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Contributors

Osler, William, Sir, 1849-1919.
Hogg, Jabez, 1817-1899
Royal College of Surgeons of England

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(21.)

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With the authors

Kind regards

AN

ACCOUNT OF CERTAIN ORGANISMS

OCCURRING IN

THE LIQUOR SANGUINIS.

BY

WILLIAM OSLER, M.D.

In many diseased conditions of the body, occasionally also in perfectly healthy individuals and in many of the lower animals, careful investigation of the blood proves that, in addition to the usual elements, there exist pale granular masses, which on closer inspection present a corpuscular appearance (Plate V. fig. 1). There are probably few observers in the habit of examining blood who have not, at some time or other, met with these structures, and have been puzzled for an explanation of their presence and nature.

In size they vary greatly, from half or quarter that of a white blood-corpuscle, to enormous masses occupying a large area of the field or even stretching completely across it. They usually assume a somewhat round or oval form, but may be elongated and narrow, or, from the existence of numerous projections, offer a very irregular outline. They have a compact solid look, and by focusing are seen to possess considerable depth; while in specimens examined without any reagents the filaments of fibrin adhere to them, and, entangled in their interior, white corpuscles are not unfrequently met with.

It is not from every mass that a judgment can be formed of their true nature, as the larger, more closely arranged ones have rather the appearance of a granular body, and it is with difficulty that the individual elements can be focused. When, however, the more loosely composed ones are chosen, their intimate composition can be studied to advantage, especially at the borders, where only a single layer of corpuscles may exist; and when examined with a high power (9 or 10 Hartnack) these corpuscles are seen to be pale round disks, devoid of granules and with well-defined contours. Some of the corpuscles generally float free in the fluid about the mass; and if they turn half over their profile view has the appearance of a sharp dark line (fig. 5, *a* & *b*). In water the individual corpuscles composing the mass swell greatly; dilute acetic acid renders them more distinct, while dilute potash solutions quickly dissolve them. Measurements give, for the large proportion of the corpuscles, a diameter ranging from one 8000th to one 10,000th of an inch; the largest are as much as one 5000th, and the smallest from one 15,000th to one 24,000th of an inch; so that they may be said to be from $\frac{1}{8}$ – $\frac{1}{2}$ the size of a red corpuscle. In the blood of cats, rabbits, dogs, guineapigs, and rats the masses are to be found in variable numbers. New-born rats are specially to be recommended as objects of study, as in their blood the masses are commonly both numerous and large. They occur also in the blood of foetal kittens.

Considering their prevalence in disease and among some of the lower animals, they have attracted but little notice, and possess a comparatively scanty literature. The late Prof. Max Schultze* was the first, as far as I can ascertain, to describe and figure the masses in question. He speaks of them as constant constituents of the blood of healthy individuals, but concludes that we know nothing of their origin or destiny, suggesting, however, at the same time that they may arise from the degeneration of granular white corpuscles. Schultze's observations were confined to the blood of healthy persons, and he seemed of the opinion that no pathological significance was to be attributed to them.

By far the most systematic account is given by Dr. Riess†, in an

* Archiv f. mik. Anat. Bd. i.

† Reichert u. Du Bois-Reymond's Archiv, 1872.

article in which he records the results of a long series of observations on their presence in various acute and chronic diseases. His investigations of the blood of patients, which were much more extensive than any I have been able to undertake, show that, in all exanthems and chronic affections of whatever sort, indeed in almost all cases attended with disturbance of function and debility, these masses are to be found. He concludes that their number is in no proportion to the severity of the disease, and that they are more numerous in the latter stages of an affection, after the acute symptoms have subsided. The former of these propositions is undoubtedly true, as I have rarely found masses larger or more abundant than I, at one time, obtained from my own blood when in a condition of perfect health. These two accounts may be said to comprise every thing of any importance that has been written concerning these bodies. The following observers refer to them cursorily:—Erb *, in a paper on the development of the red corpuscles, speaks of their presence under both healthy and diseased conditions: he had hoped, in the beginning of his research, that they might stand, as Zimmerman supposes (see below), in some connexion with the origin and development of the red corpuscles; but, as he proceeded, the fallacy of this view became evident to him. Bettelheim † seems to refer to these corpuscles when he speaks of finding in the blood of persons, healthy as well as diseased, small punctiform, or rod-shaped, corpuscles of various sizes. Christol and Kiener ‡ describe in blood small round corpuscles, whose measurements agree with the ones under consideration; and they also speak of their exhibiting slight movements. Riess §, in a criticism on a work of the next-mentioned author, again refers to these masses, and reiterates his statements concerning them. Birsch-Hirschfeld || had noticed them and the similarity the corpuscles bore to micrococci, and suggests that under some conditions *Bacteria* might develop from them. Zimmerman ¶ has described corpuscular elements in the blood, which, with reference to the bodies in question, demand a notice here. He let blood flow directly into a solution of a neutral salt, and, after the subsidence of the coloured elements, examined the supernatant serum, in which he found, in extraordinary numbers, small, round, colourless corpuscles with weak contours, to which he gave the name of “elementary corpuscles.” These he met with in human blood both in health and disease and in the blood of the lower animals; and he found gradations between the smaller (always colourless) forms and full-sized red corpuscles. He gives measurements (for the smaller ones, from one 1000th to one 800th of a line; the largest, one

* Virchow's Archiv, Bd. xxxiv.

† Wiener med. Presse, 1868, No. 13.

‡ Comptes Rendus, lxxvii. 1054. Quoted in ‘Centralblatt,’ 1869, p. 96.

§ Centralblatt, 1873, No. 34.

|| Centralblatt, 1873, No. 39.

¶ Virchow's Archiv, Bd. xviii.

500th to one 400th of a line), and speaks of them also as occurring in clumps and groups of globules. It is clear, on reading his account, that in part, at any rate, he refers to the corpuscles above described. Gradations such as he noticed between these and the coloured elements I have never met with, and undoubtedly he was dealing with the latter in a partially decolourized condition. Lostorfer's* corpuscles, which attracted such attention a few years ago from the assertion of the discoverer that they were peculiar to the blood of syphilitic patients, require for their production an artificial culture in the moist chamber extending over several days. They appear first after two or three days, or even sooner, as small bright corpuscles, partly at rest, partly in motion, which continue to increase in size, till, by the sixth or seventh day, they have attained the diameter of a red corpuscle, and may possess numerous processes or contain vacuoles in their interior. Blood from healthy individuals, as well as from diseases other than syphilis, has been shown to yield these corpuscles; and the general opinion at present held of them is that they are of an albuminoid nature.

The question at once most naturally arose, How is it possible for such masses, some measuring even one 400th of an inch, to pass through the capillaries, unless supposed to possess a degree of extensibility and elasticity such as their composition hardly warranted attributing to them? Neither Max Schultze nor Riess offer any suggestion on this point, though the latter thinks that they might, under some conditions, produce embolism.

During the examination of a portion of loose connective tissue from the back of a young rat, in a large vein which happened to be in the specimen, these same corpuscles were seen, not, however, aggregated together, but isolated and single among the blood-corpuscles (fig. 8); and repeated observations demonstrated the fact that, in a drop of blood taken from one of these young animals, the corpuscles were always to be found accumulated together; while, on the other hand, in the vessels (whether veins, arteries, or capillaries) of the same rat they were always present as separate elements, showing no tendency to adhere to one another. The masses, then, are formed at the moment of the withdrawal of the blood, from corpuscles previously circulating free in it.

To proceed now to the main subject of my communication. If a drop of blood containing these masses is mixed on a slide with an equal quantity of saline solution, $\frac{1}{2}$ – $\frac{3}{4}$ per cent., or, better still, perfectly fresh serum, covered, surrounded with oil, and kept at a temperature of about 37° C., a remarkable change begins in the masses. If one of the latter is chosen for observation, and its outline carefully noted, it is seen, at first, that the edge presents a tolerably uniform appearance, a few filaments of

* Wiener med. Presse, 1872, p. 93. Wiener med. Wochenschrift, 1872, No. 8. Article in Archiv f. Dermatolog. 1872.

fibrin perhaps adhering to it, or a few small corpuscles lying free in the vicinity. These latter soon exhibit apparent Brownian movements, frequently turning half over, and showing their dark rod-like border (fig. 5, *a, b*). After a short time an alteration is noticed in the presence of fine projections from the margins of the mass, which may be either perfectly straight, or each may present an oval swelling at the free or attached end or else in the middle (fig. 2, *b*). It is further seen that the edges of the mass are now less dense, more loosely arranged, or, if small, it may have a radiated aspect. Sometimes, before any filaments are seen, a loosening takes place in the periphery of the mass, and among these semifree corpuscles the first development occurs. The projecting filaments above mentioned soon begin a wavy motion, and finally break off from the mass, moving away free in the fluid. This process, at first limited, soon becomes more general; the number of filaments which project from the mass increases, and they may be seen not only at the lateral borders, but also, by altering the focus, on the surface of the mass, as dark, sharply defined objects. The detachment of the filaments proceeds rapidly; and in a short time the whole area for some distance from the margins is alive with moving forms (fig. 2, *c*, and fig. 3), which spread themselves more and more peripherally as the development continues in the centre. In addition to the various filaments, swarming granules are present in abundance, and give to the circumference a cloudy aspect, making it difficult to define the individual forms. The mass has now become perceptibly smaller, more granular, its borders indistinct and merged in the swarming cloud about them; but corpuscles are still to be seen in it, as well as free in the field. A variable time is taken to arrive at this stage; usually, however, it takes place within an hour and a half, or even much less. The variety of the forms increases as the development goes on; and whereas, at first, spermatozoon-like or spindle-shaped corpuscles were almost exclusively to be seen, later more irregular forms appear, possessing two, three, or even more tail-like processes of extreme delicacy (fig. 5, *k*). The more active ones wander towards the periphery, pass out of the field, and become lost among the blood-corpuscles. The process reaches its height within $2\frac{1}{2}$ hours, and from this time begins almost imperceptibly to decline; the area about the mass is less densely occupied by the moving forms, and by degrees becomes clearer, till at last, after six or seven hours (often less), scarcely an element is to be seen in the field, and a granular body, in which a few corpuscles yet exist, is all that remains of the mass. The above represents a typical development from a large mass in serum, such as that seen in fig. 3*.

We have next to study more in detail the process of development and the resulting forms. Commonly, the first appearance of activity is

* The mass from which this sketch was taken was seen in full development by several of the foreign visitors to the British Medical Association last year.

displayed by the small free corpuscles at the margins, which, previously quiescent, begin a species of jerky irregular movement, at one time with their pale disk-surfaces uppermost, at another presenting their dark linear profiles (fig. 5, *a* & *b*). Not unfrequently, some of these are seen with a larger or smaller segment of their circumference thicker and darker than the other (fig. 5, *c*).

Earliest, and perhaps the most plentiful, of the forms are those of a spermatozoon-like shape (fig. 5, *d*), attached to the mass either by the head or tail; while, simultaneously, long bow-shaped filaments appear (fig. 5, *e*), having an enlargement in the centre. Straight hair-like filaments (fig. 5, *f*) may also be seen, but they are not very numerous. The time which elapses before they begin the wavy movement is very variable, as is also the time when they break away after once beginning it. Filaments may be seen perfectly quiescent for more than half an hour before they move, and others may be observed quite as long in motion before they succeed in breaking away from the mass. Commonly it is in the smaller masses, and where the development is feeble, that filaments remain for any time adherent. The spermatozoon-like forms appear, at the head, on one view flattened and pale, on the other dark and linear (fig. 5, *d*); consequently the head is discoid, not spheroidal. The bow-shaped filaments also present a dark straight aspect when they turn over (fig. 5, *e*), and are by far the longest of the forms, some measuring as much as one 900th of an inch. Many intermediate forms between the round discoid corpuscles and those with long tails are met with in the field, and are figured at fig. 5, *g*.

Small rod-shaped forms are very numerous, most of which, however, on one aspect look corpuscular; but in others this cannot be detected, or only with the greatest difficulty; slight enlargements at each end may also be seen occasionally in these forms (fig. 5, *h*).

Usually late to appear, and more often seen in the profuse developments from large masses, are the forms with three or more tail-like processes attached to a small central body (fig. 5, *k*). Among the granules it is extremely difficult to determine accurately the number of these processes, the apparent number of which may also vary in the different positions assumed by the element. As to the ultimate destiny of the individual forms, I have not much to offer; I have watched single ones, with this view, for several consecutive hours without noticing any material alteration in them. The one represented at fig. 6 was watched for four hours, that at fig. 7 for five, and the changes sketched. The difficulty of following up individual filaments in this way is very great, not only from the ensuing weariness, but from the obstacle the red corpuscles offer to it.

With regard to the movement of the filaments, this, at first sight, bears some resemblance to that known as the Brownian, exhibited by

granules in the field, or sometimes by the red corpuscles; but an evident difference is soon noticed in the fact that, while the former (also the small corpuscles) undergo a change of place, the latter remain constant in one position or vary but little.

Movements like those of the ordinary rod-shaped *Bacteria* are not exhibited by them.

Circumstances which influence the development.—In blood, without the addition of saline solution or serum, no change takes place in the masses even after prolonged warming. A temperature of about 37° C. is necessary for the process; none occurs at the ordinary temperature, with or without the addition of fluid. Fresh serum is the medium most favourable to the process, added in quantity equal to the amount of blood. Not every mass develops when placed under conditions apparently favourable; but for this no good reason can, at present, be offered.

Fig. 8 represents the corpuscles among the red ones while in the vessel; and, as is there seen, they appear somewhat more elliptical on the profile view, and more elongated, than in blood after withdrawal, but present the same disk-like surfaces when they roll over. On adding saline solution or serum, and warming the preparation, development proceeds, but not to such an extent as from the masses. The individual corpuscles become elongated, some tailed, and they move about in the vessel. At fig. 9 they are seen in the vessel after three hours on the warm stage: the remarkable form seen at *a* was one 1300th of an inch in length, and had moved up from the opposite end of the vessel.

It must still be confessed, with Max Schultze, that we know nothing of the origin or destiny of these corpuscles; and once admit their existence as individual elements circulating in the blood, his suggestion, and Riess's assertion that the masses arise from the disintegration of white corpuscles, becomes quite untenable. We must also confess the same ignorance of the reasons of their increase in disease; nor do we know at all what influence they may exert in the course of chronic affections.

Finally, as there is no evidence that these bodies are in organic continuity with any other recognized animal or vegetable form, or possess the power of reproduction, nothing can at present be said of their nature or of their relation to *Bacteria*.

These observations were carried on in the Physiological Laboratory of University College, and my thanks are due to Prof. Sanderson and Mr. Schäfer for advice and valuable assistance.

EXPLANATION OF THE PLATE.

PLATE V.

Fig. 1. Common forms of the masses from healthy blood. (Ocular 3, Objective 5.)

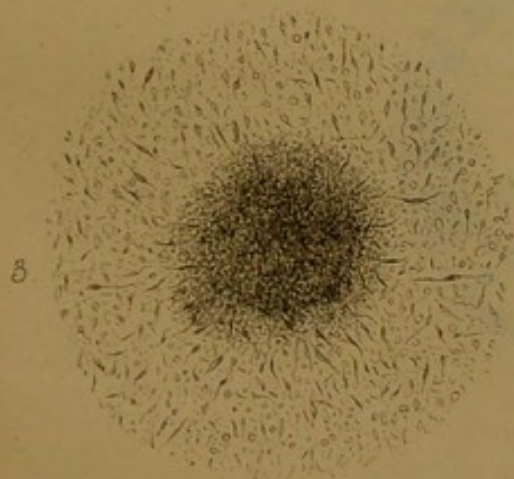
Fig. 2. A mass from healthy blood, in saline solution, showing stages of development: *a*, at 10 A.M.; *b*, at 10.30 A.M.; *c*, at 11 A.M. (Ocular 3, Objective 7.)

- Fig. 3. Mass from blood of young rat (in serum) in full development, after two hours' warming. (Ocular 3, Objective 7.)
- Fig. 4. Mass (young rat) with blood-corpuscles about it, to show the relative sizes. (Ocular 3, Objective 5.)
- Fig. 5. Some of the developed forms as seen with No. 11 Hartnack. (See text.)
- Fig. 6. Form watched for four hours. (Ocular 3, Objective 9.)
- Fig. 7. Form watched for five hours. (Ocular 3, Objective 9.)
- Fig. 8. Small vein in connective tissue from the back of a young rat, showing the corpuscles free among the red ones. (Ocular 3, Objective 7.)
- Fig. 9. Small vein from the connective tissue of a rat (in serum), showing corpuscles and developed forms. (Ocular 3, Objective 9.)

1.



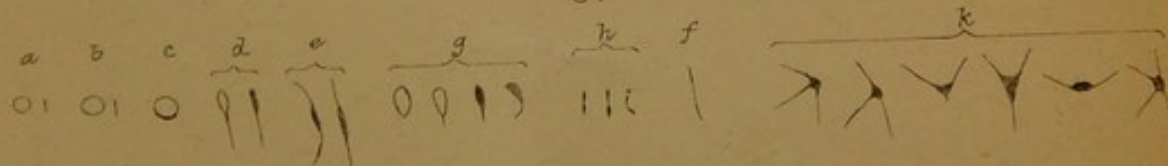
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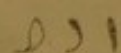
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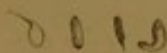
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6.



7.



8.



9.



