Wellcome Film Project

The Macrophage

The Scientific Basis of Medicine

Presented by Dr Ian Carr, University of Sheffield & Weston Park Hospital.

University of London Audio-Visual Centre, 1975.

The film sequence of macrophages in culture was made by Professor F Jacoby, Department of Anatomy, University College Cardiff.

Produced by Trevor A Scott.

Made for British Postgraduate Medical Federation.

Black-and-white

Duration: 00:37:16:10

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<**Opening titles**>

<**Dr Ian Carr, seated, to camera**>

In this programme I'm going to talk about an important phagocytic cell, the macrophage. The programme will try to answer four questions. First of all, what does it look like? And we'll have a look at the structure and, notably, the ultra structure of the macrophage. Secondly, where is the macrophage found? And we'll have a look at the sites in the human body where macrophages are found and at the origin and the circulation of the cell. Thirdly, how does the cell work at a cellular level? And we'll look at the way macrophages ingest foreign material and the effect this material has upon the cell. And fourthly, what is the role of the macrophage in bodily function? We'll look at the role of the macrophage in the physiology of the whole organism.

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The best introduction to the structure of the macrophage is to take a look at living cells as seen by phase contrast microscopy in tissue culture. And for the films that we're going to look at, I'm indebted to Professor Jacoby of the Department of Anatomy at Cardiff.

<**Carr over series of short films showing macrophage cells in action**>

The first sequence shows the rapidly undulating cell membrane of these macrophages in tissue culture, and the dark bodies being taken into the cell are blebs of fluid in pinocytic vacuoles, and look at them going into the cell at the tip of the pointer.

The second sequence shows a group of macrophages in culture, phagocytosing carbon particles; the small, bright, highly refringent particles. Now, watch these cells up here. And now watch these ones down here.

The third sequence shows a macrophage phagocytosing in sequence; several other cells are probably dead and probably macrophages. And I want you to watch this cell here.

<**Carr to camera**>

Phagocytosis of degenerate cells, as we have seen in vitro, has an important counterpart in vivo: macrophages in vivo phagocytose degenerate or dead cells in inflammatory lesions. Now the rest of the illustrations to this talk will be electron micrographs of dead, fixed tissue and it should always be remembered that such pictures are still pictures of the chemically preserved corpse of a restlessly moving cell.

Let's have a look now at the ultra structure of macrophages. Macrophages are of two basic types: freely moving and fixed. It's convenient to describe the ultra structure of the peritoneal macrophage, a typical freely moving macrophage; all macrophages elsewhere are basically of similar ultra structure.

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<**Carr over series of electron micrographs detailing the ultra structure of the macrophage, uses electronic pointer**>

In the first transmission electron micrograph the macrophage is seen to have a highly irregular surface with numerous cytoplasmic surfaces and deep cytoplasmic invaginations. These long, finger-like or flap-like processes protruding from the edge of the cell, and there are deep invaginations into the interior of the cell. You can see here numerous electron-dense bodies, or lysosomes, which we'll look at later at a higher magnification.

The cytoplasmic processes become more evident as is seen in the next illustration in cells which have been stimulated to active phagocytosis. And this is a cell in the process of active phagocytosis.

The fine cytoplasmic processes of the macrophage are well seen with the scanning electron microscope when the cell is allowed to spread out on a glass surface. Here is a macrophage, a peritoneal macrophage, which has been allowed to spread on a glass surface – notice the numerous fine processes spread over the surface of the glass; this is a red blood cell which has been caught during phagocytosis.

Well, preparations are stained with ruthenium red, which is a semi-specific stain for acidic mucous substances; a prominent cell coat is seen – the electron dense layer which is lying attached to the outer laminar of the cell membrane. And fine fibrils of this material cross deep invaginations of the cell surface, fine fibrils of cell coat substance.

When you look at the cell coat at a higher magnification, you can very often see, and this is well seen in the macrophage, globular aggregates of this presumably mucous substance, and it is convenient to suppose that this coat is a sticky layer to which foreign material tends to adhere. Recognition of many foreign substances takes place at the level of a protein layer superficial to the cell coat and this protein layer, unlike the cell coat, can be readily washed off.

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The cell cytoplasm contains large numbers of vesicles of various sizes, ranging from small, clearly micropinocytotic vesicles, about 100 nanometres or less in diameter, to large vacuoles, half a micrometer or more in diameter, which are clearly phagocytic or pinocytotic. Granular and plasmic reticulum is present in most macrophages, as here, and a prominent Golgi apparatus is visible in appropriate sections. And here you can see in the centre of the cell a large Golgi apparatus composed of flattened sections with many small vesicles around the edge. And this, of course, is evidence that the mature macrophage still has the ability to produce hydrolytic enzymes, and here it differs in an important way from the neutrophil polymorph which no longer, in its mature state, has this property.

Most macrophages contain large numbers of lysosomal-dense granules containing various acid hydrolytic enzymes. These vary from small homogeneous structures which are probably primary lysosomes, or larger heterogeneous secondary lysosomes containing evidence of partially digested phagocytosed material. And in this micrograph here, you can see small lysosomes like this one here, or this one here, or this one here, with a wholly homogeneous content, sometimes you get these in elongated forms, and these probably represent primary lysosomes containing the material secreted by the cell.

Most microphages also contain larger, heterogeneous dense bodies like this one here in which electron-dense subcomponents can be seen. The secondary lysosomes represent the combination of primary lysosomal material and partially digested phagocytosed material. And it's interesting that the primary lysosome of the polymorph is the only lysosomal material which is useful in phagocytosis, whereas in the macrophage both the primary lysosomal material and the secondary lysosomal material can be used in phagocytosis, that is to say, the lysosomal enzymes are reusable.

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As in other cells, the subcellular organelle which is principally involved in processes of movement, whether translatory movement of the whole cell or movement of organelles within the cell, is probably the 6-nanometer microfibril, presumably composed of actin. And in this micrograph here you can see the fine, strand-like microfibrils radiating throughout the cortical, the superficial, area of the cell.

Microtubules are also prominent in many macrophages, sometimes forming a meshwork. And in this micrograph you can see a meshwork of microtubules, much larger in size than the microfibrils; the function of these is not quite clear but they're probably cytoskeletal.

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<**Carr briefly to camera then over a diagram of human body marked to show where macrophages can be found. This is followed by a series of diagrams focusing on different organ locations of macrophages. Carr uses electronic pointer**>

And now I'm going to turn to look at the sites where macrophages are found throughout the body. These are illustrated in the next slide in a diagram.

In the lymph nodes, in the spleen, in the liver, in the serosal sacs, in the bone marrow, in gut associated lymphoid tissue, in the thymus, in the brain as the microglia, and scattered around about the body in connective tissue as connective tissue histiocytes.

Macrophages in lymph nodes are found in two sites: sinusoidal and interstitial. They form part of the lining of the sinus walls on the inner surface of the subcapsular sinus and in the radial and medullary sinusoids. And many of them are adherent to one another and to adjacent endothelial cells by desmosomes, that is, they are genuinely fixed macrophages. Long, cytoplasmic processes dip into the sinusoid, acting as a filtering mechanism for foreign material in the lymph. Interstitial macrophages are found scattered throughout the pulp of the lymphoid tissue, particularly obviously

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within germinal centres, where they contain prominent cytoplasmic debris derived from ingested lymphocytes – tingible body macrophages. Interstitial macrophages are found lying adjacent to the subcapsular sinus in a paravascular site.

In the spleen, the site of the macrophage is a little different. Macrophages in the spleen are entirely extravascular. The splenic sinusoids are lined by endothelial cells which are only very poorly phagocytic but whose intercellular junctions are permanently patent, so that material can readily escape from the bloodstream to be phagocytosed by the extravascular macrophages.

The macrophages of the liver, the Kupffer cells, form part of the wall of the hepatic venous sinusoids in a manner similar to the way in which lymph node macrophages form part of the wall of the lymph node sinus. The Kupffer cell and its long processes, however, project very far into the hepatic sinusoid.

<**Carr to camera**>

The macrophages of the bone marrow resemble those of the spleen in being entirely extravascular in their position, but the intracellular junctions between the sinusoidal endothelial cells in the marrow are less permanently patent than those in the spleen.

Interstitial macrophages are histiocytes in various stages of activity are found in connective tissues around the body, and these are of similar structure in general to the ones we have discussed.

The microglia, however, the macrophages of the brain, deserve a little individual mention. These are small, inconspicuous cells found in the brain substance. In the presence of inflammation or in the neighbourhood of an infarct, the microglial cells enlarge and develop into typical mature macrophages. At the same time, more macrophages are recruited into the area by immigration of circulating monocytes. The resident microglial population is believed to derive originally by immigration of blood monocytes into the brain about the time of birth. It seems likely that

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osteoclasts, the phagocytes of bone, are multinucleate bone macrophages and are of monocytic origin.

The macrophages of the lung are found in the septal wall and lying free in the alveolus and their striking peculiarity is that their metabolism and response to phagocytosis is more aerobic than that of macrophages elsewhere which are facultatively anaerobic.

<**Carr over animated illustration showing dendritic reticular cells**>

Two specialised types of macrophage, or macrophage-like cell, are found in lymph reticular tissue. Dendritic reticular cells or dendritic macrophages are found in the germinal centres of lymph or reticular tissues. They are cells with long, straight, slender processes which pass out into the surrounding tissue. The cell body is inconspicuous but resembles that of a macrophage with a moderate amount of endoplasmic reticulum and a few lysosomes. And in animals which have been previously sensitised to a specific antigen, these cells bind the antigen on their surfaces strongly, as is indicated in the diagram by the little white spots arranged around the surfaces of the processes.

Closely adjacent to these processes lie numerous lymphocytes and it is possible that these adjacent lymphocytes are immunologically competent and that they are then in a position to react with the antigen. Now, this is a nice story. It is clear that cells with this shape do exist in germinal centres and it is clear that they do bind antigen, whether they are, in fact, a specific cell type is not so certain. Whether they are, in fact, macrophages is not quite so certain but it's a nice story.

<**Carr over illustration of interdigitating cell**>

Interdigitating macrophages are much more like common-or-garden macrophages. They are found in the thymus-dependent areas of the spleen and lymph nodes, the paracortical area of the lymph node and the periarterial lymphoid tissue of the spleen. And the cell body of this cell resembles an ordinary macrophage very closely

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but there is deeply invaginated into it the cytoplasmic processes, sometimes even the whole cell bodies of lymphocytes. It has been shown in experiments involving the recolonisation of the tissues of thymectomised animals by labelled T-lymphocytes that T-lymphocytes protrude long processes into the cytoplasm of these cells; the whole lymphocyte may be within the macrophage and it is held that the T-lymphocyte matures in this site.

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<**Carr to camera, then over animated diagram showing the origin and circulation of the macrophage**>

The next thing we should consider is the origin and circulation of the macrophage. It has been clearly shown by experiments involving transfusion of marrow cells, labelled either with a radioactive isotope or with a chromosomal label, that the macrophages in inflammatory foci are of recent marrow origin.

They derive by way of the blood monocyte from a rapidly dividing marrow precursor; and there are three or more precursors before the mature circulating monocyte. Cells leave the marrow 13 to 26 hours after the last cell division, circulate for 36 to about 100 hours and leave at random. The rate of monocyte production is increased in acute inflammation, probably as a result of release of a monocytosis promoting factor. And once the monocyte is attracted out into an inflammatory focus, presumably by a chemotactic stimulus, it may divide or mature directly into a macrophage, or both.

Macrophages in other sites have been similarly demonstrated to be of marrow origin and this common origin has led to the use of the term, mononuclear phagocyte system. Usually, however, unless under exceptional and rather unphysiological stimuli, they are not of such recent marrow origin as those in inflammatory lesions. The marrow origin of macrophages in lymph nodes and spleen, while very likely, has not as yet been unequivocally demonstrated. The fact that macrophages are of marrow origin does not mean that they cannot divide locally and peripherally; there is

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clear information that macrophages in many sites – the peritoneal cavity, the liver and the lymph nodes, for instance, may divide under local stimulation. Mitosis is common in mature macrophages in inflammatory lesions, due probably to local release of chemical mediators.

<**Carr over electron micrograph showing a macrophage with broken nuclear membrane, then back to camera**>

And this micrograph illustrates a mature macrophage, with an irregular, ruffled surface and small lysosomes, in cell division – the nuclear membrane has broken down and here is the dividing nucleus; a mature macrophage in cell division, in this case within a tumour.

Once macrophages settle down in an area, it is not easy to know whether or not they spend the rest of their lives in that site. Some mature macrophages can be found in the circulating blood and it has been shown that under various circumstances macrophages pass from spleen to liver and thence to the lungs, then pass up the bronchial tree and die within the gut. The quantitative importance of this pathway is rather hard to assess.

I'm now going to look at the functions of the macrophage; the prime cellular function of the macrophage is ingestion of foreign material and this has been studied extensively in vitro and it has been shown that when macrophages are cultured in media with a high concentration of foreign protein, […]

<**Carr over an illustration of pinocytosis in a macrophage, followed by an electron micrograph showing pinocytosis in a macrophage**>

[…] they ingest the medium by an energy-dependent process within large vacuoles, cell drinking or pinocytosis. This stimulates the cell to enlarge, to mature and to produce more lysosomal enzymes and this in vitro situation is very parallel indeed to the in vivo maturation of the monocyte.

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This micrograph demonstrates extensive pinocytosis occurring in a macrophage in a tissue culture situation – the long pinocytic channels, deeply protruding into the cell. But it's uncertain how important pinocytosis is in the intact mammalian organism.

<**Carr briefly to camera, then over electron micrograph showing macrophage in phagocytosis**>

The most important way in which macrophages ingest things is phagocytosis, a process very akin to pinocytosis. Here, a solid particle, whether bacterial or inorganic, adheres to the cell surface, often by an opsonising layer of immunoglobulin. The immunoglobulin sticks to a receptor on the macrophage surface by its Fc end and this stimulates membrane movement so that the cell throws out processes which surround it.

This micrograph illustrates the phagocytosis of debris, cellular debris, in an in vitro situation. Here is the cell surface here which has been thrown into long irregular processes and there is a deep invagination here, a large phagocytic vacuole, containing cytoplasmic debris. The cytoplasmic processes fuse to form a vacuole and this is pooled into the cytoplasm. The stimulus is a local one and affects only a limited area of cell membrane. It appears likely that the mechanism behind the movement of the cytoplasmic vacuole is contraction of actin filaments attached to it. This phenomenon of phagocytosis is usually accompanied by increased oxygen uptake and a burst of output of metabolic energy. The membrane of the phagocytic vacuole then fuses with that of a lysosome, sometimes primary and sometimes secondary, and lysosomal enzymes then become available to digest, if possible, the foreign material.

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<**Carr to camera**>

Within the phagocytic vacuole, most bacteria are killed, although the mechanism of this is not clear. It is likely that the factors involved in killing of bacteria within the

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phagocytic vacuole include low pH, lysozyme and the generation of hydrogen peroxide in relation to either myeloperoxidase or catalase. Macrophage lysosomal enzymes will digest almost any complex molecule although they apparently are curiously unable to deal with sucrose. The end result is usually destruction of the ingested foreign material. Some ingested material, however, often persists and sometimes, as in the case of the micro bacteria, organs may persist and grow within the cell. Sometimes the ingested material may kill the cell as when ingested silica reacts with the lysosomal membrane and allows the release of lysosomal membranes into the cell. And a large amount of surface membrane, up to 50% of the total surface area of the cell, may be used by the cell during phagocytosis. This is resynthesised after a lag phase of between 4 and 8 hours.

An important result of pinocytosis, and probably also of phagocytosis of non-toxic materials, is that the cell is stimulated to produce more lysosomal enzymes. And, as I've said, macrophage lysosomes are reusable in the sense that secondary lysosomes will fuse with the phagocytic vacuole. Macrophages ingest foreign material in two other rather less important ways – small particles may be ingested in caveolae or vesicles, some 100 nanometres or less in diameter.

<**Carr over micrograph showing macrophage during micropinocytosis, then back to camera**>

This micrograph illustrates a macrophage, here is the cell surface, here, and here is a micropinocytotic vesicle containing clumped ferritin molecules. This is a much larger vacuole within the cell, possibly formed by fusion of micropinocytotic vesicles. The process of micropinocytosis can happen in the cold and in the presence of metabolic inhibitors and is therefore clearly not energy dependent. A variation of this process of micropinocytosis, micropinocytosis vermiformis, involves tubular invaginations of cell membrane and is probably particularly related to protein ingestion.

Lastly, macrophages in clusters sometimes relate to large foreign bodies which they cannot individually ingest; obvious examples of such foreign bodies are pieces of

suture or fragments of necrotic bone. The macrophages form a semi-permanent capsule surrounding the foreign material and around this capsule, fibroblasts lay down a layer of fibrous tissue.

<**Carr over table listing functions of macrophage, then to camera**>

The functions of the macrophage and the physiology of the organism are summarised in this table.

Phagocytosis: first of all in inflammation and repair, and secondly in the clearance of the blood stream of foreign particles of bacteria: reticuloendothelial clearance. Secondly, the involvement of the macrophage in the immune response. Thirdly, the involvement of the macrophage in lipid metabolism. Fourthly, its involvement in iron metabolism. Fifthly, its ability to secrete, and six, the role of the macrophage in the control of neoplasia. And I'm going to summarise these in a simplified and rather superficial way.

First of all, phagocytosis. Macrophages phagocytise in two important circumstances – first of all in inflammation and repair and secondly in reticuloendothelial clearance. In inflammatory regions macrophages ingest bacteria and tissue debris and characteristically are involved in the more chronic lesions such as those caused by microbacteria. This is probably not due to any affinity for such bacteria but because of their ability to survive and multiply after phagocytosis.

<**Carr to camera, then over micrograph showing macrophage in human sarcoid granuloma**>

Phagocytosis is aided by the presence of non-specific opsonins and specific antibodies in the inflammatory exudate. Macrophages are attracted to inflammatory lesions by products sometimes described as lymphokines, released when specifically sensitised lymphocytes react with antigen. The macrophages are immobilised in the site and some of them enlarge, lose much of their phagocytic ability, show evidence of marked RNA synthesis and come to contain numerous structures similar to

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secretory vacuoles, and these are then known as epithelioid cells. An example of such a lesion is illustrated in a human sarcoid granuloma.

This micrograph illustrates a large macrophage in a human sarcoid granuloma containing numerous dense bodies and related to other similar macrophages around the edge by interlocking cell membranes. The cells are held together by these interdigitating membranes, seen here at a higher magnification; there is the cytoplasm at one macrophage in the sarcoma, there is the cytoplasm at the other, and these long finger-like processes from the two sides interlock, and sometimes the cells are held together presumably even more firmly by actual well-developed desmosomes such as are seen in epithelial tissue. It is possible that these large epithelioid macrophages are secretory cells but their real significance is still, as yet, poorly understood.

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<**Carr to camera, then over micrograph showing multinucleate giant cell, then back to camera**>

A characteristic feature of many chronic inflammatory lesions or granulomas is the multinucleate giant cell. Illustrated in this micrograph, the mass of cytoplasm with several nuclei around the edge. This has been shown, under experimental circumstances, to be formed when macrophages divide without separation of cell cytoplasm. New young macrophages fuse onto the giant cell and the nuclei then divide together undergoing chromosomal pulling to form a macrophage polykaryon.

The fixed phagocytes of the liver, the spleen and the bone marrow, acting together, efficiently clear the circulation of bacteria or artificially introduced colloidal particles. The rate of clearance of particles or bacteria can be measured and this gives an index of whole body so-called reticular endothelial function. This function can be artificially stimulated or depressed. It depends on two things: the number and activity of macrophages present and the rate at which leakage occurs from the circulation

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through gaps between endothelial cells. The phagocytosis and destruction of bacteria by fixed macrophages is of great importance in bacteraemia septicaemia.

<**Carr briefly over earlier table listing function of macrophages, illustrations of different cell types. Then to camera**>

The involvement of macrophages in the immune response is complex and any statement on it will inevitably meet with the disagreement of some immunologists. There is no doubt that macrophages take up antigens. It seems likely that much of this is degraded and is of no further immunological significance. The degradation of large amounts of antigen may be of significance in inhibiting the development of immunological tolerance by preventing contact between immunocompetent lymphocytes and large pools of antigen. And it's possible that some of the ingested antigen may be altered or even complexed to RNA, and this superantigen passed to adjacent immunocompetent lymphocytes.

An alternative idea has developed from the finding that antigen persists on the surface of macrophages for a prolonged period. This is, that the surface of the macrophage merely provides a convenient scaffolding on which antigen molecules lie, allowing lymphocytes to make convenient contact with them. The dendritic macrophage, which I illustrated a minute or so ago, the dendritic macrophage is clearly suitably shaped to act in this way. The role of the macrophage in the immune response can be neatly, if vaguely, summed up in the phrase that it acts as an antigen-focusing cell.

There is good evidence that the interdigitating cell, which is probably a macrophage, acts as a maturation site for T-lymphocytes relating to this process in the same way as the Sertoli cell does to spermatogenesis. A remaining immunological function of the macrophage relates to the control of neoplasia and will be discussed in a minute.

The involvement of macrophages in lipid metabolism is complex. It is clear that macrophages possess enzymes which enable them to esterify and solubilise cholesterol and triglycerides. They can also synthesise phospholipid which

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solubilises triglyceride. And it's also known that stimulation of macrophage function inhibits atherogenesis under certain experimental circumstances and may even cause reversal of established atheromatous lesions. But it is not at present clear how important these things are in human physiology and pathology.

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Next, macrophages are involved in iron metabolism. They are responsible for the breakdown of red blood cells; they do this by removing abnormal fragments of red blood cells, so-called pitting, and also by removing whole red blood cells, so-called culling.

<**Carr over micrograph of splenic sinusoid deforming red blood cell**>

Red blood cells are considerably deformed as they pass through narrow gaps in the walls of splenic sinusoids. And this micrograph illustrates a splenic sinusoid – there is the wall there, there is the lumen there, and here is the extra-sinusoidal tissue, and here a red blood cell is passing between the gaps between endothelial cell there, endothelial cell there, there is the gap there. Now it's clear from a micrograph like that that the red blood cell is being deformed as it passes through such narrow gaps. It seems possible that aged cells are excessively distorted by this process, rendering them sensitive to phagocytosis. The ingested red blood cell, or red blood cell fragment, is broken down by lysosomal action and the iron complexed onto the storage protein apoferritin– the resultant ferritin is visible in most macrophages, both in the cytoplasm and within lysosomes.

Marrow macrophages probably pass iron to developing erythroblasts. Macrophages, it seems, may also pick up transferrin attached to iron in the blood and they may therefore be involved in the transfer of iron from iron stores, for instance in the spleen, to the site of utilisation in the marrow.

It has been known for many years that macrophages produce lysosomal enzymes whose main function is intracellular digestion of material, taken into the cell, within a

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phagosome. But it has become clear recently that this is not the only secretory function of a macrophage. It has been shown, in tissue culture, that macrophages will actively release lysosomal enzymes into the culture medium, and in chronic inflammatory lesions they may release similar enzymes into the intercellular environment.

<**Carr to camera, returning briefly to earlier table listing functions of macrophages**>

This is probably, though not quite certainly, a process of active secretion rather than cellular disintegration.

Macrophages have been clearly shown to release lysozyme and plasminogen activator, which stimulates fibrinolysis. It's clear that macrophages are the main source of the pyrogen which is the chemical mediator inducing fever in tuberculosis, and in other conditions where the leukocytic response is mononuclear rather than polymorphonuclear. Macrophages are also significant, though probably not the main source of interferon and they may produce the third component of complement.

The role of the macrophage in the control of neoplasia is controversial. It is known that macrophages are present in considerable numbers in both human and experimental animal neoplasms along with other lymphoreticular cells.

<**Carr over micrographs showing macrophage with human carcinomas, then to camera**>

The micrograph illustrates a macrophage with the usual complement of lysosomal bodies and the irregular surface, a macrophage with the usual structure, lying within a human carcinoma, surrounded by carcinoma cells. It is known that in animal systems, macrophages can kill tumour cells either non-specifically or specifically. And the attack by macrophages on an apparently viable tumour cell is illustrated in this micrograph of macrophages and tumour cells in a degenerating transplanted animal neoplasm. Here is the tumour cell in the centre, with a large nucleolus – in

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this system, by chance, the tumour cells all have rather pale cytoplasm. Around the edge there are several smaller, darker cells, with fine processes, closely related to the cytoplasm of the tumour cell. And at a higher magnification one can see a tumour cell here and the thin process of macrophage which has slid along the surface of the tumour cell and is very closely related to it at several points. And thereafter all stages of phagocytosis of the tumour cell may be seen. In this micrograph, a macrophage; here is its cell body here and nucleus, and here is the long, thin cytoplasmic process surrounding an apparently viable tumour cell; this is an early stage of phagocytosis of an apparently viable cell.

In the cases of immunologically specific killing of tumour cells, the macrophage is armed, that is, it caries on its surface a coat of specific antibody derived from a lymphocyte. The actual mechanism of killing is not quite clear, it has been suggested that the recognition of the tumour cell by the macrophage is immunologically specific and that thereafter the macrophage either lyses the tumour cell or inhibits the DNA synthesis. It seems likely that macrophage lyses of tumour cells involves early damage to the tumour cell membrane and osmotic shock. Macrophages have been clearly shown to lyse red blood cells in vitro, in a parallel manner, by releasing labile soluble factor in a molecular weight below 1000. This damages the cell membrane and destroys the cell by osmotic shock.

I want, in conclusion, to attempt to summarise the biological significance of the macrophage on a very brief table.

<**Carr over table summarising the biological significance of macrophages**>

Macrophages are a family of cells scattered throughout the body that are ultimately of marrow origin. They are narrowly phagocytic, usually survive the phagocytic experience and are stimulated by it to produce more hydrolytic enzymes. Their ultrastructure reflects their ability to ingest rapidly, to move freely and to produce hydrolytic enzymes. They have important functions in phagocytosis, in the immune response in lipid and iron metabolism, in secretion, and probably in the control of

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neoplasia. The picture of the macrophage that I want to leave in your minds is the picture of the living, ever-moving cell.

<**Short film of macrophages moving actively**>

<**End credits**>

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