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Scientific Basis of Clinical Practice

Activities of the Neutrophil Polymorph

D. B. BREWER

British Medical Journal, 1972, 2, 396-400

The neutrophil polymorphonuclear leucocyte is the most important cell in the cellular defences of the body against acute bacterial infections and it is the most important factor in the killing of invading bacteria. The killing of bacteria by the polymorphonuclear leucocytes is the result of a complex process involving a sequence of activities on the part of the polymorph, many of which depend on a variety of plasma factors.

The polymorphs are actively motile cells; indeed, they can move more rapidly than any other cell. In addition, under appropriate circumstances their movements become directed so that they will move towards bacteria. Having come into contact with bacteria, the polymorphs then phagocytose them. A vacuole is formed around the phagocytosed organisms and the polymorph granules fuse with the vacuole, releasing their contents into the vacuole and so killing the organisms. Such a complex succession of events may best be analysed by considering its parts separately.

Movement of Neutrophil Polymorphs

When moving spread out on the surface of a glass cover slip polymorphs have a very constant and typical appearance when examined by phase-contrast microscopy (Fig. 1). The anterior end, which is free of granules, is constantly pushing forward, but it does not move evenly. Different portions of the anterior edge push forward and stop, and then other portions push forward—but the sum of these irregular movements adds up to a continuous forward movement. Behind this anterior edge is the main cell body, containing cytoplasmic granules, and, usually towards the rear of the cell, the lobed nucleus. The granules stream forward but may often be seen to stop suddenly when they encounter the posterior margin of the granule-free anterior edge, as if they encounter an obstruction which prevents them moving further forward. The main cell body often tapers to a pointed posterior end, which appears dark by phase-

contrast microscopy and from which several very long thin threads can be seen projecting backwards.

There has been surprisingly little investigation of the detailed mechanism of the movement of the neutrophil polymorph. It is commonly described as amoeboid, with the implied assumption that the mechanism of movement is similar to that of the amoeba; but probably this is too facile an assumption, as, apart

FIG. 1—Two living human polymorphs moving upwards. Anterior ends free of granules pushing between other polymorphs. Main cell body full of granules. Nuclei in posterior part of cell. Phase contrast microscopy. $\times 2,000$ approx.

from anything else, the neutrophil polymorph is very much smaller than the amoeba. Even if we accept that the polymorph moves in the same way as the amoeba we are still left with several alternative hypotheses as there is no universally accepted explanation of how the amoeba moves.

According to Goldacre,¹ the amoeba is propelled forwards as a result of contraction of a plasmagel at the rear end of the cell body which causes a fluid cytoplasmic stream to flow forward in the central portion of the cell body. The contractile plasmagel after contracting at the rear becomes soluble and flows forward as a plasmasol in the

forward flowing cytoplasmic stream. When it reaches the anterior end of the cell the soluble protein becomes an insoluble fibrous protein in the cell membrane, which then with the forward movement of the amoeba gradually comes to occupy a more and more posterior position. Eventually the protein lies at the posterior end of the amoeba, when it again contracts to propel forward the cytoplasmic stream in which the protein is again soluble.

The most widely held alternative view is that of Allen,² who considers that the cytoplasmic stream is not propelled by contraction at the rear end of the amoeba but is propelled by contraction of the endoplasm in the centre of the cell body. This produces a central forward flowing stream of cytoplasm, which at the anterior end of the amoeba then turns and flows backwards in the outer zones of the cell cytoplasm. Because of this pattern of flow this hypothesis is referred to as the fountain zone contraction hypothesis.

There is no convincing evidence in favour of either of these theories in the case of the neutrophil polymorph. The appearances of the neutrophil polymorph moving on a coverslip are in fact often contrary to those implied by Goldacre's theory. Commonly the anterior end of a polymorph may be seen to push forward for quite a considerable distance while the rear end remains quite immobile. It is possible to imagine that this apparently active spreading forwards of the anterior end of the polymorph is brought about by adhesion between the surface of the polymorph and the surface of the coverslip. In fact, Carter³ has suggested that such a mechanism may underlie chemotaxis. He coated a coverslip with a film of palladium of gradually increasing thickness. The thicker the film of palladium, the more adherent the cells, and he showed that the cells moved consistently and directly from areas of lesser adhesion to areas of greater adhesion. Nevertheless, though to move on a substrate a cell must adhere, if the adherence is too great it becomes permanent and all movement ceases. To move regularly forward the cell must not only adhere but must also detach itself so that it can move forward again.

Often when the anterior end of the polymorph moves forwards the rear end remains fixed, and so the cell will obviously become elongated and narrow. Then another characteristic form of movement takes place. While the anterior end remains fixed the posterior end of the cell becomes detached from the surface of the coverslip and is pulled quite rapidly forwards by a contraction of the cell body. It is now widely accepted that such a contraction of a cell is the result of the presence within the cytoplasm of a system of microfibrils or microtubules detectable with the electron microscope that cause the cell to contract by a mechanism similar to that of muscle contraction.⁴ Such fibrillar structures have been seen in monocytes⁵ but they have not so far been described in neutrophil polymorphs. Nevertheless, it remains possible that they are present but are difficult to demonstrate as they may form and disappear according to the functional state of the cell and their detection with the electron microscope depends considerably on fixation.

Chemotaxis

It would seem inherently likely that polymorphs can move towards bacteria in a purposeful manner. This has not been conclusively shown in living tissues but several methods have now been developed to demonstrate and measure it in vitro.

METHOD OF HARRIS

Harris⁶ has devised a very simple and striking method of demonstrating chemotaxis in vitro. A coverslip to which polymorphs are adherent is mounted on a slide with a thin plasma clot between the slide and the coverslip. The movement of the polymorphs is observed by dark-ground microscopy at a magnification of about 250. Under these circumstances the polymorphs appear as bright round blobs against a black background. Their movements are recorded by exposing a photographic film continuously for 5 to 15 minutes, when the cells trace out a bright track. When no chemotactic stimulus is present the tracks are entirely random. However, when a chemotactic object is present the polymorphs may be seen to converge towards it in a most dramatic fashion. Using this technique, Harris showed that a variety of bacteria attracted neutrophil polymorphs, including *Salmonella typhi* and *Mycobacterium tuberculosis* that in vivo produce lesions notable for the absence of polymorphs.

He also demonstrated in this experimental set-up that crushed or autolysed tissues of enzymatic digests of tissues were not chemotactic. If these tissue break-down products are chemotactic in vivo, the reason for the failure to demonstrate it may be because the chemotactic substances are readily soluble and so diffuse evenly throughout the preparation.

To try to circumvent this difficulty Boyden⁷ devised another method of observing and measuring chemotaxis.

METHOD OF BOYDEN

Chemotaxis is observed in a two-compartment chamber. The compartments are separated from one another by a Millipore filter. The cells to be observed are placed in a suitable medium in one compartment and the substances under test in the other. If the substance is positively chemotactic the cells will move through the Millipore filter towards it and they can be counted on the surface of the filter.

Using the method of Boyden several workers have shown that a variety of substances are positively chemotactic. Some such as Witte's peptone, casein, and culture filtrate of *Escherichia coli* are active in the absence of serum. Others such as certain antigen-antibody complexes, heat-aggregated gammaglobulin, and glycogen require the presence of fresh serum. Keller and Sorkin⁸ have suggested that those substances active in the absence of serum should be called cytotoxins, and those that require serum cytotoxigens, it being assumed that the latter generate cytotoxins by reacting with various serum factors. The identity of the cytotoxins so formed is not fully determined, but clearly important among them are various components of complement. These include a high molecular weight complex of C'5, 6, and 7, and two low molecular weight factors—C3a formed by the action of plasmin or trypsin on the C3 component of complement, and C5a formed from C5 either by trypsin or by the interaction of the first five components of complement. This new knowledge of chemotactic properties of antigen-antibody complexes and the role of complement in this phenomenon is of great interest as it has long been known that plasma factors play an important part in phagocytosis.

Phagocytosis

The details of the process of phagocytosis have become clear in recent years as a result of several studies by electron micro-

FIG. 2—Electron micrograph of phagocytosis of staphylococci by a polymorph. Part of polymorph in left half with four spherical cocci adherent to cell membrane. Cell membrane only slightly indented in lower two. Cell membrane moving around to envelope of upper two. $\times 25,000$.

scopy.⁹ Very close adhesion develops between the outer cell membrane of the polymorph and the bacterium (Fig. 2). The gap between the cell membrane and the surface of the bacterium is very narrow, about 150 Å. By conventional electron microscopy nothing can be seen in the gap, but probably it is bridged by protein molecules. By causing adhesion in this way these protein molecules render possible the process of phagocytosis. From the initial point of adhesion the cell membrane gradually comes to cover the whole of the surface of the bacterium (Fig. 2). At this point the cell membrane, which has come to surround completely the bacterium, fuses in two layers—one to encircle the phagocytosed bacterium, and the other to complete the outer cell membrane.

In this way the bacterium comes to lie in the cell cytoplasm surrounded by a layer of cell membrane that was originally part of the outer cell membrane but is now detached from it. At this stage the cell membrane is still as closely applied to the surface of the bacterium as in the initial stages of phagocytosis but very soon a vacuole is formed (Fig. 3). This appears to involve two processes; firstly, the separation of the cell membrane from the surface of the bacterium and its expansion; and, secondly, the fusion of the polymorph granules with the membrane of the phagocytic vacuole and the release of the contents into the

vacuole. Observations on living polymorphs by phase-contrast microscopy show that these two events take place quite rapidly and almost simultaneously. However, probably the fusion of the granules takes place first and the vacuole develops very soon afterwards.

That changes occur in the cytoplasmic granules of the polymorph has been known for some time. If polymorphs and a suspension of bacteria with the necessary plasma factors are incubated *in vitro* and samples are taken at intervals, fixed, and stained, it will be seen that the cytoplasmic granules decrease in number as phagocytosis proceeds. In fact, within 30 minutes of incubation degranulation is present and is directly related to the amount of material ingested.

DEGRANULATION

Observations of the process by phase-contrast microscopy in living cells show that degranulation is a very rapid dramatic event and directly brought about by phagocytosis (Figs. 4-6). It was first described in living cells by Robineaux and Frederic¹⁰ and, though they did not demonstrate the details of the process, they suggested that it was related to the process of digestion of the phagocytosed organisms.

Hirsch¹¹ has analysed the process in some detail.

By using very thin preparations of living cells and filming at 10 frames a second he showed that the changes in the granules developed within 30 sec of phagocytosis beginning. In some instances the changes occurred before the object being phagocytosed was completely surrounded by cytoplasm. The polymorph granules, normally dark, suddenly "pop" and are transformed into bright spheres. This process takes only from 0.1 to 0.2 sec and as a result it appears almost like a bright flash of light. The bright sphere which then appears alters in shape and spreads around the phagocytosed object. Only granules adjacent to the phagosome "pop" but a succession of granules will "pop" and the resulting bright spheres will coalesce and surround the organism forming a vacuole about it.

I have repeated Hirsch's experiments. Figures 4 to 6 are from a cine film taken of living rabbit polymorphs by phase-contrast microscopy. The time interval between Fig. 4 and Fig. 5 is 0.375 sec and between Fig. 5 and 6 0.625 secs. The oval bodies being phagocytosed are empty yeast cells. At the top end of the upper yeast cell (Fig. 5) two granules have "popped" and are fusing to form a clear spherical vacuole (Fig. 6).

The structures concerned are so small that they are quite close to the limit of resolution of the light microscope, so that it is difficult to see precisely what is happening. But studies by electron microscopy of polymorphs fixed while actively phagocytosing have sometimes shown appearances suggesting fusion between the membrane about the phagocytosed organism and the membrane of the granules of the polymorph, so that as a result the contents of the granule are released into the vacuole (Fig. 3).

FIG. 3—Electron micrograph of part of polymorph. The two pale areas—one on left edge, the other on lower edge—are lobes of the nucleus. To the right of the upper lobe is a vacuole containing in its lower part a single staphylococcus and many other small dark oval and lighter bodies probably cytoplasmic granules. $\times 16,000$.

FIG. 4-6—Frames from a phase-contrast cine film of rabbit polymorphs phagocytosing yeast cells. Two polymorphs are phagocytosing two yeast cells. In Fig. 5, 0.375 sec after Fig. 4 two granules have "popped" at the upper end of the yeast cell on the right; 0.625 sec later in Fig. 6 they have fused to form a single round vacuole. $\times 2,000$ approx.

Several studies have now examined the nature of the contents of the cytoplasmic granules, some by biochemical techniques and others by histochemical methods.¹² The precise details are not completely certain. There are certainly two different types of cytoplasmic granule, and possibly three, but it is agreed that the granules may be regarded as primary lysosomes. They contain several hydrolytic enzymes—including acid and alkaline phosphatase, ribonuclease, deoxyribonuclease, cathepsin, and β -glucuronidase. They also contain lysozyme, an enzyme first discovered as an antibacterial substance in tears and nasal secretions by Fleming¹³ in 1922. It acts on a range of organisms by breaking down certain polysaccharides in the cell wall.

An important enzyme found in the polymorph granules is peroxidase. This is present in large amounts in polymorphs amounting to 5% of the dry weight of the cell. In other cells it is not present in lysosomes but is found in the microbodies. There is good evidence that peroxidase plays an important part in killing phagocytosed bacteria. Klebanoff¹⁴ has shown that in the presence of iodide and hydrogen peroxide peroxidase can bring about the iodination of bacterial protein and so kill the bacteria.

Clearly, therefore, the release of the contents of the polymorph granules into the phagocytic vacuole exposes the bacteria to many different enzymes capable of destroying a wide range of bacteria.

Disorders of Polymorph Function

In recent years an interesting two-way traffic of information has developed in the field of disorders of polymorph function. Knowledge of the normal function has provided an explanation of disorders of function, and investigation of disorders of function have in their turn provided new information on how the polymorph destroys bacteria.

The precise definition of the various disorders and their distinction one from another is still developing, so what is now regarded as a single entity may later be shown to encompass several, and what are now thought to be separate entities may later be found to be the same. Nevertheless, at present, disorders of polymorph function may be considered as resulting from: (1) an absence of plasma factors; and (2) an intrinsic defect in the polymorph.

DEFECT IN CHEMOTAXIS

Ward and Schlegel¹⁵ described a 4-year-old child who suffered from recurrent respiratory and cutaneous infections. They showed that there was impairment of chemotaxis which was due to the presence in the plasma of an inhibitory factor which impaired the chemotaxis of normal polymorphs. In normal plasma the patient's polymorphs behaved almost normally. In addition to this defect of chemotaxis the polymorphs were unable to destroy *E. coli* and *Klebsilla enter-bacter* after they had been phagocytosed. The relation between these two abnormalities in this patient is as yet unclear.

DEFECT IN PHAGOCYTOSIS

Miller *et al.*¹⁶ described this abnormality in a 3-month-old infant who suffered from diarrhoea, severe eczematoid dermatitis, recurrent local and systemic bacterial infection, and failure to thrive. Antibody formation, cellular immunity, and leucocyte bactericidal activity were all normal. They found that the patient's serum was deficient in plasma factors required for opsonization and that in normal serum the patient's polymorphs were normally phagocytic. Plasma from the patient's mother was also deficient in these factors. The administration to the patient of fresh blood or plasma was very effective in treatment.

"LAZY LEUCOCYTE SYNDROME"

In this disorder the abnormality appears to be intrinsic to the leucocyte. Miller *et al.*¹⁷ described two young children, one almost 5 years old, the other just over 2 years, who suffered from recurrent stomatitis, otitis, gingivitis, and low-grade fevers. Humoral and cellular immunity were normal. The peripheral polymorph count was appreciably reduced, 170 neutrophil polymorphs/mm³ in one and 135 neutrophil polymorphs/mm³ in the other. Polymorphs in the bone marrow were present in normal numbers but they could not be mobilized to increase the peripheral count. The polymorphs in the peripheral blood showed poor chemotaxis and also much reduced random movement, but under suitable conditions phagocytosis was normal and the phagocytosed bacteria were normally destroyed. There is as yet no explanation of this abnormality.

CHRONIC GRANULOMATOUS DISEASE

This disorder of the neutrophil polymorph has been more intensively studied than any other. It is characterized by recurrent infections that are severe but that are most often due to bacteria of low virulence. There are commonly infections of the skin; the superficial lymph nodes are enlarged; and there is often persistent pulmonary infection and enlargement of the liver and spleen, in which giant cell granulomas may be present. Throughout the reticuloendothelial system are numerous macrophages containing large amounts of lipochrome. Antibody formation is unimpaired and there may be hypergammaglobulinaemia.

Movement and phagocytosis by the neutrophil polymorphs are normal. The striking abnormality is that when the polymorphs phagocytose the bacteria they fail to kill them. There is as yet no complete explanation of this. It was originally suggested that the polymorph granules did not fuse with the phagocytic vacuole. However, careful qualitative and quantitative studies by Baehner *et al.*¹⁸ have shown normal degranulation and release of hydrolytic enzymes in polymorphs in chronic granulomatous disease.

In normal polymorphs the act of phagocytosis stimulates oxidative metabolism and the hexose monophosphate shunt. Considerable amounts of hydrogen peroxide are produced. The abnormal polymorphs in chronic granulomatous disease do not show this metabolic response and do not produce hydrogen peroxide. There is good evidence that this lack of hydrogen peroxide is the cause of the failure to kill the ingested bacteria. As already mentioned, Klebanoff showed that one important mechanism of killing of bacteria by polymorphs is the iodination of bacterial proteins by the action of peroxidase in the presence of iodide and hydrogen peroxide. Klebanoff and White¹⁹ compared the iodination by the polymorphs of chronic granulomatous disease of bacterial proteins of lactobacilli (producers of hydrogen peroxide and killed by polymorphs of chronic granulomatous disease) and of serratia (non-producers of hydrogen peroxide and not killed by polymorphs of chronic granulomatous disease). Only the lactobacilli were iodinated and these only when they were alive and producing hydrogen peroxide. Killed lactobacilli were not iodinated.

Following this line of thought Good drew attention to the fact that catalase-negative bacteria are killed by polymorphs from patients with chronic granulomatous disease while catalase-positive organisms are not. The explanation of this is that the catalase destroys the hydrogen peroxide produced by the bacteria and so prevents their iodination.

The defect in the polymorphs would therefore appear to be a failure of stimulation of metabolism by phagocytosis and a failure to produce hydrogen peroxide. The precise explanation of this in terms of the enzyme biochemistry of the polymorph is so far uncertain. The problem is reviewed in a most fascinating manner by Gray and Good.²⁰

This article is based on a lecture given in the Birmingham course under the title "The Scientific Basis of Clinical Practice" (see B.M.J., 27 November 1971, p. 510).

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Second Opinion, Please

Ankylosing Spondylitis

T. R. CULLINAN, BASIL CHRISTIE

British Medical Journal, 1972, 2, 400-401

Sydenham House, Ashford, Kent

Dear Basil,

This boy, E. F. aged 19, came to see me last week complaining of increasing pain in both tibial heads, which had been coming on for several weeks. He has no relevant personal or family history and, apart from minor complaints, has always been well.

As you will see, both tibial heads are clinically swollen anteriorly and tender to touch, though they are not markedly hot. X-ray shows no radiological change but I do not think we can escape a presumptive diagnosis of Osgood-Schlatters disease. There is no joint involvement.

The pain is now such as to affect his work as a carpenter's apprentice.

Kent and Canterbury Hospital, Canterbury

Dear Tim,

Thank you for asking me to see this patient who, I agree, appears to have bilateral Osgood-Schlatters disease. This is unusual at this age, though the upper ossification centre of the tibia may not join until the twentieth year.

X-rays of the knees show no abnormality, so I am treating him symptomatically with some short-wave therapy.

Sydenham House, Ashford, Kent

Dear Basil,

You will recall treating E.F. a few months ago for Osgood-Schlatters disease. He responded fairly well to short-wave

therapy and was left with residual stiffness only, which has been helped by indomethacin.

He now complains, however, of left hip pain which is not entirely related to the stiffness in his knees. Hip movement was full and painless today, and his hip x-ray shows no signs of Perthes's disease.

Kent and Canterbury Hospital, Canterbury

Dear Tim,

I think this boy's pain felt in his left hip, which has been present three weeks, almost certainly is referred from his back. The pain is aggravated by lumbar movements and there is some pain on full straight leg raising on the left. The hip movements are entirely normal.

The x-rays you ordered of the left hip are normal; I have had some films taken of his sacroiliac joints and these are also normal.

I am arranging some lumbar traction for him, as I think his pain must be coming from his back.

Sydenham House, Ashford, Kent

Dear Basil,

The lumbar traction you gave E.F. four months ago solved his backache for a time, but now it has returned and he also complains of a right shoulder joint pain.

Although his E.S.R. was only 15 last week, I very much fear we may be dealing with a more generalized disease than at first we thought.

Kent and Canterbury Hospital, Canterbury

Dear Tim,

This boy now has pain in his right shoulder and a recurrence of his backache. The only abnormality on examination was some tenderness of his tibial tuberosities. The remainder of the skeletal system was normal. I repeated his blood picture

Ashford, Kent

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