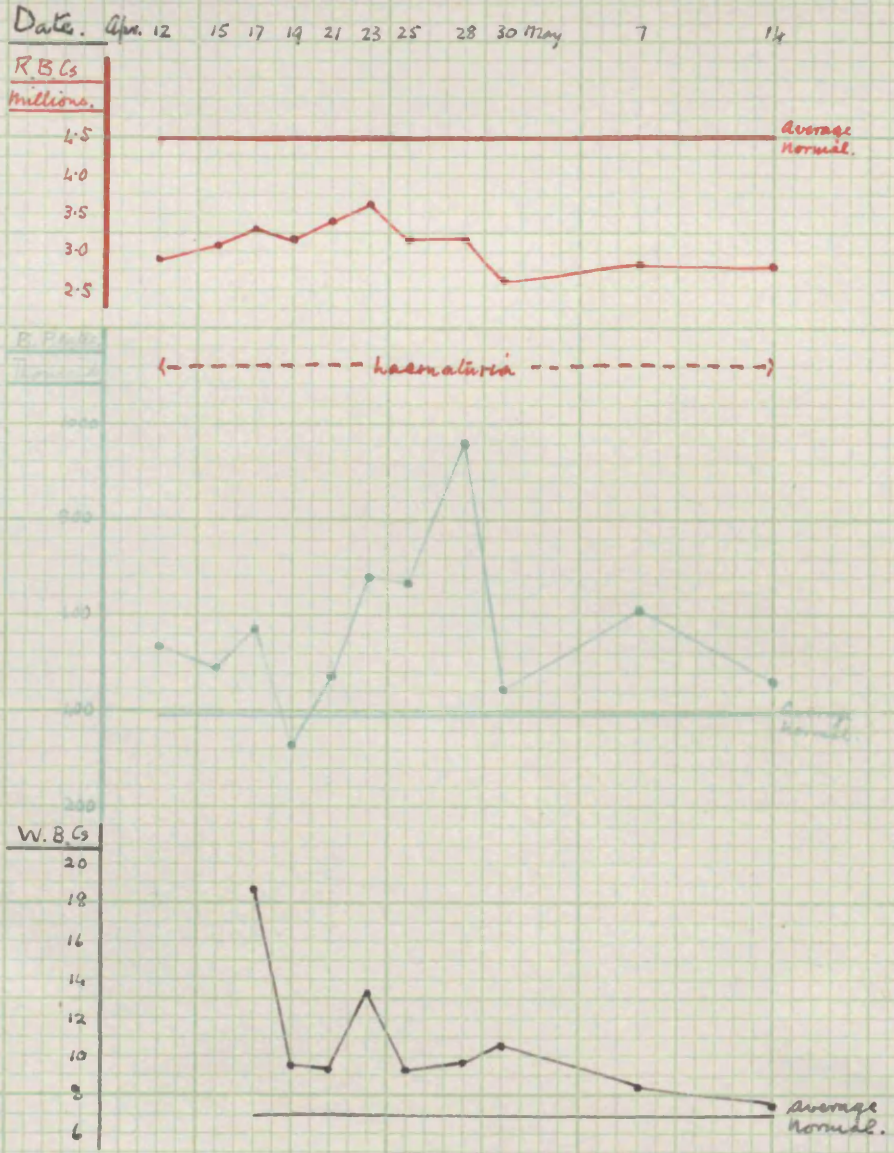
Summary. There was a slight rise in the platelet count previous to the cessation of the hæmaturia.

Bleeding time and coagulation time were not related to alteration in the number of circulating platelets.

On 27th April, the date on which the thrombocytes first increased, many large forms were observed.

Case No. 51.

Patient. A. B.



Ward No. 8. Journal No. 92, page 110. Case No. 51.

Patient. A. B., Female.
Age. 14 years.
Occupation. Factory Worker.

Diagnosis. Acute Nephritis.

Clinical notes. Patient had hæmaturia for seven days before the first platelet count was carried out. During the whole period of observation abundant blood was present in the urine.

Results of investigation of the blood.

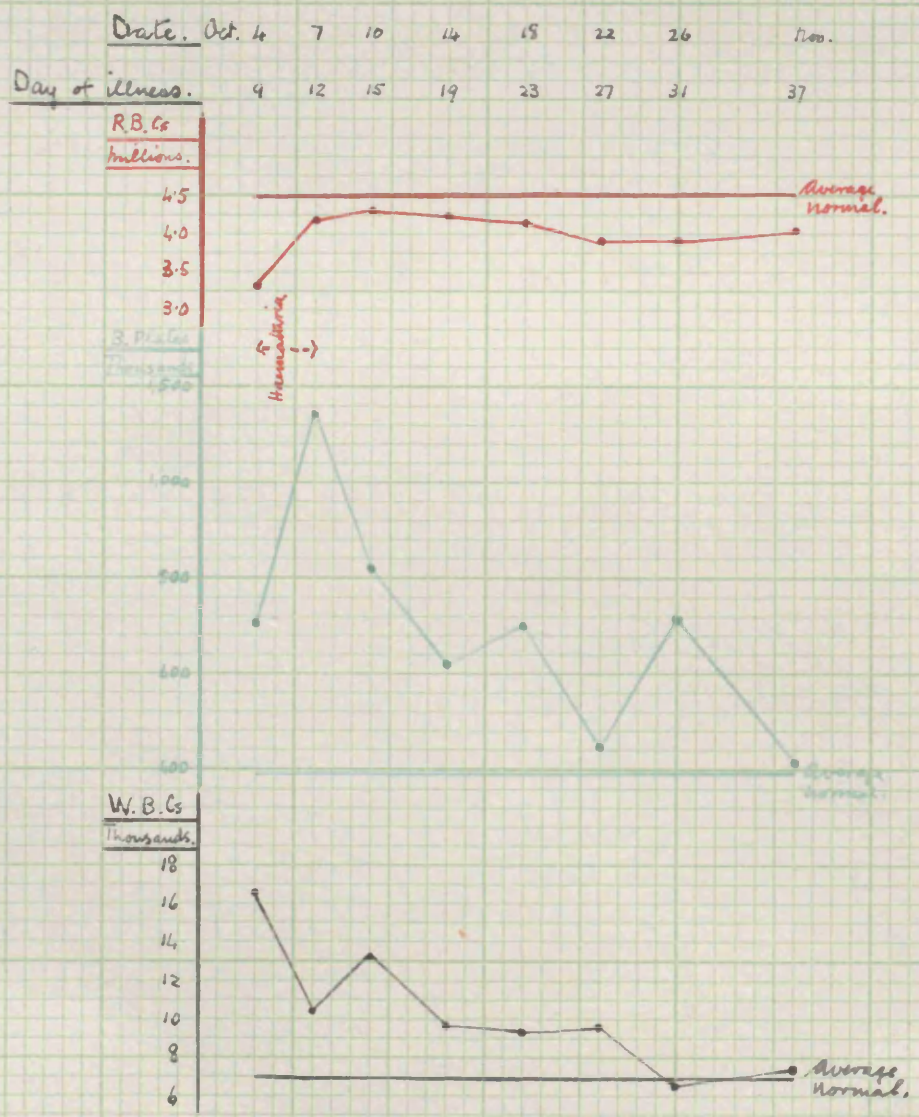
Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
*Apr. 12	2,950,000	-	525,100	-	-	*Note.
" 15	3,150,000	-	497,700	-	-	-
" 17	3,270,000	18,800	575,520	1'10" RE	1'30"	-
" 19	3,230,000	9,200	316,540	-	-	-
" 21	3,470,000	9,000	492,740	-	-	-
" 23	3,630,000	13,200	693,330	1' RE	1'45"	-
" 25	3,230,000	9,000	684,500	-	2'	-
" 28	3,230,000	9,600	972,230	-	2'	-
" 30	2,575,000	10,600	437,750	-	2'45"	-
May 7	2,880,000	8,200	622,080	1' RE	2'	-
" 14	2,760,000	7,200	453,400	-	-	-
" 20	-	-	-	-	-	***

Summary. On the whole the platelet numbers were always above normal and on one occasion they were very high. The rise in the platelet count coincided with a fall in the leucocyte count.
Bleeding time and coagulation time did not depend on the number of thrombocytes present in the blood.
Retraction of the clot was present.

*Note. On this date the blood was collected in a test-tube. No retraction of the clot was noted after 21 hours. However when this irretractile clot was gently loosened from the sides of the test-tube rapid syneresis occurred.

Case No. 52.

Patient. G. C.



Ward No. 8. Journal No. 94, page 112. Case No. 52.

Patient. G. C., Female.
Age. 5½ years.

Diagnosis. Acute nephritis.

Clinical notes. When patient was first investigated she had been ill for 9 days. She was oedematous and abundant blood was present in the urine. The hæmaturia persisted until the 7th Oct. She made a good recovery.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Oct. 4	3,360,000	16,850	710,640	1' RE	2'	***
" 7	4,220,000	10,650	1,372,800	1' RE	1'30"	-
" 10	4,300,000	13,050	817,000	-	-	***
" 14	4,250,000	9,900	605,625	1'15"RE	-	-
" 18	4,180,000	9,100	706,420	-	-	-
" 22	3,850,000	9,750	448,525	1'30"RE	2'15"	***
" 26	3,900,000	6,600	729,300	-	-	-
Nov. 1	4,160,000	7,250	407,680	1'30"RE	2'	-

Platelet Morphology.

	Size.			Granulation.				Staining.	
Date.	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Oct. 4	25	75	-	-	-	100	-	100	-
" 7	-	100	-	-	-	100	-	100	-
" 10	-	100	-	-	-	100	-	100	-
" 14	-	100	-	-	-	91	9	100	-
" 18	-	99	1	-	-	100	-	100	-
" 22	-	100	-	-	17	83	-	100	-
" 26	-	100	-	-	28	72	-	100	-
Nov. 1	-	100	-	-	-	100	-	100	-

Summary. When first investigated the platelet count was high. The numbers increased to 1,372,800 but thereafter they fell gradually to numbers which were always above normal average values. In some respects the white cell and platelet curves resemble each other

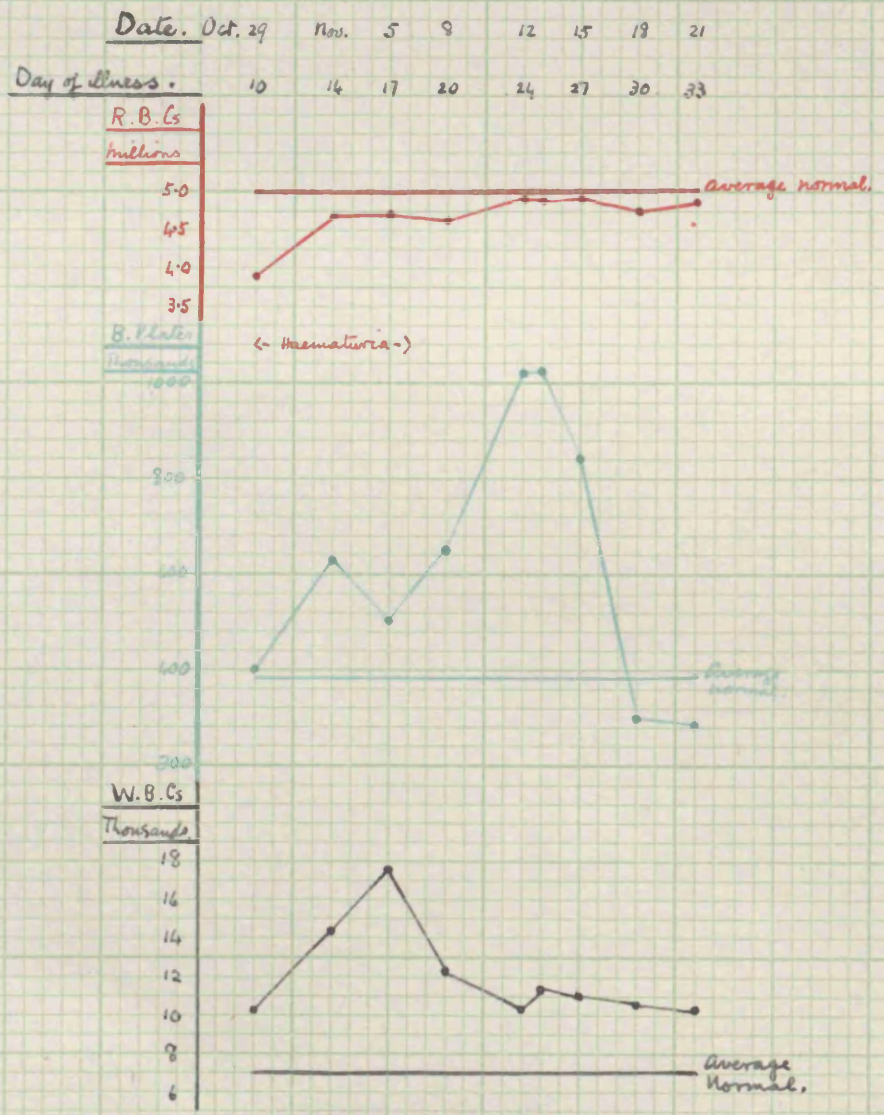
Bleeding time and coagulation time were not related to the number of circulating platelets.

Clot retraction was always "good".

On the occasion of the first observation many small but granular forms were noted. Late in convalescence there was an increase in the less granular forms. The cytoplasm was always hyaline.

Case No. 53.

Patient. P. T.



Ward No. 9. Journal No. 94, page 448. Case No. 53.

Patient. P. T., Male.
Age. 9 years.
Occupation. At school.

Diagnosis. Acute nephritis.

Clinical notes. Patient was ill for 10 days before the observations commenced. There was a fair amount of generalised oedema which cleared up by the 2nd Nov. The urine contained abundant blood up until the 6th Nov. Eventually the patient made a good recovery.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Oct.29	3,810,000	10,500	392,430	2' RE	2'	* *
Nov. 2	4,690,000	14,700	635,495	-	-	-
" 5	4,700,000	17,600	512,300	1'40"RE	1'50"	-
" 8	4,610,000	12,550	650,010	-	-	-
" 12	4,970,000	10,750	1,043,700	1'20"RE	-	-
" 13	4,820,000	11,650	1,072,450	-	2'15"	***
" 15	4,940,000	11,000	837,330	1'30"RE	-	-
" 18	4,750,000	10,950	304,000	-	-	-
" 21	4,840,000	10,750	295,240	-	1'50"	***

Platelet Morphology.

Date.	Size.			Granulation.				Staining.	
	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Oct.29	-	100	-	-	6	94	-	94	6
Nov. 2	-	100	-	-	-	100	-	100	-
" 5	-	100	-	-	-	100	-	100	-
" 8	-	100	-	-	-	100	-	100	-
" 12	-	100	-	-	-	100	-	100	-
" 13	-	99	1	-	-	100	-	99	1
" 15	-	100	-	-	31	69	-	100	-
" 18	-	100	-	-	10	90	-	100	-
" 21	-	100	-	-	-	100	-	100	-

Summary. During the period of blood loss the platelet numbers were high but after the hæmorrhage ceased there was a marked rise in the thrombocyte values to even higher figures. By the 30th day of illness the platelets were below average normal numbers.

In this case the the bleeding time was shortened when the platelet numbers were increased and "vice versa".

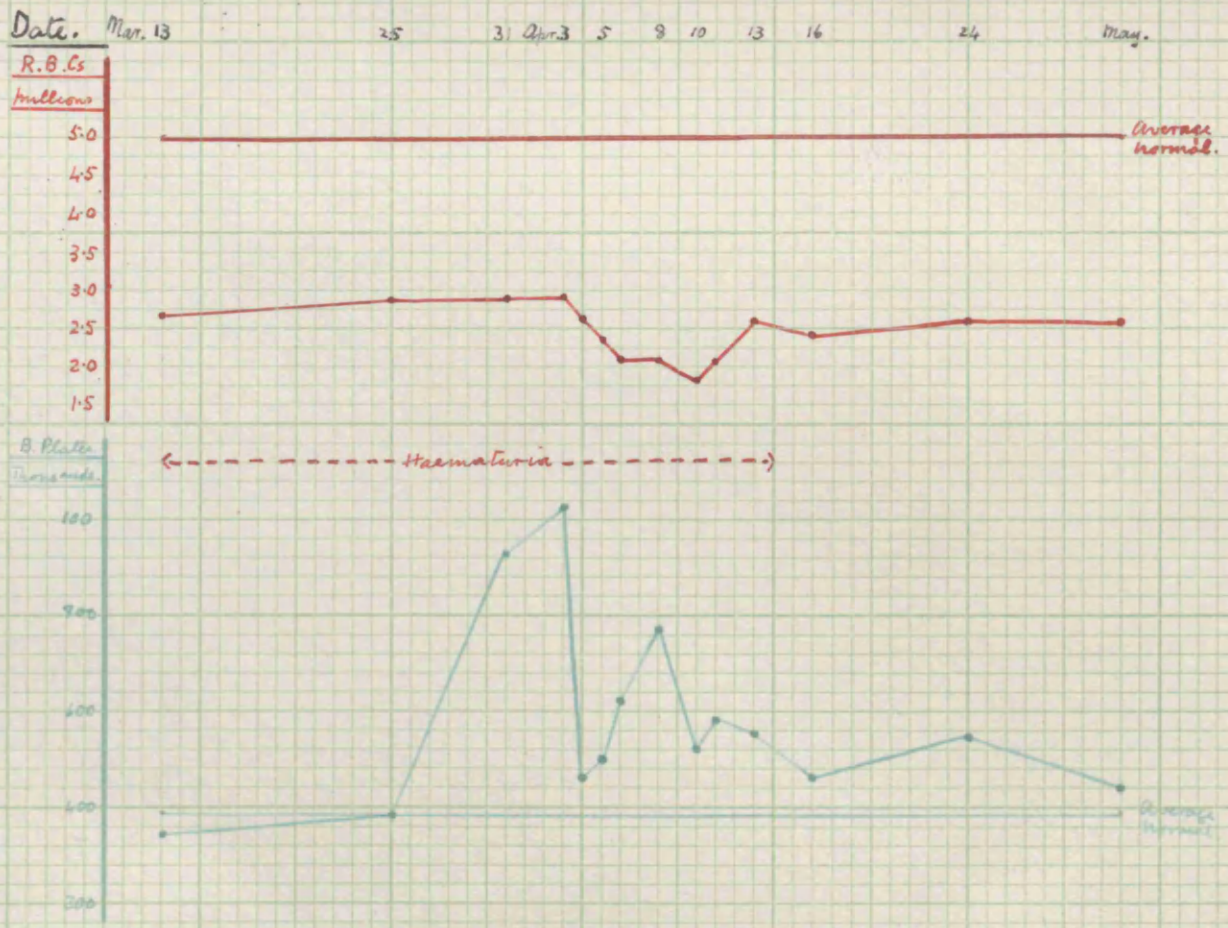
The duration of coagulation time bore no relationship to the number of thrombocytes in the blood.

Clot retraction was always present.

On the first day of observation 6% of the platelets showed basophilia and a similar percentage were deficient in granules. Diminution in the number of granules was noted also on the 15th and 18th Nov. i.e. during the period of fall in the platelet numbers. On the 13th Nov., when the thrombocyte numbers were high, one large basophil form was observed.

Case No. 54.

Patient. J. McK.



Ward No. 9. Journal No. 91, page 384. Case No. 54.

Patient. J. McK., Male.
Age. 67 years.
Occupation. Ironworker.

Diagnosis. Chronic nephritis.

Clinical notes. Patient was in hospital for about 3 weeks before the first platelet count was carried out. At that time there was marked generalised oedema and the urine contained abundant blood. On the 3rd, 4th and 5th April pus was present in the urine. Blood persisted in the urine until the 14th April but the oedema never cleared up all the time the patient was in hospital.

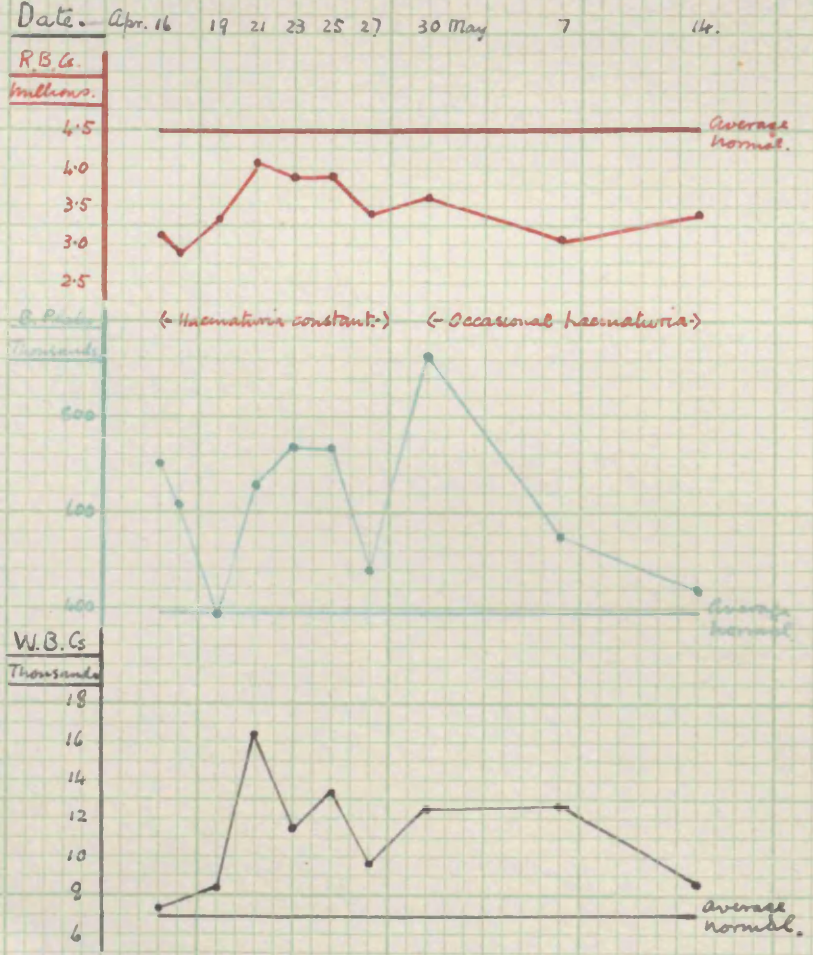
Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Mar. 13	2,670,000	-	355,110	-	-	-
" 25	2,800,000	-	392,000	-	-	-
" 31	2,850,000	-	931,950	-	-	-
Apr. 3	2,890,000	-	1,182,010	-	-	-
" 4	2,530,000	-	465,520	-	-	-
" 5	2,390,000	-	506,240	-	-	-
" 6	2,100,000	-	638,400	-	-	-
" 8	2,110,000	-	776,180	-	-	-
" 10	1,760,000	-	520,000	-	-	-
" 11	2,090,000	-	593,560	-	-	-
" 13	2,610,000	-	566,775	-	-	-
" 16	2,450,000	-	460,600	-	-	-
" 24	2,680,000	11,700	557,440	1'15"RE	2'	-
May 2	2,530,000	12,400	432,630	1'30"RE	1'30"	-

Summary. This case shows the great daily variation which may occur in the number of circulating thrombocytes and records a rise in the platelet values to over 1,000,000 with a sudden drop in the space of one day to average normal figures. This great diminution coincided with the appearance of pyuria which lasted for 3 days.

Case No. 55.

Patient. M. C.



Ward No. 8. Journal No. 92, page 142. Case No. 55.

Patient. M. C., Female.
Age. 26 years.
Occupation. At home.

Diagnosis. Chronic nephritis.

Clinical notes. On admission patient was oedematous and abundant blood was present in the urine. Except for 2 days - the 28th and 29th April - blood in varying amounts was present in the urine during the whole period of observation. While in hospital patient did not improve to any great extent.

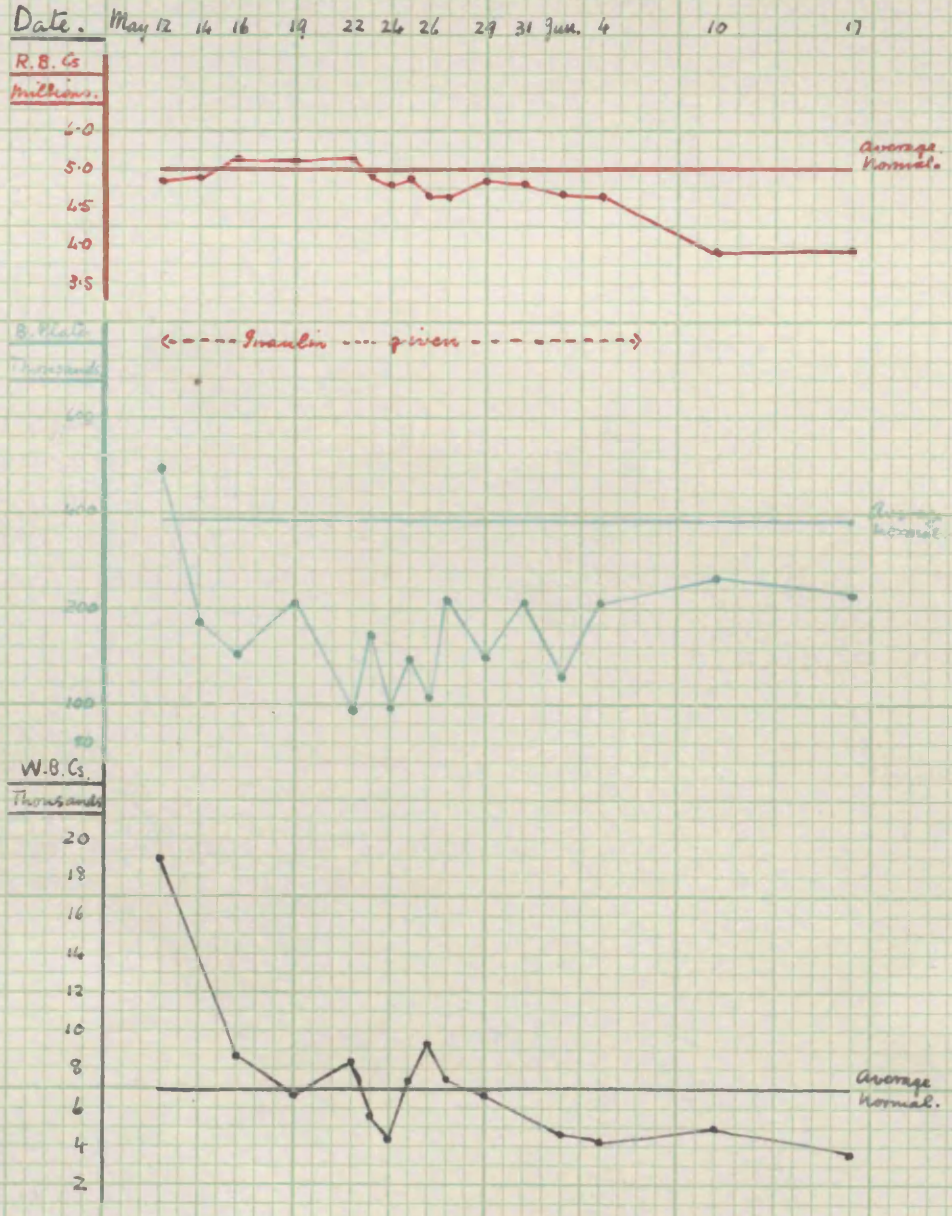
Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Apr.16	3,170,000	-	757,630	-	-	***
" 17	2,850,000	7,400	621,300	-	-	-
" 19	3,310,000	8,400	397,200	-	-	-
" 21	4,085,000	16,600	669,940	-	-	-
" 23	3,800,000	11,466	741,000	1' RE	1'30"	***
" 25	3,850,000	13,200	731,000	-	1'45"	-
" 27	3,400,000	9,600	482,800	1'15"RE	2'	-
" 30	3,620,000	12,400	933,960	-	2'30"	-
May 7	3,020,000	13,000	552,660	1' RE	2'15"	-
" 14	3,420,000	8,800	434,340	-	-	***

Summary. Although the platelet numbers varied greatly they tended to be high especially during the period of constant hæmaturia ending on 28th April. The highest platelet count was however recorded on 30th April.
Bleeding time and coagulation time did not depend on the number of platelets in the circulation.
Syneresis of the clot was always "good".

Case No. 56.

Patient. S. D.



Ward No. 9. Journal No. 93, page 64. Case No. 56.

Patient. S. D., Male.
Age. 13 years.
Occupation. At school.

Diagnosis. Diabetes mellitus.

Clinical notes. Patient received injections of insulin from 11th May until the 7th June.

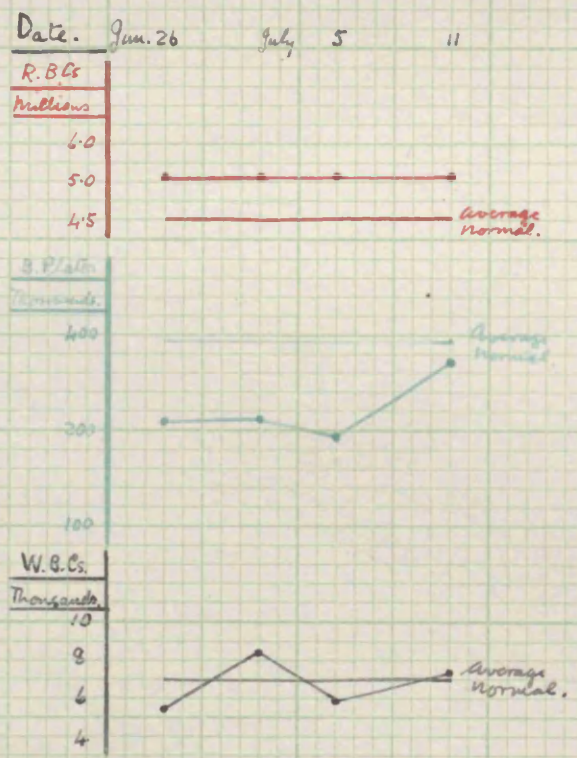
Results of investigation of the blood.

Date. 1929	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
May 12	4,760,000	19,000	495,040	1' RE	2'	-
" 14	4,880,000	-	185,440	-	-	-
" 16	5,150,000	8,800	149,350	-	-	-
" 19	5,180,000	6,800	212,380	-	-	-
" 22	5,330,000	8,450	95,840	1' RE	1'20"	* *
" 23	4,900,000	5,700	171,500	-	-	-
" 24	4,760,000	4,450	99,960	-	-	-
" 25	4,840,000	7,350	150,040	-	-	-
" 26	4,690,000	9,200	107,870	-	-	-
" 27	4,620,000	7,400	221,760	1'30"RE	2'30"	-
" 29	4,830,000	6,950	144,900	-	-	-
" 31	4,790,000	-	210,180	-	-	-
Jun. 2	4,700,000	4,900	131,600	1' RE	2'	-
" 4	4,670,000	4,150	219,690	45"RE	2'30"	-
" 10	3,890,000	5,000	270,355	-	-	-
" 17	3,980,000	3,400	232,730	-	-	-

Summary. Apart from the first observation the platelet numbers were always considerably below average normal values.
Bleeding time and coagulation time were not related to increase or decrease in the number of thrombocytes.
Retraction of the clot on one occasion was "fair".
The platelets were small and granular.

Case No. 57.

Patient. S. McK.



Ward No. 8. Journal No. 93, page 28. Case No.57.

Patient. S. McK., Female.
Age. 58 years.
Occupation. At home.

Diagnosis. Diabetes mellitus.

Clinical notes. Patient was treated by dieting alone. No insulin was given.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Jun.26	5,160,000	5,250	211,500	1' RE	1'45"	* *
Jul. 1	5,120,000	8,400	235,520	1' RE	1'15"	-
" 5	5,090,000	6,000	185,785	-	-	-
" 11	5,100,000	7,500	334,050	-	-	-

Platelet Morphology.

Date.	Size.			Granulation.				Staining.	
	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Jun.26	-	100	-	-	-	100	-	100	-
Jul. 1	-	100	-	-	2	98	-	100	-
" 5	-	97	3	-	1	99	-	99	1
" 11	-	99	1	-	-	96	4	100	-

Summary. With the exception of the last count, the platelets were rather lower than average normal values. On the 11th July the patient was on full diet and feeling very well.
Estimations of bleeding time and coagulation time showed nothing of note.
Retraction of the clot on one occasion was "fair".
A few large thrombocytes were observed. The distribution of the granules was somewhat irregular.

Ward No. 9. Journal No. 93, page 350. Case No. 58.

Patient. J. McK., Male.
Age. 47 years.
Occupation. Steelworker.

Diagnosis. Diabetes mellitus.

Clinical notes. During the period of observation no insulin was given.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Jul.10	4,350,000	4,950	267,525	1' RE	2'10"	-
" 17	4,440,000	5,720	162,060	-	-	-
" 24	4,520,000	4,400	262,160	-	-	***

Platelet Morphology.

Date.	Size.			Granulation.				Staining.	
	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Jul.10	-	100	-	-	2	88	10	98	2
" 24	-	93	7	-	12	82	6	95	5

Summary. The number of platelets was rather below average normal values.
Bleeding time and coagulation time were normal.
Retraction of the clot was "good".
Some of the platelets were large. There was an increase in the number of basophil forms. The distribution of granules was irregular.

Ward No. 8. Journal No. 93, page 422. Case No.59.

Patient. M. N., Female.
Age. 55 years.
Occupation. At home.

Diagnosis. Diabetes mellitus.

Clinical notes. During the period of observation no insulin was given to this patient.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Sept12	6,150,000	6,250	218,325	1' RE	2'	* *
" 19	5,480,000	5,000	356,200	-	-	-

Platelet Morphology.

	Size.			Granulation.				Staining.	
Date.	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Sep.12	-	100	-	-	2	96	2	100	-
" 19	-	100	-	-	-	100	-	100	-

Summary. There is nothing worthy of note in these observations except perhaps the slight degree of irregularity in the distribution of the granules on 12th Sept.

Ward No. 8. Journal No. 89, page 270. Case No. 60.

Patient. M. C., Female.
Age. 25 years.
Occupation. Saleswoman.

Diagnosis. Diabetes mellitus.

Clinical notes. On the dates of observation the patient was on diet and receiving injections of insulin.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Sep.20	4,260,000	6,200	264,120	2' RE	1'45"	* *
" 27	4,420,000	7,100	227,630	-	-	-

Platelet Morphology.

	Size.			Granulation.				Staining.	
Date.	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Sep.20	-	100	-	-	10	82	8	100	-
" 27	-	100	-	-	64	36	-	100	-

Summary. The platelet numbers tended to be somewhat low.
Nothing worthy of note was made out regarding bleeding time or coagulation time.
Retraction ofthe clot was "fair".
There was a marked increase in the number of less granular forms.

Ward No. 9. Journal No 82, page 190. Case No. 61.

Patient. D. F., Male.
Age. 54 years.
Occupation. Unemployed.

Diagnosis. Diabetes mellitus.

Clinical notes. Between the 3rd and 17th Oct. patient was receiving injections of insulin.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Sep.26	5,370,000	7,300	158,410	-	-	* *
Oct. 3	4,050,000	3,950	326,025	1'30"RE	2'	-
" 10	3,720,000	5,450	236,220	-	-	-
" 17	4,190,000	4,550	429,475	-	-	***

Note. From 26th Sept. to 3rd Oct. patient was very constipated and enemata were necessary. With each stool he lost a fair amount of blood.

Platelet morphology.

	Size.			Granulation.				Staining.	
Date.	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Sep.26	-	100	-	-	-	100	-	95	5
Oct. 3	-	98	2	-	2	94	4	100	-
" 10	-	100	-	-	-	100	-	100	-
" 17	-	100	-	-	-	100	-	100	-

Summary. Before insulin was given the count was very low. Afterwards the platelet numbers were much increased.
There was nothing of note regarding bleeding time and coagulation time.
Retraction of the clot was "fair" when the count was low and "good" when the thrombocytes were almost trebled in number.
Basophilia was noted when the platelets were diminished. On another occasion increase in size and irregularity in the distribution of the granules were observed.

Ward No. 8. Journal No. 93, page 402. Case No. 62.

Patient. J. P., Female.
Age. 68 years.
Occupation. At home.

Diagnosis. Carcinoma of Ampulla of Vater.

Clinical notes. On admission the patient was jaundiced, the stools were abilious and the urine contained bile and blood. Bruising and scattered petechial spots were noted over the body. Just previous to death on the 17th Sept. a good deal of fresh blood was passed per rectum and per urethram.

Post-mortem examination disclosed the presence of bleeding into the pelves of the kidneys, rectum, vagina and bladder.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Sep.13	3,550,000	10,600	800,525	1'30"RE 2+ hrs LE	9'	***
" 15	3,270,000	15,850	703,050	-	-	-
" 17	2,350,000	33,700	794,300	-	-	* *

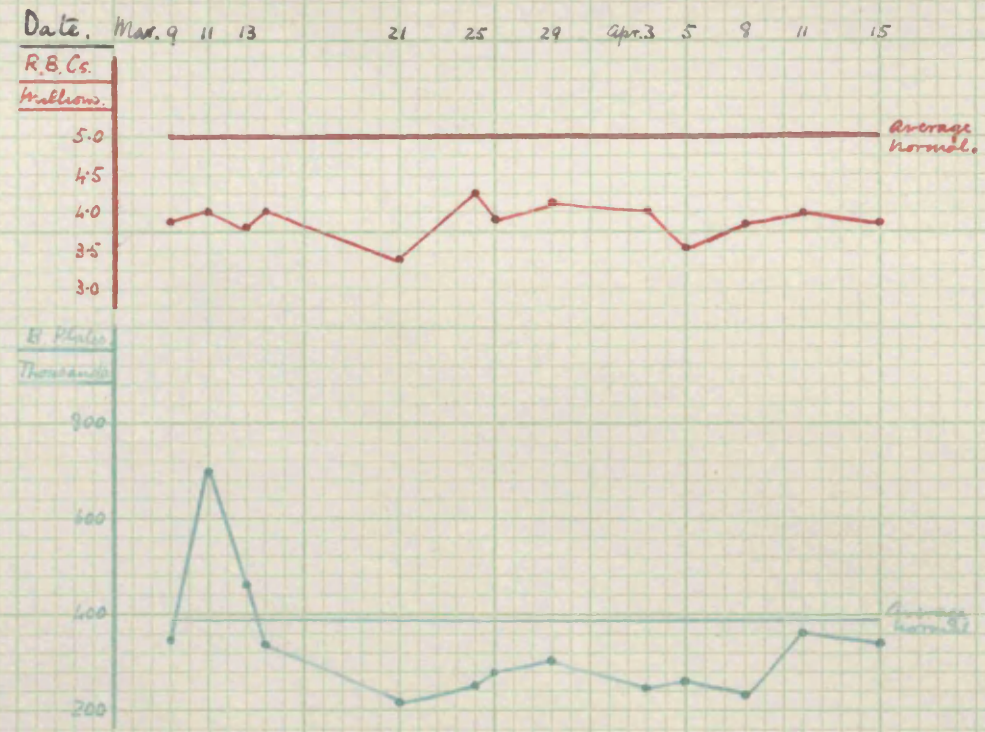
Platelet Morphology.

Date.	Size.			Granulation.				Staining.	
	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Sep.13	-	99	1	-	-	100	-	100	-
" 15	-	99	1	-	1	99	-	100	-
" 17	-	100	-	-	-	100	-	100	-

Summary. The platelet count was always high.
The bleeding time was greatly increased, the bleeding from the puncture wound of the left ear continuing for approximately 36 hours. It was only stopped with difficulty and it was thought inadvisable to repeat the estimation of the bleeding time on subsequent dates. Bleeding time varied with the site of puncture.
The coagulation time was also increased.
Retraction of the clot was present.
Apart from the tendency for the platelets to be rather larger than normal the platelet morphology was otherwise without note.

Case No. 63.

Patient. T. F.



Ward No. 9. Journal No. 92, page 26. Case No. 63.

Patient. T. F., Male.
Age. 59 years.
Occupation. Porter.

Diagnosis. Carcinoma, ? of pancreas.

Clinical notes. Patient complained of abdominal pain, loss of weight, asthenia, anorexia and nausea. He was juandiced, the stools were abilious and the urine contained bile. While in hospital the pain become increasingly severe and he became very emaciated. He was sent home at his own request.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Mar. 9	3,920,000	-	352,800	1' BE	3'15"	-
" 11	4,090,000	-	709,840	-	-	-
" 13	3,760,000	-	458,720	1' RE	-	-
" 14	4,030,000	-	338,520	-	-	-
" 21	3,360,000	-	211,680	-	-	-
" 25	4,270,000	-	262,950	1'25"RE	-	-
" 26	3,910,000	-	281,520	-	2'45"	-
" 29	4,180,000	-	309,330	-	-	-
Apr. 3	4,040,000	-	246,440	1'15"RE	2'30"	-
" 5	3,570,000	-	264,180	-	-	-
" 8	3,840,000	-	284,160	-	-	-
" 11	4,030,000	-	382,850	1'30"RE	2'45"	-
" 15	3,860,000	-	347,400	-	-	-

Summary. On 11th Sept, a rather high platelet count was recorded but thereafter the thrombocyte numbers fell to between 200,000 and 300,000
Bleeding time was never prolonged.
Coagulation time was slightly increased on 9th March.

Ward No. 9. Journal No 94, page 388. Case No. 64.

Patient. J. F., Male.
Age. 51 years.
Occupation. Unemployed.

Diagnosis. Jaundice, ? cholecystitis.

Clinical notes. Patient complained of pain in the region of the gall bladder. He was jaundiced, the stools were abilious and bile was present in the urine. On the 26th Oct. the jaundice had disappeared and the urine was bile-free.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Oct.18	5,510,000	7,300	365,650	1'30"	3'	* *
" 21	4,970,000	8,650	362,810	1'30"	2'	* *
" 26	5,150,000	10,450	206,000	-	-	-

Platelet Morphology.

	Size.			Granulation.				Staining.	
Date.	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Oct.18	-	100	-	-	5	95	-	100	-
" 21	-	100	-	-	10	90	-	100	-
" 26	-	100	-	-	34	66	-	100	-

Summary. Apart from the observation that the platelets were deficient in granules investigation of this case did not disclose anything worthy of note.

Ward No. 8. Journal No. 94, page 222. Case No. 65.

Patient. M. S., Female.
Age. 45 years.
Occupation. At home.

Diagnosis. Jaundice.

Clinical notes. On admission patient was jaundiced. Bile was present in the stools and in the urine. A petechial rash was noted on the flexor aspects of both arms. The Wassermann reaction was positive. Patient improved under anti-specific treatment.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Oct.19	4,180,000	3,900	234,080	3' LE 2' RE	1'30"	***
" 22	3,950,000	5,700	240,950	2'30" BE	4'45"	***

Platelet morphology.

	Size.			Granulation.				Staining.	
Date.	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Oct.19	-	95	5	-	-	99	1	96	4
" 22	-	93	7	-	-	100	-	95	5

Summary. Both observations were made when the jaundice was intense.
The number of platelets was only very slightly diminished.
The duration of bleeding time reached to the higher limits of normal.
Coagulation time was slightly prolonged on the 22nd Oct.
Retraction of the clot was always "good".
Capillary resistance test was negative.
A fair percentage of large basophilic forms was noted.
The platelets were always granular.

Ward No. 8. Journal No. 92, page 424. Case No. 66.

Patient. M. G., Female.
Age. 35 years.
Occupation. At home.

Diagnosis. Cirrhosis of the liver.

Clinical notes. On admission jaundice and ascites were present. Post-mortem examination showed the patient to have suffered from irregular cirrhosis of the liver.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot. retraction.
1929						
Jun. 5	4,140,000	8,000	260,820	2'30"RE	2'30"	***
" 8	4,670,000	13,050	403,955	-	-	***
" 10	4,540,000	13,800	283,750	2'15"RE	2'	-

Summary. Nothing worthy of note was observed.

Ward No. 9. Journal No. 94, page 244. Case No. 67.

Patient. J. H., Male.
Age. 25 years.
Occupation. Linotype operator.

Diagnosis. Lymphosarcoma.

Clinical notes. Patient died on 9th Oct. A post-mortem examination confirmed the diagnosis.

Results of examination of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Oct. 1	4,890,000	7,250	391,200	2' RE	2'30"	* *
" 8	5,380,000	13,950	476,130	2' RE	-	-

Note. On 8th Oct. there was evidence of stasis of the venous circulation.

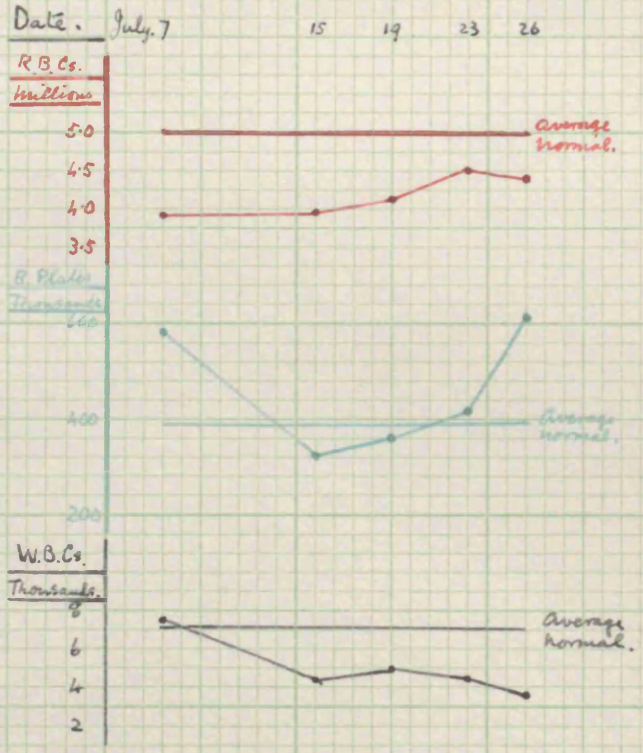
Platelet morphology.

Date.	Size.			Granulation.				Staining.	
	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Oct. 1	-	99	1	-	31	68	1	100	-
" 8	9	91	-	-	29	71	-	100	-

Summary. There was no diminution in the number of platelets.
Bleeding time and coagulation time were normal.
Retraction of the clot was "fair".
On the day before death occurred the platelets tended to be smaller in size. Deficiency of granulation was however noted on both occasions.

Case No. 68.

Patient. A. F.



Ward No. 9. Journal No. 93, page 412. Case No. 68.

Patient. A. F., Male.
Age. 45 years.
Occupation. Surface worker.

Diagnosis. Retroperitoneal endothelioma.

Clinical notes. Patient died and the diagnosis was made at post-mortem examination.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Jul. 7	3,870,000	7,400	590,240	1' RE	2'	***
" 15	3,950,000	4,550	323,900	-	-	-
" 19	4,170,000	5,000	366,960	1'15"RE	-	-
" 23	4,550,000	4,500	418,600	-	-	-
" 26	4,430,000	3,800	606,910	1'30"RE	-	-

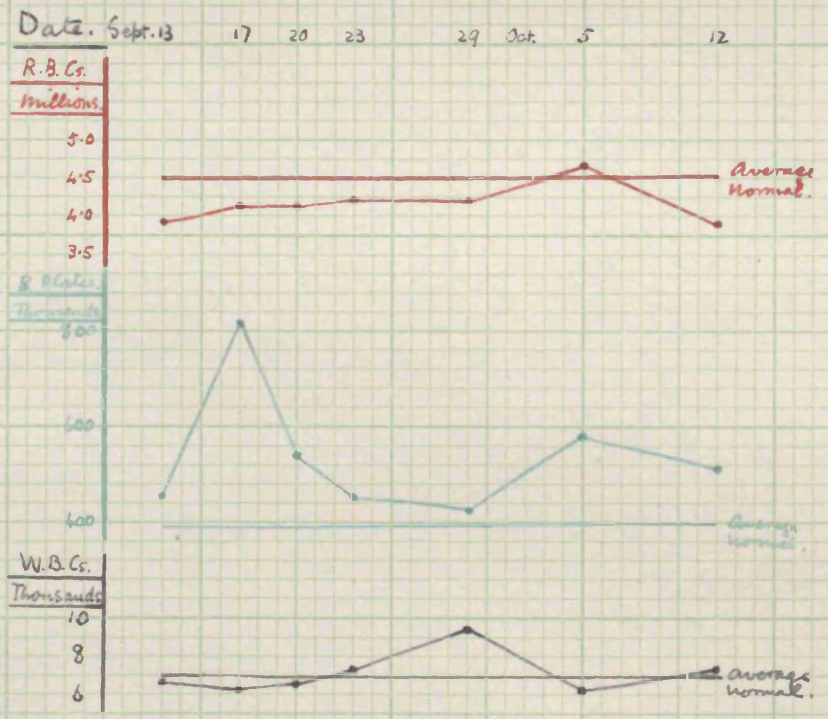
Platelet morphology.

	Size.			Granulation.				Staining.	
Date.	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Jul.15	-	99	1	-	1	59	40	100	-
" 19	-	100	-	-	-	100	-	100	-
" 23	-	100	-	-	7	84	9	97	3
" 26	-	99	1	-	2	97	1	99	1

Summary. The platelet numbers were never low and they varied within wide limits. On the occasion of the first platelet count the patient came up as an out-patient.
Bleeding time did not vary in any characteristic way with alteration in the number of platelets.
Coagulation time was normal.
Syneresis of the clot was "good".
Large platelets were occasionally seen. Distribution of the granules was markedly irregular. Some basophilia was also noted.

Case No. 69.

Patient. M. McL.



Ward No. 8. Journal No. 94, page 52. Case No. 69.

Patient. M. McL., Female.
Age. 54 years.
Occupation. At home.

Diagnosis. Carcinomatosis of bone marrow.

Clinical notes. X-ray examination showed mottling of the lumbar vertebræ and the posterior part of the pelvis and sacrum. Normoblasts and myeloblasts were present in the blood.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Sep.13	3,940,000	6,950	480,680	1' RE	2'	* *
" 17	4,170,000	6,650	825,660	-	-	-
" 20	4,200,000	6,850	537,600	1'15"RE	2'10"	-
" 23	4,250,000	7,350	452,625	-	-	-
" 29	4,240,000	9,400	428,240	1' RE	1'50"	* *
Oct. 5	4,710,000	6,150	586,395	-	-	-
" 12	3,870,000	7,350	514,710	1'20"RE	1'50"	-

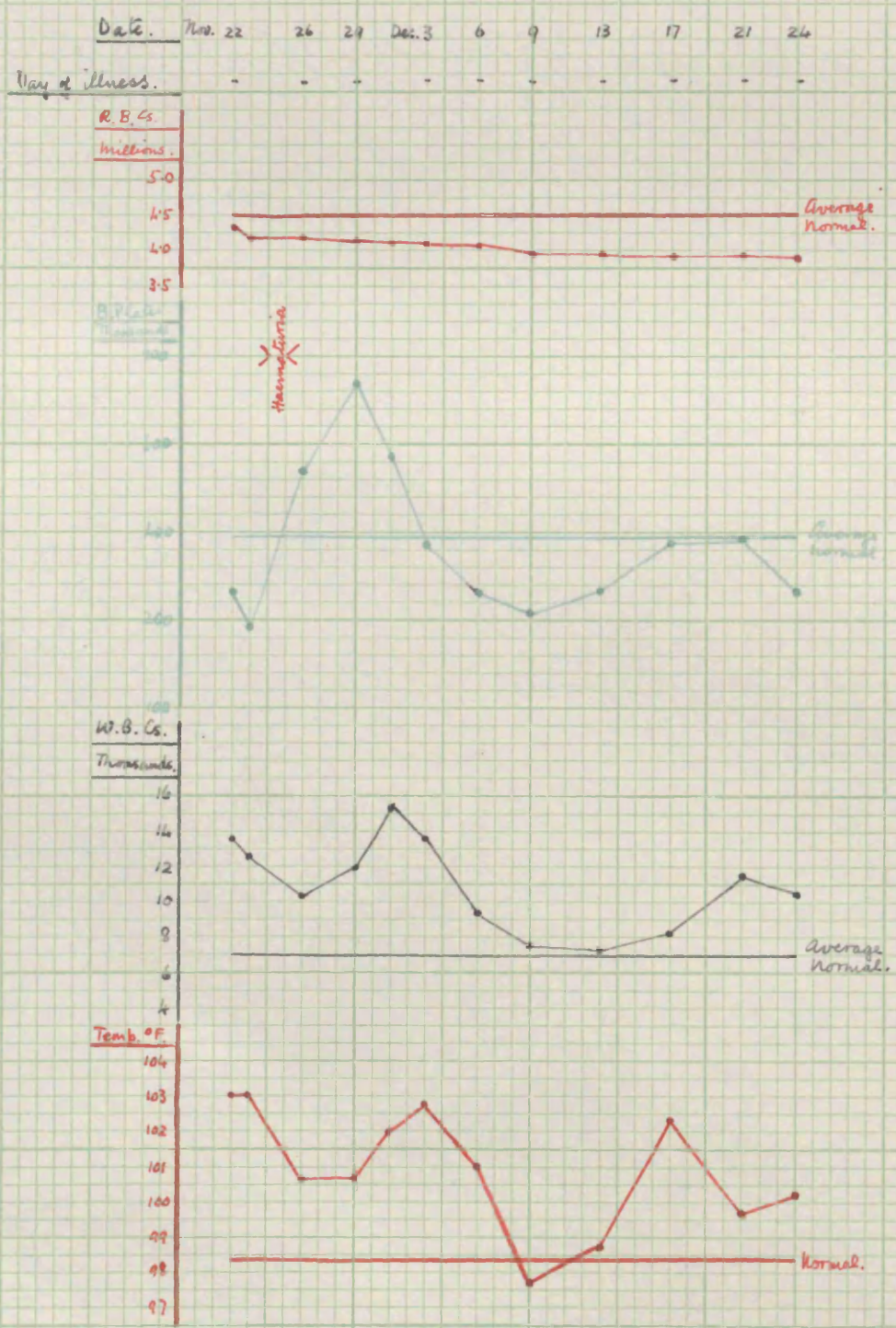
Platelet morphology.

	Size.			Granulation.				Staining.	
Date.	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Sep.13	-	100	-	-	-	97	3	100	-
" 17	-	100	-	-	-	100	-	100	-
" 20	-	100	-	-	-	100	-	100	-
" 23	-	99	1	-	-	98	2	100	-
" 29	-	99	1	-	-	100	-	100	-
Oct. 5	-	100	-	-	5	95	-	100	-
" 12	-	100	-	-	-	100	-	100	-

Summary. With the exception of one occasion when the thrombocytes numbered over 800,000 they varied between 420,000 and 580,000. The numbers were always high.
The platelets varied independently of the red and white cells.
Bleeding time and coagulation time did not depend on the number of platelets in the circulation.
Retraction of the clot was "fair".
Platelet morphology did not show any distinctive change. There was slight irregularity in the distribution of granules.

Case No. 70.

Patient. A. M.



Ward No. 8. Journal No. 94, page 362. Case No. 70.

Patient. A. M., Female.
Age. 46 years.
Occupation. At home.

Diagnosis. Pelvic sepsis.

Clinical notes. While in the ward the patient had a high degree of fever and she was always toxic looking. A large quantity of pus was present in the urine, and on 24th and 25th Nov. a fair quantity of blood was also found in the urine. She had a lacerated cervix and was transferred to the surgical wards for further treatment.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Nov. 22	4,290,000	13,600	270,070	2' RE	-	* *
" 23	4,210,000	12,900	191,555	2' RE	-	-
" 26	4,240,000	11,100	532,120	2' RE	-	-
" 29	4,140,000	12,050	743,130	1'50" RE	1'15"	-
Dec. 1	4,110,000	15,500	566,180	-	-	-
" 3	4,070,000	13,700	372,405	-	-	-
" 6	4,070,000	9,350	262,515	1'45" RE	-	* *
" 9	3,930,000	7,600	212,220	-	1'30"	-
" 13	3,930,000	7,150	269,205	-	-	-
" 17	3,870,000	8,250	379,260	-	-	-
" 21	3,970,000	11,500	393,030	2' RE	2'	* *
" 24	3,910,000	10,400	265,880	-	-	-

Platelet morphology.

	Size.			Granulation.				Staining.	
Date.	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Nov. 22	-	100	-	-	8	92	-	97	3
" 23	-	100	-	-	-	100	-	100	-
" 26	-	100	-	-	-	100	-	100	-
" 29	-	100	-	-	-	100	-	100	-
Dec. 1	-	100	-	-	-	100	-	100	-
" 3	-	100	-	-	-	100	-	100	-
" 6	-	100	-	-	-	100	-	100	-
" 9	-	99	1	-	1	99	-	99	1
" 13	-	100	-	-	-	100	-	100	-
" 17	-	100	-	-	-	100	-	100	-
" 21	-	100	-	-	-	100	-	100	-
" 24	-	100	-	-	-	100	-	100	-

Summary. An increase in the platelet count followed the appearance of blood in the urine. There was a degree of similarity between the white cell and platelet curves.
The duration of the bleeding time and coagulation time was not dependent on the number of platelets in the circulation.
Retraction of the clot was "fair".
Nothing characteristic was noted regarding the morphology of the thrombocytes.

Ward No. 9. Journal No. 95, page 214. Case No. 71.

Patient. A. P., Male.
Age. 14 years.
Occupation. At school.

Diagnosis. Pyæmia.

Clinical notes. On admission patient was very ill and toxic looking. On his right internal malleolus was an ulcerated wound which he had received about two weeks previously. Staphylococcus aureus was grown on blood culture. The patient died on the fourth day after admission and a post-mortem examination was held.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Dec. 7	4,600,000	14,150	204,700	-	-	-
" 8	4,710,000	-	120,055	2' RE	1'30"	* *
" 10	4,760,000	7,625	111,860	-	-	* *

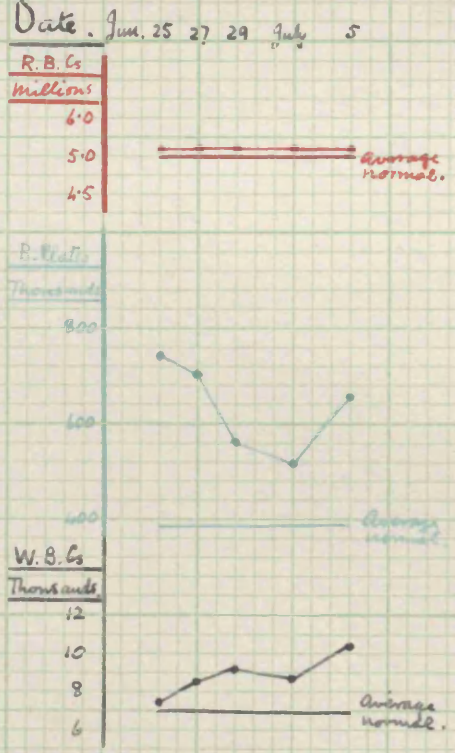
Platelet morphology.

	Size.			Granulation.				Staining.	
Date.	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Dec. 7	-	100	-	-	7	93	-	100	-
" 8	-	98	2	-	9	91	-	100	-
" 10	-	100	-	-	-	100	-	100	-

Summary. The platelet numbers were low and they diminished progressively until death.
Bleeding time and coagulation time were both within normal healthy limits.
Syneresis of the clot was "fair".
Apart from the presence of some poorly granular platelets nothing of note was observed regarding the morphology of the platelets.

Case No. 72.

Patient. W. A.



Ward No. 9. Journal No. 93, page 282. Case No. 72.

Patient. W. A., Male.
Age. 10 years.
Occupation. At school.

Diagnosis. Tabes mesenterica.

Clinical notes. Patient complained of swelling of the abdomen, abdominal pain and alternating attacks of constipation and diarrhoea.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929.						
Jun.25	5,030,000	7,400	751,985	1'30"RE	2'	***
" 27	5,040,000	8,900	705,600	-	-	-
" 29	5,080,000	9,200	561,340	1'30"RE	2'15"	-
Jul. 2	5,040,000	8,700	529,200	-	-	-
" 5	5,110,000	10,250	666,855	-	-	-

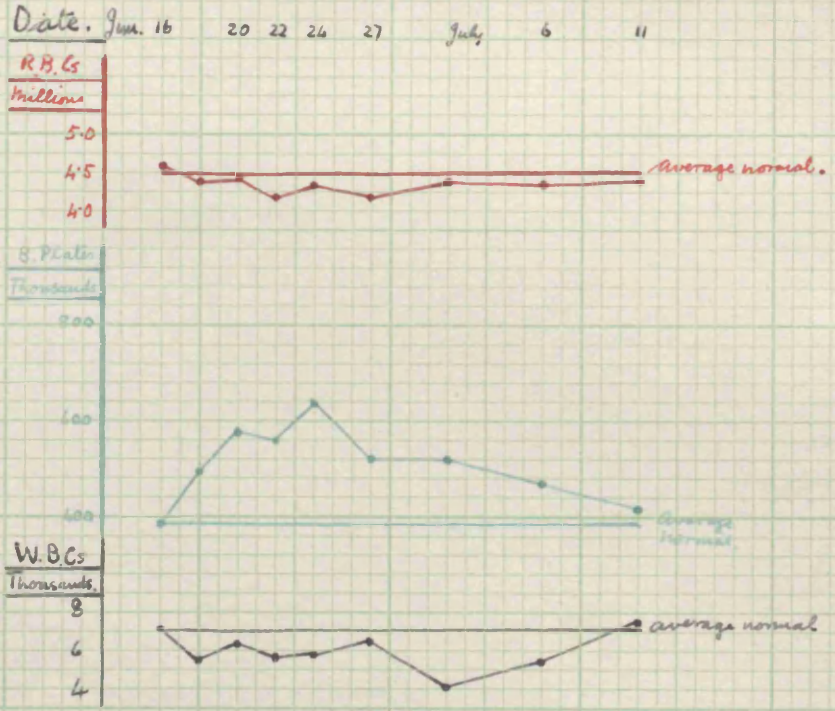
Platelet morphology.

Date.	Size.			Granulation.				Staining.	
	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Jun.25	-	100	-	-	-	100	-	100	-
" 27	-	100	-	-	-	100	-	96	4
" 29	-	100	-	-	-	100	-	87	13
Jul. 2	-	99	1	-	-	99	1	99	1
" 5	-	100	-	-	-	100	-	100	-

Summary. The platelet count was always high.
Bleeding time and coagulation time did not show any alteration worthy of note.
Retraction of the clot was "good".
The platelet picture showed a fair number of basophil forms on various occasions.

Case No. 73.

Patient. S. S.



Ward No. 8. Journal No. 92, page 470. Case No. 73.

Patient. S. S., Female.
Age. 36 years.
Occupation. At home.

Diagnosis. Tuberculous peritonitis.

Clinical notes. On admission patient had some ascites. Although the ascites did not clear up completely it diminished in amount and the patient was ultimately dismissed from hospital feeling much improved in general health.

Results of investigation of the blood.

Date.	Red cells.	White cell.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Jun. 16	4,510,000	7,000	396,880	1'30"RE	2'	***
" 18	4,360,000	5,350	492,680	-	-	-
" 20	4,420,000	6,300	585,650	-	-	-
" 22	4,230,000	5,700	554,130	-	-	-
" 24	4,300,000	5,900	647,800	1'30"RE	2'	-
" 27	4,210,000	6,350	522,040	-	-	-
Jul. 1	4,350,000	4,000	524,175	1'30"RE	1'30"	-
" 6	4,310,000	5,500	474,410	-	-	-
" 11	4,370,000	7,700	406,410	-	-	-

Platelet morphology.

	Size.			Granulation.				Staining.	
Date.	Small.	Normal.	Large.	0	+	+ +	+++	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Jun. 22	-	100	-	-	-	100	-	100	-
" 24	-	100	-	-	4	96	-	99	1
" 27	-	100	-	-	-	100	-	100	-
Jul. 1	-	100	-	-	20	80	-	96	4
" 6	-	99	1	-	-	93	7	100	-
" 11	-	100	-	-	-	100	-	100	-

Summary. With improvement in the general condition of the patient there was an increase in the number of thrombocytes. Thereafter there was a gradual diminution in the numbers until the original level was reached.

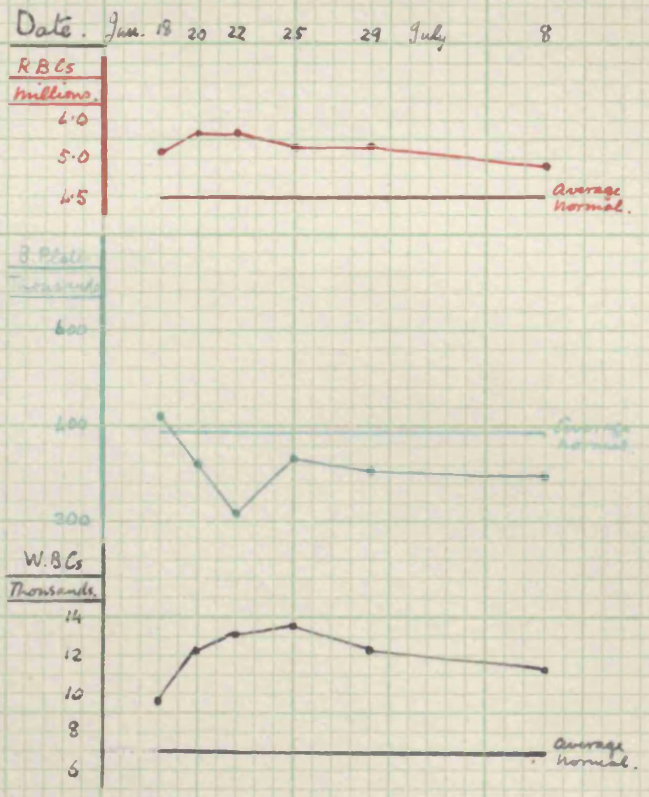
Bleeding time and coag ulation time did not vary with changes in the platelet count.

Syneresis of the clot was "good".

During the period of observation a number of poorly granular forms and a few basophil platelets were noted.

Case No. 74.

Patient. A. W.



Ward No. 8. Journal No. 92, page 436. Case No. 74.

Patient. A. W., Female.
Age. 17½ years.
Occupation. Domestic servant.

Diagnosis. Hyperthyroidism.

Clinical notes. Nil.

Results of investigation of the blood.

Date.	Red cells.	White cells.	Platelets.	Bleeding time.	Coagulation time.	Clot retraction.
1929						
Jun.18	5,280,000	9,900	427,680	-	-	***
" 20	5,510,000	12,250	314,070	1'20"RE	1'30"	-
" 22	5,630,000	13,050	204,495	-	-	-
" 25	5,320,000	13,800	327,180	1' RE	1'40"	-
" 29	5,435,000	12,400	309,795	1' RE	1'30"	-
Jul. 8	4,920,000	11,100	295,200	-	-	-

Platelet morphology.

	Size.			Granulation.				Staining.	
Date.	Small.	Normal.	Large.	0	-	- -	---	Hyaline.	Basophil.
1929	%	%	%	%	%	%	%	%	%
Jun.22	-	96	4	-	3	97	-	95	5
" 25	-	100	-	-	-	100	-	97	3
" 29	-	99	1	-	-	100	-	100	-
Jul. 8	-	100	-	-	-	100	-	100	-

Summary. There was nothing characteristic in the platelet count.
Bleeding time and coagulation time did not vary with variation in the number of platelets.
Retraction of the clot was "good".
On the whole the platelets tended to be rather large.
On two occasions a fair amount of basophil forms was noted.