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Research Article

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Leukokinetic Studies. XI. Blood Granulocyte Kinetics in Polycythemia Vera, Infection, and Myelofibrosis *

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Although it seems evident that the neutrophilic leukocytosis commonly encountered in patients with purulent infections, polycythemia rubra vera, and a variety of other clinical disorders probably indicates an increased mass of neutrophils in the blood and increased neutrophil production, turnover, and utilization, it has not been possible to quantify these processes directly until recently. In normal subjects it was demonstrated that approximately one-half of the neutrophilic granulocytes in the blood are circulating freely [circulating granulocyte pool (CGP)], whereas the remainder adhere to the walls of small venules [marginal granulocyte pool (MGP)] (1). Since these two pools were shown to be in rapid equilibrium with each other they may be considered to form a single total blood granulocyte pool (TBGP) for kinetic purposes. These facts together with the finding that neutrophilic granulocytes disappear from the blood in a random manner (2) have made it possible to approximate the rate of production and destruction of neutrophils in normal man.

In the present study the size of the TBGP, the distribution of cells in the two subcompartments, the CGP and the MGP, the blood granulocyte half disappearance time ($t_{\frac{1}{2}}$), and the granulocyte turnover rate (GTR) were measured in patients with polycythemia vera, myelofibrosis, chronic infections, and diseases of other kinds. Studies in patients with chronic myelocytic leukemia are the subject of a separate report (3). We sought to determine whether there is a characteristic granulocyte kinetic pattern in any of these diseases and whether the observed granulocytosis reflects an absolute increase in TBGP size, an intravascular redistribution of cells, or some combination thereof. In addition an elevated GTR was encountered in many of these studies, and the mechanism by which this is sustained was evaluated. Several preliminary reports of these studies have been published (4, 5).

Methods

Sixty studies were carried out in patients with the disorders mentioned. All patients were studied by means of the *in vitro* diisopropyl fluorophosphate (DFP^{32}) granulocyte labeling technic (2). TBGP size was measured by the isotope dilution principle and calculated in two ways. The "determined" TBGP was calculated from the mean of triplicate blood granulocyte radioactivity values obtained 5 minutes after completion of the infusion (t_0). The "extrapolated" TBGP was calculated from the blood granulocyte radioactivity at t_0 obtained by extrapolating the blood granulocyte disappearance curve back to the ordinate. Since the determined TBGP appears to be the more accurate value (3), only these values are given in the tables. The sizes of the CGP and the MGP were determined as previously described (1). The $t_{\frac{1}{2}}$ was obtained from a semilogarithmic graph of the blood granulocyte specific activity (BGSA)[1] curve. The GTR was calculated from the TBGP and $t_{\frac{1}{2}}$ measurements as described previously (6).

Since it is extremely difficult to evaluate kinetic parameters measured in a nonsteady state, only studies on subjects with stable absolute granulocyte counts (less than 20% variation in most studies and less than 53% in all studies) and a stable clinical course are included in the evaluations presented here (Tables II, III, IV, and V).

Repeated leukocyte and 200 cell differential counts were done on each patient while under study. The differential counts in these subjects were characterized by relatively little shift to the left with the exception of

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[1] Expressed as counts per minute per milligram granulocyte nitrogen.

four studies in patients with myelofibrosis (Table V). In 18 of the 56 studies 0.5 to 2.5% myelocytes were found. Metamyelocytes were present in the blood of most of the patients, but in only six were as many as 5 to 9.5% of these forms present. The remainder of the neutrophils were segmented or juvenile forms. A patient was considered to have granulocytosis if his absolute granulocyte count exceeded 7,500 per mm^3 (7).

Results

Types of blood granulocyte radioactivity curve encountered. As in studies on patients with chronic myelocytic leukemia (3), the DFP^{32}-labeled, granulocyte disappearance curves in these 60 studies were of three types (Figure 1). In 41 studies a single exponential blood granulocyte disappearance (type "A") curve was observed. In 12 studies a rapid fall in blood granulocyte specific activity (BGSA) occurred during the first several hours after infusion of the labeled blood. Thereafter the BGSA decline could be described by a single exponential curve, type "B" curve. In seven studies a changing granulocyte disappearance rate was observed and a single $t_{\frac{1}{2}}$ could not be obtained, type "C" curve. The number of times the several curve types were encountered in the several diseases studied is shown in Table I. In type A curves the two TBGP values were the same. In type B curves the extrapolated TBGP values were larger than the determined values. In type C curves no extrapolated TBGP was calculated.

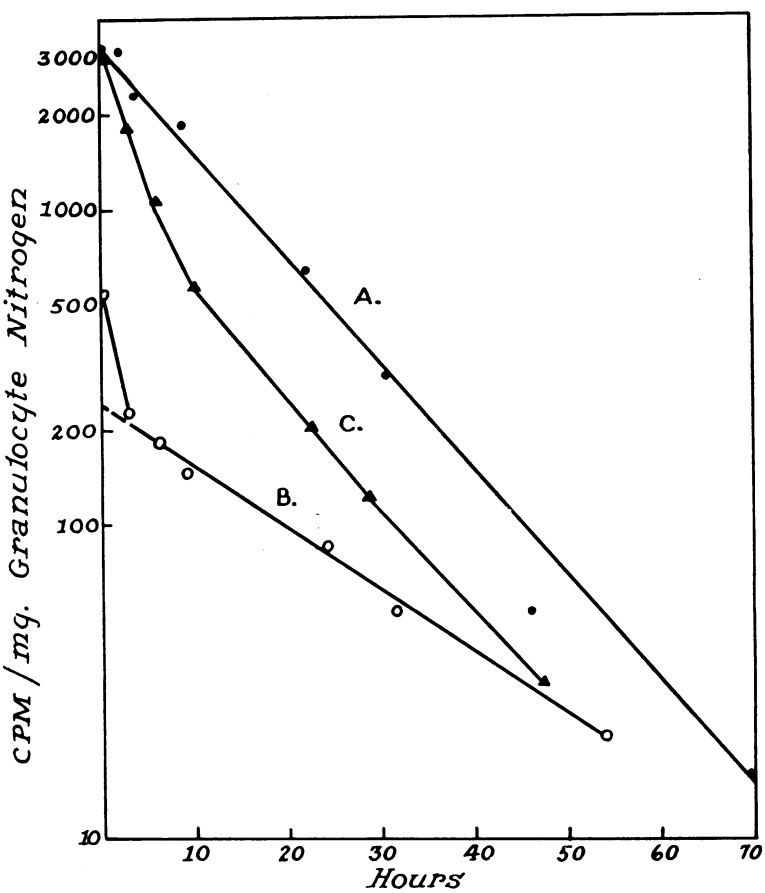

FIG. 1. REPRESENTATIVE EXAMPLES OF THE THREE TYPES OF BLOOD GRANULOCYTE DISAPPEARANCE CURVES OBSERVED IN PATIENTS WITH NEUTROPHILIC GRANULOCYTOSIS. Curve A is the single exponential disappearance curve usually obtained; note that the "determined" and "extrapolated" t_0 values are the same. Curves B and C were encountered less frequently. In the B curves the extrapolated t_0 value is considerably lower than the determined t_0 value.

TABLE I

Incidence of the several types of curves in normal and diseased subjects

Normal	Total studies 59	Curve A 56	Curve B	Curve C 3
Polycythemia vera	16	11	3	2
Infection	17	11	2	4
Miscellaneous conditions	20	14	5	1
Myelofibrosis	7	5	2	0
Total	60	41	12	7

Only the determined TBGP values are given in the tables since they are the more accurate, as will be discussed.

Normal subjects. The mean granulocyte kinetic values obtained in 56 normal subjects are summarized in Table II for ready reference. These data were selected from 66 complete blood granulocyte kinetic studies carried out on apparently normal subjects. Seven of the 66 studies were discarded because the subjects were found to have granulocyte counts outside the 95% limits of normal as given by Osgood and co-workers (7). In 56 of the remaining 59 normal subjects the BGSA curve followed a single exponential decline. In three subjects a BGSA curve with a changing disappearance rate (Figure 1, curve C) was encountered.

Polycythemia rubra vera. TBGP values ranging from normal to 12 times the normal mean were encountered in patients with polycythemia vera (Table II). In all 13 studies on patients with granulocytosis the TBGP was larger than normal. In one of the three patients with normal blood granulocyte concentration the TBGP was also larger than normal. The correlation between the blood granulocyte concentration and determined TBGP size was good ($r = +0.85$, $p = < 0.001$). In addition, at increased TBGP values the size of the MGP was enlarged to a greater degree than was the CGP. As a result, the CGP/TBGP ra-

TABLE II

*Blood granulocyte kinetic values in patients with polycythemia vera as compared to normal subjects**

Study no.	G	TBGP	CGP	$t_{\frac{1}{2}}$	GTR	Type of curve
	per mm³	*× 10⁷ G/kg*		*hrs*	*G/kg/day × 10⁷*	
Mean 56 normals	4,650	62.5	31.4	6.7	163	
95% limits	2,250–6,600	14–108	19–44	4–10	50–340	
Polycythemia vera (16)						
IV-166	23,900	610	154	11.0	923	A
V-34	21,400	805	161			C
III-6	20,830	513	171	9.5	899	A
IV-36	19,300	411	137	14.2	498	A
V-178	13,973	429	85	11.3	631	B
V-140	13,300	238	98	7.8	503	A
VI-32	12,700	189	85	9.3	336	A
VI-80	12,000	379	126†	10.5	600	A
V-122	11,910	204	87	9.2	367	A
IV-94	11,540	397	109†	11.2	582	A
V-144	10,340	175	71†	9.0	323	A
IV-62	9,540	316	72	15.5	340	B
VII-58	8,325	139	50	8.0	291	A
V-32	6,190	272	42†	15.0	302	B
IV-124	5,030	104	55†			C
VI-74	5,000	52	45	7.4	118	A

* G = granulocytes; TBGP = total blood granulocyte pool; CGP = circulating granulocyte pool; GTR = granulocyte turnover rate.

† These CGP values were calculated from Cr^{51} blood volume values determined at the completion of the study.

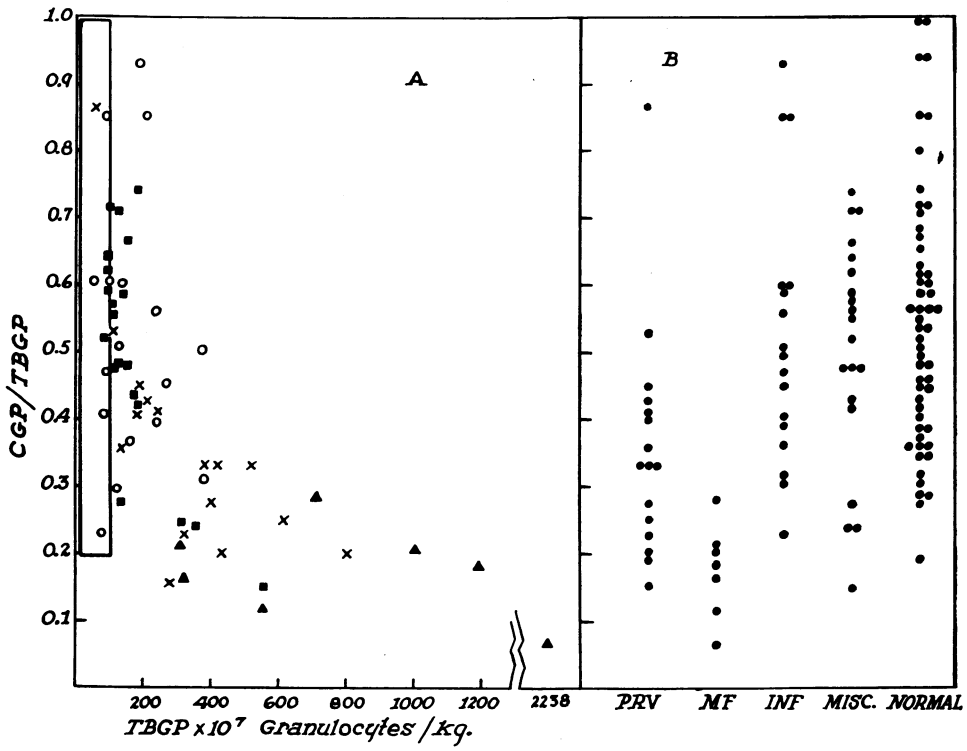

FIG. 2. A. RELATIONSHIP BETWEEN THE PROPORTION OF GRANULOCYTES IN THE TBGP THAT ARE CIRCULATING, AS REPRESENTED BY THE CIRCULATING GRANULOCYTE POOL/TOTAL BLOOD GRANULOCYTE POOL (CGP/TBGP) RATIO, AND THE TBGP SIZE IN 60 STUDIES ON PATIENTS WITH DISEASE AS COMPARED TO NORMAL SUBJECTS. The rectangle encompasses 95% of normal studies. Patients with polycythemia vera = ×. Patients with infection = ○. Patients with miscellaneous disorders = ■. Patients with myelofibrosis = ▲. B. COMPARISON OF THE DISTRIBUTION OF CELLS IN THE TBGP OF PATIENTS WITH DISEASE AS COMPARED TO NORMAL SUBJECTS, AS INDICATED BY THE RATIO CGP/TBGP. PRV = polycythemia rubra vera. MF = myelofibrosis. INF = infection. MISC. = miscellaneous diseases.

tio was less than 0.45 in all 13 subjects with granulocytosis (Figure 2, A and B). When the TBGP was enlarged, the GTR was usually increased (Figure 3) while the $t_{\frac{1}{2}}$ remained normal or was only moderately prolonged (Figure 4).

Infection. In the 17 patients with subacute to chronic infections determined TBGP values ranging from normal to six times the normal mean were encountered. In ten of the eleven patients with granulocytosis the TBGP was larger than normal (Table III). Only one patient with a normal granulocyte count had a slightly enlarged TBGP; presumably the count was normal due to a shift of cells to marginal sites. The correlation between blood granulocyte concentration and determined TBGP size was good ($r = +0.74$, $p = < 0.001$). The distribution of cells between circulating and marginal sites varied considerably and was similar to the distribution encountered in normal subjects (Figure 2B). The $t_{\frac{1}{2}}$ remained normal or was moderately prolonged in all of the patients with infection. In no instance was the $t_{\frac{1}{2}}$ shorter than normal (Table III). When the TBGP was enlarged the GTR was usually also increased, but there was considerable overlap with the normal range of values (Figure 3). GTR values in these patients with subacute and chronic infections did not exceed twelve times the normal mean.

Miscellaneous diseases. In most of the 20 studies carried out on patients with a variety of diseases only modest elevations in granulocyte concentration were noted (Table IV). The TBGP was also either normal or only moderately elevated

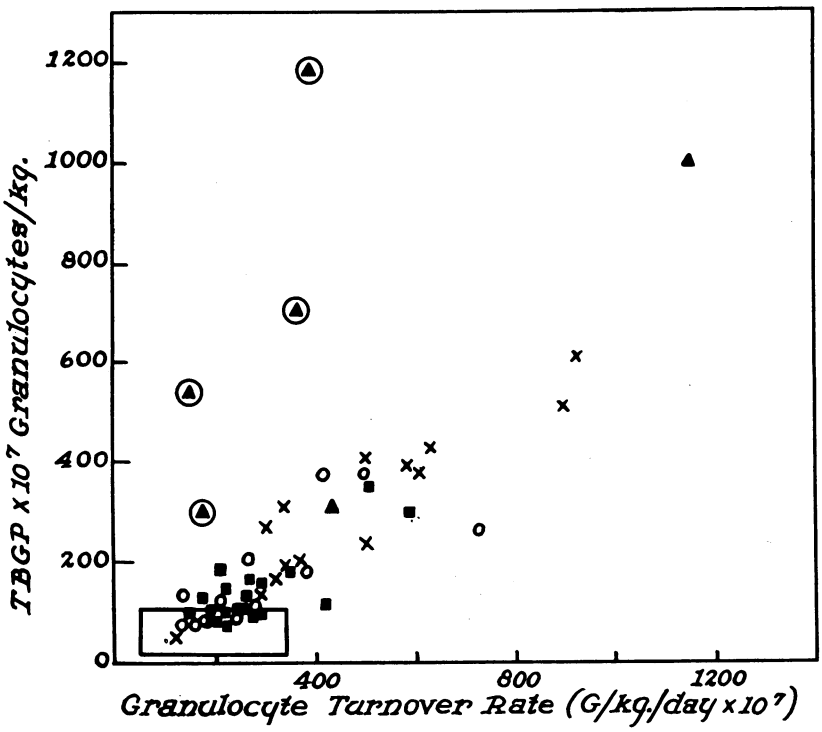

FIG. 3. RELATIONSHIP BETWEEN TBGP SIZE AND THE GRANULOCYTE TURNOVER RATE (GTR) IN 60 STUDIES ON PATIENTS WITH DISEASE. The rectangle encompasses 95% of normal subjects. Patients with polycythemia vera = ×. Patients with infection = ○. Patients with miscellaneous disorders = ■. The first three myelofibrosis studies in Table V are designated by ▲; the last four studies are designated by (▲). The second study on Patient II-236, Table V, is not included because of the very large values: TBGP = 2,238, GTR = 1,987.

TABLE III

*Blood granulocyte kinetic values in patients with infection**

Study no.	Diagnosis	G	TBGP	CGP	$t_{\frac{1}{2}}$	GTR	Type of curve
		per mm³	*× 10⁷ G/kg*		*hrs*	*G/kg/day × 10⁷*	
I-161	Empyema	30,100	208	177	13.0	267	A
VII-78	Perisplenic abscess	23,770	182	169	8.0	378	A
IV-2	Cholecystitis-subacute	23,370	373	187	15.0	414	A
I-157	Lung abscess	17,780	373	115	12.5	496	A
VII-84	Ca of lung with abscess	17,690	232	130			C
II-124	Pyelonephritis	16,600	262	118	6.0	727	A
VII-52	Pneumonitis	11,520	234	92			C
III-178	Lung abscess-septicemia	10,350	131	78	16.0	136	A
IV-66	Colitis	9,330	151	55			C
VII-80	Abscess of chest wall	9,320	126	64	10.0	209	A
VII-86	Genitourinary infection	7,690	87	74	8.0	181	B
VII-12	Diabetes, pneumonitis	5,430	87	41	8.0	181	A
VII-36	Genitourinary infection	6,720	98	59	6.8	240	A
I-168	Genitourinary infection	4,300	79	32	9.0	146	A
II-174	Genitourinary infection	4,180	119	35	7.1	280	A
IV-84	Pyelonephritis	3,790	48	29			C
VI-68	Pyelonephritis	2,200	74	17	8.0	154	B

* See Table II for abbreviations.

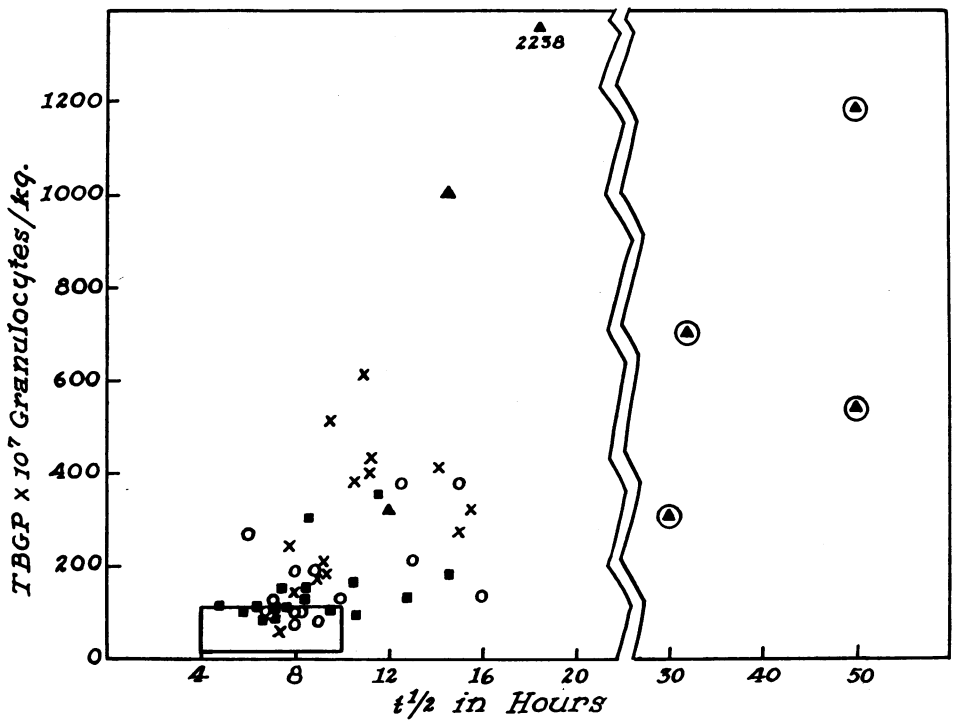

FIG. 4. RELATIONSHIP BETWEEN TBGP SIZE AND $t_{\frac{1}{2}}$ IN 60 STUDIES ON PATIENTS WITH DISEASE. See Figure 3 legend for symbols. Note the change in scale on the abscissa between 20 and 30 hours.

TABLE IV

*Blood granulocyte kinetics in patients with miscellaneous clinical conditions**

Study no.	Diagnosis	G	TBGP	CGP	$t_{\frac{1}{2}}$	GTR	Type of curve
		per mm³	*× 10⁷ G/kg*		*hrs*	*G/kg/day × 10⁷*	
III-100	Unexplained leukocytosis	20,950	181	134	14.5	208	A
IV-162	Hodgkin's disease	12,840	146	97	7.6	218	A
V-160	Unexplained leukocytosis	12,100	348	84	11.5	503	B
III-40	Hodgkin's disease	11,760	187	79	9.0	345	A
V-174	Hodgkin's disease	10,560	551	83			C
VI-150	Unexplained leukocytosis	10,450	303	73	8.6	586	B
IV-6	Unexplained leukocytosis	10,400	166	72	10.5	264	A
V-170	Laënnec's cirrhosis	10,400	132	77	12.8	171	A
VII-24	Unexplained leukocytosis	9,890	101	72	7.0	239	B
VI-38	Pulmonary infiltrate, unknown etiology	9,500	107	76	6.4	278	A
VI-36	Pulmonary coin lesion	9,020	102	58	5.9	286	A
VI-160	Unexplained leukocytosis	8,840	110	61	7.5	243	A
VII-40	Cushing's disease-adenoma	8,500	148	71	8.5	290	A
V-176	Hodgkin's disease	8,000	107	51	9.5	187	B
II-98	Unexplained leukocytosis	7,980	87	54	7.1	205	A
III-124	Pulmonary infiltrate unknown etiology	7,600	92	59	7.1	216	A
IV-170	Giant follicular lymphoma	7,540	94	55	10.6	148	A
II-210	Hodgkin's disease	6,850	86	45	6.6	217	A
VI-30	Hodgkin's disease	6,600	117	56	4.7	414	B
V-38	Hodgkin's disease	6,000	130	36	8.3	260	A

* See Table II for abbreviations.

TABLE V

*Blood granulocyte kinetic values in patients with myelofibrosis**

Patient no.	G	Myelo	Meta	Juv	Seg	TBGP	CGP	$t_{\frac{1}{2}}$	GTR	Type of curve	Leukocyte alkaline phosphatase	Fibrosis on bone marrow biopsy
	per mm³	%	%	%	%	× *10⁷ G/kg*		*hrs*	*G/kg/day* × *10⁷*			
II-236	30,660		2.5	35.0	54.0	999	208	14.5	1,146	A	NA	NA
†	21,680	1.0	0.5	52.0	36.0	2,238	147	18.5	1,987	A	271	No
III-122	8,000	2.5	4.5	24.5	50.0	314	52	12.0	435	A	186, 204, 192	Yes
V-46	30,730	5.0	20.0	28.0	26.0	705	199	32.0	367	B	68	No
VI-40	27,600	5.0	17.5	29.0	32.0	1,184	218	50.0	394	A	107, 17, 28	Yes
V-158	9,770	3.0	10.5	27.5	18.5	305	65	30.0	173	A	11, 4	Yes
‡	9,800	4.5	8.0	36.0	25.0	544	64	50.0	151	B	261, 38, 324	NA

*See Table II for abbreviations. Myelo = myelocytes; Meta = metamyelocytes; Juv = juvenile forms; Seg = segmented neutrophils, NA = not available.
† The second study was carried out 21 months after the first.
‡ The second study was carried out 2 years after the first.

in these patients. The correlation between determined TBGP and granulocyte concentration was poor in this group ($r = +0.30$, $p = < 0.2$), probably because of the narrow range of TBGP and granulocyte concentration values and the variation in distribution of granulocytes in the TBGP (Figure 2B). The $t_{\frac{1}{2}}$ values were normal or moderately prolonged in these patients, and the GTR values were within the normal range in all but four studies.

Myelofibrosis. Seven studies were carried out on patients thought to have myelofibrosis (Table V). The largest TBGP values encountered were in this group, and as with the other patients the large TBGP values were found in patients with high blood granulocyte counts. One distinguishing feature of the myelofibrosis patients was the marked shift of granulocytes into the MGP so that the CGP/TBGP ratio was less than 0.28 in all seven studies (Figure 2B).

The $t_{\frac{1}{2}}$ values were large in all patients with myelofibrosis but were so strikingly prolonged in four (30 to 50 hours) that granulocyte kinetics in these patients appear to be completely different from the findings in the other patients described (Figure 4). These patients were in every way similar to the others considered to have myelofibrosis except for the somewhat larger proportion of myelocytes and metamyelocytes in their blood. The net result of the large TBGP and the very long $t_{\frac{1}{2}}$ values in these four studies is a normal or only slightly increased GTR (Figure 3). The results in these four studies are similar to those encountered in patients with chronic myelocytic leukemia in relapse (3).

All groups combined. If all the data are examined together, several features are apparent. When the blood granulocyte concentration is increased, the TBGP size is usually increased also (Figure 5), and the correlation between these parameters is fairly good ($r = +0.60$, $p = < 0.001$). At larger TBGP values the granulocytes were distributed unevenly between the CGP and the MGP. This is seen in Figure 2A where the CGP/TBGP ratio is compared with TBGP size. However, this impression may reflect the fact that most of the larger TBGP values were seen in patients with myelofibrosis and polycythemia vera.

In patients with infection the $t_{\frac{1}{2}}$ was normal or prolonged rather than shortened. This was also the case in the other disorders studied (Figure 4). The longest $t_{\frac{1}{2}}$ encountered in any of these patients (excluding the four myelofibrosis studies in which $t_{\frac{1}{2}}$ values were long) was 18.5 hours. No patient had a $t_{\frac{1}{2}}$ value less than normal. The correlation between TBGP size and $t_{\frac{1}{2}}$ was $+0.59$ ($p = < 0.001$). The four studies in patients with myelofibrosis in whom the $t_{\frac{1}{2}}$ values were long were excluded from this calculation.

The excellent correlation between TBGP size and GTR can be seen in Figure 3 ($r = +0.95$, $p = < 0.001$). The four studies in myelofibrosis in which very long $t_{\frac{1}{2}}$ values were observed were again excluded since they do not appear to belong to the same population (Figure 3).

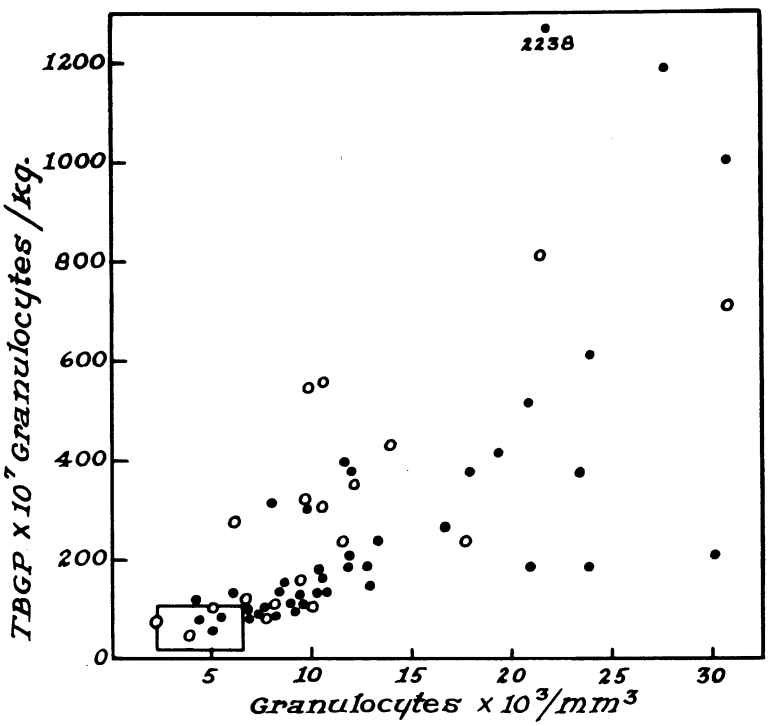

FIG. 5. RELATIONSHIP BETWEEN THE SIZE OF THE TBGP AND THE BLOOD GRANULOCYTE COUNT IN 60 STUDIES ON PATIENTS WITH POLYCYTHEMIA RUBRA VERA, CHRONIC INFECTION, MYELOFIBROSIS, OR ONE OF A NUMBER OF OTHER MISCELLANEOUS CONDITIONS STUDIED. The solid dots (●) indicate values obtained from type A curves. The circles (○) indicate values calculated from determined t_0 values in patients with type B and C curves. The rectangle includes 95% of normal subjects.

Discussion

Because of the close similarity in granulocyte kinetic findings in the various disorders studied, they will be discussed as a whole except for the four studies in patients with myelofibrosis which differed from the remainder. These will be considered separately.

From the relationship between TBGP size and granulocyte count shown in Figure 5 it can be seen that, as the blood granulocyte count increased, the TBGP also increased ($r = +0.60$, $p = < 0.001$). As the TBGP increased, the $t_{\frac{1}{2}}$ remained normal or became prolonged but never decreased (Figure 4). Finally, as the TBGP increased the GTR increased (Figure 3) ($r = +0.95$, $p = < 0.001$). All three of these relationships appear to be continuous, with no clear segregation of values by disease type. These data may be reviewed for possible clues as to the physiologic mechanisms controlling granulocyte behavior in pathologic states.

The findings of greatest interest were the normal or slightly prolonged $t_{\frac{1}{2}}$ values encountered in all patients studied and the excellent correlation between the blood GTR and the size of the TBGP.

GTR values in these patients ranged from normal to 14 times normal. Since the disappearance of granulocytes from the circulation of normal subjects has been demonstrated to be a first order process (2), one would expect the turnover of cells to depend on the number present in the blood (TBGP). However, from the formula for calculation of the GTR [GTR = 0.693 × TBGP × 24 (hours)/$t_{\frac{1}{2}}$ (hours)] it can be seen that an increase in GTR could result from an increase in fractional turnover rate (i.e., a short $t_{\frac{1}{2}}$) as well as from an increase in TBGP size or from certain combinations of these two

parameters. The absence of an increase in fractional turnover rate (short $t_{\frac{1}{2}}$) in any of these studies suggests that it is unusual for the GTR to be increased by this means. The major factor influencing GTR in these patients appeared to be the size of the TBGP.

The accumulation of large numbers of neutrophils at sites of injury and inflammation is a common clinical occurrence. Therefore, it is of interest that in patients with extensive purulent processes (Patients VII-78, I-157, and III-178 in Table II) the GTR may be only one to three times the normal mean. Since large but unknown numbers of granulocytes accumulate in and are discharged from such areas of inflammation, larger GTR might have been anticipated. However, it must be kept in mind that the GTR represents the total blood granulocyte turnover per day. Since the normal mechanisms and sites of blood granulocyte removal are largely unknown, it is quite possible that under appropriate conditions a marked reduction in clearance of granulocytes through normal channels and a shift of these cells to the site of injury may occur, thus providing many times the normal number of cells to an injured tissue with little increase in GTR. For example, if we assume a 5 to 10% clearance of granulocytes in the normal lung (8), it seems quite possible that with the development of pneumonia, the lung clearance fraction could be increased greatly, perhaps to 70 or even 80%. Such a change would increase the cells removed by the lung seven- or eightfold without any increase in over-all GTR. If the GTR were simultaneously increased threefold, more than a twentyfold increase in the number of cells accumulated in the lung would result. Such a scheme could explain the rather modest increase in GTR encountered in patients with extensive purulent infections and is compatible with the demonstration by Allison, Smith, and Wood that neutrophils selectively accumulate at sites of tissue injury (9).

The slightly prolonged $t_{\frac{1}{2}}$ encountered in some of these patients seems related to the size of the TBGP (Figure 4). It has not been possible to demonstrate a relationship between the prolonged $t_{\frac{1}{2}}$ noted in some of them and the presence of slightly increased numbers of myelocytes and metamyelocytes in their blood. This may be due to the lack of any relationship between these two parameters or to the limited number of these immature cells (less than 11.5%) in the blood of the patients studied. The markedly prolonged $t_{\frac{1}{2}}$ values in four of the patients thought to have myelofibrosis have already been mentioned. The prolonged $t_{\frac{1}{2}}$ values and the increased number of immature cell forms present in their blood are similar to the findings in patients with chronic myelocytic leukemia in relapse (3). The possible explanations for the markedly prolonged $t_{\frac{1}{2}}$ in such patients have been discussed (3). Some factor in addition to enlarged TBGP size must be invoked to explain the marked divergence of these four studies (Figure 4) from the findings in other patients studied. This factor is presumed to be the presence of immature cell forms in the blood. In any case, it is apparent that leukokinetic studies do not differentiate some patients with what appears to be myelofibrosis from patients whose findings are those of classical chronic myelocytic leukemia.

In 40 of 48 studies carried out on patients with a stable, persistent granulocytosis the TBGP was enlarged, and in all subjects with a granulocytosis greater than 10,000 per mm^3 the TBGP was enlarged. In 8 of 16 studies on patients with normal TBGP, elevated granulocyte counts were encountered. It is possible that these 8 studies represent a clinical counterpart to previously reported experimental situations in normal subjects in whom a transient intravascular shift of cells from the MGP to the CGP resulted in a granulocytosis in the presence of a normal TBGP (1). Three patients with larger than normal TBGP but normal granulocyte counts were also encountered. That such intravascular shifts of cells would be seen in disease states in which fever, tachycardia, and alterations in blood flow and viscosity occur seems likely. However, since even in normal subjects there was wide variation in the distribution of granulocytes between the MGP and CGP with from 19 to 99% of the cells circulating in the CGP (Figure 2B), proof that a persistent granulocytosis may result from an altered distribution of cells is difficult to obtain. From Figure 2A it might be inferred that a shift of cells from the CGP to the MGP occurs with increasing TBGP size. However, this conclusion

may not be valid since the largest TBGP values were found in patients with myelofibrosis and polycythemia vera. A TBGP larger than 400 $\times 10^7$ granulocytes per kg was seldom encountered in the other diseases studied. Only in patients with myelofibrosis does it seem clear that a shift of granulocytes into the MGP occurs regularly (Figure 2B). A lesser shift of granulocytes may be characteristic of patients with polycythemia vera, but this was not clearly demonstrated in the small group studied. When the blood granulocyte concentration and TBGP values were compared, the correlation between these two parameters was fairly good ($r = +0.60$, $p = < 0.001$). The divergence of occasional values from the main group (Figure 2) is probably due to intravascular shifts of cells.

A significant proportion of the granulocyte radioactivity curves in these patients did not follow a single exponential line (types B and C, Figure 1). Type B curves appear to reflect the presence of damaged cells in the labeled, infused blood (3). The damaged cells are removed from the blood within several hours of infusion, whereas the undamaged cells remain. The finding that in subjects with type B curves the TBGP calculated from determined t_o values is usually compatible with the granulocyte count (Figure 5) whereas the TBGP calculated from extrapolated t_o values is unusually large is consistent with this interpretation. The same phenomenon was seen in patients with chronic myelocytic leukemia (3). Type C curves may also reflect cell damage. However, no such curves were encountered in studies in which cells were intentionally damaged and then infused (3). Therefore it seems more likely that these curves reflect a nonsteady state that is not evident in the blood granulocyte concentration values. In favor of this interpretation is the finding that in patients in whom skin inflammations were produced, type C curves were common (10).

Summary

Sixty studies of blood granulocyte kinetics have been carried out by means of the *in vitro,* diisopropyl fluorophosphate (DFP^{32})-labeled granulocyte technic in patients with polycythemia rubra vera, subacute and chronic infection, myelofibrosis, and miscellaneous diseases. The results are compared with values in 56 normal subjects. An increase in total blood granulocyte pool size was observed in all subjects with blood granulocyte counts persistently greater than 10,000 per mm^3. In 8 of 16 patients with normal total blood granulocyte pools (TBGP) the granulocyte count was moderately elevated (7,500 to 9,890) and in three patients with moderately elevated TBGP the granulocyte concentration was within normal limits. These last two groups of studies presumably reflect intravascular shifts in granulocyte distribution.

In patients with myelofibrosis and in some patients with polycythemia rubra vera there was a tendency for the granulocytes to accumulate disproportionately in marginal sites, and this tendency was particularly noticeable when the total blood granulocyte pool values were high.

In all but four of the 60 studies the $t_{\frac{1}{2}}$ values were normal or moderately increased. In no study was the $t_{\frac{1}{2}}$ less than normal. The daily granulocyte turnover rate ranged from normal to twelve times normal. The increase in granulocyte turnover rate in these studies appears to be associated with an increase in the size of the blood granulocyte pool rather than an accelerated blood granulocyte pool renewal rate.

In four studies on patients with myelofibrosis very long $t_{\frac{1}{2}}$ values of 30 to 50 hours were found. These values are comparable to those encountered in patients with chronic myelocytic leukemia in relapse.

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