Observations and Reports (*continued*).

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"Note on some Changes in the Blood of the General Circulation consequent upon certain Inflammations of acute and local Character." By C. S. Sherrington, M.D., F.R.S., Lecturer on Physiology, St. Thomas's Hospital, Professor-Superintendent of the Brown Institution, London. Received December 11, 1893,—Read December 14, 1893.

[Plate 1.]

In result of an acute inflammatory process of even limited local extent alterations, that have been long recognised, take place in the blood of the general circulation. These alterations are (1) hyperinosis, or increased yield of fibrin; (2) leucocytosis, or numerical increase of leucocytes.

Of all the phenomena of inflammation the most fundamental, apart from the local degeneration of the involved tissue, is, without doubt, abnormal exudation of intravascular fluid. The latter process must produce changes in the blood in general circulation, as well as in that in the vascular area locally disturbed. It is these general hæmic changes incident on local inflammation with which my experiments deal, especially with certain features of the inflammatory leucocytosis.

I. Methods.

The inflammatory lesion I have established by trauma of one or other kind, induced generally by thermal means. When the seat chosen for the lesion has been in the limb, the procedure has been as follows.

The animal being deeply anæsthetised, the nerves to the limb have been carefully severed, in order to destroy sensation in the limb. Then the main artery to the limb (femoral or brachial) has been occluded by digital compression, and the extremity of the member immersed in water at 52° C. for five minutes. The limb has then been wiped dry, the animal allowed to recover from anæsthesia, and replaced in its stall.

The blood was examined at least once before establishment of the lesion. Afterwards a series of examinations were made, and these, with records of body-temperature and respiration, furnish the chief observations obtained from the experiments.

When the site of the lesion has been in an abdominal organ the same general plan has been followed, except that, as a rule, no nerve has been severed. Sponges steeped in 0·6 per cent. aqueous NaCl solution at 52° C. were applied for five minutes to a knuckle of intestine, brought to a small incision in the linea alba; the gut was then carefully replaced, and the wound closed, the whole performed with strict precautions for asepsis. In several instances, instead of the above plan, mechanical trauma was employed in the form of ligation of the knuckle of intestine. In several experiments where inflammation, primarily of a mucous surface, was requisite, use was made of specific chemical irritants in the form of cathartics administered by the stomach; but I have for the present endeavoured to avoid the use of chemical and bacterial irritants.

For the examination of the blood "drop" methods have been used throughout; the withdrawal of even quite small quantities of blood from the circulation induces rapid alteration in the circulating blood itself. By "drop" methods this source of error is avoided. Moreover "drop" methods have the advantage of not necessitating any binding down or tying of the animal, and it has by several authorities* been shown that these fixations of the animal, especially when continued over longish periods, induce of themselves severe changes in the composition of the blood. The animals employed have been the dog and cat, and occasionally the rabbit. The drop of blood required for examination has been almost always taken from the pinna of the ear.

For the counting of corpuscles I have used a selected pair of previously tested Thoma-Zeiss "counters." The instruments are guaranteed to vary in capacity by less than 1 per cent. of the capacity of each, *i.e.*, by less than 0·001 mm.. My pair showed no difference measurable under the magnification of the Zeiss Objective D. I have therefore discarded enumerations which have not tallied on the two counters within 10 per cent. I have not used the Thoma-Zeiss pipette, but one by Hawksley, containing no bead, and of a different shape from the Thoma-Zeiss pipette. Objec-

* *Cf.* especially Löwit, 'Studien zur Physiologie u. Pathologie des Blutes u. der Lymphe,' p. 9, &c.

tions to the Thoma-Zeiss pipette are, the large surface relatively to cubic content, the difficulty of drying the bead quickly enough for use in successive observations, and the presumption that leucocytes will adhere to the bead.

I have always *counted both chromocytes and leucocytes in the same film of the diluted blood, and in the same film enumerated the representatives of the various kinds of leucocytes distinguishable, e.g., finely granular, coarsely granular, large hyaline, small hyaline.* I imagine the carrying out of the enumeration of all the elements on *one and the same* film to be a point of importance. The methods of counting in which the enumeration of chromocytes is carried out in one film, that of leucocytes in a second, and the determination of the numerical proportion between varieties of leucocytes in a third and fourth, let a number of possible and probable variants into the observation which are excluded in carrying out the whole operation upon one and the same large film. Certain countings it is naturally impossible to combine in one and the same film; for instance, those dependent on the colour reactions introduced by Ehrlich cannot be combined with enumerations on a living film; but it is possible to translate the one results into the other, and to make in that way the two modes of counting yield, as it were, control observations.

For diluting the blood, I have used the following solution :—

Distilled water................	300 grams.
Sodium chloride	1·2 „
Neutral potass. oxalate.........	1·2 „
Ehrlich's purified methyl blue ..	0·1 gram.

The chromocytes are not laked in it for several hours at the ordinary temperature of the room. The leucocytes of the dog, cat, and rabbit are not killed by immersion in it for several hours; they are reduced to a sluggish condition, and at the ordinary temperature of the room do not locomote over the floor of the counter. This fluid is preferable to Thoma's 0·3 per cent. acetic solution, which soon kills the leucocytes outright, and rapidly destroys much of their finer structural character. The object of the acid solution is to render invisible the chromocytes by laking them. When blood is diluted only ten times, as is usual for counting leucocytes in the Thoma-Zeiss apparatus, the number of chromocytes present tends to obscure the leucocytes. Myself, I met that difficulty in my earlier countings (although chromocytes and leucocytes were always, both of them, enumerated in one and the same film), by rendering the chromocytes, after counting them, invisible by freezing, and proceeding to count the leucocytes. The freezing was done by placing the counter on a carefully levelled freezing microtome, freezing the film for a few seconds, and then letting it thaw again. Most of the chromocytes are thus laked, and the leucocytes are most of them little altered. The difficulty arising from condensation of moisture on the cover glass is met by using the water immersion objective. It seems better, however, to dilute the blood more freely than ten times, and not to freeze the film. I have latterly always used the solution in the proportion of 49 parts to 1 part of blood. This admixture allows of the chromocytes being easily counted, the normal blood of the dog offering then about 33 chromocytes per square on the floor of the counter.

In counting leucocytes one of the most serious mishaps that can occur is for the leucocytes to cluster or "ball." It is obvious that where this has happened the enumeration is useless. The hyaline leucocytes seem less sticky than do the granular leucocytes. There is always, however, a tendency for all leucocytes to clump in this way. In the above fluid in the above proportion, I have had to reject very few observations on account of clumping. The basis obtained for numerical calculation is, of course, reduced by increase of dilution. This

I have remedied by increasing the area for enumeration on the floor of the counter. I have always counted all the leucocytes found *on the whole ruled floor-space of the two counters*, *i.e.*, not merely on the squares, but outside them, as far as the ruled lines extended. The area thus obtained was in one of the counters (Counter A) $5\frac{3}{4}$ that of the squared area. In the other counter (Counter B) it was $4\frac{504}{507}$, the size of the squared area; this I have treated as 5. As basis for calculation, I have had, therefore, instead of the usually ascertained actual number of leucocytes in 0·01 mm. of blood, the actual number in 0·0215 mm. of blood, a basis more than twice as wide. The counting has been made on the Zeiss movable stage on his Stativ IV, 1, with the dry 4 mm. apochromatic objective, usually combined with ocular 8. Countings have been occasionally carried on on the warm stage (Israel's).

The amount of hæmoglobin in the blood I measure by the Gower's instrument, by the light of a Welsbach lamp reflected from a vertical sheet of white paper not otherwise illuminated.

The specific gravity of the blood is estimated by Roy's* method, as in the observations by Copeman and myself.† The specific gravity of the blood serum is also observed by Roy's method. The blood is previously centrifuged in capillary tubes. Havilland and Lloyd Jones‡ have both employed the centrifuge for separating corpuscles from fluid in minute quantities of blood received into capillary tubes.

The exact procedure with me has been as follows. A drop of blood, as it exudes from a prick in the skin, is taken by capillarity into a fine, freshly drawn glass tube, like a vaccine tube, but longer, and bent into a U shape. The capillary U-tube is then placed with its bent end downwards into a "bucket" on the centrifuge, or in a radial slot on a vulcanite disc ; the two open ends will then lie toward the centre of rotation, and in a few minutes a clear layer of serum or plasma is obtained in each limb of the tube. The specific gravity of the supernatant fluid can be readily ascertained by Roy's method. I say serum or plasma, because it is surprising how often no trace of fibrin seems to exist in the clear layer, even on standing for a long time.

The clear fluid I have often found to be absolutely cell free. I shall refer to the fluid as serum, but I suspect that in several instances it was pure plasma.

Where the temperature is recorded, the rectal temperature in degrees centigrade is meant. By respiratory rate is meant number of inspirations per minute.

II.

The varieties of hæmic leucocytes which I have attempted to distinguish are explained more fully on pp. 186—194. The nomenclature adopted is based on Wharton Jones§ and Max Schultze.||

* 'Journal of Physiology,' vol. 5, p. 9, 1884.

† 'Journal of Physiology,' vol. 9, p. 8, 1890.

‡ 'British Medical Journal,' September 23, 1893.

§ "The Blood Corpuscle considered in its different Phases of Development," 'Phil. Trans.,' 1846, p. 64.

|| 'Archiv für Mikroskopische Anatomie,' vol. 1, p. 1, 1863.

1. Finely granular leucocytes.
2. Coarsely granular leucocytes.
3. Hyaline leucocytes: α. Large.
   ,, ,, β. Small.

Differences between Cat's Blood and Dog's Blood.

The number of chromocytes per unit volume blood is greater in cat's blood than in dog's blood. The individual chromocytes are smaller in the former; according to Gulliver,* the average diameter in cat is 1/4404 in.; in dog, 1/3542 in. The ratio of leucocytes to chromocytes in normal cat's blood is distinctly lower than in dog's blood; this is probably a result of the greater number of the smaller chromocytes per unit volume of cat's blood.

In the blood of nearly one half of the dogs I have examined, a few nucleated chromocytes have been met with. It has been so in some instances with old dogs (in half-grown puppies they are found in numbers); in all instances the dogs were not known to be ailing; some were certainly very active and well-nourished. The nucleated chromocytes were always of the kind called normoblasts. In adult cats the blood seems to contain nucleated chromocytes less commonly, but I have met with them

The specific gravity of the serum of cat's blood has in my experiments averaged distinctly higher than that of dog's blood.

The coarsely granular leucocyte appears rather more numerous in cat's blood than in dog's. Certain differences between the coarsely granular leucocytes in the two species will be mentioned in a short description of the leucocytes (p. 189.)

(1.) *The Seat of Acute Local Inflammation is in the Limb.*

The inflammation was induced in the extremity of the limb in the way above described.

The results on the blood will be best shown by quoting some examples.

Example.

Dog.

10.30 A.M. Temperature, 38·8°. Respiration, 20.

Sp. gr. of blood from artery in ear	1·065
Hæmoglobin value	72
Sp. gr. of blood serum	1·025
Number of chromocytes per mm. blood	6,553,332
,, leucocytes per mm. blood	6,608
,, hyaline leucocytes per mm. blood	302
,, coarsely granular leucocytes per mm. blood	435
,, irregularly nucleate leucocytes per mm. blood	6,281

* 'Proceedings of the Zoological Society of London,' June 15, 1875.

Ratio of leucocytes to chromocytes	1 : 993
,, hyaline leucocytes to chromocytes	1 : 21,844
,, coarsely granular leucocytes to chromocytes	1 : 15,065
,, hyaline leucocytes to total leucocytes	5·2 per cent.
,, coarsely granular leucocytes to total leucocytes	6·8 ,,

11—11.15 A.M. Temperature, 38·8°. Respiration 20.
Lesion established in both hind legs.

12.40 P.M. Temperature, 38°. Respiration, 18.

Sp. gr. of blood of ear	1·078
Hæmoglobin value	95
Sp. gr. of blood serum	1·024
Number of chromocytes per mm. blood	8,600,000
,, leucocytes per mm. blood	15,304
,, hyaline leucocytes per mm. blood (the small kind very scarce)	802
,, coarsely granular leucocytes per mm. blood	404
,, irregularly nucleate leucocytes per mm. blood	14,400
Ratio of leucocytes to chromocytes	1 : 562
,, hyaline leucocytes to chromocytes	1 : 10,750
,, coarsely granular leucocytes to chromocytes	1 : 21,500
,, hyaline leucocytes to total leucocytes	5·2 per cent.
,, coarsely granular leucocytes to total leucocytes	2·6 ,,

3.15 P.M. Temperature, 38°. Respiration, 16.

Sp. gr. of blood from ear	1·0795
Hæmoglobin value	98
Sp. gr. of blood serum	1·0235
Number of chromocytes per mm. blood	9,175,000
,, leucocytes per mm. blood	17,913
,, hyaline leucocytes per mm. blood (small kind less scarce relatively)	378
,, coarsely granular leucocytes per mm. blood	168
,, irregularly nucleate leucocytes per mm. blood	17,502
Ratio of leucocytes to chromocytes	1 : 512
,, hyaline leucocytes to chromocytes	1 : 24,132
,, coarsely granular to chromocytes	1 : 53,970
,, hyaline leucocytes to total leucocytes	2·2 per cent.
,, coarsely granular leucocytes to total leucocytes	0·9 ,,

5.15 P.M. Temperature, 38°. Respiration, 14.

Sp. gr. of blood from ear	1·081
Hæmoglobin value	106
Sp. gr. of blood serum	1·0235
Number of chromocytes per mm. blood	10,200,000
,, leucocytes per mm. blood	32,956
,, hyaline leucocytes per mm. blood	890
,, coarsely granular leucocytes per mm. blood	none found.*
,, irregularly nucleate leucocytes per mm. blood	32,100
Ratio of leucocytes to chromocytes	1 : 309
,, hyaline leucocytes to chromocytes	1 : 11,460
,, ,, ,, total leucocytes	1 : 37

* "None found" refers, unless otherwise stated, to search in the two counters.

12 noon next day. Temperature, 37·8°. Respiration, 22.

Sp. gr. of blood from ear	1·0785
Hæmoglobin value	96
Sp. gr. of blood serum	1·0235
Number of chromocytes per mm. blood	8,800,000
„ leucocytes per mm. blood	29,410
„ hyaline leucocytes per mm. blood	1,430
„ coarsely granular leucocytes per mm. blood	none found.
„ irregularly nucleate leucocytes per mm. blood	28,110
Ratio of leucocytes to chromocytes	1 : 290
„ hyaline leucocytes to chromocytes	1 : 6,153
„ „ „ total leucocytes	1 : 20·5

The smaller kind of hyaline leucocyte forms about 15 per cent. of all the hyaline leucocytes.

12 noon next day. Temperature, 34°. Respiration, 24.

Sp. gr. of blood from ear	1·078
Hæmoglobin value	91
Sp. gr. of blood serum	1·024
Number of chromocytes per mm. blood	8,300,000
„ leucocytes per mm. blood	12,630
„ hyaline leucocytes per mm. blood	1,280
(Of these about 25 per cent. are the small variety.)	
„ coarsely granular per mm. blood	none found.
„ irregularly nucleate per mm. blood	11,070
Ratio of leucocytes to chromocytes	1 : 657
„ hyaline leucocytes to chromocytes	1 : 6,484.

Example.

Dog.

9.30 A.M. Temperature, 39°. Respiration, 24.

Sp. gr. of blood taken from ear	1·066
Hæmoglobin value	69
Sp. gr. of blood serum	1·0245
Number of chromocytes in mm. blood	8,126,600
„ leucocytes in mm. blood	7,500
„ hyaline leucocytes in mm. blood	1,100
„ coarsely granular in mm. blood	417
„ irregularly nucleate leucocytes per mm. blood	6,330
Ratio of leucocytes to chromocytes	1 : 1,083
„ hyaline leucocytes to chromocytes	1 : 7,387
„ coarsely granular leucocytes to chromocytes	1 : 19,480
„ hyaline leucocytes to total leucocytes	1 : 6·8
„ coarsely granular leucocytes to total leucocytes	1 : 18

10.30 –10.45 A.M. Lesion established in one limb only.

11.15 A.M. Temperature, 38·6°. Respiration, 20.

Sp. gr. of blood taken from ear	1·072
Hæmoglobin value	78
Sp. gr. of blood serum	1·025
Number of chromocytes in mm. blood	8,910,000
„ leucocytes in mm. blood	6,670
„ hyaline leucocytes in mm. blood	1,060
„ coarsely granular leucocytes in mm. blood	330

Number of irregularly nucleate leucocytes in mm. blood	5,580
Ratio of leucocytes to chromocytes	1 : 1,186
,, hyaline leucocytes to chromocytes	1 : 8,800
,, coarsely granular leucocytes to chromocytes	1 : 27,000
,, hyaline leucocytes to total leucocytes	1 : 6·2
,, coarsely granular leucocytes to total leucocytes	1 : 20

12.45 P.M. Temperature, 39·2°. Respiration, 24.

Sp. gr. of blood from ear	1·071
Hæmoglobin value	76
Sp. gr. of blood serum	1·025
Number of chromocytes in mm. blood	8,440,000
,, leucocytes in mm. blood	13,166
,, hyaline leucocytes	1,140
,, coarsely granular leucocytes in mm. blood	174
,, irregularly nucleate in mm. blood	1,200
Ratio of leucocytes to chromocytes	1 : 639
,, coarsely granular leucocytes to chromocytes	1 : 48,506
,, hyaline leucocytes to total leucocytes	1 : 11
,, coarsely granular leucocytes to total leucocytes	1 : 79

3.15 P.M. Temperature, 40·2°. Respiration, 28.

Sp. gr. of blood from ear	1·0725
Hæmoglobin value	85
Sp. gr. of blood serum	1·0245
Number of chromocytes in mm. blood	8,626,000
,, leucocytes in mm. blood	28,833
,, hyaline leucocytes in mm. blood	980
,, coarsely granular leucocytes in mm. blood	152
,, irregularly nucleate leucocytes in mm. blood	27,800
Ratio of leucocytes to chromocytes	1 : 299
,, coarsely granular leucocytes to chromocytes	1 : 56,750
,, hyaline leucocytes to total leucocytes	1 : 29
,, coarsely granular leucocytes to total leucocytes	1 : 173

6 P.M. Temperature, 39·4°. Respiration, 25.

Sp. gr. of blood from ear	1·072
Hæmoglobin value	84
Sp. gr. of blood serum	1·023
Number of chromocytes in mm. blood	8,561,000
,, leucocytes in mm. blood	29,583
,, hyaline leucocytes in mm. blood	1,200
,, coarsely granular in mm. blood	none found in the counters.
,, irregularly nucleate in mm. blood	28,200
Ratio of leucocytes to chromocytes	1 : 289
,, hyaline leucocytes to total leucocytes	1 : 24

3 P.M. next day. Temperature, 38°·6. Respiration, 20.

Sp. gr. of blood from ear	1·073
Hæmoglobin value	85
Sp. gr. of blood serum	1·0235
Number of chromocytes in mm. blood	9,142,000
,, leucocytes in mm. blood	32,330

Number of hyaline leucocytes in mm. blood	1,080
" coarsely granular in mm. blood	none found in counter.
" irregularly nucleate in mm. blood	31,100
Ratio of leucocytes to chromocytes	1 : 283
" hyaline to total leucocytes	1 : 31
" coarsely granular to total leucocytes	1 : 850

Example.

Cat.

10 A.M. Temperature, 38°·6. Respiration, 26.

Sp. gr. of blood from ear	1·0535
Hæmoglobin value	44
Sp. gr. of blood serum	1·0305
Number of chromocytes in mm. blood	7,160,000
" leucocytes in mm. blood	14,232
" hyaline leucocytes in mm. blood	3,581
" coarsely granular leucocytes in mm. blood	1,395
" irregularly nucleate leucocytes in mm. blood	13,380
Ratio of leucocytes to chromocytes	1 : 504
" hyaline leucocytes to chromocytes	1 : 1984
" coarsely granular leucocytes to chromocytes	1 : 5114
" hyaline to total leucocytes	1 : 4
" coarsely granular to total leucocytes	1 : 10

10.30—10.45 A.M. Lesion established in one leg.

11.50 A.M. Temperature, 38·2°. Respiration, 30.

Sp. gr. of blood from ear	1·059
Hæmoglobin value	52
Sp. gr. of blood serum	1·0295
Number of chromocytes in mm. blood	9,520,000
" leucocytes in mm. blood	26,140
" hyaline leucocytes in mm. blood	2,790
" coarsely granular leucocytes in mm. blood	930
" irregularly nucleate leucocytes in mm. blood	23,280
Ratio of leucocytes to chromocytes	1 : 364
" hyaline leucocytes to chromocytes	1 : 3412
" coarsely granular leucocytes to chromocytes	1 : 10236
" hyaline to total leucocytes	1 : 9·4
" coarsely granular to total leucocytes	1 : 28

5.15 P.M. Temperature, 39°·3. Respiration, 37.

Sp. gr. of blood from ear	1·0575
Hæmoglobin value	51
Sp. gr. of blood serum	1·0275
Number of chromocytes in mm. blood	9,160,000
" leucocytes in mm. blood	32,420
" hyaline leucocytes in mm. blood	1,618
" coarsely granular leucocytes in mm. blood	47
" irregularly nucleate leucocytes in mm. blood	30,690
Ratio of leucocytes to chromocytes	1 : 282
" hyaline leucocytes to chromocytes	1 : 5654
" coarsely granular leucocytes to chromocytes	1 : 194893
" hyaline to total leucocytes	1 : 20
" coarsely granular to total leucocytes	1 : 697

6.30 P.M. Temperature, 39°·2. Respiration, 35.

Sp. gr. of blood from ear	1·058
Hæmoglobin value..	51
Sp. gr. of blood serum	1·0275
Number of chromocytes in mm. blood	9,140,000
" leucocytes in mm. blood	34,100
" hyaline leucocytes in mm. blood	1,840
" coarsely granular leucocytes in mm. blood. None found in the counters, and none in cover-glass films, nor in counting 10,000 leucocytes from the leucocyte layer in a centrifuged specimen; but one of typical normal appearance seen in examining specimens from the leucocyte layer of the centrifuged blood.	
Number of irregularly nucleate leucocytes in mm. blood.......	32,150
Ratio of leucocytes to chromocytes........................	1 : 268
" hyaline leucocytes to chromocytes	1 : 4967
" hyaline leucocytes to total leucocytes...............	1 : 18

Under the conditions of experiment the changes in the blood generally circulating were as follows:—

1. The specific gravity of the blood was increased.

2. The specific gravity of the serum was slightly lessened or remained not obviously altered.

3. The hæmoglobin content of the unit volume of blood was increased.

4. The number of chromocytes in the unit volume of blood was increased.

5. The numerical ratio of leucocytes to chromocytes in the unit volume of blood was always increased, sometimes after a preliminary decrease of the ratio.

6. The number of leucocytes in the unit volume of blood was at first slightly diminished and then increased; much later there was sometimes a fall to below normal.

7. The numerical ratio of coarsely granular leucocytes to chromocytes in the unit volume of blood was diminished.

8. The number of coarsely granular leucocytes in the unit volume of blood was diminished.

9. The numerical ratio of coarsely granular to the rest of the leucocytes was diminished.

10. The numerical ratio of finely granular to the rest of the leucocytes was greatly increased after a certain time.

11. The number of hyaline leucocytes in the unit volume of blood became less.

12. Hæmoglobin in solution appeared in the plasma of the blood, and of the lymph in the thoracic duct, and of the exudation fluid in the limb.

13. There seemed to be a certain small number of nucleated

chromocytes added to the blood of general circulation, but whether this was always the case I am not certain.

14. The rapidity of clotting of the blood was increased, and the lymph also clotted well.

(2.) *The Seat of the Local Inflammation is in the Abdominal Cavity.*

The inflammation was induced as above described in a tract of the small intestine. The following are examples of the experiments :—

Example.

Dog.

9.35 A.M. Temperature, 38°·5. Respiration, 23.

Sp. gr. of blood from ear	1·0515
Hæmoglobin value	47
Sp. gr. of blood serum	1·023
Number of chromocytes in mm. blood	4,575,000
" leucocytes in mm. blood	7,750
" hyaline leucocytes (large) in mm. blood	780
" " " (small) in mm. blood	282
" coarsely granular leucocytes in mm. blood	1,010
" irregularly nucleate leucocytes in mm. blood	5,630
Ratio of leucocytes to chromocytes	1 : 590
" hyaline leucocytes to chromocytes	1 : 4,480
" coarsely granular leucocytes to chromocytes	1 : 4,604
" hyaline to total leucocytes	1 : 7·3
" coarsely granular to total leucocytes	1 : 7·7

10.20 A.M. Piece of jejunum sponged.

11.15 A.M. Temperature, 38°. Respiration, 19.

Sp. gr. of blood from ear	1·055
Hæmoglobin value	60
Sp. gr. of blood serum	1·0225
Number of chromocytes in mm. blood	6,750,000
" leucocytes in mm. blood	6,690
" hyaline leucocytes in mm. blood	1,148
" coarsely granular leucocytes in mm. blood	438
" irregularly nucleate leucocytes in mm. blood	5,160
Ratio of leucocytes to chromocytes	1 : 1,009
" hyaline leucocytes to chromocytes	1 : 5,869
" coarsely granular leucocytes to chromocytes	1 : 15,340
" hyaline to total leucocytes	1 : 5·9
" coarsely granular to total leucocytes	1 : 13

1.15 P.M. Temperature, 38°·6. Respiration, 22.

Sp. gr. of blood from ear	1,058
Hæmoglobin value	66
Sp. gr. of blood serum	1·0225
Number of chromocytes in mm. blood	7,990,000
" leucocytes in mm. blood	14,522
" hyaline leucocytes in mm. blood	1,320
(About 25 per cent. of these are the small kind).	

Number of coarsely granular leucocytes in mm. blood	370
„ irregularly nucleate leucocytes in mm. blood	13,100
Ratio of leucocytes to chromocytes	1 : 552
„ hyaline leucocytes to chromocytes	1 : 6,053
„ coarsely granular leucocytes to chromocytes	1 : 21,594
„ hyaline leucocytes to total leucocytes	1 : 11
„ coarsely granular leucocytes to total leucocytes	1 : 39

3.45 P.M. Temperature, 38°·2. Respiration, 20.

Sp. gr. of blood from ear	1·060
Hæmoglobin value	70
Sp. gr. of blood serum	1·0225
Number of chromocytes in mm. blood	8,010,000
„ leucocytes in mm. blood	32,087
„ hyaline leucocytes in mm. blood	764
„ coarsely granular leucocytes in mm. blood	260
„ irregularly nucleate leucocytes in mm. blood	31,200
Ratio of leucocytes to chromocytes	1 : 250
„ hyaline leucocytes to chromocytes	1 : 10,540
„ coarsely granular leucocytes to chromocytes	1 : 30,808
„ hyaline leucocytes to total leucocytes	1 : 42
„ coarsely granular leucocytes to total leucocytes	1 : 123

5.45 P.M. Temperature, 38°·2. Respiration, 20.

Sp. gr. of blood from ear	1·060
Hæmoglobin value	71
Sp. gr. of blood serum	1·0225
Number of chromocytes in mm. blood	8,040,000
„ leucocytes in mm. blood	43,565
„ hyaline leucocytes in mm. blood	854
„ coarsely granular leucocytes in mm. blood	none found in the counters.
„ irregularly nucleate leucocytes in mm. blood	42,600
Ratio of leucocytes to chromocytes	1 : 184
„ hyaline leucocytes to chromocytes	1 : 9,458
„ hyaline leucocytes to total leucocytes	1 : 51

„ coarsely granular leucocytes to total leucocytes must have been very low. No coarsely granular were found in the "counter" nor in two cover-glass preparations, but one example was found in a film from the leucocyte layer of a sample of centrifuged blood.

7.30 P.M. Temperature, 38°·3. Respiration, 20.

Sp. gr. of blood from ear	1·0595
Hæmoglobin value	70
Sp. gr. of blood serum	1·0225
Number of chromocytes in mm. blood	7,785,000
„ leucocytes in mm. blood	55,304
„ hyaline leucocytes in mm. blood	922
„ coarsely granular leucocytes in mm. blood	none found.
„ irregularly nucleate leucocytes in mm. blood	54,320
Ratio of leucocytes to chromocytes	1 : 140
„ hyaline leucocytes to chromocytes	1 : 8,462
„ hyaline leucocytes to total leucocytes	1 : 60

Next day. Noon. Temperature, 38°. Respiration, 19.

Sp. gr. of blood from ear	1·058
Hæmoglobin value	64
Sp. gr. of blood serum	between 1·022 and 1·0225
Number of chromocytes in mm. blood	7,450,000
„ leucocytes in mm. blood	30,400
„ hyaline leucocytes in mm. blood	760
„ coarsely granular leucocytes in mm. blood	none found.
„ irregularly nucleate leucocytes in mm. blood	29,700
Ratio of leucocytes to chromocytes	1 : 245
„ hyaline leucocytes to chromocytes	1 : 9,802
„ hyaline leucocytes to total leucocytes	1 : 43

In the examination of cover-glass films two coarsely granular cells were found after much search, but 1,000 leucocytes were counted without meeting one.

2.30 P.M. Temperature, 38°·4. Respiration, 18.

Sp. gr. of blood from ear	1·058
Hæmoglobin value	62
Sp. gr. of blood serum	1·0223
Number of chromocytes in mm. blood	7,380,000
„ leucocytes in mm. blood	33,000
„ hyaline leucocytes in mm. blood	650
„ coarsely granular leucocytes in mm. blood	none found.
„ irregularly nucleate leucocytes in mm. blood	32,300
Ratio of leucocytes to chromocytes	1 : 224
„ hyaline leucocytes to chromocytes	1 : 11,354
„ hyaline leucocytes to total leucocytes	1 : 50

No coarsely granular leucocytes met with at all.

6 P.M. Temperature, 39°. Respiration, 18.

Sp. gr. of blood from ear	1·060
Hæmoglobin value	67
Sp. gr. of blood serum	1·0223
Number of chromocytes in mm. blood	7,800,000
„ leucocytes in mm. blood	46,600
„ hyaline leucocytes in mm. blood	775
„ coarsely granular leucocytes in mm. blood	none found.
„ irregularly nucleate leucocytes in mm. blood	45,800
Ratio of leucocytes to chromocytes	1 : 168
„ hyaline leucocytes to chromocytes	1 : 10,060
„ hyaline leucocytes to total leucocytes	1 : 59·8

Noon, next day. Temperature, 38°·6. Respiration, 18.

Sp. gr. of blood from ear	1·056
Hæmoglobin value	52
Sp. gr. of blood serum	1·0223
Number of chromocytes in mm. blood	4,860,000
„ leucocytes in mm. blood	31,480
„ hyaline leucocytes in mm. blood	787
„ coarsely granular leucocytes in mm. blood	none found.
„ irregularly nucleate leucocytes in mm. blood	30,300

Ratio of leucocytes to chromocytes	1 : 154
„ hyaline leucocytes to chromocytes	1 : 6,152
„ hyaline leucocytes to total leucocytes	1 : 40

Example.

Cat.

6.30 P.M. Temperature, 38°·6.

Sp. gr. of blood from ear	1·049
Hæmoglobin value	51
Sp. gr. of blood serum	1·027
Number of chromocytes in mm. blood	6,040,000
„ leucocytes in mm. blood	10,610
„ hyaline leucocytes in mm. blood	1,913
„ coarsely granular leucocytes in mm. blood	1,044
„ irregularly nucleate leucocytes in mm. blood	8,600
Ratio of leucocytes to chromocytes	1 : 570
, hyaline to total leucocytes	1 : 5·5
„ coarsely granular leucocytes to total leucocytes	1 : 10

7 P.M. Piece of ileum sponged.

7.40 P.M.

Sp. gr. of blood from ear	1·052
Hæmoglobin value	54
Sp. gr. of blood serum	1·0265

9.30 A.M. Temperature, 38°·8. Respiration, 40.

Sp. gr. of blood	1·059
Hæmoglobin value	60
Sp. gr. of blood serum	1·026

One coarsely granular leucocyte met in counting through 2,000 leucocytes in cover-glass preparations. The films, both fresh and dried, show obvious but not extremely severe leucocytosis.

Under these conditions of experiment the changes in the blood of the general circulation resembled in their main features the results observed in the experiments of series (I). I will not therefore recapitulate the results. I will merely add that the addition of nucleated chromoblasts to the blood seemed less uncertain in these experiments than in the experiments on the limb.

A modified form of the experiment consists in simply ligating the knuckle of intestine, and returning it with aseptic precautions into the peritoneal cavity. This modification, although the same main changes in the blood were as before brought about, did not give quite the same sequence of events. I quote examples.

Example.

Dog.

9 P.M. Was fed at noon. Temperature, 39°. Respiration, 22.

Sp. gr. of blood from ear	1·058
Hæmoglobin value	50
Sp. gr. of blood serum (slightly milky)	1·0275
Number of chromocytes in mm. blood	2,502,000
„ leucocytes in mm. blood	6,260

Number of hyaline leucocytes in mm. blood	1,740
,, coarsely granular leucocytes in mm. blood	180
,, irregularly nucleate leucocytes in mm. blood	4,500
Ratio of leucocytes to chromocytes	1 : 400
,, hyaline leucocytes to chromocytes	1 : 1,438
,, coarsely granular leucocytes to chromocytes	1 : 13,900
,, hyaline leucocytes to total leucocytes	1 : 3·6
,, coarsely granular leucocytes to total leucocytes	1 : 34

9.30 P.M. Ligature placed on jejunum.

9.30 A.M. Temperature, 38°·4. Respiration, 32.

Sp. gr. of blood from ear	1·069
Hæmoglobin value	74
Sp. gr. of blood serum (not milky)	1·0270
Number of chromocytes in mm. blood	6,960,000
,, leucocytes in mm. blood	16,700
,, hyaline leucocytes in mm. blood	560
,, coarsely granular leucocytes in mm. blood	none found.
,, irregularly nucleate leucocytes in mm. blood	16,120
Ratio of leucocytes to chromocytes	1 : 417
,, hyaline leucocytes to chromocytes	1 : 12,428
,, hyaline leucocytes to total leucocytes	1 : 30

12.45 P.M. Temperature, 38°. Respiration, 28.

Sp. gr. of blood from ear	1·0705
Hæmoglobin value	77
Sp. gr. of blood serum	1·028
Number of chromocytes in mm. blood	6,980,000
,, leucocytes in mm. blood	8,700
,, hyaline leucocytes in mm. blood	390
,, coarsely granular leucocytes in mm. blood	none found.
,, irregularly nucleate leucocytes in mm. blood	8,280
Ratio of leucocytes to chromocytes	1 : 802
,, hyaline leucocytes to chromocytes	1 : 17,900
,, hyaline leucocytes to total leucocytes	1 : 22

3.30 P.M. Temperature, 33°. Respiration, 20.

Sp. gr. of blood from ear	1·074
Hæmoglobin value	83
Sp. gr. of blood serum	1·029
Number of chromocytes in mm. blood	8,293,000
,, leucocytes in mm. blood	4,868
,, hyaline leucocytes in mm. blood	540
,, coarsely granular leucocytes in mm. blood	none found.
,, irregularly nucleate leucocytes in mm. blood	4,300
Ratio of leucocytes to chromocytes	1 : 1,703
,, hyaline leucocytes to chromocytes	1 : 15,360
,, hyaline leucocytes to total leucocytes	1 : 9

6.15 P.M. Temperature, 30°·2. Respiration, 17.

Sp. gr. of blood from ear	1·072
Hæmoglobin value	80
Sp. gr. of blood serum	1·0295
Number of chromocytes in mm. blood	7,100,000
,, leucocytes in mm. blood	2,610

Number of hyaline leucocytes in mm. blood	650
" coarsely granular leucocytes in mm. blood	none found.
" irregular nucleate leucocytes in mm. blood	1,900
Ratio of leucocytes to chromocytes	1 : 2,730
" hyaline leucocytes to chromocytes	1 : 10,923
" hyaline leucocytes to total leucocytes	1 : 4

Example.

Dog.

12.45 P.M. Temperature, 38·4°. Respiration, 22.

Sp. gr. of blood from ear	1·059
Hæmoglobin value	55
Sp. gr. of blood serum (no molecular base)	1·0265
Number of chromocytes in mm. blood	5,800,000
" leucocytes in mm. blood	15,900
" hyaline leucocytes in mm. blood	3,200
" coarsely granular leucocytes in mm. blood	1,600
" irregularly nucleate leucocytes in mm. blood	11,000
Ratio of leucocytes to chromocytes	1 : 368
" hyaline leucocytes to chromocytes	1 : 1,812
" coarsely granular leucocytes to chromocytes	1 : 3,625
" hyaline leucocytes to total leucocytes	1 : 5
" coarsely granular leucocytes to total leucocytes	1 : 10

1.15 P.M. Jejunum ligated.

1.40 P.M. Temperature, 38·2°. Respiration, 22.

Sp. gr. of blood from ear	1·059
Hæmoglobin value	55
Sp. gr. of blood serum	1·0265
Number of chromocytes in mm. blood	5,815,000
" leucocytes in mm. blood	15,600
" hyaline leucocytes in mm. blood	3,280
" coarsely granular leucocytes in mm. blood	1,540
" irregularly nucleate leucocytes in mm. blood	11,400
Ratio of leucocytes to chromocytes	1 : 372
" hyaline leucocytes to chromocytes	1 : 1,762
" coarsely granular leucocytes to chromocytes	1 : 3,776
" hyaline leucocytes to total leucocytes	1 : 4·7
" coarsely granular leucocytes to total leucocytes	1 : 10

3.40 P.M. Temperature, 38·4°. Respiration, 22.

Sp. gr. of blood from ear	1·059

4.30 P.M. Temperature, 38·7°. Respiration, 22.

Sp. gr. of blood from ear	1·059
Hæmoglobin value	56
Sp. gr. of blood serum	1·0255
Number of chromocytes in mm. blood	5,850,000
" leucocytes in mm. blood	15,820
" hyaline leucocytes in mm. blood (more than 50 per cent. are the "small" variety.)	5,270
" coarsely granular leucocytes in mm. blood	700
" irregularly nucleate leucocytes in mm. blood	10,400
Ratio of leucocytes to chromocytes	1 : 389

Ratio of hyaline leucocytes to chromocytes	1 : 1,110
„ coarsely granular leucocytes to chromocytes	1 : 8,357
„ hyaline to total leucocytes	1 : 3
„ coarsely granular leucocytes to total leucocytes	1 : 22·5

6.30 P.M. Temperature, 39°. Respiration, 22.

From examination in stained films the nucleated red blood corpuscles are not so numerous; and the proportion of hyaline leucocytes to total leucocytes is lower, *i.e.*	1 : 4·5

8.30 P.M. Temperature, 38·6°. Respiration, 26.

Sp. gr. of blood from ear	1·0605
Hæmoglobin value	65
Sp. gr. of blood serum	1·0255
Number of chromocytes in mm. blood	6,150,000
„ leucocytes in mm. blood	34,350
„ hyaline leucocytes in mm. blood	1,720
„ coarsely granular leucocytes in mm. blood	108
„ irregularly nucleate leucocytes in mm. blood	32,600
Ratio of leucocytes to chromocytes	1 : 179
„ hyaline leucocytes to chromocytes	1 : 3,578
„ coarsely granular leucocytes to chromocytes	1 : 56,944
„ hyaline leucocytes to total leucocytes	1 : 20·6
„ coarsely granular leucocytes to total leucocytes	1 : 318

10.30 A.M. Temperature, 38°. Respiration, 24.

Sp. gr. of blood from ear	1·067
Hæmoglobin value	74
Sp. gr. of blood serum	1·0253
Number of chromocytes in mm. blood	8,175,000
„ leucocytes in mm. blood	16,700
„ hyaline leucocytes in mm. blood	1,850
„ coarsely granular leucocytes in mm. blood	none found in counter.
„ irregularly nucleate leucocytes in mm. blood	14,800
Ratio of leucocytes to chromocytes	1 : 489
„ hyaline leucocytes to chromocytes	1 : 4,418
„ hyaline leucocytes to total leucocytes	1 : 9
„ coarsely granular leucocytes to total leucocytes; as judged by counting cover-glass preparations, the proportion was about	1 : 650

Example.

Dog.

6.30 P.M. Temperature, 38·5°. Respiration, 22.

Sp. gr. of blood from ear	1·059
Hæmoglobin value	55
Sp. gr. of blood serum	1·024
Number of chromocytes in mm. blood	5,913,300
„ leucocytes in mm. blood	12,610
„ hyaline leucocytes in mm. blood	2,250
„ coarsely granular leucocytes in mm. blood	790
„ irregularly nucleate leucocytes in mm. blood	10,300
Ratio of leucocytes to chromocytes	1 : 468
„ hyaline leucocytes to chromocytes	1 : 2,628

Ratio of coarsely granular leucocytes to chromocytes	1 : 7,485
„ hyaline leucocytes to total leucocytes	1 : 5·8
„ coarsely granular leucocytes to total leucocytes	1 : 16

7 P.M. Ligation of piece of ileum.

8.45 A.M. Temperature, 39·2°. Respiration, 28.

Sp. gr. of blood from ear	1·072
Hæmoglobin value	72
Sp. gr. of blood serum	1·025
Number of chromocytes in mm. blood	7,966,000
„ leucocytes in mm. blood	29,600
„ hyaline leucocytes in mm. blood	1,233
„ coarsely granular leucocytes in mm. blood	none seen.
„ irregularly nucleate leucocytes in mm. blood	28,300
Ratio of leucocytes to chromocytes	1 : 269
„ hyaline leucocytes to chromocytes	1 : 6,476
„ hyaline leucocytes to total leucocytes	1 : 24

12.30 P.M. Temperature, 38·2°. Respiration, 25.

Sp. gr. of blood from ear	1·0735
Hæmoglobin value	78
Sp. gr. of blood serum	1·0255
Number of chromocytes in mm blood	8,540,000
„ leucocytes in mm. blood	21,820
„ hyaline leucocytes in mm. blood	910
„ coarsely granular leucocytes in mm. blood	none found in the counters.
„ irregularly nucleate leucocytes in mm. blood	20,760
Ratio of leucocytes to chromocytes	1 : 380
„ hyaline leucocytes to chromocytes	1 : 9,490
„ hyaline leucocytes to total leucocytes	1 : 24·5

3.30 P.M. Temperature, 39·2°. Respiration, 32.

Sp. gr. of blood from ear	1·073
Hæmoglobin value	81
Sp. gr. of blood serum	1·025
Number of chromocytes in mm. blood	8,520 000
„ leucocytes in mm. blood	23,043
„ hyaline leucocytes in mm. blood	1,210
„ coarsely granular leucocytes in mm. blood	none found.
„ irregularly nucleate leucocytes in mm. blood	21,700
Ratio of leucocytes to chromocytes	1 : 370
„ hyaline leucocytes to chromocytes	1 : 7,100
„ hyaline leucocytes to total leucocytes	1 : 19

5.45 P.M. Temperature, 39·6°. Respiration, 42.

Sp. gr. of blood from ear	1·073
Hæmoglobin value	82
Sp. gr. of blood serum	1·025
Number of chromocytes in mm. blood	8,490,000
„ leucocytes in mm. blood	21,000
„ hyaline leucocytes in mm. blood	1,060
„ coarsely granular leucocytes in mm. blood	none found.
„ irregularly nucleate leucocytes in mm. blood	19,900

Ratio of leucocytes to chromocytes	1 : 404
„ hyaline leucocytes to chromocytes	1 : 8,480
„ hyaline leucocytes to total leucocytes	1 : 20

(3.) *The Inflammation is located in the Gastro-intestinal Mucous Membrane.*

The inflammation was induced from the internal surface of the bowel in the manner above described. The following will serve as an example of the effects upon the blood:—

Example.

Cat.

10 A.M. Temperature, 39°. Respiration, 30.

Sp. gr. of blood from ear	1·053
Hæmoglobin value	41
Sp. gr. of blood serum	1·0285
Number of chromocytes in mm. blood	6,970,000
„ leucocytes in mm. blood	7,210
„ coarsely granular leucocytes in mm. blood	1,115
Ratio of leucocytes to chromocytes	1 : 968
„ coarsely granular leucocytes to chromocytes	1 : 6.335
„ coarsely granular leucocytes to total leucocytes	1 : 6·4

11 A.M. 0·3 gram. calomel and 12 grams magnes. sulphate is given by mouth.

11.45 A.M. Temperature, 39°. Respiration, 32.

Sp. gr. of blood from ear	1·0535
Hæmoglobin value	41
Sp. gr. of blood serum	1·0285
Number of chromocytes in mm. blood	7,200,000
„ leucocytes in mm. blood	6,920
„ coarsely granular leucocytes in mm. blood	845
Ratio of leucocytes to chromocytes	1 : 1,040
„ coarsely granular leucocytes to chromocytes	1 : 8,520
„ coarsely granular leucocytes to total leucocytes	1 : 8·2

(Hyaline leucocytes are rather numerous.)

12.45 P.M. Temperature, 38·6°. Respiration, 32.

Sp. gr. of blood from ear	1·0535
Hæmoglobin value	42
Sp. gr. of blood serum	1·0285
Number of chromocytes in mm. blood	7,340,000
„ leucocytes in mm. blood	7,200
„ coarsely granular leucocytes in mm. blood	780
Ratio of leucocytes to chromocytes	1 : 1,019
„ coarsely granular leucocytes to chromocytes	1 : 9,410
„ coarsely granular leucocytes to total leucocytes	1 : 9·2

(Hyaline leucocytes are rather numerous.)

3.15 P.M. Temperature, 38·4°. Respiration, 30.

Sp. gr. of blood from ear	1·0545
Hæmoglobin value	45
Sp. gr. of blood serum	1·0285
Number of chromocytes in mm. blood	7,460,000

Number of leucocytes in mm. blood	13,535
„ coarsely granular leucocytes in mm. blood	420
Ratio of leucocytes to chromocytes	1 : 552
„ coarsely granular leucocytes to chromocytes	1 : 17,760
„ coarsely granular leucocytes to total leucocytes	1 : 32·2

4.45 P.M. Temperature, 38·6°. Respiration, 32.

Sp. gr. of blood from ear	1·055
Hæmoglobin value	46
Sp. gr. of blood serum	1·0285
Number of chromocytes in mm. blood	7,486,000
„ leucocytes in mm. blood	14,700
„ coarsely granular leucocytes in mm. blood	One example found in the two counters together; several examples found in fresh and stained films.
Ratio of leucocytes to chromocytes	1 : 508

9 P.M. Temperature, 38·5°. Respiration, 30.

Sp. gr. of blood from ear	1·0545
Hæmoglobin value	44
Sp. gr. of blood serum	1·0285
Number of chromocytes in mm. blood	7,200,000
„ leucocytes in mm. blood	12,200
„ coarsely granular leucocytes in mm. blood	93
Ratio of leucocytes to chromocytes	1 : 590

12 noon next day.

Sp. gr. of blood from ear	1·053

(Plenty of coarsely granular leucocytes in blood, but not enumerated.)

The results in this series have followed in their broad features those of the previous. The difference from those seems one of degree rather than of kind.

Heidenhain* has observed that in the intestinal mucous membrane of the dog the number of cells with oxyphil granulation is increased by a purgative. He leaves it open whether his cells are the same as the oxyphil cells of the blood, and Ehrlich could not give a definite opinion on the point. A notable feature in my experiments, of this series as of the others, has been the great numerical reduction of the oxyphil (α-granulation, coarsely granular) leucocytes in the circulating blood. I believe that a similar though much less marked diminution of these cells follows the ingestion of a full meal, and also that abstinence from food causes in the blood a higher percentage of the cell (*vide infra*, p. 205).

* "Beiträge zur Histologie u. Physiologie der Dünndarmschleimhaut." 'Arch. f. Gesammte Physiologie,' vol. 43, Supplem. Heft.

III. Remarks on the Hæmic Changes observed.

In this note I propose to remark briefly on the significance to be attached to the above hæmic changes.

(I.) *The Apoplasmia of the Blood.*

The measurements shew that consequent upon an acute local inflammation the circulating blood becomes inspissated in the sense that it loses some of its plasma, while its chromocytes do not escape, or at least not in direct proportion to the loss of plasma. There results, therefore, an *apoplasmia* of the blood, referable, doubtless, to increased exudation through the vascular membrane in the inflamed area. The amount of fluid lost to the circulation by the vascular leakage at the *locus læsionis* is thus shown to be not equalised by increased entrance of lymph into the circulation, *viâ* thoracic duct, &c. The local tumor itself consists partly of fluid exudation, whence it is obvious that not all the actual fluid exuded is returned forthwith by the lymph drainage system. It is conceivable that the loss of fluid from the blood, threatening as it must, an upset of various mechanical arrangements in the circulation, would be remedied at once or very soon by call upon the tissue lymph of various other regions, especially as Heidenhain has shown that such a call can be made by chemical means appealing through the circulation. The above observations negative this idea. The plasma of the blood as regards quantity is neither maintained nor speedily re-established. The facts show that the call on the lymph of other parts, if made, does not at least suffice to speedily restore to the blood its normal quantity of fluid. Nor is the phenomenon simply a case of lost time between the escape of the fluid from the circulation and its return again into the circulation; it persists for too considerable a period. In one experiment the blood for more than sixty hours was apoplasmic to the extent that its specific gravity remained heightened 0·021 (water 1·000) above normal, while the specific gravity of its serum (plasma) was not heightened at all, indeed was 0·002 less than at outset of experiment. Nor need it be extreme in order to be long-lasting, as the following exemplifies:—

Dog, young; in good condition.

3 P.M. Fed at noon, chiefly lean meat.

Sp. gr. of blood from ear	1·054
,, ,, serum from ear	1·023

Two days later. 3.15 P.M. Temperature, 39°. Respiration, 20. Not fed to day, in view of surgical operation.

Sp. gr. of blood from ear	1·054
,, ,, serum from ear	1·023

Halstead's operation of intestinal anastomosis then performed with full antiseptic precautions and under complete anæsthesia, by Messrs. Ballance and Edmunds.

4.30 (after operation).

Sp. gr. of blood from ear	1·062
„ „ serum from ear	1·023 (or a little less).

3 P.M. Temperature, 39·2°. Respiration, 30. Took a little milk this morning.

Sp. gr. of blood from ear	1·060
„ „ serum from ear	1·023

Next day, noon. Temperature, 39·8°. Respiration, 20.

Sp. gr. of blood from ear	1·059
„ „ serum from ear	1·023

Next day, noon. Temperature, 39·8°. Respiration, 20.

Sp. gr. of blood from ear	1·0585
„ „ serum from ear	1·023

Next day, noon. Temperature, 39·5°. Respiration, 20.

Sp. gr. of blood from ear	1·0565
„ „ serum from ear	1·023

Next day, noon. Temperature, 39·4°. Respiration, 20.

Sp. gr. of blood from ear	1·055
„ „ serum from ear	1·023

Although never extreme in degree, the apoplasmia of the blood here lasted through five days, in consequence of a carefully-conducted surgical operation accompanied by no untoward event, and soon ending favourably.

The degree of apoplasmia appears to depend in some measure upon the extent of the vascular area involved in the inflammation. For example, when both feet are involved in the lesion the apoplasmia is more severe than in experiments affecting one foot only.

Such an apoplasmia must notably increase the friction-coefficient of the blood.

Whether apoplasmia of the blood is an accompaniment in appreciable degree of all extensive local inflammation I cannot yet say. It has occurred as yet, without exception, in all my experiments, excluding three performed on the pleural cavity of the cat. The particular features of these exceptional experiments are fairly exhibited by the following example :—

Example.

Cat.

9.30 A.M. Temperature, 39°. Respiration, 30.

Sp. gr. of blood from ear	1·055
Hæmoglobin value	46
Sp. gr. of blood serum	1·029
Number of chromocytes in mm. blood	7,260,000
„ leucocytes in mm. blood	17,210

Number of hyaline leucocytes in mm. blood	2,760
,, coarsely granular leucocytes in mm. blood	1,080

11.45 A.M. Temperature and respiration as before.

Sp. gr. of blood and serum as before.

Hæmoglobin value estimated at 47.

Number of chromocytes in mm. blood	7,450,000
,, leucocytes in mm. blood	16,960
,, hyaline leucocytes in mm. blood	2,700
,, coarsely granular leucocytes in mm. blood	1,110

11.45—12 noon. Lesion established in right pleural cavity.

1 P.M. Temperature, 36·4°. Respiration, 40.

Sp. gr. of blood from ear	1·0545
Hæmoglobin value	45
Sp. gr. of blood serum	1·029
Number of chromocytes in mm. blood	7,100,000
,, leucocytes in mm. blood	39,120
,, hyaline leucocytes in mm. blood	2,600
,, coarsely granular leucocytes in mm. blood	610

2.30 P.M. Temperature, 37·2°. Respiration, 32.

Sp. gr. of blood from ear	1·0545
Hæmoglobin value	46
Sp. gr. of blood serum	1·0285
Number of chromocytes in mm. blood	7,600,000
,, leucocytes in mm. blood	44,410
,, hyaline leucocytes in mm. blood	2,415
,, coarsely granular leucocytes in mm. blood	585

6.30 P.M. Temperature, 39·2°. Respiration, 34.

Sp. gr. of blood	1·0495
Hæmoglobin value	41
Sp. gr. of blood serum	1·028
Number of chromocytes in mm. blood	6,840,000
,, leucocytes in mm. blood	48,560
,, hyaline leucocytes in mm. blood	2,530
,, coarsely granular leucocytes in mm. blood	138

Autopsy made at 7 P.M. revealed no hæmorrhage; I suspected the fall in the specific gravity might be due to hæmorrhage, and so performed autopsy at once to see the seat of it. There was a not very copious exudation into the pleural cavity; the pleural surface showed patches of inflammatory cells, but among these not many coarsely granular were found in my examination of them.

It is noticeable that, although the apoplasmia of the blood was here absent, there was, nevertheless, a great reduction in the number of coarsely granular leucocytes, not merely relatively to the rest of the leucocytes, but absolutely per unit volume of blood.

In the experiments with the ligation of a piece of intestine and mesentery, the apoplasmia developed later than in the other series. Copeman and myself* have noticed that in the rabbit the operation

* *Loc. cit.*, and 'Journ. of Physiol.,' vol. 14, p. 52.

of ligation of the vessels of the spleen, and various other forms of experimental interference with the contents of the abdominal cavity, including even the simple opening of the cavity by an incision through the linea alba, are all followed by increase in the specific gravity of the blood. In these cases there occurred increase in the specific gravity usually detectible in thirty minutes or less from the completion of the operation. I was therefore somewhat surprised to meet so long a latent period for the reaction in the case of the ligation of the intestine or mesentery of the dog. But in the rabbit interference with the abdomen so disturbs the normal respiration (in rabbits respiration is almost entirely abdominal) that complications arise which are far more considerable than in the dog; *e.g.*, in the rabbit the blood pressure often exhibits under these conditions a considerable temporary depression, and the respiratory rate is very greatly hurried. W. Hunter* has observed in this animal an increase of specific gravity of the blood to follow interperitoneal transfusion. By Copeman and myself it was suggested that this inspissation of the blood is a concomitant, or even a symptom, of "abdominal shock." Subsequent observations by Mr. Grünbaum and by myself, but especially by Professor Roy and Dr. Cobbett, have confirmed its association with abdominal operations, but I would now extend its scope to a large number of other inflammatory lesions.

(II.) *Changes in the Total Number of the Leucocytes.*

That the number of leucocytes per unit volume of circulating blood is increased in many cases of acute local inflammation is a fact established by the researches of numerous observers. Some of the most recent and detailed observations on this point are by v. Limbeck† and by Rieder.‡ They supply careful measurements of the degree of this "inflammatory leucocytosis." With a number of their observations my own are fully in accord. In two respects, however, our observations do not agree.

V. Limbeck states that leucocytosis always commences prior to the occurrence of any inflammatory exudation; the exudation is a result of the leucocytosis; to my mind his observations do not prove the fact. Certainly, from a number of my experiments, I should conclude rather the reverse, because the blood became obviously apoplasmic prior to any increase of the number of leucocytes in it.

Löwit,§ in discussing Limbeck's and Rieder's observations, remarks

* 'Journ of Physiol.,' vol. 11, p. 115.

† 'Arch. f. Heilkunde,' vol. 10, p. 392, 1890.

‡ 'Beiträge z. Kenntniss d. Leukocytose,' Leipzig, 1892. Rieder gives a very complete review of previous observations and opinions on "inflammatory leucocytosis;" I will not, therefore, recapitulate them here.

§ *Op. cit.*

that, although the fact is not mentioned by them nor obtainable from their measurements, he would expect a diminution in the number of leucocytes in the circulating blood to precede the leucocytosis. I have a number of observations which demonstrate the accuracy of this supposition by Löwit. It seems the rule for inflammatory leucocytosis to be preceded by a *leucocytopenia* (Löwit's term). This preliminary leucocytopenia of the blood is the more remarkable when, instead of the number of leucocytes per unit volume of blood, the numerical ratio of leucocytes to chromocytes is studied. If the total number of leucocytes remained the same there would, as a result of the apoplasmia at this time, appear to be an increased number of them per unit volume of blood.

The *degree* of leucocytosis which occurred in the experiments was often very considerable. The number of leucocytes per unit volume of blood was in some instances increased sevenfold. A small part only of such an increase as this can be accounted for by the coexisting degree of apoplasmia of the blood. The highest ratio of leucocytes to chromocytes observed in my experiments has been 1 : 136, a proportion corresponding very closely with the highest observed in Löwit's* experiments, dealing with another form of leucocytosis, viz., that following intravenous injection of albumoses, &c. But the ratio 1 : 136 was observed in the dog, and is not nearly so abnormal a ratio as the ratio 1 : 140 observed in one of the experiments on the pleural cavity of the cat. Löwit experimented on rabbits, so that my ratios are not strictly comparable with his. The largest number of leucocytes met with per c. millimeter of blood has been in my experiments 55,000, the number at the outset of the particular experiment being 7,750.

The statement by v. Limbeck,† supported by Gottlieb Pick,‡ that inflammatory leucocytosis does not appear in inflammations accompanied by slight exudation, but accompanies those causing marked exudation, has not been found to hold good in my experiments, *e.g.*, in case of inflammation in pleural cavity hardly any exudation but marked leucocytosis.

Frequently the leucocytosis is followed by a final leucocytopenic phase (*cf.* Example on page 175). This does not always occur, but it is occasionally very marked. I have only seen it happen when the temperature has fallen below normal, and the *exitus lethalis* is not far off. In one instance the leucocytes fell to less than 2000 per c. millimeter.

* *Op. cit.*

† 'Zeitschrift für Heilkunde,' vol. 10, p. 392, 1890.

‡ 'Prager Med. Wochensch.,' 24, p. 303, 1890.

(III). *Disturbance of the numerical Ratios normal between the various kinds of Hæmic Leucocytes.*

Before attempting to consider the nature of the upset produced in the ratios normal between the various sets of leucocytes in the blood, it seems necessary to give some characteristics of the different sorts of hæmic leucocytes I have endeavoured to distinguish. The confused condition of the terminology applied to the subject has led of late more than once to the misapprehension of an observer's descriptions. This I would hope to avoid by prefacing my summary with a short account of the varieties of hæmic leucocytes which I have studied.

I have for the present confined the observations requiring the sorting of the leucocytes to experiments on the dog and cat. I wish it to be understood that, except where distinctly otherwise stated, this brief description is applied to the blood of those two species.

The classification followed has been based on that by Wharton Jones,* who was the first to discriminate varieties of white blood-corpuscles in the blood, the "finely granular" and the "coarsely granular." Some years later Rindfleisch† and then Max Schultze‡ corroborated Wharton Jones' separation of the two kinds of cell, and through the work of the last authority the distinction became widely known. M. Schultze noted besides the above certain other "smallest" and "small" kinds of leucocytes. These I have followed him in keeping apart from the "finely granular" of Wharton Jones; them, together with certain of the large leucocytes, I put into a class recognised by all recent observers as scarcely at all granular, and therefore conveniently termed "hyaline" (M. Foster).§

A. *The Finely Granular Leucocyte.*

Large or medium in size, rarely small. Nucleus almost always obscured when the living cell is spheroid and unstained, but obvious when the cell is spread and crawling, or when half dead or tinged with nuclear dyes; the nucleus is usually polymorphous or polymerous, the lobes of it usually (almost invariably) united by bonds of chromatin. The irregularity of the nucleus is not a sign of reproduction nor of degeneration. It is, as Arnold|| first suggested, and a number of later observers (Korschelt,¶ Dekhuysen,** Gulland,††

* *Op. cit.*

† 'Pathologische Histologie,' 1861.

‡ *Op. cit.*

§ 'Text-book of Physiology,' Part I, p. 47, Edition 6.

|| 'Archiv f. Mikroskopische Anatomie,' vol. 30, p. 226, 1887.

¶ 'Zool. Jahrb., Abtheilung f. Anat. u. Ontogenie der Thiere,' vol. 4, 1889.

** 'Verhandlungen d. Anatom. Gesellschaft,' 1890.

†† 'Lab. Rep. Roy. Coll. Phys., Edin.,' vol. 3, 1891.

M. Heidenhain*) succeed in proving, a sign and result of the amœboid activity of the cell. If the cell is allowed to quiet slowly down before it is killed, I have shown† that the nucleus then very usually returns to spheroidal form. Of course the cell body becomes spheroidal much sooner than the nucleus. In the slowly killed cell the nucleus usually becomes excentric in situation as well as spherical in shape. It is also especially liable to smear. In the counting solution the nucleus of this cell does not tinge so readily as does that of the hyaline leucocyte. Under certain circumstances, when kept for a number of hours *in vitro*, the nucleus of this leucocyte frequently presents a curious appearance I have not found described. The appearance is shown in figs. 6 and 7 (Plate 1). A number of portions of the nucleus are set in a wreath-like manner around the approximate centre of the cell. I have never observed this arrangement in the nucleus of the coarsely granular or hyaline leucocyte.

Cell body: finely granular. The granulation of the cell body has been called "neutrophil" by Ehrlich,‡ Rieder,§ &c. In the cat, under the prolonged action of aqueous methyl blue solutions, some granules, especially in the neighbourhood of the nucleus, take on a bright rose tint, and ultimately a considerable amount of rose-coloured substance in rounded masses, some of large size, appears in the cell. But the cell is much altered when this happens, and a good deal of plasmoschisis has gone on. With less departure from the normal a good deal at least of the granulation of this cell can by pushing eosin or rubin be coloured by these acid dyes; Kanthack and Hardy consider them, strictly speaking, oxyphil.

This cell is amœboid. I have previously pointed out|| that at low (16° C.) temperatures, it appears to be more amœboid than is the coarsely granular leucocyte. If kept for an hour or so in hanging drop at 42° C. this cell shows well the "*excroissances sarcodiques*" of Dujardin, that, as Ranvier¶ has pointed out, are not to be confused with pseudopodia. Besides the quaint fixed finely granular excrescences there are protruded from the cell at a slightly lower temperature, quickly rising, clearer, vesicular-looking processes; these are thrust out in succession from various points of the periphery, one falling as a later rises. They lead to no locomotion of the cell. I mention them here because I have never seen the coarsely granular leucocyte or the hyaline leucocytes produce either of these excrescences, although under the same conditions, and in the same

* 'Kern u. Protoplasma,' Leipzig, 1892.

† 'Proc. Internat. Congress of Physiologists,' Liège, 1892.

‡ 'Arch. f. d. Physiologie,' 1879; 'Zeitsch. f. klin. Medicin,' 1880; later papers

§ *Op. cit.*

|| *Loc. cit.*

¶ 'Traité Technique d'Histologie,' p. 156.

drop or film. They therefore seem to me to help toward distinction between these kinds of leucocytes.

The cell can ingest particles, even hours and days after its removal from the body. In oxalated blood these cells can often be seen with crystals inside them as well as adherent to them. Rarely I have seen them contain a chromocyte. Both crystals and chromocytes, when contained in the leucocytes, lie usually in obvious vacuoles. I have occasionally seen in some of these cells fresh from the circulation some sparse small vacuoles, but they are quite uncommon in blood freshly drawn. On the other hand after some hours, or better, one or two days *in vitro*, the cell frequently becomes riddled with small vacuoles (see figs. 2 and 3, Plate 1), so as even to resemble a flake of froth. The nucleus is then hard to discover in the fresh cell, but on staining with basic dyes becomes at once obvious, and is then found to be no longer markedly polymerous. The cell in this frothed condition is still amœboid, although not *very* actively, so far as I have seen. On the warm stage it however travels fairly in this condition. In a great number of the vacuoles fine particles can be seen, and these show that the vacuoles contain fluid, for the particles inside them exhibit Brownian movement. Most of the vacuoles are spherical and small, some are large, as these are for the most part oval in outline. In a number of the vacuoles *no* particles are visible.

The granules in the normal cell never, so far as I have seen, exhibit Brownian movement, but, when the cell is dead or dying, Brownian movement often affects its granules in a most marked degree, the cell body acquiring a shimmering appearance from the dancing of the granules. This is doubtless due to lowered vitality, or perhaps lethal acidification of the cell giving its protoplasm over to imbibition of the aqueous surrounding. Brownian movement of the granules of a leucocyte is, in my experience, one of the signs that the cell is nearly dead, and I have been interested to find it present in many of the cells of certain exudation fluids and pus, although invariably absent from the leucocytes of normal blood and lymph.

In these samples of pus leucocytes with spherical excentrically set nuclei occur, and the nuclei have an especial tendency to smear, just as in leucocytes which have slowly died *in vitro* (see fig. 4, Plate 1).

By irrigation of such weakened cells with various saline solutions that affect the normal leucocyte but little and leave it still actively amœboid, the cell body, and very often the nucleus as well, can be burst with an explosive discharge of the cell contents, the nucleus remaining as a shrunken film attached to a fragment of cell-body.

The finely granular leucocyte forms in the dog and cat about 70—90 per cent. of the hæmic leucocytes. The vast majority of the finely granular are always, without doubt, those designated "neutrophil" by Ehrlich and his pupils; generally, I believe all of them

are. But among the finely granular there may be sometimes included the scanty basophil cells which are so rare as hardly really to be considered normal hæmic leucocytes. It must be remembered that Howell* and Gulland† have shown that in its earliest history the blood is devoid of all leucocytes. Essentially all the hæmic leucocytes are therefore vagrants wandering through blood as through the other tissues; thus it becomes difficult to set a sharp line between leucocytes normally hæmic and leucocytes only abnormally hæmic. Ehrlich includes the basophil cell as an occasional hæmic leucocyte. Basophil cells I have seen in the blood of an emaciated dog which was undergoing treatment by thyroid injections after thyroidectomy. That subvariety of basophil cells termed by Ehrlich "mastzellen," I have never met with in normal mammalian blood, but I have found them sparsely in the blood of patients dying in the reaction stage of Asiatic cholera,‡ and at that time the inflamed submucosa and mucosa of the intestine I found often contain large numbers of these cells.

B. The Coarsely Granular Leucocyte.

This is among the largest of the leucocytes.

Nucleus is usually somewhat less deeply stained by nuclear dyes than the nucleus of the finely granular leucocyte; is often reniform, often irregular, and appearances intermediate between the reniform and completely irregular are common. The nucleus is always more or less obvious even when the living cell is spheroid because of absence of the characteristic granulation in its region.

Cell-body, in its greater part, contains a number of granules, more or less regularly arranged. The granules are highly refracting (especially in the cat, but much less so in the horse); the granules vary in size considerably in the same individual cell, but usually the largest is not more than thrice the size of the smallest. The shape of the granules is usually in the rabbit and dog spherical, in the cat cylindroid, in the horse roughly cuboid, but in the cat and horse many spheroid granules are often present. The average size of the cell is about the same in these three types, but the cylindroid granule of the cat is larger than the spheroid of the dog, and the cuboid granule of the horse is much larger (diameter about 2μ—4μ) than the cylindroid of the cat. In the normal cell the granules never exhibit Brownian movement, but in abnormal conditions Brownian movement sets the particles dancing freely. Under imbibition the granules usually lie trembling in the surface-sheet of the cell-body, but some-

* "The Life History of the Formed Elements of the Blood," 'Journ. Morph.,' vol. 4, p. 1, 1890.

† *Op. cit.*

‡ 'Roy. Soc. Proc.,' 1886.

times they are withdrawn in a mass to the neighbourhood of the nucleus which is often excentric in the cell. It is possible, with care, when the granules are dancing at the surface of the cell, to so hold the cell between object slide and cover-slip that the dancing of the granules at the upper and under poles of the cell is arrested while the dancing in the equatorial region is unhindered. This proves, I think, not only that the granules are then very close to the surface of the cell, but that they lie not free under a cell membrane as Ranvier* suggests, but actually in a thin cortical layer of the cell.

As to the nature of the substance composing these granules, the idea put forward by A. Schmidt,† that it is closely allied to hæmoglobin, has by Pouchet‡ and Hayem§ been pushed so far as for them to consider the granules to be hæmoglobin and pieces of broken chromocytes. That it is not actually hæmoglobin is proved by the absence of colour from it. Ehrlich and Schwarze|| have also found it does not give the staining reactions of the chromocytes. The granules tinge yellow over osmic vapour, but various reactions show that they are not fat. They contain a certain amount of water (Ehrlich and Schwarze); they are not soluble in alcohol or ether. In the dried corpuscles they melt (?) and run together, but at a very high temperature only (Ehrlich). As the water is driven off from them by slow heat they display a greater and greater affinity for acid stains (Schwarze). In the living cell they, in rabbit's blood, became deeply tinted (to a maroon colour) on irrigation with dilute Ehrlich-Biondi stain. In the fresh condition in the cat's blood, mixed with dilute aqueous methyl blue, it has often appeared to me, when using powerful systems, that each granule is coated with a thin film of substance which becomes blue-violet with this basic dye, and also will stain with acid fuchsin, a film, in fact, of amphophil substance. I find the granule is soluble in acetic acid, but not in distilled water. It appears to give the ammoniomolybdate reaction used to reveal phosphorus by Lilienfeld and Monti¶. The granulation of the finely granular leucocyte does not yield this reaction, though the cell-body of the hyaline leucocyte does usually give a faint reaction. The granules of the coarsely granular leucocyte yield the reaction readily without previous treatment to liberate the phosphorus. The granules

* *Op. cit.*, p. 168.

† 'Arch. f. d. Gesammte Physiologie,' vol. 9, p. 353.

‡ 'Journ. de l'Anat. et de la Physiologie,' 1880.

§ 'Du Sang,' Paris, 1889.

|| *Op. cit.*

¶ 'Verhandlungen der Physiologischen Gesellschaft zu Berlin,' Sitzung am Juni, 1892. Professor Halliburton, who has had considerable experience of the microscopical application of this test for phosphorus, has been so kind as to look over some of my preparations, and he endorses the opinion that the reaction is given faintly but distinctly by the coarse oxyphil granule.

of the cell give a deeper yellow than does the nucleus itself. If, as Rénaut* concluded, the granules are albuminous, perhaps they are of the nature of *nucleo-albumin.* Ranvier† has suggested that they are similar to the yolk-granules in ova, but I find those granules for by far the most part basophil.

In the description appended by Stricker to his well-known "Photogramm eines farblosen Blutkörpchen"‡ (a coarsely-granular leucocyte of Proteus), he states that the particles sometimes show branching processes, which occasionally unite forming a network of which he sees evidence in his photogram. The granules are always really absolutely discrete, as shown in the photogram appended (Plate 1, fig. 1).

The number of granules per cell varies considerably. In the dog and cat it averages between 30 and 60; in the latter animal I have counted 78 granules and 97 granules in individual cells. In the horse the number is smaller, usually 12—20, but the granules are much larger (up to 4μ) approaching in size the huge mucin granules discovered by Reid§ in the slime glands of *Myxine.*

In the dog I observe four morphological varieties of this leucocyte, detectable chiefly by the granulation.

1. The typical large cell, the body packed with granules, 30—60 in number.

2. The cell contains, instead of granules of fairly uniform size, one or two large, highly refracting masses, with a scanty number of the usual granules: I have found the larger masses oxyphil, and reacting to the Lilienfeld-Monti method like the usual granules.

3. The cell contains, in addition to the highly refracting granules, a few somewhat smaller rounded granules that appear in the fresh and unstained condition indistinguishable from spherical vacuoles, because the substance they contain hardly refracts more than the cell plasma. These also are oxyphil, like the highly refracting granules, and sometimes are amphophil.

4. The cell is quite small; contains a simple vesicular nucleus; the nucleus is rather large in proportion to the cell body. In the latter are coarse, highly refracting oxyphil granules, and these are distributed throughout. Dekhuysen has recently pointed out similar cells in amphibian blood. He looks upon them as the young form of the coarsely granular leucocyte; but he points out that, if I understand him rightly, the granules are amphophil, not oxyphil. In this connexion we must remember that Ehrlich has himself pointed out that the granules of his typical oxyphil cell are sometimes amphophil.

Varieties 2, 3, and 4 are, in my experience, uncommon in the blood; when 2 does occur it seems usual for the examples of it to be fairly numerous in the blood of the animal at the time; but in most dog's blood it is not to be found at all.

* 'Archives de Physiologie Normale et Pathologique,' vol. 13, p. 649, 1881.

† *Loc. cit.*

‡ 'Arbeit. a. dem Path. Instit. zu Wien,' 1890.

§ "Mucin Granules of Myxine," 'Journ. Physiol.,' vol. 14, p. 340, 1893.

In cat's blood I would note three varieties of the cell.

1. The typical large cell, with its cell body packed with large cylindroid grains.

2. A cell resembling in all respects the former, except that the granules are not of the same highly refracting quality, and are generally smaller. These granules are oxyphil, like the typical ones. Variety 2 is not so frequent as 1, but it not unfrequently forms 10 per cent. of all the coarsely granular leucocytes.

3. A variety, small, and like 4 of the dog, but with granules tending to be cylindroid, instead of spheroid.

The coarsely granular leucocyte is amœboid. Myself, from what I have seen of it on the warm stage, I should incline with Lavdowski,* to consider it the most actively amœboid of all hæmic leucocytes, were it not for two difficulties. 1. At and below the ordinary temperature of the room, the cell is usually less actively amœboid than the finely granular leucocyte. 2. As a rule, when fixed immediately after withdrawal from the circulation the nucleus is less distorted from a regular figure than is that of the majority of the finely granular leucocytes, it is very usually of a simple horse-shoe shape; now the degree of irregularity of form of the nucleus may be taken as a rough index of the amœboid activity of the cell at the time of fixation.

I have never, either in freshly drawn blood or in blood kept for a time *in vitro*, seen an unmistakable vacuole in the coarsely granular leucocyte. This stands in striking contradistinction to one's experience of the finely granular leucocyte. Related to this absence of vacuolation appears the fact that a number of observers, including Metschnikoff,† admit the want of evidence that the coarsely granular hæmic leucocyte is phagocytic. In my own preparations, when, after being fed with bacteria *in vitro*, the great majority of hæmic leucocytes have ingested the bacteria (and other particles besides), the coarsely granular leucocytes have not contained any.

I think there is little doubt that, as Müller‡ says, this coarsely granular cell is Ehrlich's cell with α-granulation—Ehrlich's true oxyphil cell—the only question is whether his amphophil cell is not also included. I gather from Ehrlich's papers, that both his cells with α-granulation (true oxyphil) and his cells with β-granulation must really be included in Wharton Jones's "coarsely granular leucocytes," and therefore I have included both of them together under that head in my countings.

It is a little difficult to assign to this cell a normal percentage in the blood, because it appears especially subject to numerical variation. In cat's blood I have found the cell usually rather more numerous than in dog's blood. Considering the two kinds of blood together, I

* 'Virchow's Archiv,' vol. 96, p. 61.

† 'Leçons sur l'Inflammation,' Paris, 1892.

‡ "Zur Frage der Blutbildung," 'Sitzungsb. d. Kais. Akad. Wien,' Abth. III, vol. 98, 1889.

should estimate the ordinary frequence as between 10 per cent. and 1·2 per cent. of all hæmic leucocytes.

C. The Hyaline Leucocytes.

This class is probably a less homogeneous collection than either of the other two. Two subdivisions of it are important. I. Small cells, lymphocytes. II. Larger cells, myelocytes. One however often meets with individuals in whose case one feels hesitation before deciding as to which of the two subdivisions they shall be assigned.

I. *Small Cells.*—These are, for the most part, M. Schultze's "smallest" cells; the nucleus is spherical, and stains deeply; the cell body is small, sometimes a mere film coating the nucleus. The cell body is apt to stain deeply with methyl blue and other basic dyes. I agree with Schultze that this cell is not amœboid in the blood. It also seems less sticky than the other leucocytes. In the counting solution the nucleus of this cell is the first living structure to become tinged with colour. When platelets (precipitate) are present these tinge even earlier, but of a violet colour, whereas the nucleus of the small hyaline cell takes at first a pure light blue; and there is no evidence that the platelets are living structures.

II. *Larger Cells.*—Some are among the largest of hæmic leucocytes. The cell body encloses a spheroid, ovoid, or reniform nucleus, the chromatin of which is patchily distributed, and not so condensed as in the partinucleate leucocytes. The cell body tinges in many individuals deeply and evenly with basic dyes, but in other individuals, as Everard, Demoor, and Massart* have especially pointed out, hardly at all. This cell is, in my experience, sluggishly amœboid. It is, however, phagocytic.

I have very frequently noted that in specimens in which the large hyaline leucocyte is numerous the small hyaline is also more numerous than in specimens in which the large hyaline cell is scanty. The two varieties seem to vary in the same direction. The number of hyaline leucocytes varies greatly in normal blood; I estimate it to average (in dog and cat) at between 5, 7, and 20 per cent. of the total leucocytes. When their number is large the blood is usually of low specific gravity, of low hæmoglobin value, and contains a relatively poor number of chromocytes, *i.e.*, the blood is polyplasmic.

The hyaline leucocytes probably correspond pretty closely with Löwit's† "mononuclear" class.

All hæmic leucocytes appear to me to be to a large extent anaërobic organisms. The amœboid varieties, for instance, continue amœboid

* "Sur les Modifications des Leucocytes dans l'Infection et dans l'Immunisation," 'Annales de l'Institut Pasteur,' p. 165, February, 1893.

† *Op. cit.*

for hours in sealed cells in which the hæmoglobin of the chromocytes exists in a reduced condition.

Having thus attempted to state definitely some characters on which I have depended for distinguishing one variety of hæmic leucocyte from another, I will proceed to a more detailed summary of the alteration in the numerical relations of the varieties, resulting from various forms of acute local inflammation.

As already pointed out, there occurs a diminution of the total number of hæmic leucocytes (a leucocytopenic phase), followed by an increase of the total number of hæmic leucocytes (a leucocytotic phase); finally, in some experiments there is again a leucocytopenic phase.

First.—The Leucocytopenic Phase.

This phase has in my experiments always been observable when the blood analysed was taken within a short time, *e.g.*, less than an hour, after the establishment of the lesion.

The decrease in leucocytes affects the finely granular more than the hyaline, indeed, my countings do not show any absolutely indubitable decrease of the hyaline leucocytes. Remembering, however, that the apoplasmia of the blood is being established at this time, and that were the hyaline leucocytes to remain undiminished their number per unit volume of blood would be thereby increased, the actually slight fall of their number in my countings looks as if they did actually diminish in number, although to a less extent than do the granular varieties. The fall in their proportion to the chromocytes supports this belief, and seems larger than attributable to the errors inherent in estimations by sample.

Interpretations of the significance of the leucocytopenia seem to be still but doubtful inferences. The term leucocytopenia has been introduced by Löwit,* and expresses conveniently any relative scantiness of leucocytes such as that observed. Whether this inflammatory form of leucocytopenia is really the same in nature as the form consequent on binding down the animal, prolonged exposure, cooling, &c., described by Löwit, is not clear. Under those circumstances Löwit discovered the decrease of leucocytes to be especially due to decrease of the mononuclear variety (= broadly, the hyaline, in my countings). Whether, further, the inflammatory leucocytopenia is related to the other form of leucocytopenia (called, on theoretical grounds, leucolysis), admirably studied by Löwit, demands more attention here.

It has long been known that intravenous injection of a number of

* *Op. cit.*

substances, *e.g.*, fibrin ferment,* hæmoglobin,† septic fluids,‡ pus, lymph cells,§ hemialbumose,|| peptones,¶ pepsin,¶ nucleic acid, nuclein,** leech extract,†† tuberculin,‡‡ pyocyanin,¶¶ curare,§§ uric acid,§§ urates,§§ dead bacterial cultures,|||| bacterial extracts,|||| bacterial proteins (Buchner),¶¶ filtered yeast cultures,§§ carmine in suspension,*** produce more or less pronounced and rapid—often immediate—diminution of the number of leucocytes in the blood of the general circulation. This diminution has been shown by Löwit††† to be preliminary to a subsequent increase, and the phase of leucocytopenia, on account of its short duration, seems to have escaped the attention of many observers who have well recognised the much longer lasting subsequent leucocytosis. The diminution is sometimes enormous in degree. In some of Löwit's experiments the number of leucocytes fell in five seconds from the time of injection to less than one-twentieth the number circulating immediately previous to the injection. Löwit has discovered that the diminution, whether great or small, is at expense of the polynuclear leucocytes (the granular leucocytes of my countings). He opines that the diminution is due to destruction (he says the dissolving up) of these leucocytes. His conclusion harmonises with the view of the Dorpat school, according to which hæmic leucocytes are easily destroyed by a number of experimental procedures, some not obviously severe. As to curare, Drosdoff‡‡‡ asserted, many years ago, that frog's leucocytes rapidly break down in blood serum (mammalian !) containing curare.

* Birk, 'Das Fibrin-Ferment im lebenden Organismus,' Dorpat, 1880.

† Bojanus, 'Exp. Beiträge z. Physiol. u. Pathol. d. Blutes,' Dorpat, 1881.

‡ Hoffman, 'Ein Beitrag z. Physiol. u. Pathol. d. farblosen Blutkörperchen,' Dorpat, 1881.

§ Samson-Himmelstjerna, 'Exp. Stud. ü. d. Blut in physiol. u. pathol. Beziehung.,' Dorpat, 1882.

|| Löwit, *op. cit.*

¶ Groth, 'Ueber die Schicksale d. farblosen Elemente im kreisenden Blute,' Dorpat, 1884; Löwit, *op. cit.*; Wright, 'Roy. Soc. Proc.,' February 9, 1893.

** Horbacewski, 'M. f. Chemie,' &c., Vienna, 1891, vol. 12, p. 221. Löwit, *op. cit.*

†† Löwit, *op. cit.* (But Wright (*loc. cit.*) finds that intravenous injection of leech extract does not reduce the number of leucocytes.)

‡‡ Tchistowitsch, 'Berlin Klin. Woch.,' p. 838, 1891; Botkin, 'Deutsch. Med. Woch.,' 1892, No. 15; Rieder, *op. cit.*

§§ Löwit, *op. cit.*

|||| Hankin and Kanthack, 'Proc. Cambridge Philosoph. Soc.,' January, 1892; Kanthack, 'Brit. Med. Journal,' 1892.

¶¶ Werigo states that the injection of the filtered cultures does not give the reaction. Rieder, *op. cit.*

*** Werigo, "Les Globules Blancs comme Protecteurs du Sang," 'Annal. Instit. Pasteur,' 1892.

††† *Op. cit.*

‡‡‡ Hofmann und Schwalbe, 'Jahrsb.,' 1873, p. 67.

Rieder* has, however, urged that the leucocytes are not destroyed, but are merely collected or collect in some region of the circulation. This region they leave after a time, and then become again distributed generally through the circulation, when, according to Rieder, substances inducing positive chemotaxis reappear in the blood. Löwit points out that the *locus* of collection of the leucocytes is not made out by Rieder. Werigo,† on the other hand, has suggested that the leucocytes, after the intravenous injection of particulate material, crowd into and remain for a time in the liver, spleen, and lungs; for the lungs this has been proved by the recent work of Goldscheider and Jacob (*Verhandl. der Physiol. Gesellsch. zu Berlin*, xix, 1893). Everard, Demoor, and Massart‡ point out that the medulla of bone must be included in the loci of collection, and that the view can be extended to the results of injection of substances dissolved, as well as particulate. The recent experiments of Verhoogen§ are particularly interesting in this connection. Moreover, Wright|| has lately shown that in the case of admixture of peptone with blood this diminution of leucocytes does not occur when the admixture is made, not in the circulation, but in blood withdrawn from the circulation. We cannot consider it as proven that the phenomenon of disappearance of leucocytes from the blood of the general circulation is really due to direct disintegration and dissolution of them, although the manner of their withdrawal from the general circulation has not yet been elucidated. Until the dissolution is proven, it is obvious that leucocytopenia is a better term for the observed phenomenon than is leucocytolysis.

A relation between the above "injection leucocytopenia" and the "inflammatory leucocytopenia" of my experiments seems indicated by the fact that in both the diminution is chiefly of the irregularly nucleate or granular cells. The connection is rendered still more probable from observations by Everard, Demoor, and Massart.¶ These investigators find a leucocytopenia (their hypoleucocytosis) usually precede the leucocytosis induced by subcutaneous and intraperitoneal injections, in considerable quantity, of bacterial cultures and culture fluids. This they attribute not to destruction of leucocytes, but to the leucocytes crowding into the blood vessels of the liver, spleen, and marrow, in virtue of chemotactic reaction. They conclude, further, that in their experiments, the leucocytopenia was chiefly due to diminution of the irregularly nucleate leucocyte, another point of resemblance between the leucocytopenia of the two procedures.

* *Op. cit.*

† *Op. cit.*

‡ *Op. cit.*

§ 'Travaux faits à l'Institut Solvay, Université de Bruxelles,' 1893.

|| *Loc. cit.*

¶ *Op. cit.*

It is important in interpreting the significance of the inflammatory leucocytopenia to remember that the granular (= irregularly nucleate) hæmic leucocytes appear more adhesive than the hyaline (mononuclear, regularly nucleate). In the "balling" of leucocytes which so readily occurs in peptone blood, I have often noticed that the clumps of leucocytes may be formed almost exclusively of granular leucocytes, while many hyaline leucocytes are free in the plasma. In oxalated blood the granular leucocytes adhere to the masses of platelets disproportionately in comparison with the lymphocytes; they are not merely adherent to the surface of the masses but many are entangled and often remain for a time hidden *in* the masses. It is interesting to watch how those temporarily buried work their way to the surface. At first they appear like fusiform fibroblasts directed so as to radiate from the centre of the ball-shaped mass as it lies flattened between object-slide and cover-slip. The elongated nucleus is the chief sign of the cell, and this can be noted slowly slipping toward the periphery of the ball. As it approaches the free surface of the mass the cell glides more quickly, and finally it emerges with an almost sudden plunge and ranges itself beside the other similar leucocytes already sticking to the surface of the clump. Had one not seen the steps of the process one might have imagined that the cells covering the mass of precipitate had wandered to it on account of its nutritive nature (proteid) and in obedience to positive chemotaxis. As a fact however most at least of the cells have been merely mechanically entangled in the mass and gradually get out of it and then stick for a while to its free surface.

It must be remembered also that the hyaline leucocytes are not so amœboid as the granular; the small variety of them not at all. Emigration will remove from the circulation more individuals of the granular than of the hyaline types. The granular leucocytes tend disproportionately numerously to adhere and escape in the vascular region of the local inflammation. This would increase the relative number of hyaline cells to granular in the general circulation.

Other possible factors may be briefly alluded to. Many of the substances that when injected into the circulation cause leucocytopenia are the *lymphagogues* of Heidenhain.* They belong to that class of lymphagogues which increase the flow of lymph from the thoracic duct by hastening the transfer of fluid from the blood into the lymph spaces. Heidenhain showed that in the dog these lymphagogues, although increasing the volume and organic richness of the output of lymph, *viâ* thoracic duct, reduce the volume and organic richness of the serum of the blood itself. Löwit† has shown that in the rabbit, as result of intravenous injection of albumose, &c., the

* *Op. cit.*

† *Op. cit.*

leucocytopenia and the lymphorrhœa occur together; but he does not find the apoplasmia of the blood noted by Heidenhain. In my experiments throughout the leucocytopenic phase of the blood the apoplasmia of it was obvious and steadily progressive. I have not yet systematically examined the flow of lymph from the duct in my form of experiment, but I have noted that the flow is sometimes increased, and that the lymph may contain hæmoglobin in solution. The absence of obvious increase, indeed the estimated decrease, of the ratio of hyaline leucocytes to chromocytes, as well as of hyaline leucocytes to granular leucocytes, indicates that any increased addition of hyaline hæmic leucocytes that may occur, *viâ* the thoracic duct, is out-balanced during the leucocytopenic phase by increased conversion of hyaline leucocytes into granular. There is, I take it, little doubt that many of the granular leucocytes are developed from the hyaline form (Kölliker, Virchow, &c.); and an increased rate of development si probable at the beginning of many forms of leucocytosis (Römer's* "*formativer Reiz*.")

In my experiments I have not found the leucocytopenia bear any very constant relation to the fever as judged by body temperature and respiratory rate. It may bear a closer relation to the process of apoplasmia; it seems to be slight when the apoplasmia is only slight.

Second.—The Leucocytotic Phase.

The time of onset of leucocytosis varied. It became obvious in something later than three-quarters of an hour after the establishment of the local lesion. In the ligation experiments it was particularly late. I did not detect any very constant relation between it and body-temperature or respiratory rate.

Its duration varied. It may be prolonged for several days and without much abatement.

The anatomical details of inflammatory leucocytosis have been recently reviewed and studied by Rieder.† I will merely point out that in my observations as in his the increase in the total hæmic leucocytes has been accompanied by upset of the normal numerical ratio of granular to hyaline (in his observations polynuclear to mononuclear) in favour of the granular leucocytes. Rieder saw the proportion rise sometimes to 20 : 1. I have seen it rise from 6·2 : 1 to 19·4 : 1.

In this feature again there is a resemblance between this form of leucocytosis and that ensuing upon injection of albumoses, bacterial cultures, &c., into the circulation. Hankin and Kanthack‡ have

* 'Virchow's Archiv,' 1892.

† *Op. cit.*

‡ *Op. cit.*

pointed out that the leucocytosis after bacterial injections is chiefly due to increase of the granular leucocytes; Löwit* has since shown the same thing for the leucocytosis following injections of albumose, nuclein, &c. In one of his experiments the polynuclear were to mononuclear leucocytes as 87 to 13. V. Limbeck,† and Everard, Demoor, and Massart‡ note the same feature in the leucocytosis resulting from subcutaneous injections of bacterial cultures.

As to interpreting the meaning of the leucocytosis, Römer§ has asserted that the increase of leucocytes is due to rapid multiplication of the leucocytes in the blood, especially in the blood of the veins. Kanthack‖ was, however, unable to confirm Römer's statement that the venous blood showed greater leucocytosis than the arterial; and Löwit¶ has recently pointed out well-founded objections to Römer's observations. Löwit considers the leucocytosis due to increased supply of young leucocytes to the blood, these developing into the polynuclear form. Löwit supposes that the excessive production of leucocytes following their diminution (in his view their dissolution) is due to chemical stimulation of leucocyte-forming organs (lymph-glands, &c.) by substances shed into the blood plasma at the time of disintegration of the hæmic leucocytes. He considers this explanation applicable to all forms of leucocytosis, and from it argues the probability that "inflammatory leucocytosis" will be found to be preceded by a diminution of hæmic leucocytes. My experiments bear him out in that point; but, as to basing inflammatory leucocytosis on a previous dissolution of hæmic leucocytes my observations lend no help, and are capable of interpretation in other ways.

I think in my experiments the degree of leucocytopenia has not always been similarly proportioned to the succeeding leucocytosis. Since reproductive division of leucocytes, inclusive of the granular, polynuclear, or adult form, has now been shown to occur in the blood, the finely granular leucocytes may, therefore, increase in number by reproduction within the circulation.

Third.—Behaviour of the coarsely-granular Leucocyte.

A striking and I believe hitherto unrecorded feature of the change in the leucocytic elements of the blood relates to Wharton Jones's "coarsely-granular cell."

This leucocyte, like the other granular leucocytes, suffers numerical

* *Op. cit.*

† *Op. cit.*

‡ *Op. cit.*

§ *Op. cit.*

‖ "Acute leucocytosis produced by bacterial products," 'Brit. Med. Journ.,' June 18, 1892, p. 1301.

¶ *Op. cit.*

reduction in the leucocytopenic phase, indeed it would appear to undergo even greater numerical decrease than the ordinary granular leucocyte with fine granules. But when the leucocytopenic phase passes off and the total number of granular leucocytes in the blood becomes greatly increased, their increase is due entirely to the "finely granular" cell, and there is no accompanying increase of the "coarsely granular" cell. On the contrary the number of the latter becomes still fewer, not merely in comparison with the rest of the polymorphic, but also in proportion to the number of chromocytes and, more striking still, absolutely as measured per unit volume of the steadily concentrating blood.

The diminution proceeds to such a degree that usually after the seventh hour from the time of establishment of the local lesion this species of leucocyte has been in my experiments only with some difficulty demonstrable in the blood. It disappears from the small samples used in the Thoma-Zeiss counters, and often from the larger samples employed in fresh and dried films spread on $\frac{5}{8}$ in. circular cover-slips. If the blood be examined by drawing 3 c.c. into a test-tube, oxalating, centrifuging, and making films from the separated layer of leucocytes, examples can usually be then found without very prolonged search, but at the ninth hour and later I have several times failed to find any, even by prolonged search, after separation by the centrifuge.

It seems, therefore, that in consequence of severe local inflammation the "coarsely-granular" hæmic leucocyte of Wharton Jones may practically disappear from the general circulation, although at the same time his "finely granular" hæmic leucocyte may be enormously increased in number.

As to the significance of this disappearance, two possibilities arise at once for consideration.

1. The cell may have become caught and so to say hidden in some part or parts of the vascular system, or have wandered out of the blood circulation altogether.

2. The cell may have become so altered in appearance that it is not recognisable by the criteria I adopt for distinguishing it. Or its resistance to the procedures employed in looking for it may have become so lowered that it is destroyed in the process of search.

To take the last hypothesis first. I consider the coarsely granular hæmic leucocyte of the mammalian blood I have examined, to be normally one of the most resistant and easily preserved cells in the body. It can be frozen and thawed again, irrigated with 33 per cent. alcohol, with saturated ammonium molybdate solution, with strong aqueous solution of pyrogallic acid, with ammonium sulphide solution, with 0·3 per cent. acetic acid; it can be heated after partial drying to 120° C., and higher, and yet its granulation not be lost or characters distinctive of them destroyed, or the cell itself altered

beyond recognition. Now when the cell is discoverable only in scanty number in the blood, those individuals still present offer the same strikingly resistant quality as do the similar cells obtainable from normal blood. Yet in order on the above view to explain its disappearance from the blood, we have to suppose that in the simple process of the shedding of a drop of blood direct upon a clean cover-glass, and the spreading of the drop into a film under the action of capillarity when the cover-glass is dropped upon the glass slide, the cell forthwith disappears to leave behind no recognised trace. This seems improbable, the more so as the search for the cell was in my case often commenced less than twenty seconds after it left the circulation.

The supposition that the appearance of the cell is altered, and that for that reason the cell, although still circulating, escapes recognition, merits more consideration.

Ehrlich was, I believe, the first to suggest that the coarsely granular leucocyte is a unicellular gland. From this suggestion one passes by a step, which is easy in the light of Heidenhain's and Langley's discoveries of phases of granularity in secreting cells, to the supposition that the granules of the coarsely granular leucocyte may disappear from it at certain periods of its activity. Recently Kanthack and Hardy* have most importantly extended some suggestive work by Hankin, and have proved that under bacterial irritation the coarsely granular leucocyte of the frog does actually change its appearance, and that the granules disappear from it more or less completely, while the surrounding microbes suffer damage.

Although bacteria were certainly never in the blood in my experiments it is impossible to suppose that this coarsely granular leucocyte discharges itself of granules under irritation of a bacterial kind only. The local inflammation in my experiments it is conceivable adds substances to the blood which may irritate these cells in the same way. If so it might be expected that in the frequent and prolonged examinations of these cells in living films, in hanging drops, &c., some good and indubitable evidence of the phenomenon should have met me. In the blood, say at the fifth hour, when the numerical disappearance of the cell is already advanced, there might have been expected, unless the disappearance of the granules is almost momentary, a certain number of cells in which the removal of the granules is incomplete. I have never observed any such appearance. In this connection I have especially borne in mind the occurrence of the subvarieties of the cell already mentioned. It is obvious that these subvarieties may be merely phases of development or degradation of charging or discharging of the cell; one of them certainly seems an

* 'Roy. Soc. Proc.,' December, 1892.

early phase of development. But I have never satisfied myself that the individuals of a subvariety became more numerous or less numerous in proportion to the typical cell. All of these forms appeared to be removed together.

Nor do I believe that the cell without its granules would have in most cases escaped recognition and passed muster with the other leucocytes. As stated above, the granules are far from being the only distinctive feature of the cell.

It is quite certain that, when the cells are being or have been reduced to a minimum in the blood, the remaining individuals are usually of perfectly normal granular appearance, active and unimpaired in their amœboid action. I have, in the stage just previous to the disappearance of the cell from ordinary films, made a dozen such films and left them, at various temperatures, protected from evaporation, and then examined them at different intervals of time to see if they did lose their granulation.

Many hæmic leucocytes, under certain circumstances, live a long time after removal from the body (frog's leucocytes nine weeks *in vitro*,* dog's leucocytes three weeks, kept cool, *in vitro*†). It might therefore have been expected that, if blood containing leucocytes which had freed themselves of their secretion granules were removed and kept alive *in vitro* for a time, the granules might be reformed. I placed samples of blood in which I was unable to find any leucocytes containing coarse granules *in vitro* under appropriate conditions, and examined it at repeated intervals; but I did not succeed in obtaining any reappearance of the coarsely granular cell. A great number of the leucocytes do, and before very long, become granular with fine and medium sized granules, and these granules are highly refractive and not basophil (*i.e.*, not micrococci). I have not satisfied myself that they are fatty. The mode of their appearance seems to be as follows:—

A great number of the finely granular leucocytes gradually become, as above mentioned, vacuolated. The vacuoles contain fluid, and are for the most part small and spherical, but some are larger and oval in shape. In most of the small vacuoles a single, fine, highly refracting particle, the size of a small micrococcus, is to be found, dancing under Brownian movement. In many of the vacuoles no particle at all is discoverable. In the larger vacuoles are obvious ingesta, but the bright particles in the small vacuoles do not seem to be ingesta because the plasma in which the cells lie is generally quite free from particles. The cells seem to exhibit the same vacuolation whether they have remained spherical and inactive as regards amœboid move-

* 'Zahn; *cf.* V. Kahlden, 'Ber. u. d. Verhandlungen der Path. Anat.,' Sect. a. d. 10 Intern. Medic. Congress, Berlin, 1890.

† Sherrington, 'Intern. Congress of Physiol.,' Liège, 1892.

ment or not. The evidence rather indicates that the particles in the fine vacuoles are produced within the cells and not ingested. But that the particles are related to the granules of the coarsely granular cell there is no evidence to show. In cat's blood, where the true α-granule is cylindroid, the small round particles appearing in the leucocytes *in vitro* are *not* cylindroid nor are they so highly refracting; besides, they are much smaller, and their fineness leaves me in doubt over the phosphorus and oxyphil reactions of them.

If substances produced at the seat of local injury and inflammation leak into the circulation and there irritate the coarsely granular cell and produce lysis of its granules, some imitation of the process might be expected from the following experiment. Blood from which, when it circulated, the coarsely granular leucocytes were disappearing at an estimated rate of more than half a million per minute, was drawn and centrifuged, and the plasma obtained from it was added to normal blood containing plenty of coarsely granular cells. The coarsely granular cells 6, 12 and 24 hours afterwards, did not seem appreciably altered in number. In one instance two particular individuals of the cell were observed at intervals for 32 hours, sketched, and their granules counted; no change in size or number of their granules occurred.

I feel justified in believing, therefore, that the disappearance of the coarsely granular cell in inflammatory blood does not go on in such blood when placed *in vitro*.

Some observers hold that the various forms of hæmic leucocytes are not distinct species or varieties, but that they merely present the various aspects of one pleomorphic organism. If all kinds of hæmic leucocyte are thus transitionally related, it is possible that the coarsely granular cell can become actually one of the other hæmic cells. Unless this transition is wont to be effected very suddenly, the arguments I have adduced against, in the present instance, the disappearance of the cell from the circulation being due to lysis of its granules, apply for the most part against explanation by the pleomorphism hypothesis also.

An explanation that may be suggested is that chemical substances generated at the *locus læsionis* act on the blood just as Löwit* believes albumoses, &c. act when injected *intra venam*, *i.e.*, altogether destroy and dissolve certain of the leucocytes. The substances produced in the particular inflammations studied might destroy especially the coarsely granular forms. Does the coarsely granular form of leucocyte suffer even more severely than the finely granular when albumoses are injected intravenously? To test this I observed the leucocytes in samples of carotid blood drawn 3—6 minutes after injection of 2 grammes of hemialbumose (Grübler) (5 per cent. in 0·7 per cent.

* *Op. cit.*

aqueous NaCl solution) into the jugular vein of a small dog weighing 6 kilos. The countings showed the diminution of leucocytes to fall, as Löwit describes, chiefly on the polynuclear (granular) leucocytes, but the ratio of coarsely granular to finely granular forms did not appear indubitably altered.

Ehrlich* suggested that the hæmic leucocytes which contain his α-granulation (the "coarsely granular" of this Note) are derived from the oxyphil cells of bone-marrow. In one form of leucocythæmia the blood seems certainly to be laden with the oxyphil marrow cells. But the coarsely granular cell of the blood is not *exactly* an oxyphil marrow cell, for the latter is, as Rieder† and Muir‡ have pointed out, not an amœboid cell. That the granulation is in both the cells oxyphil does not establish the identity of the cells, nor even of the granulation; a variety of substances are of the eosinophilous class. Dékhuysen§ failed to find any connexion between the hæmic leucocytes with α-granulation and the oxyphil granular plasma cells and connective tissue corpuscles.

Yet Ehrlich's view is supported by several facts. Thus I find the oxyphil granules of the marrow yield the Lilienfeld-Monti reaction to the same extent as the coarse granules of the hæmic cell. There is, too, correspondence between the shape of the granules in the cells from both sources; thus I find

In the dog and rabbit, *small spheroid* granules in the coarsely granular leucocyte *and* in the oxyphil marrow cells.

In the horse, *huge granules, spheroid, occasionally almost cuboid* in the coarsely granular leucocyte *and* in the oxyphil marrow cells.

In the cat, *cylindroid granules* in the coarsely granular leucocyte *and* in the oxyphil marrow cell.

But I have not been able to satisfy myself in my experiments that the oxyphil cells of the marrow are affected even when Ehrlich's α-granulation practically disappears from the blood.

As the coarsely granular leucocyte is not destroyed, or altered so as to escape preparation or recognition, it must be withdrawn from the general circulation, either by becoming fixed in some particular vascular region or by passing out of the blood vessels altogether. I have not yet sufficiently examined the anatomical character of the exudations to criticise these possibilities. The cellular characters of the exudation have seemed to vary greatly; sometimes many cells closely resembled the coarsely granular hæmic leucocyte, but sometimes only a few.

* *Op. cit.*

† *Op. cit.*

‡ 'Journ. Path. and Bact.,' vol. 1, p. 133, 1892.

§ 'Verhandl. der Anat. Gesellschaft,' 1892. 'Anat. Anzeiger.'

The duration of the period of extreme poverty of the blood in this cell has varied in my observations between 18 hours and 6 days. In prolonged inflammation they may probably be scanty for much longer periods.

The degree of numerical elimination of the cell is illustrated by the following reckoning. In one experiment the cells fell from 13 per cent. of all leucocytes to less than 1 per 100 in the course of 12 hours. The animal was a large cat. Steinberg estimates the blood in the cat at 9 per cent. of the body weight; the animal weighed a little over 4 kilo. This would give 360 c.c. blood. In each mm. of blood there were at beginning of experiment about 15,300 leucocytes or 1,200 of the coarsely granular kind, making a total of 432 millions of the coarsely granulate in the circulation. Nine hours later no coarsely granular were found in the specimens examined on either of the two Thoma-Zeiss counters, nor were any found in several cover-glass preparations, but in specimens of blood centrifuged two of the cells were found in films of leucocytes from the leucocytic layer. In counting at random through these films 10,000 leucocytes were met with without meeting one coarsely granular cell. Allowing, however, that one existed for every 12,000 of the leucocytes, and knowing that the number of leucocytes had then risen to 36,100 per mm. of blood, the number of coarsely granular leucocytes in the circulation may be estimated at 1,080,000. On this calculation more than 400 millions of them had been withdrawn from the circulating blood in the course of nine hours. In the above example no allowance is made for the diminution in volume of the total blood (the specific gravity had increased from 1·056 to 1·061) which must have occurred but cannot have amounted to many c.c. The example is an extreme one, because the original percentage of these cells in the blood was high. But it gives an idea of the degree of impoverishment of the blood in these cells, and of the rate of their withdrawal (average rate of more than half a million per minute) from the general circulation. I detect at present no clear relation between the diminution of the number of coarsely granular leucocytes and the apoplasmia of the blood. When the apoplasmia developed late (ligation experiments) the withdrawal of coarsely granular leucocytes seemed hardly deferred. In the three experiments on the lung and pleural cavity apoplasmia was not produced, but the numerical reduction of the coarsely granular cells, though not so marked as usual, was unmistakable.

Under certain conditions, other than the above experimental ones, I have found the blood to contain very few coarsely granular leucocytes. I have already noted that fasting does not appear to decrease the number of them, but appears rather to increase it. At the same time, if prolonged to starvation point, fasting certainly appears to

greatly reduce the number of these cells. I judge so from their practical absence from the blood of three animals admitted into the Brown Institute in a destitute and starving state. Two of these animals did not recover, and autopsy revealed nothing but evidence of starvation, and slighter cases of the kind are not infrequently admitted at the Institution. I have also found the cell abnormally scarce in the blood at a late stage after thyroidectomy. The cell was scarce in the blood of a bitch which had thrown puppies twenty-four hours previously, though her temperature was normal. In a dog with a large subcutaneous abscess and in a horse with submaxillary abscess, I had great difficulty in finding any coarsely granular leucocytes, but the last two examples come under the same category as my own experiments, except that the local inflammatory conditions were subacute.

Canon* has concluded that the number of eosinophilous cells in the blood is increased in all diseases of skin. In a dog admitted with a severe scald of the back I found the blood almost destitute of these cells (coarsely granular), and it remained so for the first four days after admission. In the experiments in which skin was involved in the lesion (Series I) the diminution of the cells was as marked as in experiments where skin was not involved. Felsen† noticed in three cases of croupous pneumonia that at the height of the "fever" eosinophilous cells seemed absent from the blood. Noorden,‡ on the other hand, has seen a great increase in the number of eosinophilous cells in bronchial asthma at the time of the attack.

Hankin§ has made an interesting observation that the blood clots rapidly when the coarsely granular cell is scanty in the blood. I have pointed out|| that the coarsely granular cell does not initiate clotting in dog's blood. In the present experiments the blood, at a time when almost (perhaps actually) free from coarsely granular leucocytes, clotted very speedily and firmly, as is well known for blood in inflammation.

DESCRIPTION OF PLATE 1.

I wish here to thank very heartily Mr. A. F. S. Kent, to whose skill is due the success of the photomicrograms appended in illustration of some points described in the text.

FIG. 1.—"Coarsely granular" hæmic leucocyte of cat. Photographed while living. × 1000. The usual horseshoe shaped nucleus and the cylindroid granules are obvious. Zeiss apochromatic 2 mm.

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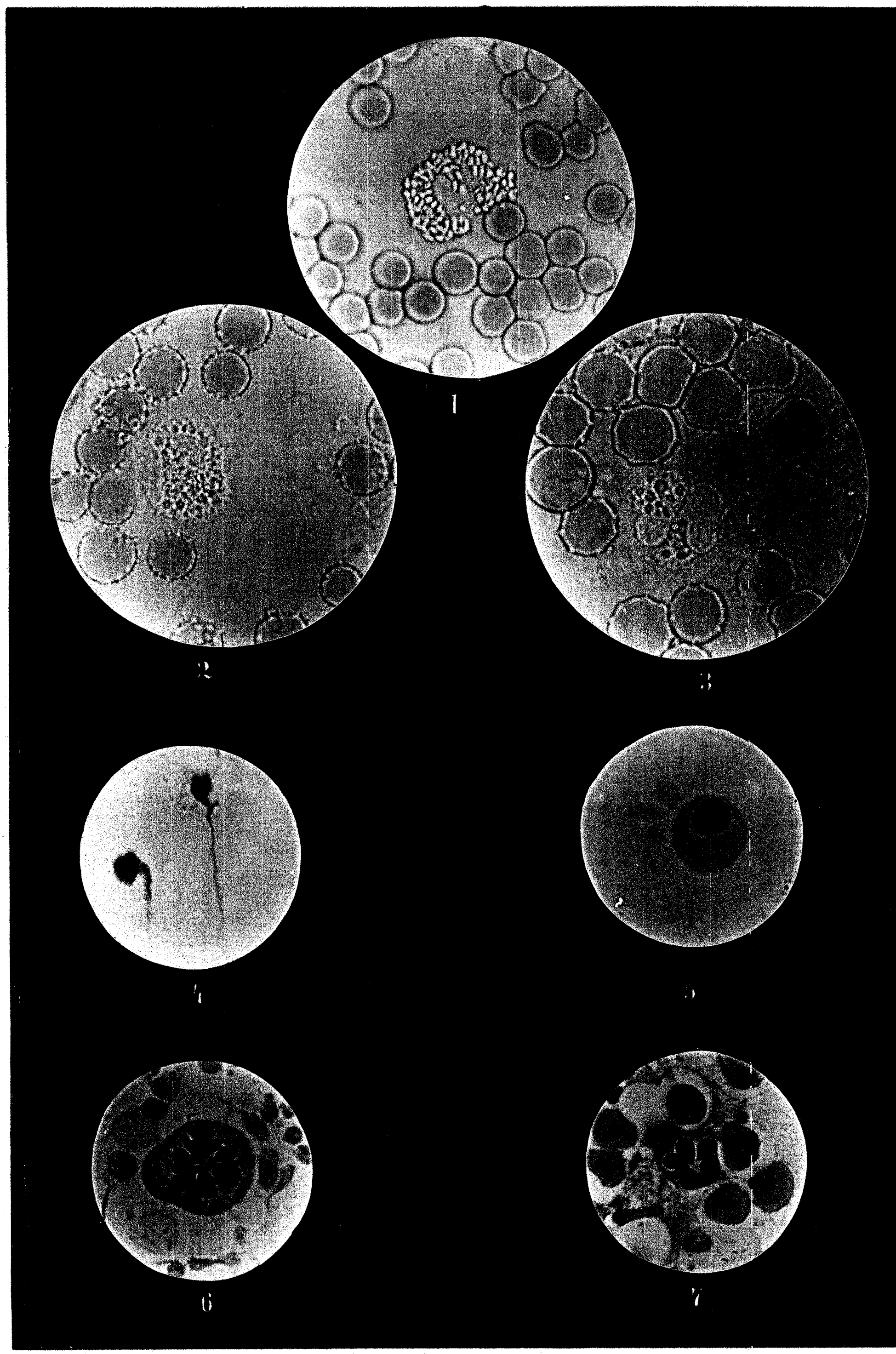
* 'Deutsche Medic. Wochen.,' p. 206, 1892.

† 'Archiv f. Kinderheilkunde,' vol. 15, p. 78, 1892.

‡ 'Zeits. f. klin. Med.,' vol. 20, Part II, 1892.

§ 'Centralblatt f. Bacteriol.,' vol. 12, p. 777, 1892.

|| *Loc. cit.*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FIGS. 2 and 3.—"Finely granular" hæmic leucocytes (cat), incubated for twenty-four hours at 30° C, and beginning to undergo "vacuolation." In most of the vacuoles no particles are visible. Photographed while living. × 1000.

FIG. 4.—Two incubated leucocytes. In each the outline of the cell body is just visible; the nucleus, darkly stained with methylene blue, has been made to smear; before incubation the nuclei of the leucocytes would not smear.

FIG. 5.—"Finely granular" hæmic leucocyte (dog), killed very slowly (5° C, ten days). The nucleus has become spheroidal and excentric in position. When fresh the granules of the cell-body were exhibiting Brownian movement. Osmic vapour, then Ehrlich's logwood. × 1000.

FIGS. 6 and 7.—"Finely granular" hæmic leucocytes (dog), showing "rosette" form of nucleus commonly assumed. Blood oxalated and incubated for forty-eight hours. Fixation by drying over osmic vapour. Hæmatoxylin and eosin. × 1000.

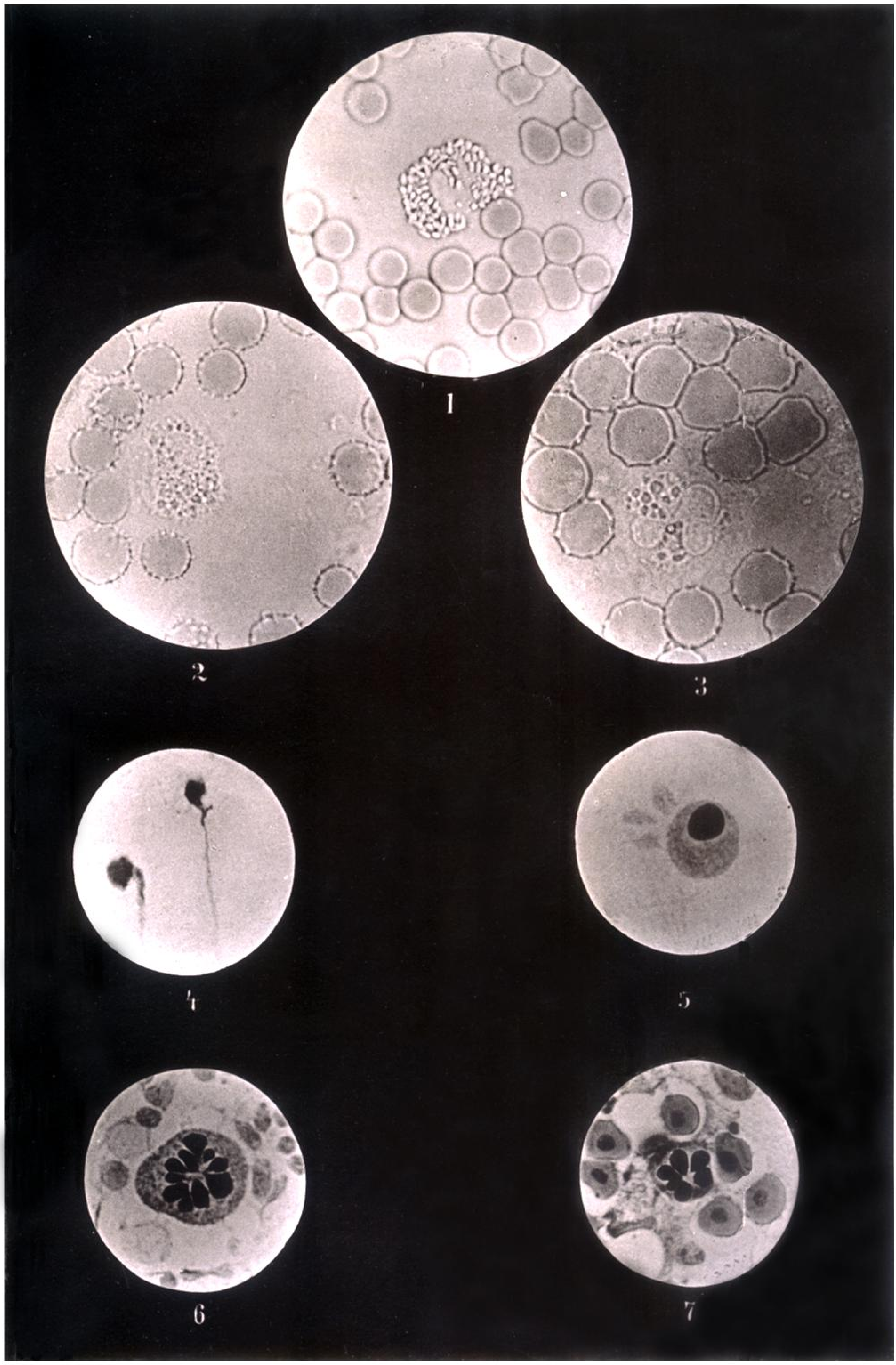
March 1, 1894.

Dr. PERKIN, Vice-President, in the Chair.

A List of the Presents received was laid on the table, and thanks ordered for them.

In pursuance of the Statutes, the names of the Candidates for election into the Society were read, as follows:—

Bateman, Sir Frederic, M.D.
Bateson, William, M.A.
Beevor, Charles Edward, M.D.
Bell, Robert.
Boulenger, George Albert.
Bourne, Professor Alfred Gibbs, D.Sc.
Bovey, Henry Taylor, M.A.
Bradford, John Rose, M.D.
Bryan, George Hartley, M.A.
Burdett, Henry Charles.
Buzzard, Thomas, M.D.
Callaway, Charles, D.Sc.
Callendar, Hugh Longbourne.
Cheyne, William Watson, F.R.C.S.
Clarke, Sir George Sydenham, Major R.E.
Clowes, Professor Frank, D.Sc.
Corfield, William Henry, M.D.
Darwin, Leonard, Major R.E.
Dibdin, William J., F.C.S.
Downing, Arthur Matthew Weld, M.A.
Edgeworth, Professor Francis Ysidro, M.A.
Etheridge, Robert, F.G.S.
Froude, Robert Edmund.
Gray, Andrew, M.A.
Griffiths, Ernest Howard, M.A.
Haddon, Professor Alfred Cort, M.A.
Heycock, Charles Thomas, M.A.
Hickson, Sydney John, M.A.
Hill, George Henry, M.Inst.C.E.
Hill, Professor M. J. M., M.A.
Hinde, George Jennings, Ph.D.
Howes, Professor George Bond, F.L.S.
Jones, Professor John Viriamu, M.A.



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