

## Übersichten

### Number and Distribution of Lymphocytes in Man. A Critical Analysis

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*Summary.* The number and distribution of lymphocytes in man has not yet been determined quantitatively. But there is limited information available on the cell number or the size of single compartments of the human lymphoid cell system. The problem is to derive knowledge about the quantitatively unknown compartments from other data. This is done by extrapolation of data on rats to man after having confirmed that lymphocyte numbers in rat and man are comparable under certain conditions.

Two independent approaches lead to an estimate of the total number of lymphocytes in normal young adult men of  $400-500 \times 10^9$ . According to conclusions derived from man data and extrapolation from the detailed studies in rats, the lymphocytes in young adult man should be distributed as follows: 2.2% in the circulating blood, 41.3% in the lymph nodes and tonsils, 15.2% in the spleen, 4.3% in the gut-associated lymphoid tissue, 10.9% in the thymus, 10.9% in the bone marrow and about 15% in other tissues.

*Key words:* Lymphocytes' distribution.

*Zahl und Verteilung der Lymphocyten des Menschen. Eine kritische Analyse.*

*Zusammenfassung.* Die Zahl und Verteilung der Lymphocyten innerhalb und außerhalb der lymphatischen Organe des

Menschen ist quantitativ noch nicht bestimmt worden. Es liegen lediglich Messungen einzelner Lymphocytencompartments und Größenbestimmungen einzelner lymphatischer Organe vor. Theoretisch ist es möglich, die quantitative Charakterisierung der noch nicht untersuchten menschlichen Lymphocytencompartments durch Extrapolation von Tierdaten zu erreichen. Voraussetzung dafür ist, daß die entsprechenden Tierdaten mit den schon vorliegenden Teildaten des Menschen vergleichbar sind. Das trifft auf die Lymphocytenzahl und -verteilung bei der Ratte zu.

Zwei voneinander unabhängige Schätzmethode ergeben für den jung erwachsenen normalen Menschen eine Gesamtlymphocytenzahl von 400—500 Milliarden. Aufgrund von Primärdaten vom Menschen und Extrapolation von der Ratte ist folgende durchschnittliche Verteilung der Lymphocyten beim jüngeren Menschen wahrscheinlich: 2,2% im zirkulierenden Blut, 41,3% in den Lymphknoten und Tonsillen, 15,2% in der Milz, 4,3% im lymphatischen Gewebe des Darmtrakts, 10,9% im Thymus, 10,9% im Knochenmark und etwa 15% in anderen Geweben.

*Schlüsselwort:* Lymphocyten.

Every physician knows that the blood lymphocyte count in healthy adult people is about  $2000/\text{mm}^3$ . By means of this value and the blood volume of 5 l it can easily be calculated that the total circulating blood contains  $10 \times 10^9$  lymphocytes. But this represents only the peak of the iceberg: the total number of lymphoid cells in the body is much larger. Not only the lymphoid organs in the strict sense, lymph nodes, spleen, Peyer's patches and the tonsils, also lymphoid organs in a wider sense like the thymus and the bone marrow and last not least the diffuse connective tissue apparently lodge large numbers of lymphocytes.

There is need to have an exact measurement or at least an orientating estimate of the number and distribution of lymphocytes in normal man: The clinicians would like to know how many percent of lymphocytes they remove from the body by splenectomy, by thoracic duct drainage or leukophoretic procedures. The pathologists are not able to compare quantitatively the lymphocyte count in the tissues of patients with the lymphocyte numbers in the normal state, because normal values are lacking. The immunologists may be interested to compare in quantitative terms their data on cellular events in immune reactions in rodents with observations in man. Experimental haematologists working in the field of kinetics of lymphocytes ex-

press their data only in relative values because of a lacking absolute baseline of reference.

There is, to my knowledge, no study reporting exact measurements of the lymphocyte content of the total human body. Excellent work, however, concerning the amount of lymphoid tissue in the spleen (Hellman, 1926; Krumbhaar *et al.*, 1939), the wall of the gut (Hellman, 1921; Duker *et al.*, 1926; Cornes, 1965) the thymus (Hammar, 1936) and the bone marrow (Donohue *et al.*, 1958; Harrison, 1962) has been published in the older literature.

The only animal species, which is examined quantitatively in this respect is the rat. By comparison of the data of the relative lymphocyte content of different lymphoid and non-lymphoid tissues of man and rat and extrapolation from rat data to man it should be possible to fill the gaps that still exist in our knowledge of the lymphocyte number and distribution in normal man. The result will be a relatively reliable estimate, as is shown in the following.

#### *Number and Distribution of Lymphocytes in Rats*

At first, it will be necessary to consider the results in rats. The data are presented in Table 1.

The methods employed to determine the lymphocyte numbers in rats were as follows: Microscopic count-

Table 1. Reported or derived data on the lymphocyte content of different lymphoid organs and tissues in normal young adult rats of 200 g weight

Authors		Kindred (1942) × 10 <sup>9</sup>	Monden (1958) × 10 <sup>9</sup>	Everett (1964) × 10 <sup>9</sup>	Ford (1969) × 10 <sup>9</sup>	Average × 10 <sup>9</sup>
Lymph nodes	(absolute number)	2.1	1.7			1.9
	(/kg body weight)	10.5	8.5			9.5
Spleen	(abs.)	0.2	1.1	0.3	0.7	0.6
	(/kg)	1.0	5.5	1.5	2.8	3.0
Peyer's patches	(abs.)	0.03	0.4			0.22
	(/kg)	0.15	2.0			1.1
Thymus	(abs.)	1.0	1.1	1.8		1.3
	(/kg)	5.0	5.5	9.0		6.5
Total lymphocytes in lymphoid tissue	(abs.)	3.33	4.3			4.0
	(/kg)	16.60	21.5			20.0
Bone marrow	(abs.)	0.9		0.7		0.8
	(/kg)	4.5		3.5		4.0
Blood	(abs.)	0.08	0.13			0.11
	(/kg)	0.4	0.7			0.55
Total lymphocytes in lymphoid tissue, bone marrow and blood	(abs.)					4.9
	(/kg)					24.5

ing of lymphocytes in defined volumes of tissue sections and multiplying these values by the volumes of the lymphoid organs (Kindred, 1942); Determination of the DNA content of lymphoid organs, divided by the DNA content of the small lymphocyte, multiplied by the proportion of lymphocytes in those organs (Monden, 1959; Everett and Caffrey, 1964); Counting of the lymphocytes in single-cell-suspensions of spleens (Ford, 1969); Calculation of the number of bone marrow lymphocytes by multiplication of the estimated number of bone marrow cells (Donohue *et al.*, 1958) by the proportion of lymphocytes in the marrow (Everett and Coffrey, 1964); Calculation of the blood lymphocyte content by multiplying the lymphocyte count by the measured blood volume (Kindred, 1942; Monden, 1959).

#### *Extrapolation from Rat to Man*

Which quantitative data on lymphocyte numbers in human tissues can be compared to these rat data?

There are two kinds of information available concerning lymphocyte content of lymphoid organs in normal man: 1. calculations of lymphocyte numbers on the basis of relative lymphocyte counts in the organ or compartment under study and the known volume or size of the organ and compartment. This is the case with the determination of the lymphocyte number in the blood and bone marrow. 2. specifications of the weight or volume of lymphoid organs or organ structures. Data of this type are compiled in Table 2. This kind of quantitative description of special parts of the lymphoid tissue has been done very precisely in several hundred of healthy young people having died suddenly by violence.

Table 2. Quantitative data on number, weight or size of lymphoid organs in normal young adult man

Authors	Leiber (1961)	Hellman (1921/1926)	Krumb- haar (1939)	Cornes (1965)	Hammar (1936)
Lymph nodes	460/man				
Spleen (total)		136 g	154 g		
White pulp		18 g			
Peyer's patches (Total area)		150/man		200/man	
Thymus		90 cm <sup>2</sup>			26 g

These data could—in part—be expressed in terms of lymphocyte numbers per organ if the density of lymphocytes per volume of lymphoid tissue or the number of lymphocytes per weight unit of lymphoid tissue would be known. Regarding these values estimates can be derived from other data. Since the human blood lymphocyte has a volume of about 150  $\mu^3$  (Thom, 1972; Marshall *et al.*, 1965) and a density of about 1.065 g/ml (Thom, 1972) 1 ml of extremely packed lymphocytes contains  $6.67 \times 10^9$  cells whereas 1 g contains  $6.25 \times 10^9$  cells. Use of this value would lead to an overestimation of the lymphocyte density in the lymphoid organs, for in the biological tissues the cells are much less concentrated than in such an artificially packed cell concentrate.

In rats and guinea pigs the lymphocyte content of lymphoid tissues was described to be about  $1.5 \times 10^9$ /g in the lymph nodes and Peyer's patches (Monden, 1959;

Table 3. Estimate of the average values of lymphocyte numbers in different tissues of rat and man (young adult individuals)

		Rat <sup>a</sup> (200 g) $\times 10^9$	Man ( $\leq 70$ kg) $\times 10^9$	Ratio rat:man
Spleen	(absolute number)	0.6	72.5 <sup>c</sup>	
	(/kg body weight)	3.0	1.03	2.9:1
	(/m <sup>2</sup> body surface) <sup>b</sup>	20.0	39.4	0.5:1
Lymphoid tissue of the gut	(abs.)	0.22	18.5 <sup>d</sup>	
	(/kg)	1.1	0.26	4.2:1
	(/m <sup>2</sup> )	7.3	10.0	0.7:1
Thymus	(abs.)	1.3	52.0 <sup>e</sup>	
	(/kg)	6.5	0.74	8.8:1
	(/m <sup>2</sup> )	43.3	28.3	1.5:1
Bone marrow	(abs.)	0.8	50.0 <sup>f</sup>	
	(/kg)	4.0	0.71	5.6:1
	(/m <sup>2</sup> )	26.6	72.2	1.0:1
Blood	(abs.)	0.11	10.0	
	(/kg)	0.55	0.14	3.9:1
	(/m <sup>2</sup> )	3.7	5.4	0.7:1
Total	(abs.)	3.03	203.0	
	(/kg)	15.2	2.9	5.2:1
	(/m <sup>2</sup> )	101.0	110.0	0.9:1

<sup>a</sup> Average rat values from Table 1.

<sup>b</sup> Body surface of a 200 g rat  $\sim 0.03$  m<sup>2</sup> (Kibler *et al.*, 1942 and of a normal man 1.84 m<sup>2</sup> (Geigy-Tabellen 1960).

<sup>c</sup> Calculated from the data of Hellman (1926) and Krumbhaar *et al.* (1939).

<sup>d</sup> Calculated from the data of Hellman (1921), Dukes *et al.* (1926) and Cornes (1965).

<sup>e</sup> Calculated from the data of Hammar (1936).

<sup>f</sup> Calculated from the data of Donohue *et al.* (1958), Harrison (1962) and Baserga (1964).

Everett *et al.*, 1964; Rosse *et al.*, 1971, about  $0.7 \times 10^9$ /g in the spleen (Everett *et al.*, 1964; Ford, 1969) and about  $3 \times 10^9$ /g in the thymus (Monden, 1959; Everett *et al.*, 1964; Rosse *et al.*, 1971). Human lymphocytes being somewhat larger than rodent lymphocytes, it is estimated that in normal man the lymph nodes and Peyer's patches contain  $1 \times 10^9$  lymphocytes/g, the spleen  $0.5 \times 10^9$ /g and the thymus  $2 \times 10^9$ /g.

Using these values, the number of lymphocytes in the examples of human spleens and thymuses can be calculated. The same is possible with the organized lymphoid tissue of the gut. Assuming a thickness of the Peyer's patches of 1 mm, the volume of the patches is obtained and this forms the basis for calculation of their lymphocyte content. Besides the larger Peyer's patches there are about 30000 smaller but macroscopically visible solitary lymphoid nodules with a mean diameter of 1 mm in the human gut (Hellman, 1921; Dukes *et al.*, 1926). Their cell content is combined with that of the Peyer's patches as „lymphoid tissue of the gut". In addition, the simple calculations of the lymphocyte content of the blood (see above) and of the bone marrow assuming a percentage of 5% lymphocytes and  $1 \times 10^{12}$  nucleated bone marrow cells in the normal adult man, (Donohue *et al.*, 1958; Harrison, 1962; Baserga, 1964) are made. The results of these calculations are given in Table 3. For reasons of comparison, the lymphocyte numbers are not only expressed in absolute values but also as number/

tissue/kg body weight and as number/tissue/square meter of body surface. The ratio of the lymphocyte numbers of rats/lymphocyte numbers in man per unit of body weight or surface is also indicated.

From the comparison of data in Table 3 the following conclusions can be drawn:

1. Man has fewer lymphocytes than rats relative to body weight and more lymphocytes relative to body surface. Extrapolation from lymphocyte numbers of rats to man on basis of body surface area would be closer to reality than simple extrapolation according to the unit of body weight.

2. The ratio of lymphocyte numbers per organ per kg body weight of rats to the corresponding lymphocyte numbers of man is relatively similar in the case of blood, spleen, lymphoid tissue of the gut and bone marrow. The only exception is represented by the thymus, which is more developed in rats (and mice) than in man (and most other mammals). Despite this asymmetry caused by the thymus, the "thymolymphatic system" (Hammar, 1936; Andreasen, 1943) is considered to be a unity. Therefore, the average ratio of the numbers of rat and human lymphocytes in the compared lymphoid compartments per kg body weight, in this case 5.2:1, is taken to extrapolate from rat to man. Since only the number of lymph node lymphocytes in man is unknown, it is, in principle, an extrapolation of the relation found in rats between the numbers of lymph node lymphocytes to the number

of lymphocytes in the rest of the lymphoid organs. The "total" lymphocyte number of rats,  $24.5 \times 10^9/\text{kg}$ , is divided into the average ratio of rat to human lymphocyte numbers equal to 5.2. The resulting value of  $4.74 \times 10^9$  cells/kg is the basis of extrapolation. Multiplication by 70 kg gives  $332 \times 10^9$ . That is our first estimate of the total of lymphocytes in the lymphoid organs, the lymphoid tissue of the gut, the bone marrow and the blood in normal man.

A second approach to extrapolate from the precise data in rats to man could be the use of the proportion of the blood lymphocytes to the lymphocyte number in the whole lymphocyte pool. This seems to be a physiologically relevant relation because relatively constant ratios of about 1:20 have been found between the blood lymphocyte number and the recirculating lymphocyte pool rats in (Ford and Gowans, 1969) and man (Review by Trepel, 1974). The proportion of blood lymphocytes to the mass of lymphocytes in the lymphoid tissues plus the lymphocytes in the bone marrow and the blood is 2.2% in the rat. It is interesting to note that the corresponding value in rabbits derived from the data of Hammar (1932) and Donohue *et al.* (1958) is 2.4%. This leads to the second extrapolation from rat to man. According to the assumed constant relation between the blood lymphocyte number and the lymphocyte number in the lymphoid organs and fluids a normal man with 20 years of age and 70 kg of weight should have  $10 \times 10^9 \times 45 = 450 \times 10^9$  lymphocytes in his lymphoid tissues, his bone marrow and his blood. Both estimates, 332 and  $450 \times 10^9$ , are of the same order of magnitude. The mean would be  $391 \times 10^9$ .

The proposed number of cells does not contain the lymphocytes outside the lymphoid tissue, the bone marrow and the blood, particularly those diffusely or nodularly distributed in the mucous membranes of the respiratory and urogenital tract, in the liver and the subcutis. There is only one quantitative study on the number of lymphocytes in tissues and this evaluation was restricted to intestinal mucosa of rats (Kindred, 1942). A number of  $1.25 \times 10^9$  lymphocytes/kg body weight, distributed diffusely outside the Peyer's patches was determined. That was three times more than the number of blood lymphocytes in the same animals. This value is surely not representative of the other tissues of the body because the intestinal mucosa is especially lymphocyte-rich. Only the mucous membrane of the respiratory tract is supposed to contain a similarly high concentration of lymphocytes (Hayek, 1970). A further basis for a discussion of the concentration of diffusely distributed lymphocytes is the concentration of lymphocytes in the peripheral (or afferent) lymph of the different tissues. It seems to be a reasonable assumption that the concentration of cells in the tissue lymph depends on the concentration of lymphocytes in the tissues and that both concentrations are possibly similar or at least not very different.

The concentration of lymphocytes in the peripheral lymph of different tissues has so far only been measured in sheep (Smith *et al.*, 1970). On the average, the lymphocyte concentration in the peripheral lymph was about one tenth of that in the blood. A similar relation can be expected in man, where only the particularly lymphocyte-poor lymph of the leg has been measured (Engeset *et al.*, 1973). Basing on an average concentration of 200 lymphocytes/mm<sup>3</sup> in the pooled tissue lymph streams and on a tissue mass of 70 kg minus 7 kg of bone, 2 kg of gut and lung, 5.4 kg of blood and 1 kg of lymphoid tissue and bone marrow resulting in 54.6 kg drained tissue, a number of  $11 \times 10^9$  ( $200 \times 10^6 \times 54.6$ ) diffusely distributed lymphocytes in the rest of the body can be calculated. Thus, we arrive at a rough estimate of the lymphocytes in the tissues outside the lymphoid organs, the bone marrow, the organized (nodular) lymphoid tissue of the gut and the blood:  $30 \times 10^9$  in the intestinal mucosa,  $30 \times 10^9$  in the mucosa of the respiratory tract and  $10 \times 10^9$  in the rest of the body giving a total of  $70 \times 10^9$  cells.

#### *Number and Distribution of Lymphocytes in Man*

After these derivations we can summarize all estimates of lymphocyte numbers and distribution in normal human adults (Table 4).

These estimates must be confirmed or corrected by measurements which have been begun by others and by ourselves. The only experimental approach, so far, to study more than one compartment of lymphocytes in man quantitatively is in complete agreement with the estimates reported here: By prolonged drainage of thoracic duct lymphocytes in uraemic patients (with the aim of immunosuppression before kidney transplantation) 200 to  $300 \times 10^9$  lymphocyte have been removed from the body, leading to an extreme lymphocytopenia of the lymph nodes and the spleen (Sarles *et al.*, 1967, 1970), which should contain in normal persons according to our estimates exactly the same amount of lymphocytes.

Admittedly, corrections could shift the predicted values of lymphocyte number to 300 or  $700 \times 10^9$ , particularly because of variations in individual cases. Larger deviations seem to be very unlikely in normal man of young and middle age. But it must be emphasized that our estimate concerns only an idealized man of about 20 years of age and normal health and weight. It is sure, that children have relatively more lymphocytes per kg weight while older people show a diminished number of lymphocytes (Hellman, 1926; Hammar, 1936; Krumbhaar, 1942). Possibly the estimate of total lymphocyte number on the basis of a presumed blood lymphocyte/tissue-lymphocyte ratio of 1:45 is also valid in children and old people, perhaps even in pathologic conditions: blood lymphocyte number and the manifold larger mobilizable lymphocyte pool are correlated not only under normal conditions but apparently also in lymphopenic patients with chronic

Table 4. Number and distribution of lymphocytes. Estimate in a normal young adult man

Blood	$390 \times 10^9$	$10 \times 10^9$	2.2%
Lymph nodes		$190 \times 10^9$	41.3%
Spleen		$70 \times 10^9$	15.2%
Lymphoid tissue of the gut		$20 \times 10^9$	4.3%
Thymus		$50 \times 10^9$	10.9%
Bone marrow		$50 \times 10^9$	10.9%
Other tissue		$70 \times 10^9$	15.2%
Total lymphocytes/70 kg		$460 \times 10^9$	100%

uraemia (Revillard *et al.*, 1968) or with Hodgkin's disease (Engeset *et al.*, 1971).

Thus far, only one approach has been undertaken to estimate lymphocyte number and distribution in man. This was done by Osgood (1954) in a theoretically impressive but purely speculative way, assuming a doubly overestimated lymphocyte volume, a fourfold overestimated number of bone marrow cells and a phantastic ratio of the lymphocytes in the lymphoid organs to the lymphocytes in the extralymphoid tissues of 1:10. This summation of errors led to an extremely high estimate of  $6 \times 10^{12}$  lymphocytes in man (more than the tenfold value of our estimate) with 85% of all lymphocytes being diffusely distributed in the extralymphoid tissues representing in total a pure lymphocyte mass of 1500 g. It is hoped that the present attempt to make up the balance of the lymphocyte numbers in man will help to establish lymphocyte research in man on a more quantitative basis.

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