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## Zanvil Alexander Cohn 1926-1993

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ZANVIL ALEXANDER COHN  
1926–1993



*An Appreciation of the Physician-Scientist*

The Macrophage in Cell Biology and  
Resistance to Infectious Disease



A Complete Bibliography

## Summary

Zanvil Alexander Cohn, an editor of this *Journal* since 1973, died suddenly on June 28, 1993. Cohn is best known as the father of the current era of macrophage biology. Many of his scientific accomplishments are recounted here, beginning with seminal studies on the granules of phagocytes that were performed with his close colleague and former editor of this *Journal*, James Hirsch. Cohn and Hirsch identified the granules as lysosomes that discharged their contents of digestive enzymes into vacuoles containing phagocytosed microbes. These findings were part of the formative era of cell biology and initiated the modern study of endocytosis and cell-mediated resistance to infection. Cohn further explored the endocytic apparatus in pioneering studies of the mouse peritoneal macrophage in culture. He described vesicular inputs from the cell surface and Golgi apparatus and documented the thoroughness of substrate digestion within lysosomal vacuoles that would only permit the egress of monosaccharides and amino acids. These discoveries created a vigorous environment for graduate students, postdoctoral fellows, and junior and visiting faculty. Some of the major findings that emerged from Cohn's collaborations included the radioiodination of the plasma membrane for studies of composition and turnover; membrane recycling during endocytosis; the origin of the mononuclear phagocyte system in situ; the discovery of the dendritic cell system of antigen-presenting cells; the macrophage as a secretory cell, including the release of proteases and large amounts of prostaglandins and leukotrienes; several defined parameters of macrophage activation, especially the ability of T cell-derived lymphokines to enhance killing of tumor cells and intracellular protozoa; the granule discharge mechanism whereby cytotoxic lymphocytes release the pore-forming protein perforin; the signaling of macrophages via myristoylated substrates of protein kinase C; and a tissue culture model in which monocytes emigrate across tight endothelial junctions. In 1983, Cohn turned to a long-standing goal of exploring host resistance directly in humans. He studied leprosy, focusing on the disease site, the parasitized macrophages of the skin. He injected recombinant lymphokines into the skin and found that these molecules elicited several cell-mediated responses. Seeing this potential to enhance host defense in patients, Cohn was extending his clinical studies to AIDS and tuberculosis. Zanvil Cohn was a consummate physician-scientist who nurtured the relationship between cell biology and infectious disease. He guided with a warm but incisive manner the careers of many individuals. He was deeply committed to several institutions of biomedical research; to medicine in the developing world; to The Rockefeller University, especially its programs for graduate study and patient-oriented research; and to the energy and spirit of this *Journal*.

## **Zanvil Alexander Cohn, 1926–1993**

This is the first volume since 1973 for which Zanvil Cohn has not served as an editor of *The Journal of Experimental Medicine*. Zan died suddenly on June 28, 1993. He gave the *Journal* years of leadership and energy, and his unique style enlivened our weekly deliberations. His incisive manner, his admiration of clever new experiments, his sense of fairness and respect, and his wit all will be sorely missed. A review of his scientific contributions and the environment in which these came about, some feelings about the man, including his love for this *Journal*, and a complete bibliography seem a fitting tribute to our friend and colleague.

### **Recruitment to Infectious Diseases and to Phagocytes**

A devotion to infectious diseases came quickly to Zan at Harvard Medical School. Prior to starting the curriculum, he spent a year in the Department of Microbiology. He then continued to do independent laboratory work and produced a thesis entitled "A Biochemical Study of the Interaction of the Influenza A Virus and the Chorioallantoic Membrane of the Hen's Egg." The work was supervised by Monroe D. Eaton and Boris Magasanik, and led to his first publication (1). In the introduction to his thesis, Zan announced what would be a life-long scientific interest, the host–parasite relationship. Zan's M.D. degree in 1953 was one of a very few to be awarded summa cum laude in the history of Harvard Medical School.

Zan trained in medicine from 1953 to 1955 at the Massachusetts General Hospital. From 1955 to 1957, he met his military obligations, rising to Chief of the Division of Rickettsial Biology, Walter Reed Army Institute, and Captain in the Army Medical Corps. In the laboratory of Joseph Smadel, Zan explored several topics with rickettsiae that were prescient of his subsequent work (2–5, 8), with emphasis on respiratory enzymes, the microbial cell wall, and the penetration of *Rickettsia tsutsugamushi* into a mammalian cell line in vitro (5). The latter was the first of Zan's 128 contributions to the *Journal*.

Either in medical school or during his postgraduate training, Zan developed his intense admiration of René Dubos of The Rockefeller Institute for Medical Research. Dubos was an eminent microbiologist who emphasized the host–parasite interplay, the microenvironment of inflammation, and the need for new therapies that would enhance host defense. Zan heard Dubos's Warren Triennial Lecture at Massachusetts General in 1953, which was incorporated in his monograph

*Biochemical Determinants of Microbial Diseases* (1954, Harvard University Press). After the lecture, Zan approached Dubos for a position at the Rockefeller. This was eventually granted, although Dubos urged Zan not to work on viruses!

In 1957, Zan joined Dubos's laboratory, which was affiliated with The Rockefeller Hospital. James Hirsch was part of the team and was fully engaged in studies of phagocytes in vitro. In 1960, Hirsch became professor and organized a new Laboratory of Cellular Immunology. Zan, Stephen Morse, and Louis Siltzbach were the first members of the new lab. Cohn participated in the lab's clinical studies in the Hospital on sarcoidosis (14, 15, 44) that standardized the use of the Kveim reagent in the diagnosis of this disease.

Dubos and Hirsch, themselves former editors of this *Journal*, must have had a substantial influence on Zan's style. All three had a similar dedication to the broad reaches of the host–parasite interplay. All three coupled a seriousness of scientific purpose and a high regard for experimentation with an affable and sometimes skeptical manner. All three had a real optimism tempered by a respect for the unknown.

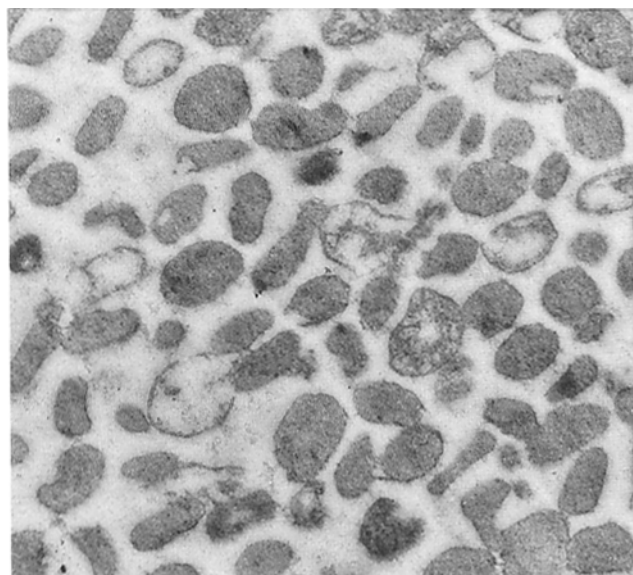
Zan began his studies of the phagocyte–microbe interaction with Morse (6, 9, 10). They utilized Hirsch's methods for obtaining homogeneous populations of neutrophils in large numbers, especially glycogen-elicited, rabbit peritoneal exudates. Cohn and Morse adapted methods of Ole Maaløe to segregate the two phases of white cell resistance, ingestion and killing. Neither phase was readily amenable to analysis in vivo since the white cell populations were mixed, blood and tissue fluids could have complicating effects, and quantitation was difficult. Cohn and Morse were able to separate cells from nonbound organisms in vitro and thereby to quantitate ingestion and killing. They observed the three basic outcomes: phagocytosis with killing (*Staphylococcus albus*, *Escherichia coli*, and certain streptococci), phagocytosis without killing (*Mycobacterium smegmatis*), and no phagocytosis at all (*S. aureus* and group A streptococci). Glycolysis was critical, as were serum opsonins in the case of *S. aureus*. Lipopolysaccharide (LPS) or endotoxin increased phagocytic activity. The approach taken by Morse and Cohn, the quantitative and direct study of the phagocyte–microbe interaction in vitro, was to bear fruit quickly.

### **Phagocyte Granules Are Lysosomes That Degranulate and Digest Microbes**

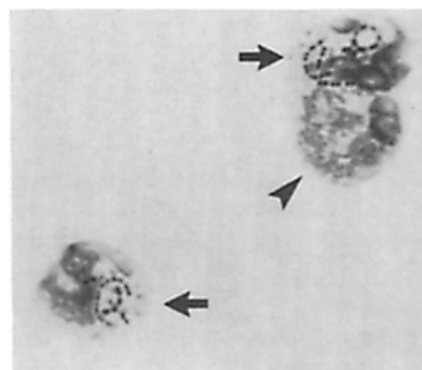
Cohn and Hirsch, focusing on events after ingestion, approached the most striking morphologic feature of the poly-

morphonuclear leukocyte, or “poly,” the abundant granules. Three historic papers appeared together in *The Journal of Experimental Medicine* (11–13). Using the techniques that were being pioneered by Albert Claude, Christian de Duve, and George Palade at The Rockefeller Institute, Zan and Jim were able to isolate a morphologically homogeneous population of granules by differential centrifugation (11) (Fig. 1). They wrote that “the efficient but relatively nontraumatic disruption” of the polys in cold 0.34 M sucrose was key, and they used the classic combination of high specific activity and recovery to establish that the granules were the location for a group of hydrolytic enzymes active at low pH. They showed that the acid hydrolases exhibited “latency,” requiring disruption by freezing and thawing for activity, and they observed the limiting membrane of the granules by electron microscopy. So the granules of the phagocyte, an object of tinctorial delight for decades, were now a biochemical and cell biological entity, identical to the lysosomes described by de Duve and colleagues.

Hirsch and Cohn next worked out methods that proved that polys degranulated during phagocytosis (12). By first applying the leukocytes to a surface, and then applying the organisms, they observed that degranulation took place only in cells that had ingested organisms (Fig. 2). To visualize degranulation more vividly, Hirsch produced elegant films of live phagocytes. These films, which remain an ideal component for many courses in biology, allowed Zan and Jim to propose that granule lysis played a key role in the destruction of microorganisms. Cohn and Hirsch then used cell fractionation to solidify the notion of granule discharge (13). They found that in phagocytosing populations, a large proportion of the acid hydrolases moved from a pellet fraction to a soluble fraction. Later (see below) they realized that this “solubilization” was a manifestation of lysosome–phagosome fusion.



**Figure 1.** A representative field taken from a sectioned granule pellet shows lysosomes enriched from neutrophils.  $\times 23,000$  (11, Fig. 1).



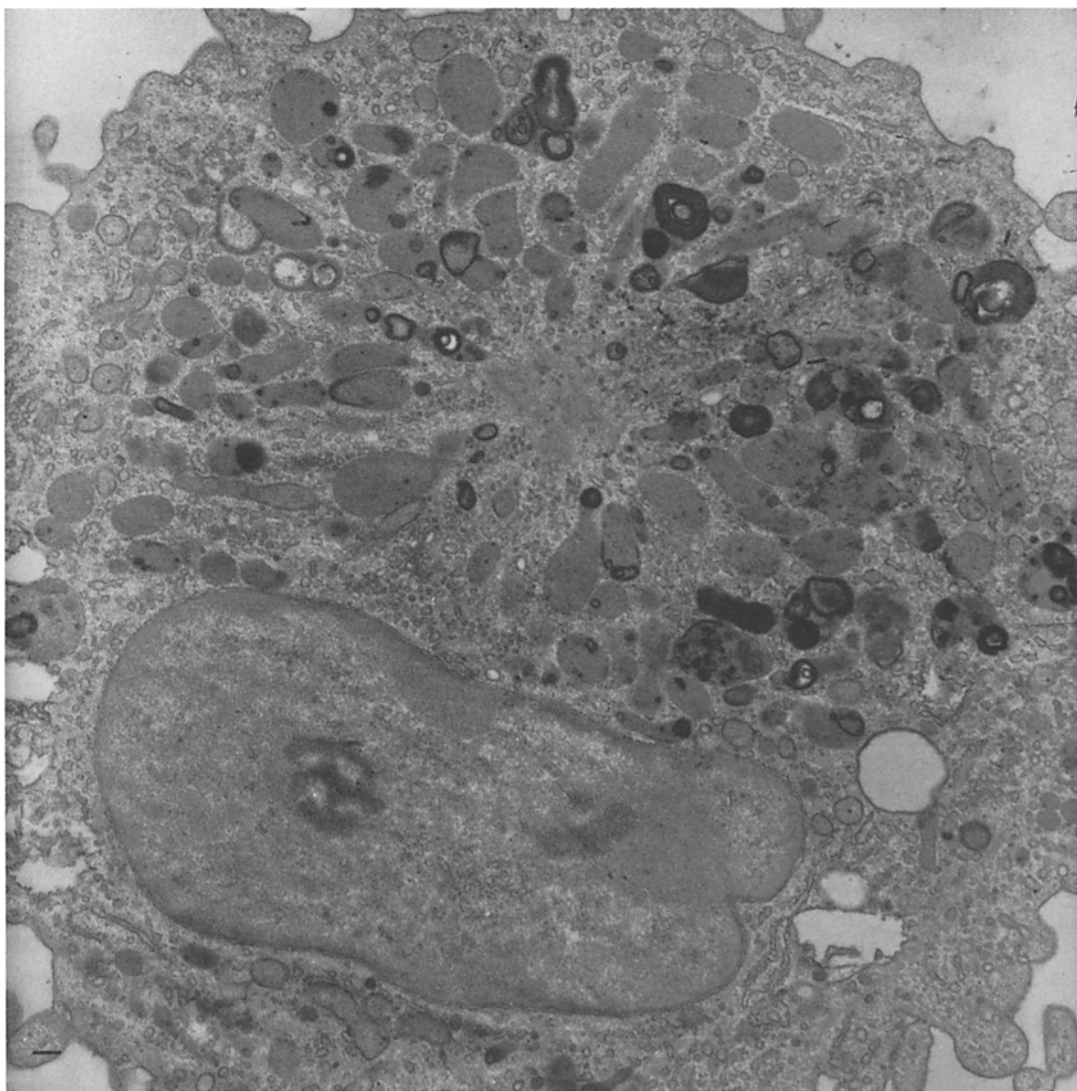
**Figure 2.** Degranulation of polymorphonuclear leukocytes during phagocytosis. Note the loss of cytoplasmic granules in two rabbit white cells that have ingested chains of streptococci (arrows), and the presence of granules in a cell that has not phagocytosed organisms (arrowhead).  $\times 1,080$  (12, Fig. 1 c).

Zan took a biochemical approach to extend the concepts of granules as lysosomes that discharged and digested microbes during phagocytosis. He radiolabeled the nucleic acids and proteins of bacteria with  $^{32}\text{P}$  and  $^{14}\text{C}$ , respectively. He found that ingested organisms first lost their pools of acid-soluble metabolites and, within three hours, 70% of the acid-insoluble constituents were converted to TCA-soluble products (22). Once the organisms were internalized, a variety of metabolic inhibitors could not slow digestion (23).

Then, with Edith Wiener, a postdoctoral fellow from Jerusalem, Zan isolated the particulate hydrolases of macrophages (24, 25). To secure an abundant and homogeneous cell source, Cohn and Wiener elicited rabbit alveolar and peritoneal macrophages with BCG and with mineral oil, respectively. Then they separated the granules of macrophages from the other major organelles, especially mitochondria, on isopycnic sucrose gradients. They proved that macrophage granules, like those of their polymorphonuclear cousins, are a particularly rich source of de Duve’s lysosomes. One of Zan’s favorite images was an early electron micrograph of the abundant lysosomes in a BCG-elicited alveolar macrophage (Fig. 3).

When Zan followed the response of macrophage lysosomes to particle ingestion (25), he again observed a solubilization of the particulate hydrolases. Zan had the benefit of unpublished electron micrographs from his friend David Luck, who documented the continuity of the phagolysosomal compartment in macrophages. This was soon followed by the seminal micrographs of Dorothy Zucker-Franklin, who together with Hirsch visualized lysosome–phagosome fusion in neutrophils. So Zan concluded that phagocyte granules were lysosomes that discharged their contents into the phagosome containing the ingested organism. The membranes of this phagolysosome, or digestive compartment, were rupturing during cell homogenization, accounting for the observed solubilization of hydrolases during phagocytosis.

Zan wrote of these experiments, “once a foreign substance has been taken into the cytoplasm of the macrophage and segregated within a membrane system, its fate may depend



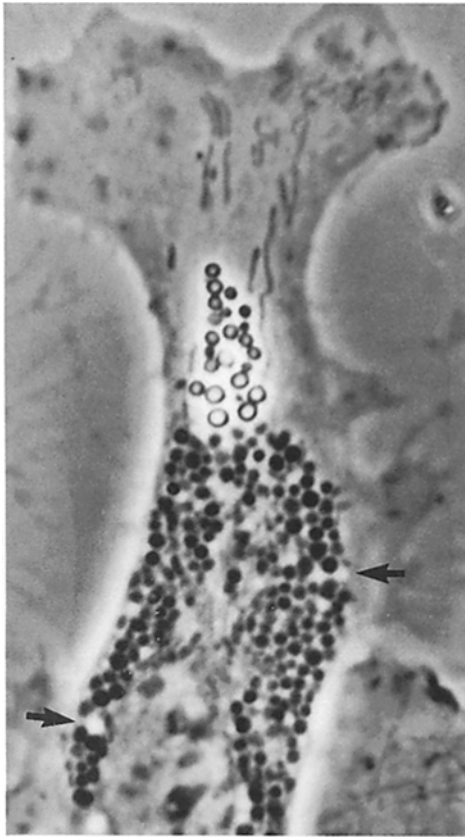
**Figure 3.** An electron micrograph of a typical BCG-induced alveolar macrophage that shows abundant lysosomal granules. Granules of various size, density, and internal structure are arranged in a rosette-like fashion in the perinuclear region. These particles vary from a uniform electron density to multivesiculated structures and myelin figures.  $\times 12,000$  (24, Fig. 1).

in part upon its susceptibility to macrophage enzymes. Certain inert substances are retained, whereas others are probably degraded in short order. Such storage of material may be reflected in the accumulation of macrophages at local sites such as in tuberculous and lepromatous lesions" (25). So the cell biology of endocytosis and host resistance had begun, and reciprocally, phagocytes occupied a central place during the formative years of cell biology. Here the seeds were also sown that certain organisms might escape digestion, a topic that Zan was to pursue in the context of leprosy and tuberculosis 20 years later.

### The Formation of Lysosomes in Cultured Mouse Peritoneal Macrophages

Zan then switched from rabbit to mouse phagocytes, a change that would eventually lead to the use of the cultured

mouse peritoneal macrophage as a model for further pioneering studies in cell biology. The impetus for this switch most likely took place during studies described in the *Yale Journal of Biology and Medicine* in 1962 (16–18). In a characteristically short introduction, he points out that the intradermal and intravenous routes of infection make it hard to follow the organisms, that are being injected in vivo. In contrast, he states, the mouse peritoneal cavity might provide a more suitable milieu to follow quantitatively both cell-associated and nonassociated organisms, much as he and Morse had done with rabbit phagocytes in vitro. He worked with staphylococci, organisms that had been studied by Dubos, and verified several features in vivo. Avirulent *S. albus* were internalized efficiently, whereas the lethal *S. aureus* multiplied extracellularly, avoiding uptake, unless immune serum was added. Phagocyte mobilization or diapedesis was markedly reduced when mice were treated with cortisone, x rays, and other blockers of host re-



**Figure 4.** The differentiation of mouse macrophages in culture. A macrophage cultivated in 50% serum medium for 48 h. A well-defined collection of large lysosomal granules is present in the perinuclear region. A number of clear pinocytotic vacuoles are also apparent (arrows).  $\times 2,500$  (33, Fig. 1 a).

sistance that Dubos had described. Zan emphasized that two populations of phagocytes were at work, resident macrophages and recruited polymorphonuclear granulocytes. A major determinant of bacterial destruction was the availability of phagocytes in sufficient numbers.

Seeing that mouse peritoneal cells adhering to glass were a homogeneous source of competent and abundant phagocytes, Zan turned his full attention to this population. In 1965, he published four papers with Belinda Benson in *The Journal of Experimental Medicine* describing the “in vitro differentiation of mononuclear phagocytes” (30–33). As was now standard fare in the laboratory, high quality phase contrast microscopy spawned and/or supported virtually every experiment. Zan noted that macrophages from different sources varied enormously in their content of phase-dense granules and hydrolytic enzymes, and resident peritoneal macrophages were relatively weak in both respects. Yet he described a huge increase in phase-dense, perinuclear granules over several days in culture in glass Leighton tubes. Excellent preservation was afforded by the glutaraldehyde fixation regime developed by

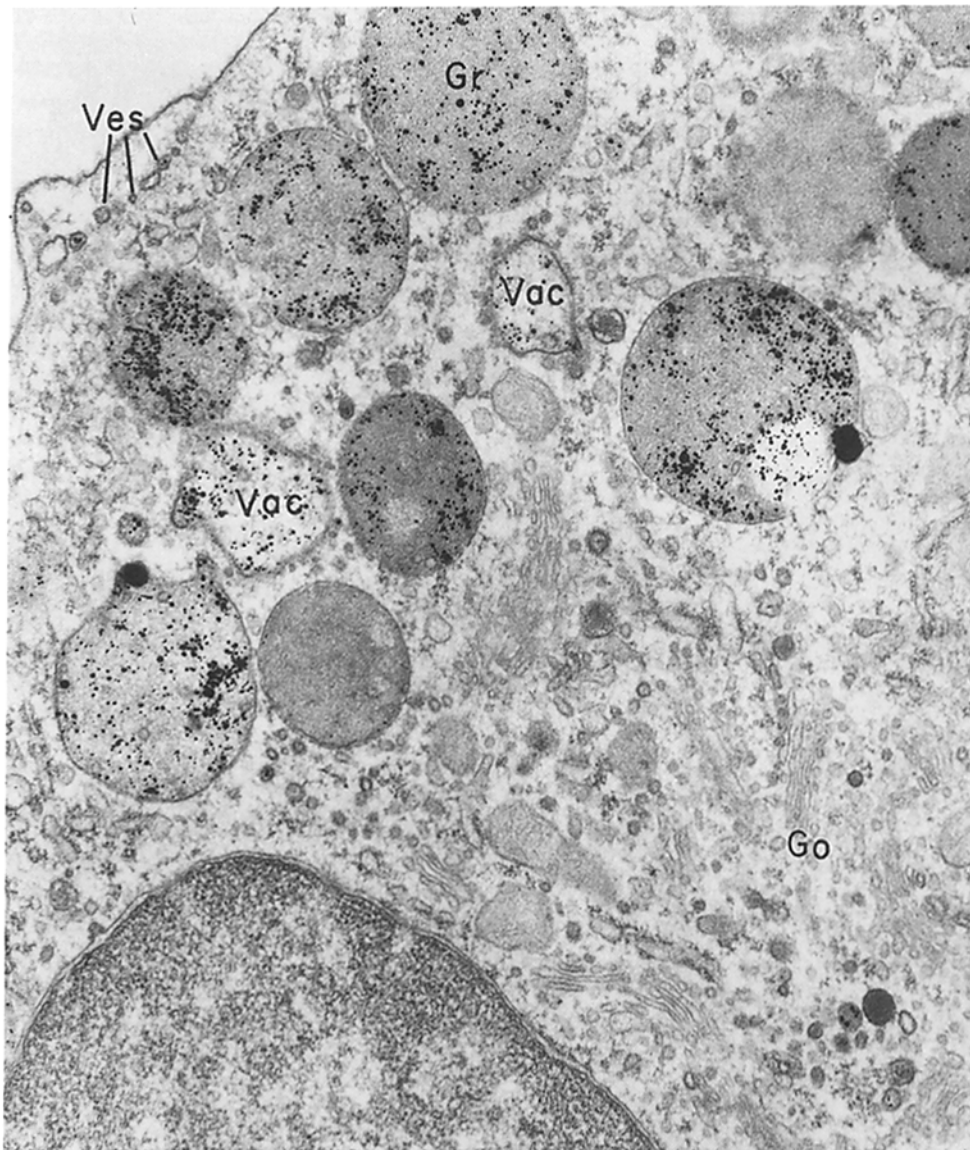
David Sabatini at Rockefeller (30). Zan distinguished the granules from rod-like mitochondria (Fig. 4) and stained the former selectively with acid hydrolase cytochemistry as outlined by Alex Novikoff. During culture of the macrophages, he also documented a marked increase in acid hydrolase activity. Zan used metabolic precursors and autoradiography to study the differentiation question (31). He showed that silver grains from radiolabeled leucine and choline accumulated over the phase dense granules. These precursors and autoradiography were just becoming available in cell biology, and the methods were being used by Lucien Caro and Palade, and by Luck, in other Institute labs.

Zan emphasized that serum in the culture medium was a major and reversible inducer of granule differentiation, and that serum also stimulated the formation of phase-lucent pinocytotic vesicles (32). After their formation at the cell periphery, the vesicles moved centripetally and gradually acquired the features of lysosomes, becoming phase dense and acid phosphatase positive. Zan applied exogenous soluble tracers, notably colloidal gold and fluorescein-modified proteins, to prove that they would accumulate in the phase-dense granules, or lysosomes (33).

With the arrival of an electron microscope in the lab, Hirsch, Cohn, and Martha Fedorko provided clear views of macrophage lysosomes (37) as well as their derivation (38). Using colloidal gold as a tracer, they could visualize the formation of small pinocytotic vesicles, their fusion into larger vacuoles, and the delivery of colloid into lysosomes (38) (Fig. 5). Using acid hydrolase cytochemistry at the electron microscope level, they described a second input, dubbed “primary lysosomes,” from the Golgi apparatus (38).

By counting pinocytotic vesicles under phase contrast, Zan returned to his quantitative haunts. In a set of four papers that would now qualify as “Brief Definitive Reports,” he described the regulation of pinocytosis in mouse macrophages: the need for energy metabolism and physiologic temperature (39), the stimulatory role of anionic substances (40), and the induction by nucleosides and nucleotides (41) and by anticellular globulins in calf serum (42). He repeatedly emphasized the link between pinocytotic activity and lysosome formation, and later, the induction of lysosomal hydrolases by phagocytosis of digestible particles (59).

A series of films emerged from the Hirsch-Cohn Lab, showing the formation and centripetal movement of pinocytotic vesicles, and their interaction with phase-dense granules. These films were somewhat less captivating than those that Hirsch made earlier to show granule discharge during microbial phagocytosis. However, Cohn’s films of pinocytosis were to prove more broadly relevant since they provide a lucid view of the formation and fate of pinocytotic vesicles, a widespread cellular activity. The distinctive feature of macrophages was not simply their pinocytotic activity but the number of lysosomes and the large flow of contents from pinocytotic vesicles to lysosomes. Equally important, the cultured mouse peritoneal macrophage was now ready to be explored by many scientists in this and other laboratories.



**Figure 5.** The vacuolar system at the electron microscope level. This macrophage was cultivated in 50% serum for 42 h and exposed to 10  $\mu\text{g/ml}$  colloidal gold for 2 h before fixation. Particles of gold are present in all structures of pinocytic origin. On the upper left, a string of pinocytic vesicles (*Ves*) contains gold, and one gold particle is present on the cell surface. Colloid is found in vacuoles scattered throughout the cytoplasm (*Vac*). The larger dense granules (*Gr*) are also labeled. In contrast, the Golgi saccules and associated vesicles (*Go*), as well as cisternae of the rough endoplasmic reticulum, are free of gold.  $\times 30,000$  (38, Fig. 1).

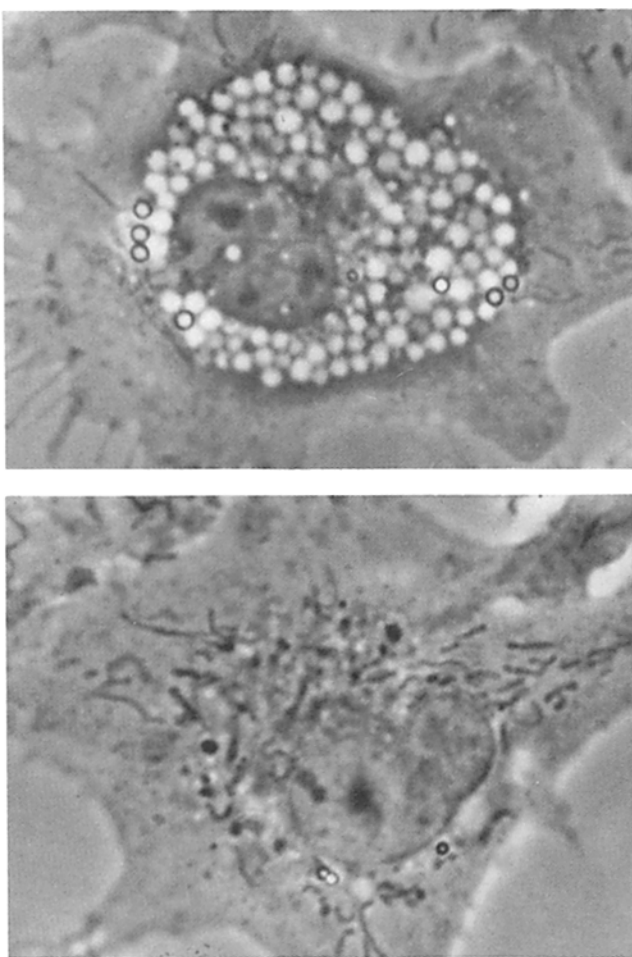
### Biochemical Features of Endocytosis and Lysosomal Digestion

In 1966, Zan became a full professor and, together with Hirsch, renamed their joint laboratory Cellular Physiology and Immunology. The Rockefeller Institute for Medical Research had just become The Rockefeller University, and the program for graduate study was underway.

Several students were to make substantial contributions in the Hirsch-Cohn Lab. The first was Barbara Ehrenreich, who, with Zan, did a remarkable group of experiments that out-

lined the basic biochemical features of the pinocytic vesicle-lysosome pathway.

Ehrenreich and Cohn fed radioiodinated human serum albumin (43) and tritiated hemoglobin (47) to mouse peritoneal macrophages so that intracellular digestion of soluble proteins could be followed. They noted uptake into phase dense granules by autoradiography. When they chromatographed the labeled material that was released from the cell, all of the label was associated with amino acids. Lysosome-mediated digestion of internalized proteins was complete!



**Figure 6.** Permeability studies of endocytic vacuoles. Following uptake by pinocytosis, the enzyme invertase dramatically shrinks vacuoles. Phase-contrast micrographs. (*Top*) Immediately after the addition of 500  $\mu\text{g}/\text{ml}$  of invertase. The cells had been cultivated for 24 h with 0.02 M sucrose and contain numerous vacuoles that have been swollen by uptake of the impermeable disaccharide sucrose. (*Bottom*) By 120 min after invertase administration, all the large vacuoles have disappeared leaving a residue of tiny dense granules.  $\times 2,500$  (57, Fig. 7, *a* and *d*).

Ehrenreich and Cohn pursued the thoroughness of lysosomal digestion by administering peptides and oligosaccharides, including nonhydrolyzable D forms. They found that the presence of undigested peptide or saccharide in the vacuolar system exerted an osmotic pressure, and the vacuoles would swell (57, 58). By monitoring vacuole swelling, Barbara and Zan could determine if the peptide or saccharide were being digested into permeable solutes, without the use of any radiolabels. They showed that most peptides and saccharides had to be digested to their amino acid and monosaccharide building blocks to avoid swelling of the vacuoles. Zan's favorite part of these experiments was the swelling induced by sucrose. By feeding invertase to the macrophage, they initiated sucrose digestion and shrinkage of the swollen vacuolar system (Fig. 6). These were some of the first experiments on the permeability of intracellular organelles. As in the studies

with radiolabeled albumin and hemoglobin, Cohn and Ehrenreich surmised that the digestive capacities of living cells had to be extensive, since it was clear that actively pinocytic macrophages could be cultured for many days without any vacuolar swelling.

Together with another graduate fellow, Zena Werb, Zan studied cholesterol uptake metabolism and distribution in mouse macrophages (69–71). They identified a cholesterol esterase with an acidic pH optimum in macrophage lysosomes. The enzyme was subsequently implicated by others in foam cell development. The contributions of macrophages to atherosclerosis was an area that Zan very much wanted to pursue further.

While lysosomes had been identified as biochemically distinct organelles in the 1950s, Zan's experiments in the 1960s put lysosomes into the dynamic context of intact cells. The interplay with the plasma membrane via endocytic vesicles was beautifully clear, and this pathway was capable of handling substrates to an extent limited primarily by an investigator's creativity. The completeness of digestion of most internalized substrates was established, and the input from the Golgi apparatus a likelihood. The distinctive potential of macrophages was the extent of their scavenging and digestive capacities, but the endocytic pathway was now opened for further experimentation in all cells.

### The Mononuclear Phagocyte System

The origin of mononuclear phagocytes *in situ* became the next focus. A starting point was the paper by William Bennett and Cohn showing that blood monocytes would develop all of the now typical features of macrophages when placed in culture (36). Similar events had been noted years before at the Sir William Dunn School of Pathology in Oxford by Robert Ebert and Howard Florey, who observed the development of extravasated monocytes *in situ*. In the 1960s at the Dunn School, Alvin Volkman and James Gowans were also providing direct evidence for the origin of tissue macrophages from blood monocytes. Zan was always fond of Oxford University, especially the Dunn School and its monumental contributions to antibiosis, experimental pathology, and cell-mediated immunity. Zan was to spend a sabbatical there in 1988 as the Newton-Abraham Visiting Professor.

With Hirsch and Ralph van Furth, Zan carried out studies that identified the blood monocyte as the precursor for tissue macrophages, and the bone marrow as the source of monocytes. van Furth worked both in Leiden and during several sabbatical visits at Rockefeller. Using [ $^3\text{H}$ ]thymidine labels newly available from Eugene Cronkite at Brookhaven, van Furth and Cohn subjected the pathway of bone marrow to blood to tissues to quantitative and direct observation. They found that monocytes were nonproliferating cells derived from proliferating precursors in the marrow (53). van Furth and Cohn monitored the movement of monocytes into the peritoneal cavity and elicited a recruitment of new macrophages with various stimuli, one being the injection of calf serum. Further studies in Leiden monitored the origin of Kupffer cells, alveolar macrophages, and spleen macrophages. Later,

van Furth, Fedorko, and Hirsch did electron microscope studies on bone marrow colonies containing precursor monoblasts and promonocytes, and they described production capacities and kinetics.

These experiments led to a redefinition of the reticuloendothelial system (RES) (78). The well-known capacity of the RES to clear colloids, organisms, and antigens could now be attributed to the endocytic pathway of the mononuclear phagocyte system. This work went beyond a new nomenclature to a redefinition based on developmental origins and cell biological features. Mononuclear phagocytes in other microenvironments were denoted and would attract Zan's attention later, for example, macrophages in the lung (202, 211, 277, 302), liver (256, 257), and spleen (328). Once cell biological criteria had been brought to the identification of mononuclear phagocytes, the foundation was in place for the laboratory to pursue other distinct cell systems, especially endothelial cells and dendritic cells.

The vital interaction with van Furth also produced five conferences on mononuclear phagocytes, held in Leiden, that brought together many investigators in the expanding macrophage universe. The volumes describing the deliberations of these meetings, all edited by van Furth (Table 1), provide a detailed survey into the Zan Cohn era of macrophage biology. Zan's honorary degree from Riksuniversiteit in Leiden in 1990 was very special to him.

### The Macrophage Plasma Membrane and Membrane Recycling

The themes of endocytosis, lysosomes, and the mononuclear phagocyte system that emerged in the 1960s are all too familiar now. Yet in 1970, the Hirsch-Cohn Lab served as a rare focus for the cell biological study of host defense (82). A group of students and postdoctoral investigators sought to work with Zan and Jim, and a flurry of new activities

emerged. The mouse peritoneal macrophage was readily accessible, and experiments became far less burdensome when tissue culture plastic replaced glassware, and CO<sub>2</sub> incubators replaced various gassed containers. While not evident from Zan's bibliography, a critical individual in the 1970s was Samuel Silverstein, who provided much expertise in cell biology and led most of the work on phagocytosis and viruses. Many individuals enjoyed both Sam and Zan as mentors, even though the two had few joint publications (83, 125, 144, 145).

By 1970, Zan's interests in the vacuolar system shifted substantially, from contents (acid hydrolases plus substrates captured by endocytosis) to containers (the plasma membrane and membranes of the endocytic apparatus). This was the time when the first plasma membrane protein, red cell glycophorin, was being characterized by Vincent Marchesi. Two peroxidase enzymes proved fruitful early on. The first, lactoperoxidase (LPO) entered the lab because of Zan's friendship with Seymour Klebanoff. Klebanoff studied thyroid metabolism at Rockefeller years earlier, and afterward found that neutrophil peroxidase, together with hydrogen peroxide, had microbicidal and halogenating activities. Zan always seemed intrigued by the fact that hydrogen peroxide, a time-honored antiseptic, is a substance used by phagocytes to kill microbes and other cells (see below).

Challenged to develop better methods for analyzing the plasma membrane biochemically and functionally (114), Zan used LPO to attach radioiodine covalently to membrane proteins in living cells. Ann Hubbard, in graduate studies with Zan, devised the relatively gentle system whereby glucose oxidase and glucose were used as a source of H<sub>2</sub>O<sub>2</sub>. She then added LPO in the cold and was able to selectively iodinate externally disposed polypeptides of the plasma membrane. Red cells were iodinated first (75) and then L cell fibroblasts (102). In the latter, it became possible to document the relatively slow turnover of most plasma membrane proteins in cultured cells. When Hubbard and Cohn coaxed L cells to phagocytose latex particles, they found that the phagocytic vacuole membrane contained a representative sample of plasma membrane polypeptides, and that phagocytosis was associated with a much more rapid turnover of these polypeptides (103). Werb made similar findings on the effect of phagocytosis on the turnover of the plasma membrane enzyme, 5'-nucleotidase (79).

The other peroxidase, horseradish peroxidase (HRP), was chosen by Ralph Steinman and Cohn because of the relative ease of quantitation (with the same enzymatic assay being used by Hubbard to standardize her LPO) and visualization (with the new electron microscopic diaminobenzidine method that had been introduced by Richard Graham and Morris Karnovsky). Steinman and Cohn used HRP to quantitate solute uptake into cultured macrophages (76) and fibroblasts (93). The method did not require radiolabels and totally replaced the counting of pinocytic vesicles that had been used in so much of the earlier work. In spite of the vigorous pinocytic activity of macrophages, Steinman and Cohn found the amounts of solute that were internalized in the fluid phase to be extremely small relative to the applied load. However, they described a dramatic enhancement of uptake when

**Table 1.** *Leiden Conferences on Mononuclear Phagocytes*

<i>Mononuclear Phagocytes</i> Blackwell Scientific Publications Ltd., Oxford, 1970 Conference: September 2–5, 1969
<i>Mononuclear Phagocytes in Immunity, Infection, and Pathology</i> Blackwell Scientific Publications Ltd., Oxford, 1975 Conference: September 2–7, 1973
<i>Mononuclear Phagocytes: Functional Aspects</i> Martinus Nijhoff Publishers, The Hague, 1980 Conference: September 17–24, 1978
<i>Mononuclear Phagocytes: Characteristics, Physiology and Function</i> Martinus Nijhoff Publishers, Dordrecht, 1985 Conference: May 9–16, 1984
<i>Mononuclear Phagocytes: Biology of Monocytes and Macrophages</i> Kluwer Academic Publishers, Dordrecht, 1992 Conference: May 13–16, 1991

HRP-anti-HRP immune complexes were administered and internalized via the Fc receptor (77).

Because internalized HRP could be visualized at the electron microscope (EM) level, Steinman and Cohn could take stereologic approaches to measure the size of the intracellular compartments that were labeled by HRP, as well as the kinetics with which these compartments filled. The phenomenon of extensive membrane recycling during pinocytosis became apparent (117). They estimated that the area of membrane surrounding newly formed pinocytic vesicles was equivalent to an influx of half the macrophage surface area every 33 minutes. Yet they found that the volume and area of the compartments in which HRP solute accumulated was considerably less than the volume and area of internalized vesicles. They made qualitatively similar findings in L cell fibroblasts, the cells in which Hubbard documented a relatively slow turnover of membrane proteins. They concluded that, during the uptake and delivery of HRP to digestive lysosomes, there likely was an enormous flow and recycling of vesicle membrane into and back out of cells (117, 231).

Graduate fellow William Muller amalgamated the LPO and HRP findings to approach the recycling of membrane proteins directly. This time Muller covalently linked LPO to latex beads, fed the beads to macrophages, added glucose-glucose oxidase to generate hydrogen peroxide, and thereby covalently linked <sup>125</sup>I to the disposed polypeptides of intravacuolar membranes (157). Muller could then observe that membrane polypeptides that had been iodinated from within the cell would rapidly return to the cell surface and then back into the cell (158, 231). Ira Mellman used internalized soluble LPO to iodinate pinocytic vesicle membranes. He found that the labeled, internal polypeptides resembled those on the plasma membrane (156). With the advent of monoclonal antibodies, specific membrane components could be identified on cell surface, phagosome, and pinocytic vesicle membranes (158, 227). Mellman documented a selective increase in the turnover of a plasma membrane receptor during Fc receptor-mediated phagocytosis (225).

In the 1970s, Zan's emphasis on the plasma and vacuolar membranes of macrophages was far from limited to these peroxidase studies. The array of approaches and topics that anteceded the peroxidase work, or were studied simultaneously, included the behavior of macrophage membrane markers following the formation of macrophage-melanocyte heterokaryons (63–66), a study that provided lovely examples of the fluid-mosaic model of membrane structure that was being developed at that time by Jonathan Singer; the uptake and turnover of the plasma membrane enzyme 5'-nucleotidase (79, 112, 113); cell surface sites accessible to lectins (87, 88), to antimacrophage antibodies (74), and to modification with trinitrophenyl groups (140); the isolation of Fc receptor-negative variants (150); uptake of cholesterol into macrophages (69–71); and the modification of fatty acids in macrophage phospholipids (121, 155). Characteristically, Zan and colleagues carried out all of these perturbations in living cells and with microscopic monitoring.

Graduate fellows Nadia Nogueira, David Lepay, and Stephen

Aley also applied the methods that were being used to study the macrophage cell surface to several microbes that were of great interest to the lab (below): *Trypanosoma cruzi* (190, 205), *Leishmania donovani* (224), and *Entamoeba histolytica* (151, 152, 239).

With graduate fellow Margaret Kielian, Zan monitored phagosome-lysosome fusion in macrophages (154, 184, 185). Perhaps of greatest interest were the anionic compounds that blocked fusion (203, 204). At the same time Hirsch, Silverstein, and Marcus Horwitz were engaged in studies where intracellular microorganisms interfered with normal fusion events. At the time of his death, Zan was poised to identify compounds used by pathogenic microorganisms to establish their unique intravacuolar environments, particularly virulent *Mycobacterium tuberculosis*.

### The Macrophage as a Secretory Cell

Zan, together with a former graduate fellow, Siamon Gordon, uncovered the profound secretory function of macrophages. The array of secretory products were to prove extraordinarily diverse. Macrophages not only used the traditional pathway of protein secretion via the rough endoplasmic reticulum but also released other products via enzymes of respiration and arachidonic acid metabolism that were associated with the plasma membrane.

The first evidence involved lysozyme (89). Prior work had shown that lysozyme, a granule-associated muramidase in neutrophils, could be regurgitated acutely during phagocytosis. Elliot Osserman had found a huge output of lysozyme in the urine of patients with monocytic leukemia. Gordon and Cohn, searching for differentiation markers for macrophages to be used in their somatic cell genetic studies (63–66), noted that many different populations of macrophages released lysozyme continuously for days and without a phagocytic challenge. The secretion rate amounted to 2.5% of total cell protein per day. Then, plasminogen activator (fibrinolytic activity in the presence of plasmin) was studied and found to be secreted copiously by thioglycollate-elicited, but not resident, macrophages. Gordon and colleagues found that, unlike the situation with lysozyme, plasminogen activator release was inducible and proceeded in a two-step fashion that was to become standard for many subsequent macrophage activities. The cells first were *primed* with LPS and then *provoked* with a phagocytic meal (90). Another important subsequent finding was that the fibrinolytic pathway could be primed during T cell-mediated immunity *in situ* (129).

Zan and colleagues, especially Carl Nathan, then turned to metabolites of oxygen, another class of products that macrophages can release (130, 142, 144–146, 160, 183). They noted differences in superoxide and hydrogen peroxide output from macrophages elicited by distinct inflammatory and immune stimuli. They associated these differences with changes in macrophage-mediated microbial and tumor killing (see below).

William Scott and Cohn uncovered and pursued a third class of macrophage secretions, arachidonic acid metabolites. Again, a major contribution was made by a graduate fellow,

Carol Rouzer. They showed that the 20-carbon polyunsaturated arachidonic acid (20:4) constituted a major fraction (25%) of the fatty acids of macrophage phospholipids. The latter could be substituted close to equilibrium by an overnight culture in [ $^3\text{H}$ ]arachidonic acid, thereby allowing the group to quantitate subsequent metabolism by the cyclooxygenase and lipoxygenase pathways. By high performance liquid chromatography (HPLC), they were able to identify many of the 20:4 products released from macrophages.

Scott, Cohn, and colleagues showed that the macrophage was in fact a major cellular source of several arachidonic acid metabolites, many of which were known to have major effects in inflammation and on smooth muscle and vascular tone. They found that in resident macrophages, particle uptake triggered the secretion of large amounts of prostaglandins, both PGE and PGF $1\alpha$  (170). Strikingly, they also proved that macrophages were an active source of the elusive leukotriene C (LTC) (169, 170). This glutathione-lipid adduct was otherwise known as one of the trace "slow reacting substances" that cause spasms of airway smooth muscle. They noted that mouse pulmonary macrophages synthesized leukotrienes C, D, and E (211), while human alveolar macrophages made substantial amounts of the chemotactic agent leukotriene B $_4$  (202). Rouzer, Scott, and Cohn discovered that the release of LTC from macrophages could be triggered by IgE-anti-IgE complexes (210, 212), a remarkable finding considering the prior emphasis that IgE immune complexes worked primarily on mast cells. Rouzer could block LTC metabolism selectively by applying buthionine sulfoximine, an inhibitor of glutathione synthesis (193, 209). Finally the group described that macrophages could utilize exogenous 20:4 and other precursors to rapidly synthesize prostacyclin and hydroxyicosatetraenoic acids (214). Interestingly, arachidonic acid metabolism was one of the few macrophage activities to be down-regulated in otherwise "activated" cells (215). This could occur locally within restricted tissue environments (277).

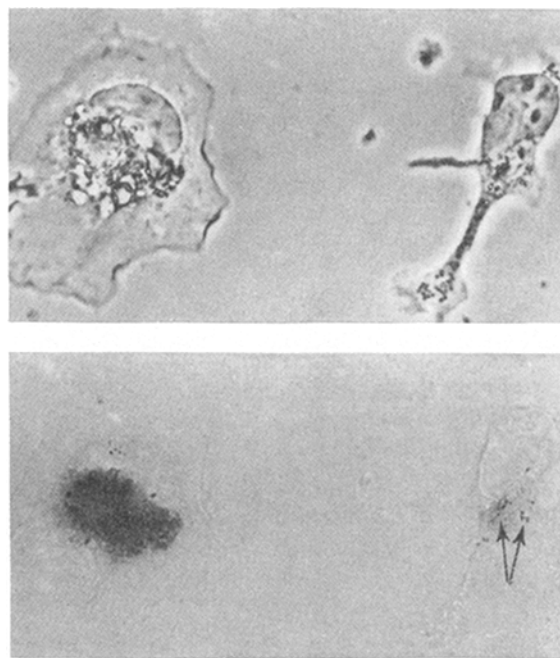
Within a period of 15 years, Zan had created a vigorous environment that was attractive to graduate students, post-doctoral fellows, junior faculty, and sabbatical visitors. This in turn led to the development of three major avenues of macrophage biology, each with substantial impact on the broader areas of cell and immunobiology: the pinocytotic-lysosome pathway, the mononuclear phagocyte *in vivo*, and several secretory roles. The function of the macrophage had changed from a "big eater" to the "versatile element of inflammation" (221). These avenues of macrophage function provided the underpinnings for several new areas (see below) that would emerge and that directly pertained to Zan's interests in host defense mechanisms.

### Discovery of Dendritic Cells

In 1966 the first success at inducing primary antibody responses was reported by Robert Mishell and Richard Dutton in mouse spleen cell suspensions. Donald Rowley and Donald Mosier found that plastic adherent cells, presumably macrophages (there were few other alternatives at the time), were

required as accessories by the immunologically competent lymphocytes. Early on, the function of the macrophage was perplexing. Zan's experiments on the distribution and fate of protein antigens in peritoneal macrophages showed that these were thoroughly degraded (43, 47, 57, 58) but failed to identify a postulated reservoir of intact protein on the macrophage cell surface (76, 77). Patrick Chen and Hirsch found that enriched populations of peritoneal macrophages could exert two effects on the antibody response. One was an enhancing effect at low doses of macrophages, but this was primarily at the level of lymphocyte viability and could be bypassed by adding 2-mercaptoethanol. A second was a strongly inhibitory function that was evident at doses corresponding to just 2–3% of the cultured cells. At the time, some papers concluded that the function of macrophages was MHC restricted, while others concluded otherwise.

Steinman and Cohn switched from peritoneal cells to spleen cells to understand the induction of immune responses in a major lymphoid organ of the mouse. They encountered an irregularly shaped population of cells, named "dendritic cells" (84). In spite of years of experience with macrophages from many tissues and species, neither Cohn nor Hirsch had ever seen a phagocyte that resembled these dendritic cells in terms of organelles (Fig. 7) and motility. At that time, there was extensive experience in the lab with the differentiated features of phagocytes. Michel Rabinovitch had pursued in some detail the abundance and phagocytic role of Fc receptors in macrophages. Hirsch and graduate fellow Sally Zigmond were



**Figure 7.** Distinguishing macrophages and dendritic cells by differences in lysosomal content. Phase-contrast (*top*) and bright-field micrographs (*bottom*) after staining for lysosomal acid phosphatase. The macrophage (note ruffles, vesicles, refractile inclusions) exhibits considerable acid phosphatase in a perinuclear position. The dendritic cell has a few small reactive granules close to the nucleus (*arrows*).  $\times 2,700$  (84, Fig. 4, *a* and *b*).

directly observing phagocyte chemotaxis and motility. Gordon and Cohn were utilizing several phagocyte differentiation markers in their macrophage-melanocyte fusion studies (63–66). When Steinman and Cohn evaluated this repertoire of known macrophage traits in dendritic cells, not a single resemblance to macrophages was apparent (91, 92). Dendritic cells lacked the abundant membrane ATPase and acid phosphatase that were typical of macrophages; the cells had little phagocytic activity in culture and in vivo; the dendritic cells detached from culture surfaces and had poor viability; their turnover in spleen was rapid; and in situ, dendritic cells were primarily localized to the white pulp instead of the red pulp (105). Soon the group noted the juxtaposition of dendritic cells with developing antibody-forming cells (106), but the turning point was a method to prepare enriched populations of dendritic cells and macrophages, both trace populations in mouse spleen suspensions (148). To do so, Steinman took advantage of the fact that dendritic cells lacked Fc receptors. Cohn, Steinman, and graduate fellow Michel Nussenzweig then documented dramatic differences between the two cell types in MHC class II expression (148), surface markers (192), and T cell stimulatory function (166). The findings in mouse spleen were evident in other tissues and species, including human blood, as studied by graduate fellow Wesley Van Voorhis (232). Dendritic cells therefore represented a new leukocyte distinct in morphology, phenotype, and function from phagocytes and lymphocytes. Mechanisms underlying the induction of primary immune responses by dendritic cells in vitro and in vivo were now accessible.

Zan played another role in uncovering the dendritic cell system, one typical of other research areas in the lab. Frequently invited to organize meetings on mononuclear phagocytes, Zan helped organize a symposium in Japan in 1980. Meetings engender new collaborations, in this case a long-standing effort with Kayo Inaba in Kyoto, which was to prove essential to the characterization of dendritic cells.

### Macrophage Activation: Antimicrobial and Antitumor Activities

Zan's early work focused on the "constitutive" microbicidal activities of phagocytes, but he often wrote in reviews about their "acquired" killing capacities. The concept of qualitative changes in macrophage antimicrobial function was pioneered by scientists at the Trudeau Institute, where Zan was a longtime advisor and trustee. George Mackaness, who had been a member of the Dubos-Hirsch Lab in the late 1950s, found that the microbicidal activity of macrophages increased during murine listeriosis and tuberculosis. Robert North provided evidence that both thymus-dependent lymphocytes and newly recruited macrophages were critical for resistance in vivo.

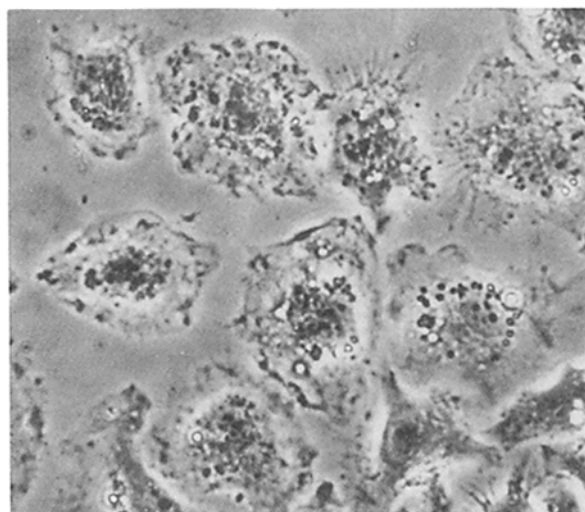
In the mid 1970s, the activation of peritoneal macrophage function took center stage, if such a thing were possible in Zan's lab! Zan emphasized that "activation" was a qualitative or quantitative increase in discrete, measurable functions relative to the baseline in resident peritoneal macrophages (126). Zan and colleagues studied many properties, and typically

in a number of populations elicited by different stimuli. Some changes included an increase in pinocytic activity (100) and turnover of the ectoenzyme 5'-nucleotidase (112) with Paul Edelson; enhanced production of plasminogen activator with Gordon (129), Jay Unkeless, and Edward Reich; enhanced release of superoxide anion (130, 183) with Richard Johnston; increased spreading (110, 138, 139) with Celso Bianco and Otto Götze; and altered plasma membrane composition and turnover (173) with Helen Yin.

However, most investigators in the field considered the pinnacle of activation to be enhanced antimicrobial and antitumor activity. Zan and colleagues encountered such capacities in macrophages taken from mice infected with viable BCG and *T. cruzi*. Zan considered the studies on *T. cruzi*, initiated with graduate fellow Nadia Nogueira, to be a high point. This obligate intracellular protozoan parasite causes Chagas' disease in humans. First they attended to the organism itself and learned to isolate the pathogenic trypomastigote form (104). Remarkably, when they followed the uptake and intracellular fate of cultured trypomastigotes, they observed that parasites escaped from the uptake vacuole and grew in the cytoplasm (115). However, in macrophages that were taken from mice that had been infected with either *T. cruzi* or BCG, and then challenged with the corresponding specific antigen (so-called "immune-boosted" macrophages), Nogueira and Cohn noted killing in 75% of the internalized parasites (123). When a lymphokine-rich conditioned medium was produced by spleen cells from infected mice and applied to otherwise nonresistant phagocytes in vitro, the group induced sterilizing resistance and other parameters of macrophage activation (Fig. 8) (124, 131). They made similar findings with human monocytes (207). Whereas prior studies with other organisms had produced bacteriostasis and/or short-lived cidal effects, Zan's *T. cruzi* work provided the precedent that products of immunologically active spleen or blood cells could change the macrophage from a susceptible to a sterilizing cell.

Henry Murray proceeded to analyze another obligate intracellular protozoan that was readily visualized, *Toxoplasma gondii*. This was familiar territory because of earlier studies by Thomas Jones and Hirsch in the lab. This class of organisms again allowed one to monitor microbial fate directly by microscopy and to ensure that microbicidal effects were occurring within the cell and not extracellularly. Murray and Cohn proceeded to outline the sensitivity of *T. gondii* to hydrogen peroxide (141), the capacity of scavengers of oxygen metabolites to block killing by immune-boosted macrophages (142, 161) (Fig. 9), and the tight correlation between enhanced oxidative metabolism and killing (160).

The work was then taken into the realm of tumor resistance by Carl Nathan, who had previously discovered with Richard Root that appropriately activated macrophages could produce as much hydrogen peroxide as polys. Along with Silverstein, the group now demonstrated extracellular, hydrogen peroxide-dependent killing following the triggering with pharmacologic agents (144, 145) and antibody-coated tumor cells (162, 163). Tumor cell killing was manifest only in appropriately activated macrophages, especially those obtained from BCG- and *C. parvum*-primed mice. Tumor cell antiox-

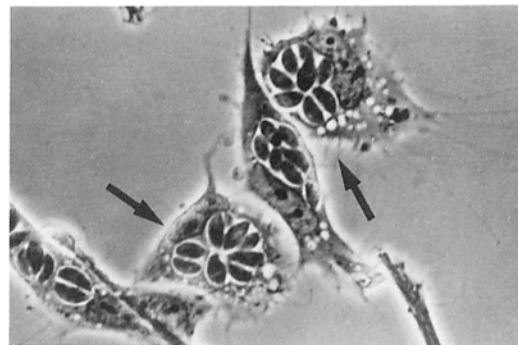


**Figure 8.** Phase-contrast micrographs of proteose peptone-induced macrophages 72 h after infection with *T. cruzi*. (Top) Cells cultivated in medium alone for the whole time. Many of the macrophages are parasitized (arrow). (Bottom) Cells cultivated in medium containing 25% of BCG-induced spleen cell factor. The burden of protozoa has been reduced by the lymphokine treatment.  $\times 600$  (131, Fig. 4).

ident defenses could be compromised in vitro and in vivo (164, 188, 199, 220, 252), and this led to enhanced killing. In other interesting experiments, the group induced killing of targets, by applying peroxidase and a halide to cells (81), and sensitized organisms with peroxidase to small amounts of  $H_2O_2$  (206). Therefore, Zan and a talented group of clinically trained individuals helped expand the long-standing topic of macrophage activation during T cell-mediated immunity to several important targets and to concrete ideas on mechanism.

### Cytotoxicity Mediated by Pore-forming Proteins

Studies on the biochemical basis for cell-mediated cytotoxicity were extended to other systems with John Ding-E Young, first a graduate fellow and then faculty member. Young



**Figure 9.** Phase contrast micrographs of macrophages 24 h after infection with *T. gondii*. (Top) Inhibition of toxoplasma replication by normal macrophages cultivated 18 h before infection in heart infusion broth (8 mg/ml) and 5% toxoplasma lymphokine. Only a few organisms are seen (arrows). (Bottom) Same macrophages after exposure to exogenous catalase (2 mg/ml) showing growth of toxoplasma (arrows).  $\times 1,200$  (160, Fig. 8).

and Cohn emphasized killing by cytolytic lymphocytes, both T and NK cells. The paradigm proved to be different from the macrophage. They showed that, instead of oxygen metabolites, killer cells released a pore-forming protein by granule-mediated exocytosis. Young isolated from killer cell granules this "perforin" (260, 285, 291), as well as two serine esterases (294). Young characterized the lesions that were created by perforin deposition in targets as large ion-carrying pores and visualized the pores by electron microscopy (292). He found these functional properties of perforin to be similar to the terminal complex of the complement cascade, to which perforin was found to have other homologies (296, 298). Young and colleagues found that the release of perforin could be induced by ionophores (299). They further identified a calcium and perforin-independent killing pathway (316) and pursued other cytolytic factors and cell types such as eosinophils (289), mast cells (312), and the agent of amoebic dysentery, *Entamoeba histolytica* (219, 262).

### Macrophage Signaling via a Major Substrate of Protein Kinase C (PKC)

The lab directed its early efforts in the signaling arena to the prototypic Fc $\gamma$  receptor, which is pivotal in triggering macrophage phagocytic and secretory functions. Mellman and Unkeless had purified the receptor some years earlier. Young

found that FcR triggering could depolarize macrophages (235) and induce ion fluxes (264), including an increase in intracellular calcium (250). Scott and colleagues showed that the secretion of arachidonic acid metabolites only required attachment of an antibody-coated particle to surface Fc receptors (168). With the arrival of Alan Aderem, the study of signal transduction for enhanced arachidonic acid, or 20:4, metabolism continued (238, 251), but an important change was to emphasize one of Zan's favorite stimuli for enhanced macrophage function (10, 17), namely the lipopolysaccharide (LPS) from the cell walls of Gram-negative organisms.

Aderem defined sequential signals for the induction of 20:4 metabolism by LPS. LPS would first prime the macrophages, and then the cells could be provoked with such triggers as PMA, latex particles, or calcium ionophore (271, 273, 319). Aderem decided to pursue the mechanism of LPS function at the level of protein myristoylation and noted specific LPS-primed species (272). He proved that a species that migrated with an apparent molecular mass of 68 kilodaltons (kD) was a major substrate of PKC (318) and was later termed myristoylated alanine-rich C-kinase substrate (MARCKS). LPS-induced myristoylation targeted MARCKS to membranes, permitting access to PKC. Aderem soon defined the capacity of MARCKS to interact with actin. The group described how interferon  $\gamma$  (IFN- $\gamma$ ), the prototype activator of macrophage function, induced the myristoylation of a distinct 48-kD macrophage protein (320). Although the link to 20:4 metabolism remained unspecified, Zan was at last seeing connections being unravelled between LPS and IFN- $\gamma$ , the macrophage surface, and the cytoskeleton.

### Endothelial Transmigration or Monocyte Diapedesis

Zan always emphasized in reviews the need to understand the recruitment of monocytes from the blood stream, a phenomenon that underlies so many contexts, including delayed-type hypersensitivity (DTH), granuloma formation in chronic infectious diseases, and perhaps atherosclerosis. Eva Cramer, Nicholas Pawlowski, and Scott were the first to approach endothelial cells in the lab. They found that the macrophage product leukotriene C could stimulate prostacyclin synthesis by endothelial cells (222) as well as the transendothelial migration of neutrophils (242). Patricia Detmers, Marco Baggiolini, and Zan showed that interleukin-8 (IL-8) could activate the integrins of neutrophils and enhance the binding of polys to endothelial cells (349, 354). Zan and colleagues then identified an experimental model in which human blood monocytes selectively bound and transmigrated through the junctional complexes of human endothelium (259, 329).

The exploration of the molecular basis for monocyte transmigration became feasible when Muller rejoined the lab to set up a vascular biology unit. He rendered the tissue culture model appropriate for quantitative studies and also developed a monoclonal antibody to an antigen that was abundant in endothelial junctions (344). Later identified as platelet/endothelial cell adhesion molecule 1 (PECAM-1), this proved

to be the first molecular species that both localizes to endothelial junctions and is required for monocyte diapedesis.

### Manipulating Cell-mediated Immunity with Lymphokines in Human Infectious Disease

Early in the 1980s, Zan was at last ready to study macrophage function directly in the setting of human infectious disease. With Gilla Kaplan, he initiated a program to study leprosy and established collaborations in Colombia, Brazil, India, Nepal, Ethiopia, and the Philippines. Suitcases packed with supplies for experiments became part of the lab environment.

Cohn and Kaplan chose leprosy for many reasons. Clinically, it remains a major scourge. Experimentally, much of the critical pathology is accessible in the skin. Biologically, the mechanisms underlying the spectrum from lepromatous to tuberculoid poles of the disease were pertinent to the lab's interests. Lepromatous leprosy was in essence an antigen-specific immunodeficiency expressed in the form of a microbially permissive macrophage, while tuberculoid disease and some reactional states were manifestations of heightened T cell immunity. So the time had come. Zan always looked forward to bringing his experiments into the realm of human disease, and he understood the reciprocal but too often forgotten principle that the study of disease stimulates new insights.

The immunologic changes in leprosy previously had been analyzed at the level of blood cells. Zan and colleagues focused on the skin lesions. Graduate fellow Van Voorhis noted that the lymphocytes in skin infiltrates were not a representative sample of those in blood. CD4<sup>+</sup> T cells predominated at the tuberculoid pole, while a scant CD8<sup>+</sup> infiltrate characterized the lepromatous pole (218). A demanding series of electron micrographs outlined the intravacuolar location of *Mycobacterium leprae* in macrophages in lepromatous disease, and the presence of what appeared to be activated lymphocytes at the tuberculoid pole (223). The group made comparable findings in examining leishmaniasis, especially in the mouse model. They noted that the makeup of infectious foci in cutaneous and visceral infections reflected the efficacy of the local immune response rather than a general sample of blood cells (307, 327).

In studies of blood cells from lepromatous leprosy patients, Zan and colleagues outlined a deficiency in the production of IFN- $\gamma$  and macrophage-activating cytokines following challenge with *M. leprae* antigens (228, 243). When they found that low levels of responsiveness in T cells from some patients could be boosted by interleukin 2 (IL-2) (254), they turned to reversing the deficit in situ. Two approaches were taken and both proved fruitful. One was to inject purified protein derivative (PPD), i.e., antigens from *M. tuberculosis*. Although lepromatous patients are unresponsive to the lepromin antigen from *M. leprae*, the patients can exhibit a typical DTH response to the tuberculin skin test antigens from *M. tuberculosis* (325). Kaplan, Cohn, and colleagues noted a substantial decrease in acid fast bacilli at the DTH site (326). So the chronically parasitized disease site did not behave as

if it were nonspecifically suppressed, a theme proposed in the literature as a result of tissue culture studies. Instead, the disease site had the potential to respond, and relatively rapidly.

The second approach was classically simple and was initiated by Cohn, Nogueira, and Nathan. Why not inject the T cell products, which lepromatous patients could not make in response to *M. leprae* antigens, directly into the skin and observe the consequences? These products had just become available as a result of recombinant DNA technology. IFN- $\gamma$  was tested first (287) and found to replay certain features of DTH. Multiple injections of IFN- $\gamma$  led to more pronounced clearance of acid-fast bacilli (304, 339).

IL-2 was tested next. Kaplan and Cohn found that remarkably, this lymphokine marshaled all the cellular changes that typified standard, antigen-elicited, DTH reactions, only faster (338). Monocytes and T cells selectively emigrated into the injection site, which became classically raised and indurated within a day (Fig. 10). Parasitized macrophages became difficult to identify by electron microscopy, dendritic cells accumulated intradermally, and the overlying epidermis changed

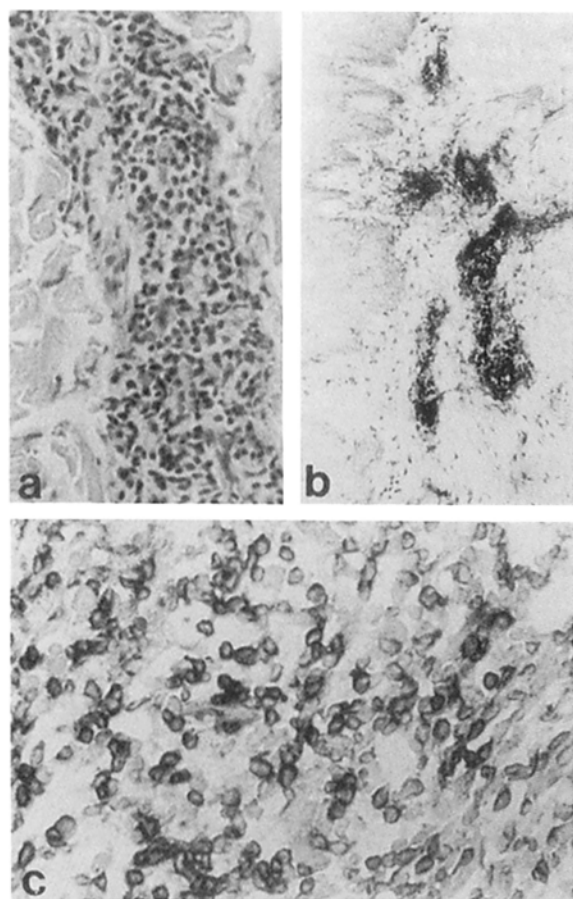
markedly (see below). So again, local *M. leprae* were not associated with nonspecific suppression of the many cellular responses to IL-2 or to PPD (337). In human cutaneous leishmaniasis, IL-2 injections also brought about a local decrease in parasite numbers (347).

Kaplan and colleagues then found that chronic, local injections of IL-2 had systemic effects as well. There were decreased bacillary numbers in slit smear preparations from the ear (357), and increased killer cells (336, 355) and responses to proliferative stimuli (348) in blood.

These experiments with relatively low doses of intracutaneous IL-2 were seminal in three respects. First, the observed responses to IL-2 provided a mechanism whereby a local response by antigen-specific T cells in DTH marshals the characteristic histologic response. Second, the response to IL-2 and to PPD unveiled changes in the keratinocytes that immediately caught the attention of Kaplan and Cohn (284). There was a marked and rapid keratinocyte hyperplasia, as well as an increase in expression of two molecules, MHC class II and a cytokine termed  $\gamma$  interferon-induced protein ( $\gamma$ -IP-10) that had been discovered by graduate fellow Andrew Luster, Unkeless, and Jeffrey Ravetch. When the effects of cytokines on keratinocyte growth were studied in vitro, GM-CSF but not IL-2 was noted to be stimulatory (324). So IL-2 injections in situ seemed to be enhancing local release of IFN- $\gamma$  and GM-CSF. Kaplan and Cohn therefore tested GM-CSF directly and uncovered striking increases in dendritic cell numbers and in the rate of wound healing (364). Third, the systemic enhancing effects of IL-2 suggested that chronic low-dose intracutaneous IL-2 might be used therapeutically in T cell deficiency states, much like chronic intracutaneous insulin is used in diabetics, Zan argued. These sets of findings that emerged by direct observation of the IL-2 injection site in leprosy are noteworthy when compared with the toxicity and limited efficacy in other studies with high dose, intravenous IL-2.

As the leprosy work progressed in the 1980s, Zan and colleagues naturally transferred attention to two major diseases in which the causative agent exhibits a tropism for macrophages, AIDS (322) and tuberculosis (368). Several clinically trained individuals joined the lab to study white cell function in HIV-1-infected patients. They documented the proliferative potential of CD4<sup>+</sup> T cells (340) and the HIV-1 burden in monocytes (358). Patient studies also were begun to evaluate the effects of intracutaneous IL-2. While IL-2 had proven ineffective in prior work, the use of high doses and the intravenous route could have been compromising. The first studies with Juliana McElrath and Hedy Teppler encouraged Zan. They found that the immunocompromised, HIV-1-infected individual could mobilize a typical cell-mediated reaction to IL-2 in the skin (350) and would show systemic effects such as a boost in IL-2-responsive killer cells (369, 370). A program to enhance the immune system of immunocompromised individuals was therefore underway.

More recently, a program in tuberculosis began under the direction of Kaplan. In one set of experiments, Anthony Molloy, the last graduate fellow to work with Zan, carefully monitored the features of human monocytes that were sup-



**Figure 10.** T cell accumulation during the response to intradermal IL-2. Histologic (hematoxylin and eosin) (a) and immunohistologic staining of sections with mAbs that recognize all T cells (CD5) (Leu-1) (b and c). Biopsies were taken 96 h after IL-2 injections ( $2 \times 10 \mu\text{g}$ ). At this early time, the majority of T cells are of the CD4<sup>+</sup> subset.  $\times 100$  (a);  $\times 50$  (b); and  $\times 200$  (c) (338, Fig. 3).

porting the growth of BCG mycobacteria. Another set of experiments was based on an outgrowth of the leprosy work, the observation that thalidomide could decrease the production of TNF in patients with erythema nodosum leprosum and in stimulated cultures of human monocytes (361). At his death, Zan was organizing an expanded and multifaceted program in tuberculosis research and was pursuing the promising initial studies in wound healing and HIV-1 infection (above). For each of these efforts, The Rockefeller University Hospital was as critical a part of the Laboratory as when Zan arrived to work with Dubos and Hirsch 35 years earlier.

### The Esprit of a Physician-Scientist

Zan's professional activities extended to many other spheres of academic medicine. He played significant editorial roles for many journals, not just this one. He was an advisor to several institutions: Bates College, where he received a B.A. in 1948; Harvard Medical School and the Massachusetts General Hospital, where he received his medical education from 1949 to 1955; the Trudeau Institute; Roswell Park Cancer Institute; the New York Blood Center; and the National Institutes of Health. Together with Jim Hirsch and Alexander Bearn, Zan organized, with Cornell University Medical College, one of the first medical scientist training programs for the combined M.D.-Ph.D. degree. Also, Zan vigorously supported The Rockefeller University Graduate Program from its inception, contributing to the professional development of numerous graduates. Ph.D. students are coauthors of 80 of his 370 publications, and their postdoctoral work is featured in dozens more. Zan's leadership of the laboratory was strengthened by his gifted assistant, Mrs. Grace Silvestri.

Two professional concerns were foremost for Zan. One was The Rockefeller University Hospital. Zan regarded himself as a "physician-scientist" who was most challenged by the biological venue of human disease. In his last 10 years, Zan was fully occupied by leprosy, AIDS, and tuberculosis, and the Hospital's in- and out-patient facilities were vital to his bench observations. Zan stressed that the Hospital served as the focal point for many of the finest accomplishments by Rockefeller investigators, whether their training was Ph.D., M.D., or both. This was more than happenstance. Problems of human disease remain intrinsically of great interest and challenging complexity, and appropriate animal models are often not available for many major illnesses. Zan therefore enthusiastically assumed the position of Vice President for

Medical Affairs in early 1992. Together with Physician-in-Chief Jules Hirsch, he was energizing a successful new Clinical Scholar Program for research in human disease, particularly the eight major conditions that currently are the Hospital's core.

The other focus for Zan was his editorial responsibility toward this *Journal*. The board meets weekly to discuss the submitted articles and the referees' reports. The editors of any journal face demanding responsibilities, but the weekly *Journal* meeting in a special way distributes the demands, provides a time to learn and to be with colleagues, and improves on fairness and consistency. Zan insisted that these pages be the place to describe the newest developments, and that there be sufficient space to document conclusions adequately and to pursue mechanisms in detail. Over the years it has become more difficult to publish the extensive work-ups that exemplified Zan's early papers. Yet the *Journal* still looks for the qualities that made Zan's work so substantial and enduring: novelty, clarity, and a mechanistic analysis that is quantitative, direct, and multifaceted.

Zan's personal qualities, of which the editors were so fond, were familiar to many. A quiet gentleman, he was known for his brevity, wit, modesty, and fairness. He was quick to share his broad experience and insight. Professionally, his greatest pleasures were the exploits of young people, and his greatest concerns were for the integrity and support of university life. He loved the sea and its wildlife, and he shared many personal interests with his wife Fern, his son David, his daughter Ellen, and numerous friends.

Zanvil Cohn was recognized in Leiden as "the founder of modern research on macrophages." His alma mater, Bates College, honored him for "his intellectual courage to explore the worlds of living cells, and for his quiet contributions of knowledge which may heal the sick." His scientific legacy extends deeply into cell biology, immunology, and infectious disease. To The Rockefeller University and the Laboratory of Cellular Physiology and Immunology, he was a warm, sensitive colleague who nurtured an array of scientific findings and who mentored the careers of dozens of individuals. To the editors of *The Journal of Experimental Medicine*, he upheld and fostered a tradition of innovation and depth, helping to guide the growth and international excellence that embrace our profession. We all miss this prince of a man.

Ralph M. Steinman and Carol L. Moberg  
For the Editors

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Several individuals helped with this tribute: Maclyn McCarty, Ralph van Furth, Samuel Silverstein, Siamon Gordon, Carl Nathan, Gilla Kaplan, Ira Mellman, William Muller, Nina Bhardwaj, Joan Muller, Judy Adams, and William Swiggard.

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