STUDY OF TRANSFUSED BLOOD.

I. The Periodicity in Eliminative Activity Shown by the Organism.

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It was hoped that some light might be thrown on the length of life of normal blood corpuscles and the mechanism of their removal from the circulation by the study of the elimination of transfused blood, which it is possible to make when the transfused blood is of a group unlike that of the recipient. This study has brought to light two facts, first, that the length of time that transfused blood remains in the circulation varies greatly; and second, that the elimination is not a continuous process but takes place in more or less cyclic crises, so that the responsibility for the disappearance of transfused blood from the circulation seems to rest more heavily on this cyclic activity of the body than upon the condition of the corpuscle.

The probable life of the blood corpuscle was reduced to 10 days or less by calculation based upon bile pigment output, made by Zoja and others, after the time of Ward-Muller, Quinck, von Ott, and Hunter, who from transfusion experiments in dogs concluded that the life of the normal corpuscle was from 14 to 26 days. The experimental results of Todd and White (1909–10) upon cattle, obtained by using an isohemolytic serum to separate out transfused blood, are in agreement with the shorter period. The work of Whipple and Hooper, however, who show that bile pigment is only in part derived from blood pigment, has made the shorter calculations based on bile pigment excretion untenable. The observations of Rous and Turner, who kept rabbit corpuscles *in vitro* for 14 days and then substituted them for a rabbit's own blood without any abnormal results, would also indicate a longer life of the corpuscles, as do my own results (1919, *a*) of the study of transfused blood in man.

As for the mechanism of blood elimination, we must undoubtedly give credit to some extent to phagocytosis, which plays a more or less important part in all

animals and appears, moreover, to be capable of extension under stimulation. Keyes finds in a wide range of animals that the physiologic destruction of the animals' own red blood corpuscles is accomplished by specialized fixed tissue phagocytes, which are confined largely to the liver or to the spleen. In birds, amphibia, and the lower mammals the phagocytic activity is most marked in the liver; in the higher animals it is most marked in the spleen. Rous and Robertson (1917) made quantitative estimates of the presence of phagocytes in the spleen of guinea pigs, cats, dogs, rabbits, *rhesus* monkeys, and man, and found that although in some of these animals phagocytic cells were present in numbers that might account for physiologic blood destruction, in the monkey and man these were few. Muir, in the study of phagocytosis in a rather large series of cases of empyema, smallpox, and pneumonia, found that phagocytosis was negligible in the bone marrow, but that in the spleen phagocytic activity was displayed against the native red blood corpuscles by cells of the splenic pulp and by certain hyaline leucocytes within the pulp. Carey, using intravenous injections of foreign red cells, and Downey, using intravenous injections of dye granules, found that under increased stimulation there is an increase in the number of cells which act as phagocytes. Downey believes that many "connective tissue" cells, may, under stimulation, become phagocytic. Carey finds under repeated stimulation an extension of phagocytic activity from cells of the spleen to those of the liver.

Rous and Robertson (1917) have recently given us knowledge of a second method of blood destruction, that of fragmentation in the blood stream with, it would seem, a filtering out of these fragments by the spleen. This they consider in man to have a greater importance than phagocytosis.

There are certain anomalous findings that suggest the possibility that a specific antibody mechanism is responsible for physiologic blood destruction. Todd and White's (1909–10) isohemolytic serum would not hemolyze ox corpuscles *in vitro* in the presence of ox serum unless guinea pig complement was added, but when injected intravenously into oxen produced massive hemolysis. Todd and White considered that this indicated the presence of some organ in the body which was able to produce the activating effect of guinea pig complement. Rous and Robertson (1918) found in some of their rabbits that had been receiving massive doses of rabbit blood that an isoagglutinin developed which caused agglutination of the corpuscles of the animals at room temperature. This agglutinin tended to appear in those rabbits which in the face of heavy blood injections developed an anemia. Davis and Macgregor both report evidence of erythrophagocytic bodies in meningitic patients, and in paroxysmal hemoglobinuria we have the isohemolysin which only unites with complement at low temperatures. Although one is tempted to speculate upon the possibility that physiologic blood corpuscle destruction is produced by some organ or organs of the body that form an antibody having lytic and opsonic qualities and so promoting fragmentation and phagocytosis, we have no evidence that any such antibody exists.

If we can draw a parallel between the elimination of transfused blood and normal blood destruction, the following study of transfused blood makes, I feel, a contribution to our understanding of blood destruction in that it would seem to connect the process with the activity of the endocrine gland system.

Method.

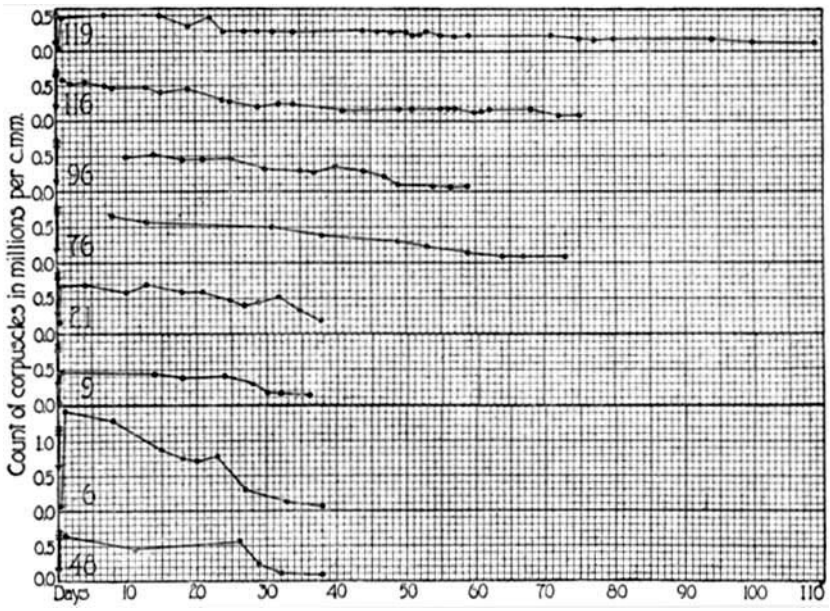
In the following work the elimination of transfused blood has been studied in individuals in Groups I, II, and III receiving Group IV transfusions. The method used was that published by me originally in *The Journal of Experimental Medicine* (1919, *a*), with certain modifications described in the *Medical Clinics of North America* (1919, *b*). It consists, in brief, of diluting the recipient's blood after transfusion with Group IV serum. This agglutinates the native corpuscles, leaving the transfused corpuscles free and capable of being counted in a hemocytometer. The dilution is made in a white blood-counting pipette, Group IV citrated serum being used as the diluent, and the mixture is expelled into Wassermann tubes. The tubes are incubated for 40 minutes with shaking, and allowed to stand at room temperature for from 15 to 30 minutes. A count is made by daylight, or, if it is necessary to use artificial light, care is taken to protect the corpuscles from its effect. All counts are made in duplicate.

Since by the use of this technique it is necessary that the transfused blood be of a different group from the recipient's blood it seemed more desirable, if it were feasible, to use the method of Todd and White (1909–10), which in cattle gives a differentiation between the blood of individuals. Patients who had received a series of from four to five 500 cc. transfusions were tested for hemolysin. Blood plasma from these patients was used both fresh without guinea pig complement and with guinea pig complement against corpuscles of the group to which the plasma belonged. Neither agglutinins nor hemolysins could be detected. This method is not applicable.

In harmony with the current conception of the behavior of native corpuscles, I assumed that transfused blood corpuscles would slowly deteriorate in the circulation and upon reaching a certain degree of degeneration either fragment or be phagocytosed, while their place was taken by new corpuscles. If this should be the case, on the injection of a normal blood into individuals not having blood disease one would expect a certain approximate equality in the length of time that expires before the transfused blood leaves the circulation, and by studying several curves of elimination to the end it seemed probable that a figure could be obtained that would roughly represent the length of life of the newest corpuscles injected.

RESULTS.

In Text-fig. 1 are given the curves of elimination of transfused blood in the eight cases of individuals without blood disease which have been studied to complete elimination or to nearly complete elimination. The time taken for elimination was approximately 100, 72, 49, 63, 38, 30, 34, and 33 days.



TEXT-FIG. 1. Curves showing the variability of the time taken by individuals without blood disease to eliminate Group IV transfused blood. ↧ indicates a Group IV transfusion.

In these data the variation in the time taken to eliminate Group IV transfused blood is so great that no time can be given as the average length of life of the transfused corpuscles. Although slight individual differences in bloods can be noted with respect to resistance to hypertonic salt solution and other hemolysins, it would hardly seem probable that so great a difference in the time of elimination as that between 100 days and 30 days could be attributed to differences in resistance of the transfused bloods, to which dif-

ferences in resistance to hypertonic salt solution might be an index. It will be noted that the longest curve, 100 days (Case 119), was obtained in the case of a man in health, while the elimination time was only 28 to 30 days in the case of a very cachectic cancer patient (Case 48). No generalization, however, can be made from this, as a patient (Case 9) whose blood had returned to normal after hysterectomy eliminated the transfused blood in 28 to 30 days, and a patient who died with long standing infection (Case 95) had shown no definite sign of elimination of the transfused blood after 46 days. The protocols of these individuals are given below.

Case 6.—A woman, aged 35 years; weight 138 pounds. An operation for fibroid of the uterus was performed, followed by two transfusions because of severe hemorrhage.

Case 9.—A woman, aged 33 years, whose normal weight was 100 pounds, was transfused previous to subtotal hysterectomy. The convalescence was satisfactory.

Case 21.—A woman, aged 45 years, weighing 87 pounds, had common duct obstruction, and tertiary syphilis of the liver.

Case 48.—A woman, aged 48 years, weighing 127 pounds, had cancer of the breast with extensive glandular involvement. The menstrual periods had been regular up to February 7, 1919. There was no further menstruation until March 28, when the menstrual flow began and continued until April 23. If the menstrual periods had continued to be regular after February, they should have occurred March 7, April 4, and May 2. On April 5 a radical operation was performed, followed by a transfusion.

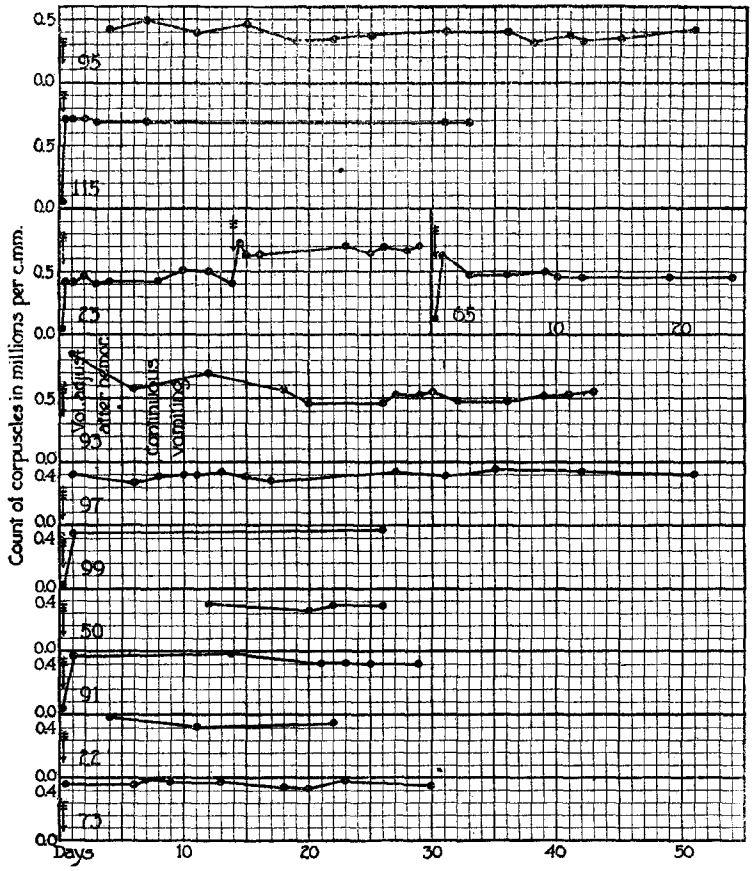
Case 76.—A woman, aged 24 years, had chondrosarcoma of the right ribs. A two-stage operation was performed for removal of the tumor. Each operation was followed by a Group IV transfusion of blood.

Case 96.—A woman, aged 40 years, had a malignant pelvic tumor. A total hysterectomy was performed, followed by a blood transfusion.

Cases 116 and 119 are given below.

With reference to the cyclic elimination of the transfused blood, my material brings out five points. (1) The curves of elimination of Group IV transfused blood do not show a gradual downward curve day by day, which would be expected if it is assumed that blood corpuscles gradually wear out and are replaced. When due allowance has been made for blood volume changes, it will be seen that the count stays on a level for a long time. (2) When the counts have been taken sufficiently close together the curve of elimination

makes a sudden drop to a lower level, at which it again remains for many days. There are longer periods of no elimination and shorter periods of elimination. (3) The nature of these drops is such that they are more likely to be due to an active destruction on the part of the body than to, what would be the other possibility, a coinci-



TEXT-FIG. 2. Curves showing that over a long period of time there is no elimination of transfused blood. ⇓ indicates a Group IV transfusion.

dent spontaneous disintegration of the corpuscles. (4) Accompanying these drops in the count of the transfused blood, there is usually an activity of the bone marrow as indicated by a rise in the total blood count. (5) In women these drops are related to the menstrual cycle.

Text-fig. 2 illustrates the fact that over a long period of time there is no elimination of transfused blood. The protocols of these cases follow.

Case 22.—A man, aged 32 years, weighing 103 pounds, had duodenal ulcer and chronic appendicitis. A posterior gastroenterostomy and appendectomy were performed, followed by a transfusion.

Case 23.—A man, aged 57 years, weighing 139½ pounds, had pernicious anemia and was given a series of transfusions.

Case 50.—A man, aged 50 years, a farm laborer of powerful build, received a transfusion after appendectomy and gall bladder operation.

Case 65.—A boy, aged 11 years, weighed 63 pounds. A diagnosis of lymphatic leucemia was made. He was transfused.

Case 73.—A woman, aged 47 years, weighing 120 pounds, had pernicious anemia. She received a series of transfusions.

Case 91.—A woman, aged 53 years, weighing 137 pounds, with pernicious anemia, received a series of transfusions.

Case 93.—A woman, aged 43 years, was given a transfusion because of post-operative hemorrhage after gall bladder operation. On the 8th and 9th days after transfusion subcutaneous injections of saline solution were given because of continuous vomiting.

Case 95.—A man, aged 31 years, had an arteriovenous aneurysm between the popliteal artery and vein, resulting from injury by a bullet. After operation secondary hemorrhage developed, necessitating a transfusion 6 days later. On the 19th day after transfusion the leg was amputated for dry gangrene. On the 55th day following hemorrhage, a pelvic exploration was done. The patient died on the 57th day after transfusion.

Case 97.—A man, aged 42 years, weighing 155 pounds, had pernicious anemia and was given a series of transfusions.

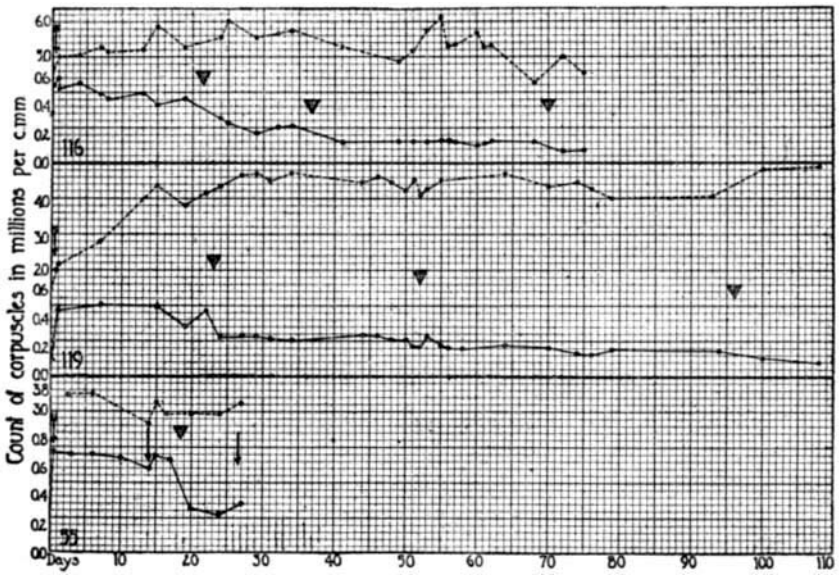
Case 99.—A girl, aged 17 years, weighing 100 pounds, was given a blood transfusion for secondary anemia due to malaria. Following medication there were no more chills.

Case 115.—A woman, aged 33 years, weighing 141 pounds, was given a blood transfusion January 26, 1920, because of secondary anemia. Normal menstruation occurred while the patient was under observation, January 26, February 27, and March 24.

The protocols of cases included in Text-fig. 3 are given below. In Cases 116 and 119 the tabulation of the blood counts, which are omitted in other instances to save the cost of reproduction, are partially given, as the length of time over which the study was made necessitated a reduction in the charts, which leaves them inade-

quate as evidence of the small changes which constitute the later drops in the count.

Case 55.—A woman, aged 51 years, whose menopause had occurred 2 years before, was completely jaundiced from common duct obstruction. There was bile in the urine.



TEXT-FIG. 3. Curves of elimination of Group IV transfused blood in two men, and a woman passed the menopause, showing that there are comparatively short periods of elimination and that these periods are irregularly cyclic. ——— Count of unagglutinated corpuscles. – – – Total red blood count. ↧ indicates a Group IV transfusion; ↓ a like group transfusion. The cross-hatched triangle calls attention to periods of elimination.

Case 116.—A man, aged 20 years, weighing 125 pounds, had been troubled with bleeding of the nose for the past 9 years. He had a bleeding time of 40 minutes and a coagulation time of 5½ minutes; platelets were 88,000, and hemoglobin 43 per cent. The diagnosis was hemorrhagic purpura. One transfusion was given January 29, 1920. On March 20 the hemoglobin was 80 per cent.

Length of time after transfusion.	No. of unagglutinated corpuscles per c.mm.
days	
0 (Transfusion with 500 cc. of Group IV citrated blood.)	
0	556,000
0	566,000
1	522,000
4	555,000
7	495,000
8	466,000
13	487,000
15	416,000
19	466,000
24	313,000
25	295,000
29	221,000
32	250,000
34	255,000
41	162,000
49	168,000
51	163,000
53	166,000
55	170,000
56	159,000
57	162,000
60	128,000
61	145,000
62	154,000
68	163,000
72	81,000
75	93,000

Case 119.—A man, aged 33 years, with a cystic tumor at the base of the tongue, came for examination because of sudden hemorrhage. The patient's blood condition rapidly returned to normal after transfusion and he was able to go to work.

Length of time after transfusion.	No. of unagglutinated corpuscles per c.mm.
days	
0	33,000
0 (Transfusion with 500 cc. of Group IV citrated blood.)	
0	441,000
1	459,000
7	500,000
15	490,000
19	350,000
22	475,000
24	270,000
27	281,000
29	282,000
31	271,000
34	260,000
44	288,000
46	281,000
48	268,000
50	272,000
51	220,000
52	223,000
53	289,000
55	224,000
56	202,000
58	211,000
60	224,000
70	222,000
74	173,000
76	157,000
79	190,000
93	184,000
100	118,000
109	118,000

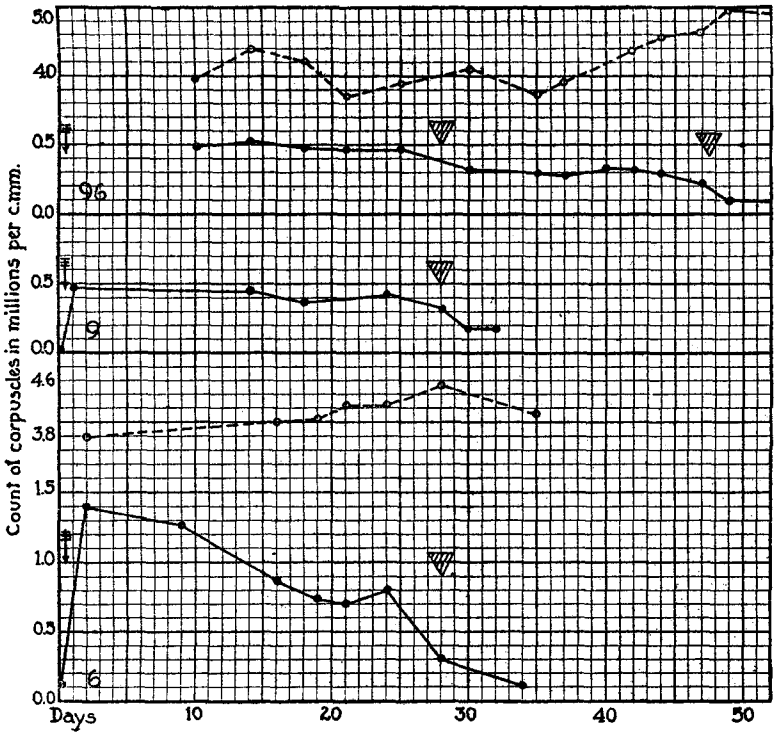
Text-fig. 4 presents the curves of Cases 6, 9, and 96, the protocols of which are given above.

Protocols of cases included in Text-fig. 5 are given below with the exception of Cases 48 and 115 which are presented above.

Case 38.—A woman, aged 32 years, weighing 133 pounds, in good general health had multiple lipomata, which were removed. The following day a transfusion of blood was given because of postoperative hemorrhage. Convalescence was excellent. Menstruation began on the 35th day after transfusion and ended on the 38th day.

Case 47.—A woman, aged 40 years, weighed 105 pounds. A partial thyroidectomy was performed, which was followed by a transfusion. The patient made an uneventful recovery. Menstruation began the 37th day after transfusion.

Case 68.—A woman, aged 36 years, weighing 82 pounds, had pernicious anemia. The patient claimed that her menstrual period was usually 24 days.

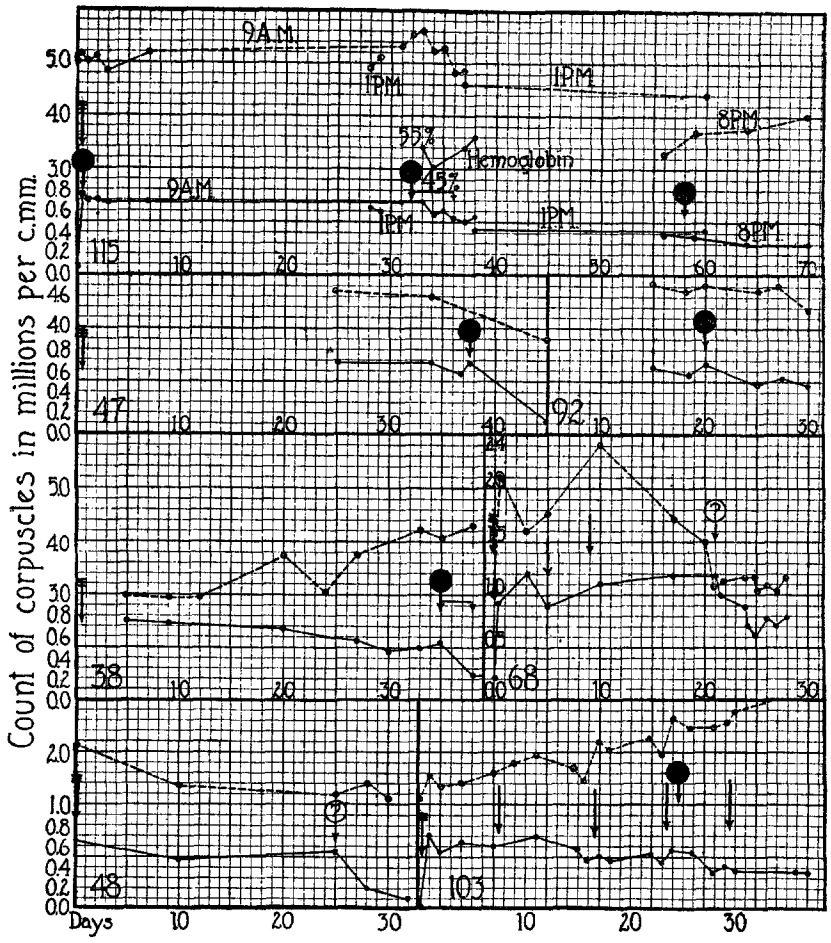


TEXT-FIG. 4. The drops in the curves of elimination of transfused blood of three women who received a transfusion with hysterectomy. The drops took place at approximately the same time after operation. ——— Unagglutinated corpuscles. – – – Total red blood count. ⇓ indicates a Group IV transfusion. The cross-hatched triangle calls attention to periods of elimination.

While she was under observation menstruation occurred, beginning 3 days before transfusion, June 24, 1919. Menstruation did not occur July 18, when the patient expected it. The patient died August 24.

Case 92.—A woman, aged 49 years, weighing 215 pounds, had bleeding uterine fibroids, marked secondary anemia, and a degenerating colloid goiter. She was

given three transfusions, two of which were of Group IV blood, after which a partial thyroidectomy was done. Menstruation began 11 days after the last Group IV transfusion, but stopped immediately, although previously bleeding had been profuse.



TEXT-FIG. 5. Curves illustrating the drop in transfused blood that takes place at the menstrual period. ↧ indicates the beginning of a menstrual period; ↧ indicates the time at which menstruation should have occurred. ——— Unagglutinated corpuscles. – – – Total red blood count. ↧ indicates a Group IV transfusion; ↓ a like group transfusion.

Case 103.—A woman, aged 32 years, had pernicious anemia and received a series of transfusions. While under observation profuse menstruation took place, beginning the 24th day after the Group IV transfusion.

In examining these curves it must be borne in mind that several factors other than blood elimination will bring about changes in the corpuscle count. Of these the most important is due to dilution from increase in blood volume. Robertson and Bock have shown, and my experience corroborates theirs, that after hemorrhage there is often only a slow return to normal blood volume. It is probable, too, that changes in the capillary circulation cause changes in the blood count taken from the ear which do not represent changes in the average corpuscle content. Robertson and Bock have shown that in cases in which the blood volume was low the difference between the capillary and vein hemoglobin might be as much as 12 per cent of the vein hemoglobin. There seem also to be daily changes in the blood volume in certain patients. Curves are very much smoother in which the counts have all been made at the same time of day.

It will be seen in Text-fig. 2 that no definite elimination is shown in the curves there represented. In Case 95 there was no change that could be interpreted as an elimination of transfused blood in 51 days. In Case 115 after a slight initial drop, presumably from blood volume adjustment, the count was constant within errors of technique for 33 days. In this instance the counts were taken at the same time of day. In Case 93 the patient was under observation for 43 days, with no definite change other than the initial blood volume adjustment and adjustment after severe vomiting. In Case 97 there was no elimination in 51 days. As these curves maintain a level for a long time, indicating that during that time there was no elimination, it is obvious that, as the blood is eventually eliminated, it is not eliminated by a continuous process but by an intermittent process.

Text-fig. 3 shows two curves of elimination of transfused blood of men, one normal and the other with purpura of several years standing, but in fairly good health, and the third, of a woman beyond the menopause, who was jaundiced. It will be seen that in these curves there are periods of elimination which are short and probably would have proved to be shorter if the counts had been taken closer

together. The first drop in Case 119 took place between two counts spaced 2 days apart. The drop in Case 55 took place between counts that were taken 3 days apart. The first drop in Case 116 took place between two counts that were 5 days apart; the apparent further drop on the following day is due to a change in technicians. It would seem, then, that these drops take place rapidly.

It will be seen that there is a periodicity, although a somewhat irregular one, in the period of elimination of the two men, ranging in the normal man from 18 to 28 or 30 days. Accompanying these drops there tends to be an increase in the total blood count.

On examining the nature of the falls in the curves it will be seen that they are such as to suggest a blood-destroying activity on the part of the body rather than a spontaneous disintegration of simultaneously formed corpuscles. For if we postulate a blood destruction which is dependent solely on the condition of degeneracy of the corpuscle, we shall have to assume not only that blood formation takes place in short periods, which may be the case, although the continued presence of reticulated corpuscles would seem to indicate that there is at least some continuous formation, but also that the individual corpuscles are so uniform that the wear and tear which they experience after 3 months (Case 119) in the circulation bring them to a simultaneous disintegration point. But even if we are willing to make this assumption, further examination of the figures does not bear out this hypothesis. For if the condition of wear and tear were wholly responsible for initiating the destruction of the corpuscles, we should expect a regularity in the rate of their disappearance. If, for instance, the corpuscles which were transfused had been formed in sharp crises every 3 weeks and their life were 12 weeks, then one-fourth of the corpuscles was due to live 12 weeks, one-fourth 9 weeks, one-fourth 6 weeks, and so on. Equal amounts should have disappeared at each period of elimination. But this was not the case; by far the largest fall came in the first periods of elimination. In Case 119 the first drop was 200,000, or nearly one-half of the blood transfused, while subsequent drops were each approximately 80,000, or one-fifth of the original blood injected. In Case 116 the first drop was 150,000, or three-eighths of the blood injected, while subsequent drops were 90,000 and 80,000, about two-tenths

of the injected blood. These figures seem to place the elimination with reference to some active process on the part of the body, probably modified by the condition of the corpuscles and the number present in the circulation.

In Text-fig. 4 are included the curves of the three women studied who received Group IV transfusions immediately before or subsequent to hysterectomy. In each case a period of elimination came between the 25th and 30th days after hysterectomy. The elimination would probably have proved to be sharper if the counts had been taken closer together. In one of these women a second period of elimination occurred about 20 days after the first. This suggests, although the series is too short to have a conclusion drawn from it, that in some way the hysterectomy initiated a cycle equivalent to the menstrual cycle, and when complete elimination did not take place the subsequent periodicity of elimination was irregular as in the case of the two men.

Text-fig. 5 summarizes all the data that I have been able to obtain on the relationship between the elimination of transfused blood and the menstrual period. Six menstruations, and two periods when menstruation should have occurred but did not, were observed. There has been no exception to the fact that elimination of transfused blood that could not be accounted for by simple blood loss from the menstrual flow occurred during the menstrual period. It has not always happened that when menstruation should have occurred but did not that there was an elimination of transfused blood. In the two cases in which the elimination did occur without the appearance of the menstrual flow, the women were in a condition of extreme anemia, and it is probable that the suppression of the flow was due to the anemia rather than to the suspension of the menstrual process.

In Case 115, which was the most intensive study made, the patient's blood volume was low and her count showed a great variation during the day, being much higher in the morning than in the evening, so that only counts taken at the same time of day were comparable. Those taken through the menstrual period that came 32 days after transfusion were made in the morning by one observer; those during the menstrual period that came 58 days after transfusion were made

by a second observer, and in the evening. The count which determines the further end of the line connecting the two menstrual periods was made by the first observer at 1 p.m. The nearer end of the line is determined from a calculated figure. It will be noted that during the earlier menstrual period, although there was a decrease in the total red blood cell count, there was some increase in the hemoglobin. At this time the transfused blood had a higher index than the patient's blood, being 0.7 per cent, while the patient's blood was 0.5. During the later menstrual period there was a rise in the total blood count. In Case 38, with a very slight menstruation, there was an elimination of more than half the transfused blood; the preliminary fall in this curve is due to blood volume adjustment. There had been massive hemorrhage, and the patient's blood volume was low. In Case 103, that of a pernicious anemia patient, although the menstrual flow was profuse, there was a moderate fall in the transfused blood and a slight increase in the total count. In Case 48, in which menstruation did not occur when it was due, there was a complete elimination of the transfused blood with a slight temporary rise in the total blood count. In Case 68, one of pernicious anemia, a big fall in the Group IV transfused blood occurred beginning the 21st day, which may have been in part due to a blood volume improvement, since the patient's blood volume had been exceedingly low, and her general condition in the face of what seemed to be a period of blood loss became no worse. There was, however, at this time a marked elimination of the native corpuscles and of like group corpuscles, since the difference between the patient's whole blood count and the count of the transfused blood became so slight that it was within the limit of experimental error. From the 21st to the 25th days the difference between the two counts increased again, which in view of the practically complete elimination of the patient's own blood must indicate a coincident blood production.

DISCUSSION.

There seems to be little doubt that the elimination of Group IV transfused blood is brought about by an active destroying process of the body which is some part of a metabolic cycle, evidenced in

women by menstruation. Whether the Group IV transfused blood is eliminated as part of a general blood-eliminating effort of the body or whether it is eliminated as a foreign body is a matter of interest. The fact that the Group IV transfused blood stays in the circulation for considerable lengths of time would be an argument against its foreign relationship to the body, but, on the other hand, in my studies of Group IV transfusions in patients with pernicious anemia, the Group IV transfused blood has remained in the circulation in the presence of destruction of the patient's own blood, and in one instance, Case 68, in the presence of destruction of transfused blood of the same group as the patient's. It would seem that if the elimination of the Group IV blood takes place because of a normal blood-eliminating process, either there must be two processes, one of which can handle the blood of the unlike group, while the other cannot, or else that a certain pressure of elimination must be attained before the threshold is reached for the elimination of Group IV which is apparently more difficult to destroy. Unless it is assumed that some Group IV transfusions are, relative to the patient's own blood, less enduring than others, the latter would not seem to be the case because in some instances we have seen complete elimination of the transfused blood in one elimination period, which would, on the assumption of a higher threshold mechanism, necessitate tremendous coincident elimination of the recipient's blood. If we assume two processes at work in the physiologic elimination of blood, one of which is more able to handle the apparently slightly foreign Group IV blood, we might conceive of it as part of a more general lytic or phagocytic function which has as one of its expressions of activity the sloughing of the endometrium and which is able to overstep the group differences. On the other hand, this periodic elimination of transfused blood may not be due to any specific blood-eliminative activity, but to a non-specific eliminative activity.

It would be a matter of great interest to know whether or not normal physiologic blood elimination also takes place in sharp cyclic crises. Satisfactory evidence on this point is difficult to obtain because if there is such blood elimination it may be masked by production, or if there is any apparent drop in the total blood count we do not at present know that it is not due to changes in blood volume or to an uneven distribution of corpuscles.

Carnot and Deflandre, Pölzl, and Sfameni, who studied the changes in the red corpuscle count over the menstrual cycle, report an increase in the count before the menstrual period, with a fall upon the onset of menstruation, which fall has no relationship to the amount of blood lost in the menstrual flow. In anemic women an improvement in the blood was noted after menstruation. Carnot and Deflandre point out that the fall may be only apparent, due to the accumulation of corpuscles in the congested pelvic organs, but call attention to the various toxic phenomena which accompany menstruation and the vitality which follows the period. It is generally conceded that menstruation is not a local but a generalized process. The numerous instances of vicarious menstruation seem to place this point beyond discussion, and there is in addition supporting evidence derived from metabolic studies, such as creatine excretion, nitrogen retention, reported by Schrader, blood calcium reported by Bell, changes in blood cholesterol reported by Gonalons, and increase in basal metabolic rate reported by Ford. The fact that some generalized change takes place at this time and with it a destruction of transfused blood is strongly suggestive that the drop in the red count reported is also due to a corpuscle destruction process rather than to a change in blood volume or an uneven distribution of corpuscles. The fact, too, that the blood picture of anemic women has been observed definitely to improve after a menstruation, in addition to being evidence in favor of the crisis in corpuscle production, supports the idea of a coincident crisis of destruction.

SUMMARY AND CONCLUSIONS.

Group IV transfused blood in a recipient of unlike group is eliminated by a blood-destroying activity of the body.

This blood-destroying activity is periodic both in men and women, and in women coincident with menstruation.

The elimination of the transfused blood probably takes place as part of a period of blood-destroying and blood-producing activity of the body, although direct evidence to this effect is so far lacking.

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