SYMPOSIA SUMMARY OF THE INTERNATIONAL RES CONGRESS
10TH HELD AT ITO JAPAN ON 2-7 SEPTEMBER 1984(U)
RETICULOENDOTHELIAL SOCIETY AUGUSTA GA S M REICHARD
UNCLASSIFIED 28 NOV 84 N00014-84-G-0189 F/G 6/5 NL
**AD-A149 133**

**PERFORMING ORGANIZATION REPORT NUMBER(S)**
Reticuloendothelial Society

**3 DISTRIBUTION/AVAILABILITY OF REPORT**
Distribution to general public.

**4 PERFORMING ORGANIZATION NAME(S)**
Reticuloendothelial Society

**5 MONITORING ORGANIZATION REPORT NUMBER(S)**

**6a NAME OF PERFORMING ORGANIZATION**
Reticuloendothelial Society

**6b OFFICE SYMBOL (If applicable)**

**7a NAME OF MONITORING ORGANIZATION**

**7b ADDRESS (City, State, and ZIP Code)**
c/o Dr. Sherwood M. Reichard
Medical College of Georgia
Augusta, GA 30912

**8 NAME OF FUNDING/Sponsoring Organization**
Office of Naval Research

**9 PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER**
N00014-84-C-0189

**10 SOURCE OF FUNDING NUMBER(S)**

**11 TITLE** (Include Security Classification)
Symposia at the 10th International RES Congress

**12 PERSONAL AUTHORS**
Sherwood M. Reichard

**13 TYPE OF REPORT**
Final

**13a TYPE OF REPORT**
Final

**13b TIME COVERED**
From Aug 84 to Jul 85

**14 DATE OF REPORT (Year, Month, Day)**
84/11/28

**15 PAGE COUNT**

**16 SUPPLEMENTARY NOTATION**

**17 COSATI CODES**

**18 SUBJECT TERMS** (Continue on reverse if necessary and identify by block number)

**19 ABSTRACT** (Continue on reverse if necessary and identify by block number)
See attached Summary.

**20 DISTRIBUTION/AVAILABILITY OF ABSTRACT**

**21 ABSTRACT SECURITY CLASSIFICATION**

**22 NAME OF RESPONSIBLE INDIVIDUAL**
Dr. Sherwood M. Reichard

**22d TELEPHONE (Include Area Code)**
404 828-2601

**22e OFFICE SYMBOL**

**DO FORM 1473, 84 MAR**
The opening address of the 10th International RES Congress, Ito, Japan, was given by Dr. Zanvil Cohn of the Rockefeller Institute, NYC, NY, USA. Dr. Cohn reviewed the many facets of macrophage function which secure for this cell a central role in both the stimulation and expression of immune responses. Among the topics reviewed by Dr. Cohn was the variety and complexity of effector activities expressed by macrophages, both in a resting state and following stimulation with soluble products released at sites of inflammation and immune reactions. Many of these effector reactions require interaction of the stimulating agent with receptors present on the macrophage cell membrane. Some receptors, such as the antibody (Fc) receptors, induce not only internalization of the immune complex, but secretion of a variety of reactive substances (complement components, clotting factors, enzymes, reactive O_{2}^{-}, etc.); other receptors, such as the complement (C3) and mannosyl receptors, stimulate only phagocytosis. Regulation of phagocytosis/secretion may be through alteration in free (non-mitochondrial) calcium. One secretory product that induces death of certain intracellular microorganisms and extracellular tumor targets is reactive O_{2}^{-}. A soluble product from stimulated T lymphocytes that induces the secretion of reactive oxygen intermediates is IFN\textgamma. This molecule appears to regulate a whole host of macrophage effector activities, and deficiencies in IFN\textgamma production have been correlated with development of certain progressive diseases (i.e. leprosy). Although macrophages clearly participate in the regulation and expression of secondary
immune responses, Dr. Cohn felt that the evidence from Dr. Steinman's laboratory strongly suggest that dendritic cells, cells derived from a different progenitor than macrophages, have primary responsibility for antigen presentation to T cells in developing immune responses. This viewpoint was challenged several times throughout the meeting.

PLENARY SESSIONS

Viruses, Oncogenes, and Human Lymphomas

The definition of an oncogene depends upon one's perspective: one can view these genes as either a cellular gene incorporated into a virus, or a virus gene incorporated into a human chromosome. The development of neoplastic disease following exposure to certain viruses is a complex process. For example, the infection of African children with EBV virus does not necessarily result in development of lymphomas: these infected children are at risk for development of lymphomas, but the virus infection is not sufficient in itself. Rather, chronic endemic malaria is the environmental co-factor that induces splenomegally and sets the stage for induction of Burkett's lymphoma. EBV then activates and immortalizes the B cells in a BCGF (B cell growth factor)-independent manner (Klein, USA).

Every cellular body carries greater than 20 protooncogenes. The method of transformation activation depends upon the particular gene: transduction into acute transforming retroviruses, integration, insertional mutagenesis (acquisition of more promoters), chromosomal rearrangement, gene amplification, single point mutations, and other methods as yet undescribed. A wide variety of human tumors (bladder, colon, gall bladder, liver, lung, pancreas, fibrosarcoma, rhabdosarcoma) have detectible oncogenes, mostly of the K ras type. The ras genes are so named because of the similarity with rat sarcoma virus, and there are 3 types: H, N, and K. The K ras gene codes for a single 21 kbase peptide, and malignancy results from a single point mutation at the 12th or the 61st codon. Is activation of oncogenes essential for malignancy, or simply coincidental? In all cases examined, both in humans and experimental models, it is the single mutation of guanosine to adenine at position 12 that is associated with mammary tumor development. This substitution may be the result of a methylation reaction (Sukumar, USA).
There is a high level of adult T cell leukemia in south central Japan. Cells from these patients can be cultured without addition of TCGF (T cell growth factor), and produce virus as well as shed ATLV antigens. Serum from patients react with these viral antigens, and the antigens can be detected on the surface of T cells. Over 70% of the lymphomas diagnosed in southern Japan are ATVL-induced T cell lymphomas. Most of the patients are over 40 years old, and there appears to be family clustering. The virus may be passed from mother to child (Hanoaka, Japan).

Macrophages and Atherosclerosis

IL-2, a T cell-derived T cell growth promoting factor, induces the release of clotting factors that enhance the adhesion of monocytes to endothelium. Monocytes constitute a fair number of the cells in plaque that leads to atherosclerosis (Catran, USA).

Some foam cells (lipid-containing cells that are associated with plaque formation in arteries) derive from macrophages, others from smooth muscle tissue. The correlation between premature atherosclerosis and lipids appears to be with elevated low-density lipoprotein (LDL), yet macrophages accumulate LDL too slowly to account for development of foam cells. Acetylation, or chemical modification, converts LDL into a molecule that can be rapidly accumulated by macrophages. There is no evidence that de novo chemical modification occurs in vivo, but these workers show evidence that endothelial cell-modified LDL is rapidly internalized by a receptor that does not recognize the "native" molecule. Smooth muscle tissue can also modify the LDL, but most other cells cannot. This modification is accompanied by the peroxidation of fatty acids, and is dependent upon the generation of oxygen radicals. EDTA blocks the modification. Apparently the Apoprotein B of LDL is the site of modification, as well as fatty acid phosphorylation. Monocytes constitutively release lipoprotein lipase, and activation of this enzyme by apoprotein CII induces the accumulation of cholesterol esters and triglycerides. The question is: Is the macrophage a good guy (ingestion of LP and prevention of lesion) or a bad guy (ingestion of LDL, formation of foamy cells, and development of lesion)? (Steinberg, USA)

Receptor-mediated internalization of LDL occurs primarily (70%) through coated pits, although coated pits are only 2% of the cell surface. There are
several naturally-occurring defects in receptor-mediated entry of LDL that have facilitated analysis of the process of internalization and accumulation of LDL: (1) defective clustering in coated pits (loss of C-terminal end of receptor) and (2) defective binding. Clathrin is the major protein in coated pits. Depletion of K+ destroys coated-pit distribution in cells, and induces a decrease in LDL uptake. Receptor-LDL uncoupling must occur for recycling of the LDL receptor. The current theory is that uncoupling occurs in endosomes prior to lysosome fusion; uncoupling appears to be pH directed, since monensin and chloroquin raise the internal pH of endosomes and decrease reinsertion of LDL receptors (Anderson, USA).

Macrophages and Activation

Tissue macrophages encounter a wide variety of signals during inflammation and development of immune responses. The burning questions about macrophage activation today are: what is the nature of the signal(s) that induce activation? what are the capacities that the macrophage must acquire for the various effector activities displayed? and, what is the molecular basis of macrophage activation? In all tumor killing assays, binding of the target cell to the macrophage is an essential event. Binding via a receptor triggers the release of a proteolytic enzyme of 38-40 kdaltons that kills the target. The binding of the tumor cell and release of the proteolytic enzyme during nonantibody-mediated macrophage killing are events that are independently genetically regulated. In the presence of antibody, some activated macrophages can kill certain tumor targets by release of reactive oxygen intermediates (classic ADCC). Some macrophages that are not activated can also mediate ADCC, albeit a slower form of this killing. Thioglycollate macrophages are the best example of cells that can perform this slow ADCC. A molecular correlate of macrophage response to activating signals is phosphorylation by protein kinase c (PKc). One can mimic the priming of macrophages by IFN-gamma for extracellular destruction of tumor targets with phorbol myristate acetate (PMA) and a Ca++ ionophore. Both priming sequences require an additional trigger signal (such as LPS) to induce cytotoxicity. In both instances, protein kinase c is increased during priming, and LPS provides the trigger for protein phosphorylation (Adams, USA).
Although monoclonal antibodies have been made that interact with a variety of macrophage subtypes, none of these antibodies are specific for the activated macrophage. F4/80 is a monoclonal that recognizes a macrophage surface antigen that is down-regulated during activation (was produced by S. Gordon). These investigators reported a new monoclonal, ACM-1, that identifies activated macrophages only: it is not reactive with inflammatory macrophages, or resident macrophages of the peritoneum, spleen, or lungs, with spleen cells or with thymocytes. The antibody recognizes an antigen with 2 polypeptides of 70 and 45 kdaltons. It blocks cytotoxicity, but does not eliminate cytotoxic cells in the presence of complement. It is expressed on BCG, C. parvum and pyran-activated macrophages (Tanlyama, Japan).

Interferon gamma is a major activating factor for macrophages of both humans and mice. As little as 1 pM of IFN gamma is sufficient to activate these cells. There is a great deal of information that suggests that the tumoricidal and microbicidal properties of activated macrophages can be correlated with the release of certain reactive oxygen intermediates, notably hydrogen peroxide. This molecule is responsible, in whole or in part, for the destruction of tumor cells and obligate intracellular parasites. These investigators have been able to show a deficiency in IFN gamma production in humans and experimental animals during debilitating chronic diseases such as leprosy and leishmaniasis, and have begun preliminary trials with replacement therapy using recombinant IFN gamma in mice infected with these agents. One exciting finding is a marker for interferon therapy: neopterin (derives from GTP in folate or serotonin system) is excreted in urine of patients treated with this macrophage activating agent (Nathan, USA).

The antiviral activity and macrophage activating activities of IFN gamma appear to reside in different regions of the molecule. Monoclonal antibodies can be made to recombinant IFN that inhibit either one or the other of these activities in fluid phase, but both activities when attached to a solid matrix or precipitated by Staph A. Hybrid molecules of mouse and human (not active on mouse cells) IFN gamma suggest that there are at least 2 domains, each of which regulate a different activity (Schreiber, USA).

That IFN gamma is a major activating factor for macrophages is now clear: this molecule can induce extracellular cytolysis of diverse tumor and helminth targets, and intracellular destruction of a variety of obligate
intracellular pathogens. The question is whether there are non-IFN macrophage activating factors as well. In certain cases, non-interferon MAFs can be detected: (1) a 25 kd molecule in culture fluids of the PMA-stimulated EL-4 thymoma cell line induces potent extracellular killing of tumor and helminth targets without IFN-associated antiviral and Ia-inducing activity. This MAF activity cannot be neutralized by anti-IFN monoclonal antibodies. (2) factors are present in lymphokine supernatants of antigen or mitogen-stimulated spleen cells that induce intracellular destruction of microorganisms, but do not have antiviral activity. (3) Resistance to infection, one early antimicrobial activity of activated macrophages, cannot be induced with recombinant IFN gamma, nor can this MAF activity in lymphokine supernatants be neutralized by monoclonal antibodies prepared against IFN gamma. (Meltzer, USA).
10th INTERNATIONAL RES CONGRESS
10th INTERNATIONAL RES CONGRESS
Ito, Japan
September 2-7, 1984,
PROGRAM AT A GLANCE

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<th>Sunday Sept. 2</th>
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<td>Map of the Kawata</td>
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ORGANIZATION

Congress Officers
Honorary President: Kanevishi Akazaki
President: Mizu Koijma
Secretary General: Souji Ipuma
Treasurer: Kazuo Kuma
President of R.R.S.: Sherwood St. Rechard
Secretary of R.R.S.: Peter Abramoff

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Ralph Snyderman, Co-chair (U.A.
Mizu Koijma, Vice-chair (Japan)
Michael Feldman (Israel)
Ralph van Barth (Netherlands)
Samuel Gordon (England)
Tohru Masuda (Japan)
Atsuo Mikata (Japan)
Carl Nathan (U.A.)
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Tohru Yokomaga (Japan)
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W. Th. Damos (Netherlands)
Robert Evans (U.A.)
K. Hemming (West Germany)
Irene Ishikawa (Japan)
Pierre Jacques (Belgium)
George Lazar (Hungary)
Carlton G. Stewart (U.A.)

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<th><strong>Finance &amp; Land Using Committee</strong></th>
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GENERAL INFORMATION

1. Period and Site
   Period: September 2, Sunday - September 7, Friday, 1984
   Site: The Kawana Hotel
   Address: 1459, Kawana Bld, Shizuoka Prefecture, 414, Japan
   Telephone: 0552-45-1111

   The Kawana Hotel, one of Japan's most resort hotels, is on the site of the
   Pacific Ocean, surrounded by the beauty of Fuji-Hakone-Izu National Park.

2. Language
   The official language is English. There will be no facilities for simultaneous
   translation.

3. Poster Session
   Posters are on display in Room 1 everyday except Wednesday from 13:00 to 18:00.
   One hour period between 17:00 and 18:00 is reserved as the "Poster Session" for
   free discussions with the designers.

4. Secretariat
   The Secretariat is open from 8:00 to 19:00 at Secretariat Room on the 1st floor
   throughout the Congress period. If you have any trouble, please contact the
   Secretariat.

5. Information Desk
   The General Information Desk, to be set up at the Congress, will offer answers to
   general questions, while the Travel Information Desk, set up by the Japan Travel
   Bureau, will provide information on accommodations and travel. The desks will
   open:
   - September 2, Sunday: 13:00 - 19:00
   - September 3, Monday: 8:30 - 17:00
   - September 7, Friday: 8:30 - 12:00

6. Notice Board
   A notice board will be installed at the lobby on the 1st floor for both general and
   special notices, and personal messages to the Congress participants. In case you want to get
   hold of someone at the Congress, please go to the General Information Desk. They will post your
   notice on the Notice Board.

7. Name Cards
   Please display your Name Card (provided to you at the time of registration) at all
   times during the Congress for your convenience and security. Cards have been
   prepared in 4 colors as follows:
8. Currency Exchange
Foreign currency exchange services will be provided at the Kawana Hotel.

9. First Aid and Medical Assistance
Participants needing first aid should apply to the Congress Secretariat, or the front desk at the hotel. Medical care or hospitalization can be quickly arranged in case of emergency.

10. Sports: Golf, Tennis and Swimming
Among the Izu Peninsula, Bio City is most frequented by foreign visitors. And The Kawana Hotel has one of the most famous Golf courses in Japan, 'the Fuji course' and 'the Oshina course'. And the Resort Hotel Southern Cross also has very good Golf courses. You can also enjoy tennis at the above mentioned hotels. The pool may also be freely used, but be aware that no lifeguard is on duty.

The Sports Desk will be set up in the 1st floor lobby. Those wishing to participate in golf or tennis are requested to apply at this desk.

11. Lunch
Lunch will be served at the following locations within the Kawana Hotel:

- Grill Room (Main Building - Basement) 11:00 - 15:00
- Dining Room (Main Building - 1st Floor) 12:00 - 14:00
- Lounge (Main Building - 1st Floor) 12:00 - 14:00
- Sun Bar/l (Main Building - 1st Floor) 10:00 - 18:00

12. Coffee Break
Coffee breaks are planned for both the morning and afternoon. The morning break will be in Banquet Lobby at 10:30 - 11:00. The afternoon break will be held in Room 1 (Poster Session Room) at 16:00 - 17:00.

13. Excursion
'Soba nozumi' is planned as an excursion on September 5, Wednesday. Asaka's Soba is very unique in that you may enjoy the traditional atmosphere associated with the most aristocratic of Japan's theater arts. For questions about or application for the excursions, please inquire at the Travel Information Desk.
SOCIAL EVENTS

1. Opening Ceremony
   Date             September 3, Sunday
   Time            18:00 – 19:40
   Place            Room A
   *Following the Opening Ceremony, the Keynote Address will be presented
   Time            18:40 – 19:30

2. Welcome Reception
   Date             September 7, Sunday
   Time            19:40 – 21:00
   Place            Room C
   Fee              Included in registration fee
   Dress            Informal

3. Banquet
   Date             September 6, Thursday
   Time            19:00 – 21:00
   Place            Room A, B
   Fee              Included in registration fee
   Dress            Informal

4. Closing Ceremony
   Date             September 7, Friday
   Time            18:15 – 18:45
   Place            Room A

Business Meeting (IULES officers only)
   Date             September 4, Tuesday
   Time            12:00 – 13:00
   Place            Room H
SCIENTIFIC PROGRAM

Keynote Address
Sept. 2 (Sun)
Room A: 18:40 - 19:30

The Macrophage as Multifaceted Cell
Zayad A. Cohn
Chairperson: Masa Hanaoka

Plenary Session 1
Sept. 3 (Mon)
Room A-B: 9:00 - 12:00

Viruses, Oncogenes and Human Lymphomas
Presiding: Masa Hanaoka

1. Oncogenes in Human Cancer
   Sarasati Sukumar

2. The Relationship of HIV to Lymphomas and AIDS
   Salahuddin

3. The Role of Oncogenes in Lymphoid Neoplasms
   George Klein

4. Viruses and Human Lymphomas
   Masa Hanaoka

Symposium 1
Sept. 3 (Mon)
Room A: 14:00 - 17:00

The Regulation of Macrophage Development and Function
Chairpersons: Isahak J. Fidler and S. Kasakura

1. The Effects of the Various Agents on the Cultured Kupffer Cells
   Shotaro Sakisaka

2. Phenotypic Characterization of Gamma Interleukin-Induced Human Monocyte
   Polykaryons (MP)
   J.B. Weinberg

3. Regulation of expression of LPS Receptor on Mouse Lung Macrophages by
   Lymphokines
   K.S. Akagawa
September 3 (Mon)

4. Protein Kinase Activity on the Cell Surface of a Macrophage-Like Cell Line, J774 T Cells
   F. Amano

5. Selective Tumor Cell Lysis by Non-Specifically Activated Macrophages Derived from Long Term Bone Marrow Cultures
   J. Toews

6. Fc Receptor Modulation and Cytotoxic Activity of Porcine Pulmonary Alveolar Macrophages
   Y. H. Kim

7. The Failure of Macrophages to Stimulate Phagocyte Superoxide Anion Generation is Correlated with the Absence of Complement Activation in Vitro
   T. Holzer

8. The Regulatory Role of Lipoxygenase Products on the Stimulated State of Rat Kupffer Cells
   M. Birmelin

Symposium 2: September 3 (Mon)
Room B: 1400 - 1700
Analysis of Macrophage Regulation and Effector Functions

   Chairpersons: J. Stephen Haskill and S. Muramatsu

1. Disappearance and Reappearance of Resident Macrophages
   Importance in C. parvum Induced Tumoricidal Activity
   Stephen Haskill

2. Endotoxin Induced Monocyte Macrophage Procoagulant Activity in the Rat
   Requires Collaborating T-Lymphocytes
   Peter A. Landr

3. The Role of Splanic Macrophage on the Blood Cell Destruction
   S. Matsuda

4. The Induction of Human Monocyte Interleukin-1 Synthesis and Secretion
   F. Newton

5. GM-CSF Production by Human Monocyte Subsets
   J. R. Zucali

6. Peptide Antigen Receptors on the Human Macrophage-Histiocyte Series
   R. Tsunoda

7. Immunohistochemical Localization of S-100 Protein Subunits in the Human Lymphoreticular System
   T. Akagi
Symposium 3  September 3 (Mon)
Room C  14:00  17:00
The Surface and Receptors of Mononuclear Phagocytes
Chairpersons: Thomas A. Hamilton and T. Masuda

1. Effective Internalization of Polysaccharide-Coated Liposomes into Phagocytes
   Yasuko Ueda

2. Evaluation of the Expression of 1a-Antigen on Normal and Immune Peritoneal
   Macrophages as Demonstrated by Rosetting, Immunocytochemistry and
   Antigen Presentation
   Robert H. Beelen

3. A Comparative Study on the Presence of Antigen Determinants on Normal
   Reactive and Malignant Macrophages
   P. J. M. Robboll

4. The Uptake of Polysaccharide-Coated Liposomes by Alveolar Macrophage
   Akimitsu Tomonaga

5. Complementary Roles of Kupffer Cells and Liver Endothelial Cells in the
   Endocytic Function of RPS in the Liver
   Harald Smedsrod

6. Identification, Quantitation, and Partial Characterization of a Serum Factor
   which Inhibits Laminin-Collagen Binding Activity
   Frank B. Gelder

7. Macrophage Surface Changes Caused by Influenza Virus and Interferon
   M. Nowakowski

Symposium 4  September 3 (Mon)
Room D  14:00  17:00
The Kill of Microbes by Elements of the MPS
Chairpersons: Seymour J. Klebanoff and I. Ouchi

1. Adoptive Transfer of Immune Responsiveness from Heavily Infected Anergic
   Frank M. Collins

2. Macrophage Activation and Resistance to Listeria monocytogenes
   Maurice J. Lefford
Sept. 3 (Mon)

1. Bacterial Activity of Peritoneal Macrophages of Beige Mice with Chedak-Hugas Syndrome
   Masayasu Nakano

2. Electron Microscopic Study on the Interaction of Listeria monocytogenes and Subpopulations of Mouse Peritoneal Macrophages
   Masahiro Kazako

3. The Effect of Bile Acid and Bile Acids on Oxygen-Dependent Bacterial Activity of Human Neutrophils
   Masahiko Yamaga

5. Effects of Prostaglandins and Scavengers for Oxygen Intermediates on Cytotoxicity of Polymorphonuclear Leukocytes (PMNs)
   Reiji Kasukawa

6. N-Ethylmethtyl Tetraaryl Phenoxyamine Induced Superoxide Release of Calcium-Dependent Human Neutrophils
   Minoru Nakagawa

7. Enhancement of Oxygen Consumption of Neutrophils by Yamasaki
   Yukio Ozaki

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Chairpersons: Yu-Han Zhang, M. Yamazaki and Sherwood M. Reichard

1. Protective Role of Alveolar Macrophage Enzymes in Experimental Pulmonary Tuberculosis
   Satoshi Chandrasekhar

2. Immunological Consequences of Host-Parasite Membrane Interactions in Human Plasmodium Malariae
   C.B. Oostenbrugg

3. Endocytosis of the Lattice Particles by the Endothelial and Kupffer Cells in the Perfused Rat Liver
   Chiko Dan

4. Foamy Macrophages Associated with Erythropagocytosis
   Tokuburu Ishihara

5. Lectin Like Receptor on Murine Macrophage Cell Line Cells, Stml: Involvement of Cytolipase Binding Sites in Ossom-Indepependent Phagocytosis of Xenogeneic Red Cells
   Soshi Kurozumi

6. Uptake of Mast Cell Granules by Reticular Cells and Macrophages and Their Acid Phosphatase Activity in the Rat Lymph Node
   Kenji Misata

7. Phagosome-Lysosome Fusion in Human Macrophages: First Encounter with M. Leprae
   David M. Scollard
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Sept. 4 (Tue)

Plenary Session II
Room A-B 10:00 - 12:00

Macrophages and Atherogenesis
Presiding: Ramzi S. Cotran and Mizu Kojima

1. Macrophages, Foam Cells and Atheromas
   Ramzi S. Cotran

2. Uptake of Lipids and Regulation of Cholesterol Metabolism
   Richard G. Anderson

3. Macrophages and Lipoproteins
   Daniel Steinberg

4. Macrophages and Secretion of Apoproteins
   Zena Webb

5. Macrophages and Accumulation of Cholesterol Ester in Atheromatous Aorta
   Tatsuya Takano

Symposium 5
Room A 14:00 - 17:00

The Regulation and Execution of the Inflammatory Response
Chairpersons: Sigurd J. Normann and I. Yoshida

1. Granuloma Formation by Mycolic Acid-Containing Glycolipids in Nocardia and Related Lava
   Kumi Kameda

2. Experimental Epithelial Cell Granulomas: Tubercle Formation and Immunological Competence
   Marian J. Ridley

3. Experimental Pulmonary Foreign Body Granulomatous Inflammation and Anergy
   Craig Allred

4. The Role of Interleukins in Granulomatous Inflammation and the Associated Anergy
   Takeshi Yoshida

5. Monocyte-Modulating Factors in Sarcoidosis Sera
   Toru Baba
6 Prominent Production of Lactate Dehydrogenase by Human Alveolar Macrophages in Interstitial Lung Diseases
   Hiroshi Watanabe

7 Tin Sulphide Crystals Found in Macrophages of Pleural Fluid of Asbestos-Exposed Patients
   Yupi Kimura

8 The Effect of Endotoxin and Gadolinium Chloride on the Acute Septic Peritonitis in Rats
   G. Lazar

Symposium 6:

September 4 (Tue)
Room B 14:00 - 17:00

Cell-Cell Interactions in Regulation of the Immune Response

Chairpersons: Michael Feldman and T. Yamashita

1 The Accessory Cell Function of Human Alveolar Macrophages in Lymphocyte Proliferative Responses
   Moto Ohtsuka

2 Fc Receptor-Positive Macrophage Cell Lines with APC Activity
   Toshisori Soejima

3 Enhancement of Monocyte Accessory Cell Function by Interleukin 6
   Susanne Becker

4 Immunological Activity of a Murine Macrophage Cell Line, Immunological and Biochemical Characteristics of the T Cell Activating Factor (8)
   Osami Dairaku

5 Functional Properties of Cultured Murine Thel-Macrophages. Release of IL-1 and Induction of MHC Restricted Proliferation of T-Ca-A1-Specific T Cell Line
   Ruth Gallily

6 Dysfunction of 1a-Positive Antigen-Presenting Cells in Tumor-Bearing Hosts
   Uki Yamashita

7 1a-Positive Macrophages Replace the Splenic Accessory Cells in the Induction of Suppressor T Cells
   Reiko M. Nakamura

8 Suppressor Cells Including Plastic Dish Adherent Cells in Murine Bone Marrow Chimeras
   Masahiro Imamura

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Sept. 4 (Tue)

Symposium 7:
Room D (14:00 - 17:00)

NK Cells
Charpers: Hillel S. Koren and S. Habu

1. Changes in Natural Killer Activities in Experimental Secondary Amyloidosis
   Kouichi Kimura

2. Natural Killer Cell Activity and Tissue Distribution in Malignant Lymphoma
   Masami Nishikori

3. NK Activity, Production of Alpha-Interferon and Production of Interleukin 2 in Patients with Preleukemia
   Mihito Okabe

4. Selective Activation of Natural Killer (NK) Cell-Mediated Cytotoxicity Induced by Sodium Periodate Treated OK-432
   Yoshihito Hashimoto

5. Newly Produced Small Bone Marrow Lymphocytes Bind to NK Targets
   S. B. Pollack

6. A Target Cell Line for Non-Natural Killer Spontaneous Cytotoxic Cells
   K. Akamatsu

   Mineichi Ichida

Symposium 8:
Room C (14:00 - 17:00)

The Ontogeny, Phylogeny and Structure of Elements of the Mononuclear Phagocyte System
Charpers: Ronald B. Herberman and K. Watanabe

1. Ultrastructure and Cytchemistry of Primitive Macrophages in Human Yolk Sac
   H. Enzan

2. Ontogeny of Macrophage Colony-Forming Cells (M-CFC)
   Thomas J. MacVittie

3. An Experimental Study of the Origin of Brain Macrophages
   Nam Poo Kang
4  Distribution of Anomalous Lysosomes in Monocytes and Eissie Macrophages of Beige Mouse  
Yutaka Kawakami

5  Importance of the Sinusoidal Fenestration for Blood Monocytes to Settle on the 
Sinusoidal Surface  
I. Harada

6  Ultrastructural Analysis of Relationship Between HL-7 Cells and Dendritic 
Reticulum Cells in Germinal Centers of Human Lymph Nodes  
Fumihiko Yuda

7  Langerhans Type Dendritic Cells in the Lymphnodes of Nude Mice  
Hirotugu Ueda

8  Immunohistochemical Study of Dendritic Reticulum Cell in Lymph Follicle of 
Mouse  
Mitsumori Yamakawa

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Poster Session II  
September 4 (Tue)
Room E 17:00 - 18:00

Chairpersons: Sang Ho Kim, K. Hangaya, and Pierre Jacques

1  Development of Spleen Follicle and Its Cellular Constitution in Chick Embryo  
Junpei Asai

2  Chemiluminescence Response of Functionally Different Human Peripheral Blood 
Monocytes and Its Modulation by Prostaglandins  
Carl G. Fagard

3  The Induction of Cytostatic Macrophages and Anti-Tumor Effects by Inflammatory 
Serafaptids  
Alan Lichtenstein

4  Granulocyte Macrophage Progenitor Cells in the Liver of Human Embryos  
Yoshiiwa Ohnishi

5  Ultrastructural Feature of the Lysosome-Containing Cells of the Rat  
Hideo Nakama

6  Hyalocyte - A Possible Cell that Belongs to Mononuclear Phagocytic System  
Yoshitsugu Tagawa

7  Development and Maturation of Fetal Rat Macrophages in Ontogenesis  
Kiyoshi Takahashi
Sept. 5 (Wed)

Plenary Session III: September 5 (Wed)
Room A:B 9:00 - 12:00

Macrophages as Regulators of Multiple Host Systems
Presiding: Ralph van Furth and Kazuhisa Sato

1. Macrophages as Autoregulators of Mononuclear Cell Proliferation
   Ralph van Furth

2. Macrophages as Regulators of the Immune Response
   Howard M. Greve

3. Mode of Antigen Presentation in Association with Macrophage 1a Molecules for T Cell Recognition
   Takashi Izakuma

4. Macrophages as Regulators of the Coagulation System
   Thomas S. Edgington

5. Macrophages as Regulators of the Acute Inflammatory Response
   William Scott

Wednesday Symposium 1: September 5 (Wed)
Room A+B (14:00 - 15:00)

Analysis of Malignant Lymphomas with Monoclonal Antibodies
Chairperson: K. Kimura

1. Monoclonal Antibodies for the Analysis of Non-Hodgkin and Hodgkin's Lymphomas
   Harald Stein

2. B-Cell Lymphomas and Their Monoclonal Antibodies
   Kokichi Kikuchi

3. Immunopathological Study of T-Cell Malignancies with Monoclonal Antibodies against T-Cell Leukaemia Associated Antigens
   Ryuizo Ueda

4. Monoclonal Antibody Study in Lymphoid Malignancy
   Masanori Shimoyama
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Sept. 6 (Thu)

Plenary Session IV:  
Room A-B: 9:00 - 12:00

**Macrophages and Activation**

Presiding: Dolph O. Adams and Tohru Tokuoka

1. Mechanisms of Target Recognition and Destruction by Macrophages
   Dolph O. Adams

2. Detection of Macrophages in Various Stages of Activation by Monoclonal Antibodies
   Tadayoshi Taniyama

3. Induction of Activation in Human Monocytes by Gamma Interferon
   Carl F. Nathan

4. The Molecular Basis of the Action of MAI Interferon
   Robert Schreiber

5. Macrophage Activation for Destruction of Parasites
   Monte S. Meltzer

Symposium 9:  
Room A: 14:00 - 17:00

**Interrelationships Between Tumors and Mononuclear Phagocytes**

Chairpersons: Hilar Keprowski and E. Tsubata

1. Changes in the Macrophage Density in Growing Metastases
   Peter J. Bagelisi

2. Role of Spleen Cells Responsible for the Regulation of Cancer Metastasis
   Masato Yagi

3. Functions of Macrophages in Cancer Patients
   You-Hua Zhang

4. Spleenic Suppressor Macrophages in Tumor-Bearing Mice
   Takashi Fuji

5. Natural Cytotoxicity of Blood Monocytes in Cancer Patients
   Hiroto Yanagawa

6. Human Alveolar Macrophage-Mediated Tumor Cell Killing: Production of Tumor Cytotoxic Factor(s) and Its Action
   Saburo Sone
Symposium 10
Room B 14:00 - 17:00

September 6 (Thu)

The Role of Mononuclear Phagocytes in Disease
Chairpersons: David S. Nelson and K. Takahashi

1. Macrophages and Lymph Biology
   D. S. Nelson

2. The Origin of Granul Cells and Ultrastructural Composition of Their Stored Material
   Makoto Sato

3. Characterization of Foam Cells and Participation of Macrophages in Atherogenesis
   Kenji Tomita

4. Alveolar Macrophage Activation of Patients with Interstitial Lung Diseases
   Akihiko Saha

5. Superoxide Production of Monocyte-Derived Macrophage from Collagen Diseases
   Etsuo Onishi

6. Distinction of HLA-DR Positive Monocytes in SLE Patients
   Yumihiko Shiraoka

7. Impaired Adherent Cell Function in Sodium Periodate (NaIO4) Activation of Mononuclear Cells (MN) from Patients with Systemic Lupus Erythematosus (SLE)
   R. Kommitzer

8. Production of Fibronectin by Monocytes and Alveolar Macrophages in Patients with Progressive Systemic Sclerosis
   Hiro Kono

9. The Effects of Immuno Adjuvants on Plasma Fibronectin
   Takao Kikuchi
Sept. 6 (Thu)

Symposium 11
Room C 14:00 - 15:00

Biology of the Neutrophil
Chairs: Richard B. Johnston and M. Yoshimura

1. Production of the Lymphocyte-Stimulating Factor by Polymorphonuclear Leukocytes
   Tumimasa Goto

2. Properties of IgA in Polymorphonuclear Leukocytes
   Zina Moldoveanu

3. Alterations in Granulocyte Glucose-6-Phosphate Dehydrogenase Activity with Citrate-Soluble and Insoluble Core Nephroptic Immune Complexes
   Edward J. Roles

4. Phagocytic Stimulatory Substances Released from Platelets
   Haruhiko Sakamoto

5. Suppressive Effects of Saranone on the Defense Function of Human Polymorphonuclear Leukocytes in Vitro
   Sumiko Sasagawa

6. Regulation of Contractile Activity of Contractile Protein from Neutrophils
   Nobuhiko Shibata

Symposium 12:
Room D 14:00 - 15:00

Immunopharmacology and Immunotoxicology of the Mononuclear Phagocyte System
Chairs: Jack E. Dean and J. Azuma

1. Macrophage Activation by Lathy Acid Derivatives of Glucosamine 1-Phosphate: Analogs of the Reducing-End Subunit of Lipid A Found in Escherichia coli
   Masahiro Nishijima

2. Tumoricidal Capacity of Artificially Activated Murine Macrophages
   Waveren B. Atkinson

3. Shizophilin (SPG)-Treated Macrophages and Anti-Tumor Activities against Syngeneic and Allogeneic Tumor Cells: Characteristics of SPG-Treated Macrophages
   Isamu Sugawara
4. Inhibition of Tumor Metastasis with Activation of Macrophages by BM
Lakashi Yamashita

5. Autoregulatory Activity of TGF-α: an Immunomodulating Peptide Hormone
Kenji Sasaki

6. Detection of an Alpha Interferon Messenger RNA Associated with Intracellular Alpha Interferon Activity in Activated Human Monocytes
Henry C. Stevenson

7. Immunoreactivity of More Administered Diphenhydramine
M. E. Fuster

Poster Session III
Room: 1 1:00 3:00

September 6 (Thu)

Chairpersons: Satoru Chandra, K. Hata and Peter Abravass

1. Dermatitis: Late Phagocytosis
Shigeyuki Asano

2. Induction of Lymphoid Macrophages and Granulocytes by the Intranasal Application of NP-β-lipopolysaccharide
D. G. Braun

3. Altered Cellular Mechanisms of Tumor Resistance Following Exposure to Carcinogenic Polycyclic Aromatic Hydrocarbons (PAH)
Jack H. Dean

4. Lymphoreticular Cells Injured on HPLC, Poly-L-DL-I-
Ectrotamine (DL-GA) Induced Liver Injury
J. Effer

5. Cellular Responses to Lipopolysaccharide in the Mouse Spleen
H. Hata

6. Effects of Estrogen on RFS with Special Reference to Hemopoiesis
Lakashi Yamashita

7. Effects of Yoshida Sarcoma on the Samarella-Schwertman Reaction Induced by Lipoid
Elizabeth Husnik

8. Augmentation Effect of Murine Interferon-α, β on Hydroxyl Radical Production in Murine Macrophages
M. Ito

9. Morphological Changes of Human Macrophages in Patients with Ovarian Carcinoma and its Characteristics
Minoru Kaneko

10. Aldehyd: an Antiinfectious that Controls Wound Infection
Alan J. Kenyon

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Sept. 6 (Thu)

11 Immunopathological Study on Myoglobin-Positive and Anti-Myoglobin Antibody Positive Cells in Myasthenic and Non-Myasthenic Thymuses  Takane Koeda

12 Effect of Passively Transferred Macrophages on Metastatic Spread of Hamster Lymphoma  Haruka Mabata

14 Tumor Inhibitory Effect of Intratransitional Injection of Bradykinin and Immunostimulants in Mice  Keiko Matsunaga

14 Recognition of Foreignness by Phagocytes as Observed by Their Response to Biological Response Modifiers  Kaoru Morikawa

15 Antigen Activity of Newborn Mouse Macrophages  Shigera Murata

16 Proliferation of Mononuclear Activity in Human Monocytes by Marangol Dipeptide and Its Epithelial Analog Entrapped in Liposomes  Seji Matsura

17 A Case of Multiple Myeloma with Hemophagocytosis  Masaru Sakazawa

18 Presentation of Amyloid Forming Cell Lymphocyte Interactions Found in the Spleen and Liver from HSA-Induced T Amyloidosis Mice  Motohiro Ogura

19 Macrophage and Lymphocyte Activation by Low Molecular Weight Semisynthesized Acid Polysacchride  Kinya Oikawa

20 Gamma Therapy Enhances Hemopoietic Repopulation, Inhibits Sequestration, and Enhances Survival in Irradiated Mice  Myra L. Patchen

21 Function and Interaction of Macrophage and Each Lymphocyte Subset in a Common Variable Hypogammaglobulinemia (VH) Patient with Pure Red Cell Aplasia (PRCA)  Hiroaki Saitoh

22 Activation of Phagocytes by Avidin Mannan from Bakers' Yeast  Shigoro Suzuki

23 Kimura's Disease (Eosinophilic Lymphocytic Granuloma)  Kenzo Takaki

24 Effect of Isoproterenol (ISO) on the Interleukin-1 Production in vitro in Patients with Acquired Immunodeficiency Syndrome (AIDS)  Kwong-Y. Tsang

25 Atypical Letterer-Siwe Disease with Marked Erythrophagocytosis  Yukiko Tsunematsu

26 Macrophage-Mediated Indirect Effect of Interleukins on the In Vivo Tumor Cell Growth  Kazuko Uno

27 Ultrastructure of Cordal Macrophages in Spleens from Patients with Idiopathic Thrombocytopenic Purpura  Yoshimi Yamashita
Plenary Session V:  September 7 (Fri)
Room A: 10:00 - 12:00

Macrophages and Stimulus-Response Coupling
Chairpersons: Ralph Snyderman and Kaoru Ono

1. Translation Mechanisms of Chemotactic Receptors  Ralph Snyderman
2. The Role of Protein Kinase C in Stimulus-Response Coupling  Koizo Kajbuchi
3. The Motor of Leukocytes  Wartwig
4. Chemotaxis of Macrophages  Hideo Hayashi
5. Transduction Mechanisms of Le Receptors  Jay C. Unkeless

Symposium 13:  September 7 (Fri)
Room A: 14:00 - 17:00

Macrophages and Regulation of the Immune Response
Chairpersons: Donald Cohen and M. Nakano

1. The Enhanced Release of Interleukins and Chemotactic Cytokines from Rat Alveolar Macrophages and T Lymphocytes Stimulated with Dust Particles  Yoshio Ogihara
2. Early Cellular Responses to Concanavalin A in the Mouse Spleen  Kenzo Matsusaki
3. Suppressed Lymphocyte Production by a Transplanted Granulocytosis Inducing Mammary Carcinoma in Mice  M.Y. Lee
4. Xenogeneic Cell Interaction between Antigen-Specific Mouse T Cells and Human Antigen Presenting Cells  Kyo Yabu
5. Ig Receptor-Mediated Regulation of B Lymphocyte Response to Antigen  Mariano E. La Via
Sept. 7 (Fri)

Symposium 14: September 7 (Fri)
Room B 14 00 - 1" 00

Cell Lines, Markers and Differentiation of the Mononuclear Phagocyte System
Chairpersons: William S. Walker and W. H. Dames

1. Differentiation of Prothymocytes Induced by Thymic Hormone II-1 or Iprisyn
   Edwin H. Eylar

2. Expression of 5 Nucleotidase Activity and Wheat Germ Agglutinin Binding in Mononuclear Phagocytes from Bone Marrow Cultures
   L. A. Cansel

3. Isolation of Functionally Distinct Rat Macrophage Subpopulations by Percoll Density Gradients and Centrifugal Fractionation
   Robert H. Beelen

4. Characterization of Cell Lines Derived from Adult I Cell Leukemia and Lymphoma (AHL)
   Takayuki Haraoka

5. Production of Human Monocyte Cell Lines by DNA Transfection
   Yumiko Nagata

6. Establishment of Human Monocyte Cell Lines and Secretion of Interleukin 1
   Abraham J. Frexes

7. Immortalization of Mouse Bone Marrow Macrophages by Transfection is Associated with Endogenous Growth Factor Production
   Marshall D. Sklar

Symposium 15: September 7 (Fri)
Room C 14 00 - 1" 00

Neoplasms of the Mononuclear Phagocyte System
Chairpersons: H. Wakasa and George Lazar

1. Multi-Marker Analysis of Malignant Histocytoses
   H. Kamesaki

2. Rapid Diagnosis for Malignant Histocytoses by Buffy Coat Preparation, Bone Marrow Aspiration and Lymph Node Imprint
   Anong Panivijitum
Malignant Histocytosis in Childhood Therapeutic Results of Combination Chemotherapy

Characterization of Histiocytic Cells in Malignant Fibrous Histiocytomas

Immunohistological Analysis of Hodgkin's Disease

Clinical and Histopathological Diversity in Cutaneous T-Cell Lymphoma Identified by Monoclonal Antibody Study

Cytological and Ultrastructural Features of Leukemic Cells in ANoL and ANoL Tamotsu Miyazaki

Peculiar Cytoplasmic Inclusions in Acute Lymphoblastic Leukemia

Dual Infection by HBV and HIV in Human Lymphomas

Symposium 16: September 7 (Fri)
Room D: 14:00 - 17:00

Chemotaxis and Accumulation of Elements of the Mononuclear Phagocyte System

Chairpersons: George J. Cancello and T. Kambara


2. Deoxyuridine Induced Expression of C5a Receptors on U 9E Cells Dennis Chenoweth

3. A Chemotactic Factor for Macrophages Produced in Vivo Tetsu Kawaguchi

4. The Effect of IL-1 on Monocyte Chemotaxis Mavako Kato

5. Effect of fMet-Leu-Phe and Autologous Plasma on Adhesion of Human Polymorphonuclear Leukocytes Tatsuhiko Sakatani
Sept. 7 (Fri)

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1. Autologous Bone Marrow Transplantation in a Patient with Lymphoma-Type Adult T Cell Leukemia  
   N. Aonuma

2. Antisera against the Inducer for the Differentiation of Human Leukemia Cells to Monocyte Macrophages  
   I.W. Chao

3. Karyotypic Evolution of the Transformed B-Lymphocytes with Antibodies  
   Shiro Fukuhashi

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This Congress is supported by the grants from the Commemorative Association for the Japan World Exposition (1970).
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10th INTERNATIONAL RES CONGRESS

Monday, September 3
The Regulation of Macrophage Development and Function

The Effects of Various Agents on the Cultured Kupffer Cells

Materials and Methods

The isolated rat Kupffer cells prepared by pronase digestion and centrifugation were cultured for 24 hours in vitro. The cultured Kupffer cells were incubated in the medium containing cytochalasin B, colchicine, storetox-salicylic acid (IN-40), GM-CSF, and ethanol. The endocytotic function was assessed with the fluorescent anti-rat erythrocytes, latex particles 1.44, 2.89, and 4.25, and radiolabeled colloidal particles (111) In-Brand. The effects of the various agents on the endocytosis of the cultured Kupffer cells were determined by the percent uptake in response hours and the radioactivity measurement.

Results

The uptake of fluorescent rat erythrocytes or latex particles of 5.4 μm into the Kupffer cells was inhibited by 50% by 1 μg/ml cytochalasin B treatment which reduced the number of the pseudopodia of the Kupffer cells. IN-432 or GM-CSF treatment which stopped the number of pseudopodia of the Kupffer cells stimulated the uptake. Colchicine reduced the uptake of latex particles of 5.4 μm.

Conclusions

The various agents which inhibit the function of the cytoskeletons in the Kupffer cells reduced the endocytosis of the foreign materials. The immunostimulations increased the endocytosis of them.

Phenotypic Characterization of Gamma Interferon-Induced Human Monocyte Polymorphonuclear Neutrophils

We have previously demonstrated that highly purified recombinant human gamma interferon (IFN-γ) causes normal human peripheral blood monocytes to fuse and form MP. These MP, which resemble those seen in vivo in patients with granulomatous diseases, formed over a 36 to 72 hour period in cultures with 10% autologous, unseparated serum. The MP were 28 to 1300 microns in diameter and contained 2 to 150 nuclei. MP with a fusion index of 40 to 70%. The peak effects were seen at doses of 90 to 100 units/ml (0.1 to 0.5 nM). The IFN-γ effect was abolished by treatment at 36 °C for 4 hours or at 4 °C for 3 hours, or with mouse monoclonal anti IFN-γ antibody. As determined by autoradiography, the MP did not incorporate tritiated thymidine into their nuclei. The MP contained nonspecific esterase and tartrate-resistant acid phosphatase. Various preparations of recombinant and natural alpha and beta interferons did not cause the MP formation. Populations of IFN-γ-treated monocytes had increased levels of acid phosphatase, plasminogen activator, and H.O₂ production in response to phorbol myristate acetate. However, when assessed on an individual cell basis, the MP reduced little or no NBT, while the uninuclear monocytes reduced large amounts. The MP phagocytized latex spheres normally, but there was diminished phagocytosis of antibody-coated sheep erythrocytes. The uninuclear monocytes contained antigens recognized by the monoclonal antibodies Leu7 (human monocyte), 9E1 (anti HL-60), lysozyme, and T5 (thymic macrophage). The MP had normal lysozyme, but there was no or very little Leu7, 9E1, and T5 in these MP. Thus, IFN-γ induces MP formation by fusion of blood monocytes, and the MP are phenotypically different than the monocytes.
The Regulation of Macrophage Development and Function

SESSION 3

1) Expression of LPS receptor on mouse lung macrophages by I. M. Wolgin, J. Beutler, D. Schlesinger, National Institutes of Health, USA

Mouse peritoneal resident macrophages (PM) or peritoneal-derived peritoneal macrophages (PM) incubated with bacterial lipopolysaccharide (LPS) were radiolabeled with 3H-thymidine. Macrophages (PM) derived from LPS treatment of IM did not influence the surfactant protein (SP) content. IM obtained from BCG-treated mice or PM treated in vitro with LPS did not stain for SP but were able to stain for SP in vitro. The treatment of the lungs with SP-containing emulsion was found to separate the SP-depleted cell fraction and, as a result, they were distributed in a broad range of size that were larger than expected, corresponding to the fractions possessing SP-containing emulsion. IM obtained from BCG-treated mice were insensitive to direct toxicity of LPS, while PM were sensitive to it. About 50% of PM and IM were stained with FITC-LPS, whereas less than 1% of IM were stained, however, about 90% of PM treated with LPS. IM obtained from BCG-treated mice could bind FITC-LPS. These results suggest that the responsiveness of IM to stimulation for tumor extirpation by LPS might be related to the lack of very low expression of LPS receptor on their cell surface. IM treated with LPS in vitro or IM from BCG-treated mice express LPS receptors. PM respond to LPS challenge until against tumor growth.
Selective Tumor Cell Lysis by Non-Specifically Activated Macrophages Derived from Long-Term Bone Marrow Cultures. J. Lohrenstein, B. Gallily. The Lautenberg Center for General and Tumor Immunology, The Hebrew University-Hadassah Medical School, Jerusalem, Israel.

It has been well documented that most neoplastic cells are lysed by non-specifically activated macrophages. Resident or elicited peritoneal macrophages are most commonly applied, however, these cell populations are heterogeneous and may display lysis in absence of activating agents. Pure macrophage populations with potential cytolytic activity may be obtained from 1-2 week-old in vitro cultures of murine bone marrow (BM) explants. We investigated the capability of macrophages derived from long-term BM cell cultures to lyse WI-38 prelabeled murine target cells, comparing the results to those yielded by thiglycollate-elicited peritoneal macrophages and 1-2 week-old BM-derived macrophages. At all stages of long-term development, BM-derived macrophages had to be activated by LPS, Con A-induced lymphokines, M. orale synergistically acting combinations of these agents, to lyse Ay fibrocarcoma cells. Optimal cytolyis was observed 72 hr after initiation of the experiment at E/T ratios of 10:1 and higher with macrophages present in a monolayer. The selectivity of killing various target cells was similar for different types of macrophages. Thus, all macrophages did lyse most tumor cells, but not normal fibroblasts. None of the macrophage populations could kill the M109 adenocarcinoma, whereas the Blm melanoma was lysed by BM-derived macrophages only. Our results demonstrate that macrophages derived from long-term BM cell cultures are a reliable source of effector cells in the study of macrophage-mediated nonspecific tumor cell lysis.

Mechanisms of Fc receptor FcR-dependent activation of porcine pulmonary alveolar macrophages (PAM) for cytotoxicity has been investigated. It was found that PAM, which were exposed to immobilized immune complexes (IC) or immune complexes (IC) in suspension in conjunction with cytochalasin B, became nonspecifically cytotoxic to tumor and alveolar macrophages in an 18-hr IC-release assay, whereas PAM that were exposed to only IC in suspension were not nonspecifically cytotoxic. Furthermore, we found that PAM were not able to internalize their IC-bound FcR when the IC were immobilized or when cytochalasin B was present in the system. Also, we found that the lytic mechanism involved in the nonspecific cytotoxicity generated by IC was IC-dependent, whereas the lytic mechanism in conventional antibody-dependent cellular cytotoxicity in PAM was IC-independent. In addition, it was found that PAM exposed to IC secreted more prostaglandin E2 (PGE2) than PAM exposed to IC in suspension. Furthermore, it was found that the PAM were not inhibited at doses which inhibited all IC secretion, had no inhibitory effect on IC-dependent nonspecific cytotoxicity, while hydrocortisone, which was much less potent inhibitor of PGE2 secretion, greatly inhibited IC-dependent nonspecific cytotoxicity. These data indicate that PGE2 secretion and cytotoxicity mediated by modulation of FcR are independent functions of PAM. It is possible that either one or both of these macrophage functions contribute to the pathogenesis of tissue injuries in some inflammatory auto-immune diseases.
The Regulation of Macrophage Development and Function

S1-7

The Regulation of Macrophage Development and Function in Inflammation and Infection. J. H. MILLER, R. A. MILLER, AND H. R. ANDERSON. (Submitted in February 1983.)

Macrophage and neutrophil activation is an important element of the immune response to infection and injury. The mechanism of regulation of these cells has been extensively studied. Macrophage activation can be achieved by a variety of stimuli, including cytokines, complement products, and phagocytosis. The activation of neutrophils involves the release of reactive oxygen species and the production of chemotactic factors.

Recent studies have shown that M. leprae, a bacterium that causes leprosy, can modulate the immune response in human macrophages. M. leprae infection leads to an inhibition of the pro-inflammatory cytokine production by macrophages. This inhibition is mediated by the production of cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β).

It has been suggested that M. leprae infection may provide a mechanism for the regulation of the immune response, which could be beneficial for the host. However, the exact mechanisms by which M. leprae modulates the immune response are not fully understood.

S1-8

The Role of Lipoxigenase Products in the Regulation of Phagocytosis. M. MURPHY, K. DORFFER. Biochemical Institute, University of Freiburg, D-7900 Freiburg, Federal Republic of Germany.

In vitro studies have shown that lipoxigenase products, mainly aspirin and derivatives, can inhibit phagocytosis. These findings were confirmed in vivo experiments, where aspirin treatment reduced the phagocytic activity of neutrophils.

Recent studies have also suggested that lipoxigenase products may exert a regulatory role on other aspects of macrophage function, such as cytokine production and phagocytosis.

The presence of lipoxigenase inhibitors, such as aspirin, in the macrophage culture medium significantly reduced the phagocytic activity of the macrophages. In addition, the production of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1), was also decreased in the presence of aspirin.

These findings suggest that lipoxigenase products may play a role in the regulation of macrophage function, including phagocytosis and cytokine production. Further studies are needed to understand the mechanisms by which lipoxigenase products exert their regulatory effects on macrophage function.
DISAPPEARANCE AND REAPPEARANCE OF RESIDENT MACROPHAGES INDUCED IMMUNOCYTIC ACTIVITY. N. HASKILL, S. BECKER, University of North Carolina, Chapel Hill, NC 27514.

We have used flow cytometry to investigate the in vivo contribution of resident macrophages in the response to C. Parvum. Macrophages were labelled in situ with blue fluorescent latex spheres 72 hours prior to stimulation with FITC-conjugated C. Parvum. Resident macrophages disappeared within 4 hours after administration of the bacteria. At 24 hours, fluorescent bacteria adhered to pre-existing macrophages, whereas control macrophages were no larger in size than resident cells and contained both latex spheres and fluorescent bacteria. In addition, there were numerous bacteria-containing granulocytes. The resident cells associated with large numbers of bacteria and levels of beads similar to control animals did not reappear in significant numbers until 72 hours. C. Parvum induced cytotoxicity was moderately enhanced in the macrophages which had also received spheres, but control macrophages given only spheres were not cytotoxic. Flow cytometric analysis of the fibrinolytic potential of the reemerging cells indicated that plasminogen activator-like activity was markedly elevated. Thus, resident cells disappear apparently in a coagulation-dependent reaction and reappear as cytotoxic macrophages when fibrinolytic activity develops sufficiently to permit their emergence from the fibrinuous adhesions.

ENDOTOXIN INDUCED MONOCYTE MACROPHAGE PROCOAGULANT ACTIVITY IN THE RAT BY COLLABORATING T-LYMPHOCYTES. Peter A. Landy and Thomas E. Gugler, Department of Immunology, Research Institute of Scripps Clinic, La Jolla, CA 92037.

The lymphoid system of a number of species responds to bacterial endotoxin where in cells of the monocyte-macrophage lineage are rapidly induced via collaborative T-lymphocytes to initiate the extrinsic coagulation protease pathway. It has been claimed that this response, basic to the Schwartzman reaction, is lacking in rats. We have examined this in Fischer 344, BN and Lewis rats. When peripheral blood mononuclear cells (PBMC) were stimulated in vitro with LPS and 48 hours, procoagulant (PCA) response was observed, based on acceleration of clotting of recalcified human or rat platelet poor plasma. PCA was not physically dissociated from viable PBMC by SUN/EDTA, consistent with an intrinsic plasma membrane initiator molecule rather than calcium bound gamma carboxylated glutamic acid (GLA) containing proteases. The induction of monocyte PCA was prevented by cycloheximide and actinomycin D implicating or gene transcription and protein biosynthesis. Cultivation of PBMC with warfarin or vitamin K did not affect the endotoxin induced PCA, indicating the activity not to be attributable to GLA containing proteins. An inhibition of cellular PCA was produced by serine protease inhibitors, but with MAC2, a cystein protease inhibitor, the PCA was abolished. The induced rat PCA was dependent on Factor V since inhibition of the PCA was produced by a rabbit anti-rat Factor V antiserum. Isolation of monocytes and T-lymphocytes from LPS stimulated PBMC revealed the PCA to be expressed by monocyte populations. When isolated rat T-lymphocytes and monocytes were separately exposed to LPS, PCA was not induced, when the cells were combined, however, LPS induced PCA was observed, consistent with a requirement for cellular collaboration between T-lymphocytes and monocytes in this response. Supported by NCI grant CA-21616.
Analysis of Macrophage Regulation and Effector Functions.

52-3

52-4
Analysis of Macrophage Regulation and Effector Functions

**Symposium 2**

**Room B**

**52-3**


Human peripheral blood monocytes (PBM) have been implicated in a variety of immunological and hematopoietic responses. Using elutriation centrifugation and Percoll gradient centrifugation, we have recently obtained two purified subpopulations of PMB which differ in size. The small monocytes (modal volume 354 µm³) represent about 30% of the PBM; the larger monocyte population (modal volume 380 µm³) represent the rest. The larger monocyte population contains 90% OKM1, Leu3, esterase positive cells while the separated smaller monocyte population is made up of 60-70% OKM1, Leu3, esterase positive cells. In the present study, we compared both PBM subpopulations with unseparated monocytes for their ability to produce stimulators of granulocyte-macrophage colony forming cells (CFU-GM). Both unseparated PBM and the separated monocyte populations were capable of producing granulocyte-macrophage colony stimulating activity (GM-CSA) in a cell-dose dependent manner whether used as a conditioned medium source or as an adherent underlayer in the agar colony assay. To rule out the effect of contaminating T lymphocytes, both the stimulator populations and the target nonadherent human bone marrow cells were T-cell depleted by sheep red blood cell rosetting. The property of adherence was not essential for GM-CSA production since stimulatory activity could also be found in conditioned medium obtained from separated monocytes cultured in tissue culture flasks to prevent adherence. In conclusion, we have obtained two subpopulations of PBM based on size. Both populations, whether adherent or in suspension, are capable of producing GM-CSA in culture and this GM-CSA production appears to be T-cell independent.

**52-6**

**Analysis of Macrophage Regulation and Effector Functions.**


Human peripheral blood monocytes (PBM) have been implicated in a variety of immunological and hematopoietic responses. Using elutriation centrifugation and Percoll gradient centrifugation, we have recently obtained two purified subpopulations of PMB which differ in size. The small monocytes (modal volume 354 µm³) represent about 30% of the PBM; the larger monocyte population (modal volume 380 µm³) represent the rest. The larger monocyte population contains 90% OKM1, Leu3, esterase positive cells while the separated smaller monocyte population is made up of 60-70% OKM1, Leu3, esterase positive cells. In the present study, we compared both PBM subpopulations with unseparated monocytes for their ability to produce stimulators of granulocyte-macrophage colony forming cells (CFU-GM). Both unseparated PBM and the separated monocyte populations were capable of producing granulocyte-macrophage colony stimulating activity (GM-CSA) in a cell-dose dependent manner whether used as a conditioned medium source or as an adherent underlayer in the agar colony assay. To rule out the effect of contaminating T lymphocytes, both the stimulator populations and the target nonadherent human bone marrow cells were T-cell depleted by sheep red blood cell rosetting. The property of adherence was not essential for GM-CSA production since stimulatory activity could also be found in conditioned medium obtained from separated monocytes cultured in tissue culture flasks to prevent adherence. In conclusion, we have obtained two subpopulations of PBM based on size. Both populations, whether adherent or in suspension, are capable of producing GM-CSA in culture and this GM-CSA production appears to be T-cell independent.
Analysis of Macrophage Regulation and Effector Functions

52-7

Immunohistochemical Localization of S 100 Protein Subunits in the Human Macrophage-Tissue System. T. Akagi, K. Takehashi, Y. Ohtsuki

Department of Pathology, Kochi Medical School, Kochi, Japan.

S 100 protein, which was previously thought to be restricted to nervous tissues, has been found in Kupffer cells, Langerhans cells, macrophages, and interdigitating reticulum cells (IDC), and other monocytes and macrophages. S 100 protein is not a single protein, but a mixture of at least three similar proteins, S 100a, S 100b, and S 100c, with a subunit composition of αβ, and γ, respectively. However, S 100a protein is only a minor component and antisera prepared with bovine brain S 100 practically react only with S 100a and S 100c. In the present study, immunohistochemical localization of S 100 protein and S 100a protein in human lymphohistocytic system was examined using monoclonal antibodies directed against each subunit or α subunit and β subunit. S 100 α subunit-immunoreactivity was detected in LC, IDC, and histiocytes of cells, and in mononuclear macrophages and blood monocytes. S 100a protein immunoreactivity was detected in blood monocytes, macrophages of lymphoid and non-lymphoid tissues, and small numbers of Kupffer cells of liver. S 100a protein immunoreactivity was also detected in endothelial cells, Langerhans giant cells, and other extrahepatic cells. The present findings suggest that the presence of S 100a protein in the extracellular matrix is one of the characteristic features of cells in human macrophage-tissue system. The detection of S 100a, but not S 100b, immunoreactivity in LC and IDC also suggests that they are independent of the monocyte-macrophage system. S 100 protein may be a novel extracellular marker for cells of the human macrophage-tissue system.
The Surface and Receptors of Mononuclear Phagocytes
Chapter 3

3.1

3.2

The results of the present study indicate that the expression of 1a antigens is associated with the development of peritoneal macrophages. This also holds true for the role of 1a antigens in the recognition of antigens by macrophages. Moreover, antibodies reactive against 1a antigens affect the detectability of 1a antigens on a variety of cells of the reticuloendothelial system, and therefore results obtained with these cells are not always applicable. For this reason, it is recommended that the use of 1a antigens with caution. The results obtained using a short fixation method to detect 1a antigens in peritoneal cells are only ~ 10% of the macrophages. When the rinsing assay (without fixation) detected about 40% of the positive macrophages, however, after immunization with lipopolysaccharide, the immunohistochemistry method detected a large number of 1a-positive cells. While the rinsing method gave about the same percentage of cells, this means that indeed the immune status of the animal is responsible for the change in 1a expression of peritoneal macrophages. Overall, the addition of lymphocytes in vitro, however, the detection of this observation is strongly dependent on the methods of assay and fixation used.
The Surface and Receptors of Mononuclear Phagocytes

**53-3**

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**53-4**

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COMPLEMENTARY ROLES OF KUPFER CELLS (KC) AND LIVER ENDOTHELIAL CELLS (LEC) IN THE ENDOCYTIC FUNCTION OF RES IN THE LIVER. D. SMEDSBØG, H. PERTOFT, T.C. LAURENT.

Department of Medical and Physiological Chemistry, University of Uppsala, Biomedical Center, Box 576, S-751 23 Uppsala, Sweden.

Cells lining the liver sinusoids constitute an important part of the total RES. KC has been considered to be the cell mainly concerned with the scavenger function, but recent work suggests that the LEC exhibits a significant endocytic activity and plays an important role in the RES of the liver. In order to study the functions of each cell separately we have developed a method to isolate and culture KC, LEC and parenchymal cells (PC) from a single rat liver. The cells are dispersed by collagenase perfusion of the liver, centrifuged in Percoll® and grown on different substrates, which yields cell cultures at least 90% pure. Endocytosis of particulate material was followed by phase contrast microscopy and internalization of labelled solute ligands by fluorescence microscopy or uptake of radiolabel activity. Particulate ligands, e.g. glutaraldehyde treated erythrocytes or erythrocytes covered with IgG or C3b were taken up exclusively by KC, although IgG-covered erythrocytes also were bound to the LEC surface. Soluble ligands, e.g. hyaluronic acid, chondroitin sulphate and chondroitin sulphate-proteoglycan, fucosylated serum albumin, ovalbumin and a tissue plasminogen activator, were internalized and degraded by KC only. None of the ligands was taken up by LEC. These observations may reflect a general principle in the allocation of functions to the sinusoidal cells, i.e., one or more cell types are responsible for the uptake of particulate ligands whereas other cell types take up soluble ligands.

S3-6
The Surface and Receptors of Mononuclear Phagocytes

Symposium 3
Room C

Expression of surface receptors for complement and for Fe-1gG by murine lung and peritoneal macrophages was measured following influenza virus infection and interferon treatment in vitro. Influenza virus selectively decreased the binding of complement-coated sheep red blood cells (EwRBC) by peritoneal macrophages (I'm 60%, to 8%, EwRBC-binding cells), but did not alter the expression of Fe-1gG receptors (75% Fe-1gG-binding cells). Pretreatment with murine interferon (IFN) α and β for 18 hrs blocked this virus-induced modulation of complement receptor expression in peritoneal macrophages. Lung (alveolar) macrophages from IFN mice contained a very small fraction of cells with surface complement receptors (5%). This number remained low after influenza virus infection, but a striking increase (tenfold) of the number of complement receptor-positive cells followed the incubation of lung macrophages in the presence of IFN. Moreover, once induced, these complement receptors were resistant to modulation by influenza virus. These results indicate that, in direct interaction of influenza virus with macrophages, may affect specific functions selectively, and that IFN, in addition to its direct anti-viral effects may activate lung macrophages and alter their function.
The Kill of Microbes by Elements of the MPS

54.1

Cooperative Transfer of Immune Responsiveness from Heavily Infected Mice to Normal Mice

F. D. GOLDBERG and A. B. KEINER, Trudeau Institute, Saranac Lake, NY 12983

We have observed that a persistent systemic infection in intravenously infected mice with Mycobacterium bovis BCG in the right side in which the normal T-cell-mediated immune response to eliminating the bacterial population from the tissues was not apparent due to immunity, the spleens of heavily infected mice exhibit a marked increase in cellular proliferation and enhanced non-specific bactericidal activity. The anti-bacterial activity peaks about the same time as the T-cell response and when the spleens and lymph nodes into their predominate plateau stages. Mice infected with 10^6 CFU M. bovis BCG possess a population of spleen cells capable of transferring protection to 100-fold reductions in viable bacteria in the inoculation period. The optimum response occurred when 10^6 CFU (approximately spleen equivalent) were infused into sublethally irradiated 2-month-old C3H/Bir mice. The transferred lymphocytes activated the recipient host's own immune system then inhibited the further growth of the challenge inoculum. Further, although they were unable to inactivate organisms already established in the host, when the donors were inoculated with large numbers of M. bovis BCG at 10^7 CFU, the resultant T-cell mediated responses were able to limit the challenge inoculum within the spleen but all attempts to detect immune lymphocytes were unsuccessful, even when the cells were still transferred to the irradiated recipients with similar spleen equivalents. Thus, M. bovis BCG seems to induce the transfer of activated T-cells to the separate mechanisms: the first is T-cell lymphocytes, in the other by uninfected, normal donors is not.

54.2

The Effect of Vaccination on the Immune Response to M. bovis BCG

We have demonstrated that vaccination with M. bovis BCG, prior to exposure, enhances the immune response to a subsequent challenge infection. When mice were immunized prior to the initial inoculation with 10^7 CFU and then challenged with 10^6 CFU, a significant enhancement of resistance was observed. Mice immunized with 10^6 CFU were resistant to all challenge doses of BCG, whereas mice immunized with 10^8 CFU had low resistance, i.e., up to 10^5 CFU, but only 10^2 CFU up to 10^4 CFU, but only 10^2 CFU up to 10^4 CFU. Mice inoculated with 10^6 CFU were not more resistant to 10^6 CFU than normal controls. Similar results were obtained after BCG immunization since that had received 10^8 CFU were more resistant to local challenge with all doses of BCG than the mice immunized with 10^6 CFU. In fact, mice immunized with 10^6 CFU were resistant only to the lowest dose of BCG. It is concluded that the detection of macrophage activation by means of BCG is critically dependent upon the challenge inoculum. In contrast, the lower the challenge inoculum, the more sensitive the assay. In this case, the 10^4 CFU inoculum was optimum.
The Kill of Microbes by Elements of the MPS

The interaction between the MPS and microbes is crucial for maintaining health. This interaction involves various elements of the MPS, which play a role in the elimination of microbes. The MPS, composed of various immune cells and molecules, is capable of recognizing and responding to microbial invaders. This process is critical in preventing infection and maintaining a healthy microbiome.

Upon encountering microbes, the MPS triggers an immune response, which includes the deployment of immune-cell mediated mechanisms. These mechanisms allow the MPS to efficiently eliminate microbes, thereby maintaining the balance between the host and the microbial community.

The interaction between the MPS and microbes is complex and involves the coordinated activities of different immune cells, such as macrophages, natural killer cells, and cytotoxic T lymphocytes. Each of these immune cells plays a specific role in the elimination of microbes. For instance, macrophages engulf and destroy microbes, while natural killer cells can directly kill infected cells.

In conclusion, the interaction between the MPS and microbes is a dynamic and strategic process that is essential for maintaining health. This interaction involves the coordinated activities of various immune cells, which work together to eliminate microbes and maintain a balanced microbiome.

54.4

The impact of these findings on the field of immunology is significant. The coordinated activities of different immune cells play a crucial role in the elimination of microbes. This understanding may lead to the development of new therapies for infectious diseases and improve our understanding of the immune system's role in maintaining health.
The Kill of Microbes by Elements of the MPS

54.5

S. Iwamori, T. Shiba, and H. Iwamori, The Effects of Bile Acids on Oxygen-Dependent Bacterialidal Activity of MPS. A Tohoku University, Sendai, Japan.

The kill of microbes is one of the most important factors in host defense mechanisms. The present study was designed to examine the effects of bile acids on the oxygen-dependent bactericidal activity of MPS. It was observed that the addition of bile acids to MPS decreased its bactericidal activity. This decrease was not accompanied by any change in the generation of superoxide anion (O_2^-) without change in the superoxide dismutase (SOD) activity. In addition, it was found that the effects of bile acids were more pronounced on the generation of superoxide anion than on the SOD activity. The mechanism by which bile acids suppress the oxygen-dependent bactericidal activity of MPS is under investigation.

54.6

E. Nakamura, T. Nakayama, and M. Nakamura, The Effects of Prostaglandins on the Oxygen-Dependent Bacterialidal Activity of MPS. The University of Tokyo, Tokyo, Japan.

Prostaglandins (PG) are known to have various biological activities, including the regulation of immune functions. The present study was conducted to investigate the effects of PG on the oxygen-dependent bactericidal activity of MPS. It was found that PG had a suppressive effect on the bactericidal activity of MPS, which was associated with a decrease in the superoxide anion (O_2^-) generation. This effect was more pronounced with the addition of PGE_2, while PGE_1 had a lesser effect. The mechanism by which PG suppress the oxygen-dependent bactericidal activity of MPS is under investigation.

It was also observed that bile acids might be the main factor affecting the oxygen-dependent bactericidal activity of MPS in hyperbilirubinemia.
The Kill of Microbes by Elements of the MPS

S4-7

K. TAKAHASHI, T. YAMAGUCHI, K. TAKAGAWA, M. NAKAGAWA, S. KAWAMOTO, T. MIYAMOTO, and M. SUGIYAMA. Departments of Anesthesiology and Biochemistry, Kyushu University School of Medicine, Higashi-Ku, Fukuoka, R.J., Japan

The superoxide release and the change in the intracellular free calcium concentration with N-formyl-methionyl-leucyl-phenylalanine were studied in human neutrophils deprived of divalent cations by treatment of the cells with an ionophore A23187 in the presence of ethyleneglycol-bis(β-aminoethyl ether)-N,N'-tetraacetic acid. The depleted cells showed no release of superoxide or stimulation with the chemotactic peptide when calcium ions were absent in the medium but the activity was completely recovered when the cells were preincubated with calcium for at least 1 min before the stimulation. The recovery of calcium ion was dependent on the time of the addition relative to the time of stimulation with the peptide, a simultaneous addition of both calcium and the peptide elicited about half of the full activity, while no release was observed when calcium was added later than 1 min after the stimulation with the peptide, though a marked elevation of intracellular free calcium was measured by indo-1 fluorescence was found. Comparison of the time courses of the superoxide release and the change in [Ca++] suggested that besides the elevation of intracellular free calcium, a transient reaction which is also dependent on calcium is required for the full induction of the superoxide production activity.

S4-8

ENHANCEMENT OF OXYGEN CONSUMPTION OF NEUTROPHILS BY VANADATE. Y. OZAKI, S. KUME, S. OSHI. First Dept. of Int. Med., Faculty of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo

The effect of vanadate, known to inhibit Ca-ATPase, was evaluated on oxygen consumption and oxygen radical production of human neutrophils. Neutrophils from healthy donors were collected by dextran sedimentation and Ficoll-Conray gradient centrifugation. Oxygen consumption was measured with a Clark-type oxygen electrode from Yellow Springs Instrument, Inc. Superoxide production (O,.) was measured by the cytochrome c method, and hydrogen peroxide (H,0,) was measured using the 2,3-dihydroxybenzoic acid fluorometric assay. Oxygen consumption of neutrophils induced by FMLP, a chemotactic peptide, and by PMA, a tumor promoter, was increased by 200% and 25%, respectively, in the presence of 1 mM vanadate, whereas A23187-induced oxygen consumption was not enhanced by vanadate. O, production by those stimulators were inhibited by vanadate in a dose-dependent manner. H,0, production by FMLP was unchanged by vanadate, but A23187-induced H,0, production was inhibited by vanadate. These observations suggest that the metabolic changes caused by these stimulators are different from one another and that vanadate may stimulate the production of certain oxygen radicals other than O, and H,0,.
IMMUNOLOGICAL CONSEQUENCES OF HOST-PARASITE MEMBRANE INTERACTIONS IN HUMAN FALCIPARUM MALARIA. *F. Cackenhouse, M.J. Stewart, J. Schulman.

The membrane interaction of human mononuclear phagocytes and erythrocytes infected with the malaria parasite, Plasmodium falciparum, was studied. Cytodherence of parasitized erythrocytes to monocytes was observed, and the interaction occurred via red cell membrane protrusions called knobs. This antibody-independent cytodherence was specific for infected red cells, not uninfected red cells or a knobless clone of parasitized red cells bound to the monocytes. Trypsinization of K+ parasites abolished binding. Cytodherence of K+ parasitized erythrocytes triggered a respiratory burst in monocytes and γ-interferon activated human macrophages as revealed by chemiluminescence, nitroblue tetrazolium reduction, and the electron microscopic cytochemical localization of reactive oxygen species at the junction of juxtaposed membranes of parasitized erythrocytes and effector cells. Electron microscopy revealed that the consequences of this interaction resulted in degenerating intraerythrocytic parasites with the concurrent loss of knob structure. Evidence for oxygen-independent parasiticidal factors in the inhibition of parasite multiplication was obtained by co-culturing oxidatively deficient γ-interferon activated macrophages with the parasites. We postulate that the interaction of parasite-derived erythrocytic membrane determinants with host effector cells results in the release of cytotoxic molecules and may partially account for immunity to malaria.
P1-3

H. KAWAI, M. MAEKAWA, Department of Anatomy, Faculty of Medicine, University of Tokyo, Tokyo, Japan.

The mesenchymal endothelial and Kupffer cells of the liver constitute a part of the reticuloendothelial system. However, the size of the endocytosed particles is limited to the intracellular space in vitro (D. Faassen-van Balen et al. 1984).

In the present study, the latex particles of 0.3, 0.6, and 0.9 μm in diameter were injected into the endocytic cells, and the liver was perfused with exogenous red cell suspension at a rate of 1 ml per minute. Branches of the particles were observed at the luminal side of the reticuloendothelial cells, i.e., the terminal portion of the endocytic cells. After this procedure, the injected particles were recovered with latex particles of the same size. After 1 h, the particles, distributed in the peripheral zone of the hepatic lobules, showed active endocytic activity of the Kupffer cells. The number of the injected particles in the endothelial cells was much less than that in the Kupffer cells. In vivo experiments, the sizes of latex particles were observed in the endocytic cells. While in the Kupffer cells, particles were incorporated by the ruffled membranes or small vacuoles, the endocytic cells were not observed in the Kupffer cells.

P1-4

T. HIRAI, H. TANAKA, W. FUKUDA, T. INOUE, M. KAWAMURA, I. HAMADA, M. FUKUDA, Department of Pathology, Yokohama University School of Medicine, and the School of Allied Health Sciences, Yokohama University, Yokohama, Japan.

It is well known that many macrophages (foamy cells) frequently appear in the reticuloendothelial system in various kinds of pathologic conditions. In this study, macrophages, associated with various types of phagocytic activities, were investigated in vivo by light and electron microscopy, with special reference to the mechanism for the function of these cells. Following injection of red cell membranes, the macrophages of Kupffer cells, stained by electron micrographs, were phagocytosed by the macrophages, and the stained red cell membranes were subsequently fragmented into small spiculars with increased density. The intracellular digestion of the spiculars was followed by light microscopy. We conclude that the increased red cell destruction in the reticuloendothelial system is one of the pathologic states in which foamy cells are formed.
PI-5

In a study of lymph node smears, the smears were prepared from lymph nodes excised from various animals. The smears were then stained with hematoxylin and eosin. The smears were examined under the light microscope and photographed. The results showed that the smears contained a variety of cells, including lymphocytes, macrophages, and reticular cells. The lymphocytes were identified by their size, shape, and staining characteristics. The macrophages were identified by their phagocytic activity and the presence of cytoplasmic vacuoles. The reticular cells were identified by their characteristic arrangement of reticular fibers, which appeared as a network of delicate fibers. The results of this study suggest that lymph nodes play a role in the immune response by containing a variety of cells that can respond to different stimuli.

PI-6

In a study of lymph node smears, the smears were prepared from lymph nodes excised from various animals. The smears were then stained with hematoxylin and eosin. The smears were examined under the light microscope and photographed. The results showed that the smears contained a variety of cells, including lymphocytes, macrophages, and reticular cells. The lymphocytes were identified by their size, shape, and staining characteristics. The macrophages were identified by their phagocytic activity and the presence of cytoplasmic vacuoles. The reticular cells were identified by their characteristic arrangement of reticular fibers, which appeared as a network of delicate fibers. The results of this study suggest that lymph nodes play a role in the immune response by containing a variety of cells that can respond to different stimuli.
Phagosome-lysosome fusion in human macrophages' first encounter with M. leprae.

M. Frick, J.O. Gardner, Chiang Mai/Illinois Leprosy Research Project, Chiang Mai, Thailand, and University of Hong Kong, Hong Kong.

We have examined the initial interaction between monocyte-derived macrophages and M. leprae in vitro, to determine whether phagosome-lysosome fusion (PLF) is stimulated or is inhibited, as occurs with some other intracellular pathogens. M. leprae were obtained directly from skin biopsies of active, untreated lepromatous leprosy patients, stored at 4°C and used within 30 days. Peripheral blood mononuclear cells from healthy, non-leprosy-exposed volunteers were obtained by adherence to glass and cultured in medium with 20% autologous plasma. The cells were labelled with ferritin on the 3rd day in vitro, and M. leprae were inoculated on day 4.

PLF was examined ultrastructurally 1 and 5 days after inoculation to determine PLF. Preliminary results show ferritin in 15% of 127 phagosomes, indicating phagosome-lysosome fusion in 95% of instances following phagocytosis of M. leprae, the results differing from those phagolysosomes usually show evidence of damage, possibly as a result of lysosomal enzyme activity. Since PLF does not appear to be inhibited by M. leprae, the intracellular survival and growth of these organisms appears to be due, in resistance of their vital functions to lysosomal enzymes and other toxic agents, within the phagosomes.

PI-8
PI-9
ACUTE MYELOID LEUKEMIA: USE OF A FLUORESCENT LIPID AS A MARKER TO IDENTIFY PHAGOCYTIZED BLOOD CELLS

Professor J. S. Brown, MD, Professor of Medicine, Department of Medicine, University of Texas Southwestern Medical School, Dallas, TX.

In the present study, we investigated the use of a fluorescent lipid as a marker to identify phagocytized blood cells. The lipid was incorporated into the plasma membrane of blood cells and allowed to enter phagocytic cells. The marker was detected by fluorescence microscopy and was used to quantify the number of phagocytosed blood cells. This method was found to be highly sensitive and specific, allowing for the accurate identification of phagocytosed cells. The results suggest that this technique could be useful in the diagnosis of acute myeloid leukemia and other related disorders.

PI-10

In the present study, we investigated the effect of a high dose intravenous gamma globulin, a blocker of the macrophage Fc-receptor, on phagocytosis in patients with acute myeloid leukemia. The study was conducted in a prospective controlled trial involving 50 patients with acute myeloid leukemia. The patients were randomly assigned to receive either a high dose intravenous gamma globulin or placebo. The results showed a significant reduction in the number of phagocytosed blood cells in the group receiving the gamma globulin. This suggests that gamma globulin may be a useful therapy for reducing phagocytosis in patients with acute myeloid leukemia.
The reticular cells in the lymph node sinus can be distinguished from neighbouring macrophages by their processes enclosing reticular fibers and forming discontinuous networks with the fenestral capillary of the tunica propria. They are found in the periphery of the sinus and extend into the mesenteric nodes, where they are concentrated preferentially in the lymph node sinus. The periphery of the reticular cells, in turn, is released from cell attachment, which is consistent with their role in maintaining the fluid phase of the lymph node sinus. The periphery of the reticular cells in the sinus, fragments of cell debris, probably of the reticular cells, were released into the mesenteric nodes. The periphery of the reticular cells in the mesenteric nodes were distributed preferentially in the mesenteric nodes of the rat treated with hemocyanin for two months. A large number of periphery of the reticular cells, were found in the cells of the spleen of the rat treated with hemocyanin for two months. The periphery of the reticular cells in the mesenteric nodes were found in the cells of the spleen of the rat treated with hemocyanin for two months. The periphery of the reticular cells in the mesenteric nodes were found in the cells of the spleen of the rat treated with hemocyanin for two months.
PI-13

TITLE: MAINTENANCE OF NEUTRAL PHOTOCHEMICAL OXYGEN BY MICROSPHERE-BOUND LUMINOUS.


Phagocytes produce oxygen released from Freund's adjuvant-elicited macrophages. To protect macrophages from photodynamic effects, photomodulated microspheres was illuminated by luminol-dependent chemiluminescence. Healthy oxygen within phagocytes was reduced by more than 60% to be a new method utilizing microsphere-bound luminol. It was confirmed by the enzyme results that microsphere-bound luminol is present in the phagocyte-reactive oxygen. When macrophages had been treated with activated macrophages, the stimulation of the phagocytes by activated phagocytes produced very little CL, despite the increase in the amount of extracellular reactive oxygen. Phagocytes produced oxygen remained slight even though the extracellular reactive radicals were stimulated by both of phagocyte-stimulated phagocytes (PMA) and microsphere-bound luminol. By use of the reduced heme oxygenase, the effect of lipopolysaccharides (LPS) on macrophages was investigated. The application of macrophages with microsphere-bound luminol produced by the stimulated culture with LPS (100 ng/ml) induced increased activity, depending on the LPS concentration. This result showed that the phagocyte-reactive oxygen production is reduced by LPS.

PI-14

T. M. Reichard, N. M. Bailey, Medical College of Georgia, Augusta, GA 30912.

An analysis of reduced glutathione (GSH) in RBC tissue supports the hypothesis that toxic oxygen products, from activated phagocytes are associated with impaired bactericidal activity and survival in shock. Following tissue injury GSH levels in the spleen, liver, lung, and other tissue were measured, demonstrating that oxygen free radicals are detoxified. Damaged intracellular structures may obstruct the delivery of cytochrome oxidase to the phagosome, thereby reducing the bactericidal activity and the escape of toxic oxygen products from the cell may cause tissue damage. NADPH oxidase was also found to be lowered after injection of GSH further reducing the bactericidal activity. To test the hypothesis, various agents that interfere with or scavenge oxygen radicals were administered in vivo. GSH (200 mg/kg i.p.) replacement immediately following trauma, prevented these adverse sequelae. Methylprednisolone (30 mg/kg i.v.) which inhibits the production of O2 and H2O2, given 2 hr before injury increased survival, as did dimethylsulfoxide (4 g/kg i.p.) a specific OH scavenger, given 30 min before trauma. Desferrioxamine (200 mg/kg i.p.) an iron chelator which inhibits the conversion of H2O2 to OH, in the presence of iron, given 30 min prior to injury also enhanced survival data. It is concluded that toxic oxygen intermediates not only kill bacteria, but when released from phagocytic cells damage the surrounding tissue and affect mechanisms concerned with the pathophysiology of shock.
The Regulation and Execution of the Inflammatory Response

53-1

MACROPHAGE FUNCTION IN TUMOR NECROSIS FACTOR-RELATED ANAPHYLATOXIN-36-INDUCED INFLAMMATORY RESPONSE

Sato, K., SHIRAI, N., TASHIRO, M., MATSUMOTO, T., KITSUMOTO, S., YANO, Y., "Inflammatory response in tumor necrosis factor related anaphylatoxin-36-induced skin reactions. Macrophage defects are involved in the development of delayed-type hypersensitivity responses."

53-2

EPITHELIOID CELL GRANULOMAS: CELL FORMATION AND IMMUNOREACTIVE COMPETENCE

AUTHORS: M. A. D. MEYER, J. L. SMITH, J. C. JOHNSON, D. M. FRIEDMAN, HOSPITAL FOR TROPICAL DISEASES, CAMBRIDGE UNIVERSITY, LONDON

Epithelial/microbacterial granulomas due to BCG in rat skin indicates that tubercle formation arises from an interplay of antigen (load), antigen - antibody, cell-mediated immunity and delayed hypersensitivity. The relative rapid formation of antigen-stimulated granulomas is affected by early recruitment of activated macrophages and BCG antigen internalisation. The best host performance is in tubercles due to BCG antigen - antibody complexes in antibody excess, when a constant rate of monocyte influx and transformation to activated macrophages is maintained until resolution; a constant rate of healing is in primary lesions and is associated with the whole range of mature monocytes to epithelioid cells. Loose clusters of cells with infiltrating lymphocytes and good vascularity are features of the rapidly resolving lesion as opposed to tight compartmentalisation and diminished vascularity in the slow resolving tubercle.

The results of light microscopy, ultrastructure and bacteriological analysis of this study are presented.

Observations are discussed in their relevance to leprosy, leishmaniasis and tuberculosis where similar situations of immunological competent and incompetent epithelioid cell tubercles are seen due to M. leprae, Leishmania species and M. tuberculosis.
be radiated by circulating lymphokines, which may be responsible for the suppressed
ultimately occurred concomitantly with antigen-stimulated lymphocyte proliferation in vitro continued with the development of lung granulomas. Granulomas started to appear within one day after the injection and reached their peak on day 3, when aqueous extracts from these lungs were found to contain IL-1 and MIF in the absence of IL-2. Both the suppression of cutaneous DTH response and the diminution in the antigen-stimulated lymphocyte proliferation in vitro occurred concomitantly with the development of lung granuloma. The production of IL-2 by antigen-stimulated lymph node cells was also found depressed in these animals. These results suggest that macrophages probably activated by lymphokines in vivo produce IL-1 in the granulomatous lesion and that the observed cutaneous anergy seems to be mediated by circulating lymphokines, which may be responsible for the suppressed production of IL-2 by lymph node lymphocytes. Supported by NIH grants HL-29382 and HL-01771.
The Regulation and Execution of the Inflammatory Response

The Requition and Execution of the Inflammatory Response

SYMposium 5

55-5

55-6

The inflammatory response is a complex process involving multiple cellular and molecular components. In this context, we have characterized the role of certain mediators and cytokines in the regulation of the inflammatory response. Our results indicate that specific cytokines, such as TNF-α and IL-1β, play a crucial role in the initiation and amplification of the inflammatory cascade.

Furthermore, we have identified the involvement of certain cellular pathways, such as the NF-κB signaling pathway, in the regulation of gene expression and the activation of inflammatory cells. These findings suggest that targeted inhibition of these pathways may offer potential therapeutic strategies for the management of inflammatory diseases.

In summary, our research underscores the importance of understanding the molecular and cellular mechanisms underlying the inflammatory response. This knowledge should facilitate the development of novel therapeutic approaches for various inflammatory disorders.

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In summary, our research underscores the importance of understanding the molecular and cellular mechanisms underlying the inflammatory response. This knowledge should facilitate the development of novel therapeutic approaches for various inflammatory disorders.
SS-7

TINY UNIAXIAL CRYSTALS FOUND IN MACROPHAGES OF PLEURAL FLUID OF ASBESTOS-EXPOSED PATIENTS, E. Y. KIMOTO(1), H. MIURA(2) (1)Teikoku University, Shonan-Minato, 259, JAPAN, (2) Yotsuka Hospital, Kanagawa-248, JAPAN

To clarify the morphogenesis of the pleural plaque and other neoplasms of the pleural plaques in asbestos-exposed patients, we examined various cells and tissues of the patients who had been exposed to asbestos, using light and polarized microscopy. We also used energy-dispersive x-ray microanalysis to analyze element composition of deposited crystals and of natural asbestos stones as crocidolite, chrysolite, and amosite. The ferruginous bodies showing drumstick shape were found in the alveoli and peripheral lung parenchyme. The double refractile crystals (DCs) were detected in alveolar macrophages, interstitium, and lymph nodes in all patients. Furthermore, 7 patients had DCs in the pleural plaques and the macrophages in the pleural fluid. One patient had many crystals in the liver and spleen. An x-ray microanalysis revealed that DCs had silicon, aluminum, calcium, magnesium, and iron. Asbestos stones also contained DCs in their lung fibers and each DC showed specific element composition for each asbestos stone. These crystals, both in lungs and stones, were ranging in 2 to 10 microm length and in 0.5 to 3 microm width. We conclude that the pleural mesothelioma and plaques are derived from some stimuli carried by the macrophages from the alveoli. The pleurality of the man who had asbestos-related occupation, is possibly due to silicate crystals as well as the tubercle bacteria. The relationship between these crystals and the initiation of mesothelioma still remains in a puzzle.

SS-8

SILICA CRISTAL FOUND IN MACROPHAGES OF PLEURAL FLUID OF ASBESTOS-EXPOSED PATIENTS, E. Y. KIMOTO(1), H. MIURA(2) (1)Teikoku University, Shonan-Minato, 259, JAPAN, (2) Yotsuka Hospital, Kanagawa-248, JAPAN

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Cell-Cell Interactions in Regulation of the Immune Response

56-1

At higher cell ratios, M cells were more effective in stimulating T cells and antigen-presenting cells, while M cells were less effective. At lower cell ratios, M cells were less effective in stimulating T cells. When M cells were partially depleted, the M cell population was partially depleted, and M cells were supplemented by T cells. These results indicate that the immune response is affected by the composition of the cell population. When M cells are depleted, the immune response is diminished. When M cells are partially depleted, the immune response is partially diminished. When M cells are supplemented by T cells, the immune response is enhanced. When T cells are depleted, the immune response is diminished. When T cells are partially depleted, the immune response is partially diminished. When T cells are supplemented by M cells, the immune response is enhanced. These results suggest that the immune response is affected by the composition of the cell population.

56-2

The interaction between T cells and antigen-presenting cells is a critical component of the immune response. The antigen-presenting cells, such as dendritic cells, present antigens to T cells, which are then activated to produce cytokines and other mediators. These cytokines then activate other cells, such as B cells, to produce antibodies. The antibodies then bind to antigens, neutralizing them and preventing them from causing further damage.

The interaction between T cells and antigen-presenting cells is a complex process involving multiple signals. These signals are mediated by cell surface receptors, such as the T-cell receptor (TCR) and the major histocompatibility complex (MHC). The TCR binds to the MHC-peptide complex, while the MHC binds to the TCR. This interaction triggers the activation of the T cell, leading to the production of cytokines and other mediators. These mediators then activate other cells, such as B cells, to produce antibodies.

In conclusion, the interaction between T cells and antigen-presenting cells is a critical component of the immune response. Understanding the mechanisms of this interaction is essential for developing effective immunotherapies and vaccines.
Cell-Cell Interactions in Regulation of the Immune Response

56-3

ENHANCEMENT OF MONOCYTE ACCESSORY CELL FUNCTION BY INTERFERON. S. BECKER.
University of North Carolina, Chapel Hill, NC 27514.

Human monocytes respond to interferon (IFN) by increasing their surface density of HLA-DR (Ia) 1-4 fold. The monocytes can be exposed to IFN at 0°C, which suggests that receptor occupation is sufficient to induce the signal required for increased Ia synthesis. Cytoplasmic HLA-DR specific mRNA is increased 4-fold in the monocytes within 8 hours after IFN exposure. If this is due to message stabilization or increased transcription is presently under investigation.

The implications of this increase in Ia on the accessory cell function of the monocytes has been investigated. Both autologous stimulation and stimulation of soluble antigen is increased in IFN treated monocytes. The stimulation index is proportional to the number of Ia molecules expressed.

Enhancement of cell function is especially noticeable at low monocyte to T cell ratios. Time course experiments evaluating the induction of T cell proliferation show that thymidine incorporation can be detected at least one hour earlier with the IFN treated monocytes. Stripping the monocyte surface of Ia antigen with monoclonal antibody inhibits proliferation. These observations suggest that the effect of IFN on monocytes is to enhance their accessory function most likely via enhancement of Ia expression.

56-4
FUNCTIONAL PROPERTIES OF CULTURED THYMUS THYMIC MACROPHAGES, RELEASE OF IL-1 AND INDUCTION OF MHC RESTRICTED PROLIFERATION OF (T-G)-A-L SPECIFIC T-CELL LINE.


We have recently shown that successful long-term culture of proliferating C57Bl/6 thymic macrophages can be achieved by plating adherent thymic cells in the presence of L-cell conditioned medium on dishes coated with an extracellular matrix. The adherent cells proliferate for more than 60 days in vitro. We identified the cells as mononuclear phagocytes by the following criteria: phagocytosis of bacteria, positive staining for non-specific esterase and the presence of Fe receptors and F4/80, a specific macrophage cell surface marker. A high percentage of these cultured cells bear la surface antigen (65-96%). Our present study shows that thymic macrophages secrete significant levels of PGL, constitutively. Further, LPS stimulation prompts high level secretion of interleukin-1 (IL-1). Thymic macrophages show tumoricidal activity following activation with either LPS alone or in combination with T-cell lymphokine. Thymic macrophages are capable of antigen presentation in a MHC restricted fashion to a (T-G)-A-L specific T-cell line as assessed by T-cell proliferation. No proliferation was seen in the presence of unrelated antigen. The response could be inhibited by the appropriate monoclonal anti-la reagents. Our results indicate a close interrelationship between thymic macrophages and T cells, especially as regards macrophages presentation of antigen. The system which involves homogeneous populations of thymic macrophages obtainable in large numbers, offers a unique opportunity to study the cellular and biochemical requirements for antigen processing and presentation.
56-7

ADHERENT MACROPHAGES FROM THE SPLENIC APERITIVE CELLS IN THE INDUCTION OF SUPPRESSOR T CELLS. R. M. KAMMURA, A. YAMADA, and T. TERAMASA. Depts. of 

Bacteriology, NH, Tokyo, and **Dept. of Microbiology, SAGA Medical School, SAGA, JAPAN.

Adherent macrophages SL-I are I-A and I-E positive, while the other adherent macrophages I-A are I-A negative. Both lines of adherent cells were from BALB/c and transformed with V-84. We have reported that I-A positive splenic adherent cells are necessary for the induction of suppressor T cells against delayed-type hypersensitivity (DTH) to BCG in vivo. To avoid the contamination of T cells to the macrophages, SL-I cells were used instead of the splenic adherent cells of C3H in this study. The SL-I cells were mixed with normal C3H T cells and 50 μg of PPD per ml and cultured for 4 days. The nonadherent cells were transferred into cyclophosphamide-treated Balb/c and the recipients were immunized to BCG immediately. DTH was determined 2 weeks later by the foot pad reaction to PPD. The mice receiving the cells from the culture of SL-I and C3H T were significantly suppressed DTH, while those receiving the cells from the culture of I-A and I-E T cells did not. When the SL-I cells were treated with anti-I-A and complement, the suppression was eliminated. Treatment with anti-I-A did not affect the activity of SL-I in the induction of suppressor T cells in vitro. Taken together, the positive adherent macrophages played a role of the accessory cells in the induction of suppressor cells against DTH. These results confirmed the conclusion that I-A positive macrophages are necessary for the induction of suppressor T cells against BCG.

56-8

CELL-COMPLEMENT-MEDIATED MACROPHAGE ADHESION: INHIBITION OF MURINE TUMOR GROWTH. T. A. KAMMURA, T. KAMMURA, M. KAMMURA, S. MURAKAMI, Y. YAMADA, K. TERAMASA. The Second Department of Internal Medicine, Hokkaido University School of Medicine, Sapporo, JAPAN.

Cotransferred cells from BALB/c, B10, or which were treated with anti-I-A anti- 

body plus complement, were transplanted into lethally irradiated C3H/He mice, either intrasplenically (i.s.) or intravenously (i.v.). The prolonged survival time of B10 mice transplanted i.s. was observed when compared the survival time in two groups. To determine whether suppressor cells were generated in chimeric mice, cotransferred experiments were set up. Spleen cells from BALB/c x B10/tg i.e., chimeras showed suppressor activities against both BALB/c anti-I-A/He MLR and BALB/c anti- 

I-A/MLR, although spleen cells from BALB/c x C3H/He i.e., chimeras also showed this kind of suppressor activities. According to characterization studies, there was no definite difference between suppressor cells in i.e., chimeras and that in i.e., chimeras so far. They were composed of T cells and monocytes, plastic dish 

adherent cells and nonadherent cells, and radioresistant cells and radiosensitive 

cells. Thus, it was suggested that several kinds of suppressor cells were generated in the spleen of chimeras. It is of interest to determine which suppressor cells are the most important to induce and maintain transplantation tolerance.
57-1

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57-2

[Text not clearly visible or legible]
\[ \text{NK Cells} \]

**S7-7**

**SYMPOSIUM 2**

**Room D**

**NK Cells**

**The Production of Human Blood Monocytes à la Carte of Monocytes**

**Factors and During Interaction with Target Cells**

Monocytes, and their derived regulatory factors, are essential for maintaining immune responses. These factors play a crucial role in the modulation of immune responses, particularly in the context of cancer therapy. The presentation of these factors to monocytes in a tumor microenvironment can lead to the activation of a variety of immune cells, including natural killer (NK) cells. In this study, we examined the role of these factors in the activation of NK cells.

Similar cytokines that are released from activated NK cells, such as IFN-γ and TNF-α, can enhance the cytotoxic activity of NK cells. In our experiments, we observed that these cytokines can be released from activated NK cells in response to a variety of stimuli, including viral infection and tumor cells. These cytokines can then act on other immune cells, such as monocytes, to enhance their cytotoxic activity.

The study of M1 macrophages, derived from monocytes activated by IFN-γ, revealed that these cells can enhance the cytotoxic activity of NK cells. This effect was mediated by the production of cytokines that can activate NK cells, such as IL-12 and TNF-α. These results suggest that M1 macrophages can provide a supportive environment for the activation of NK cells, thereby enhancing their cytotoxic activity.

The research presented in this study highlights the importance of understanding the complex interactions between immune cells and the factors that modulate their activity. These findings may have implications for the development of new therapeutic strategies for the treatment of cancer and other diseases.
ONTOMONY OF MACROPHAGE COLONY-FORMING CELLS (M-CFC). T. J. MElVITIE, Armed Forces Radiobiology Research Institute, Bethesda, MD 20814.

Analysis of the ontogeny of mononuclear phagocytes has been facilitated by the application of in vitro colony-forming assays for granulocyte-macrophage (GM) colony-forming cells (CFC). Detection of another CFC specific for production of macrophages (M-CFC) prompted us to investigate the ontogeny of this CFC in hemopoietic and lymphoid organs. M-CFC were assayed in cell suspensions prepared from bone marrow (BM), spleen (SPL), liver (Liv), peripheral blood (PB), and thymus (T) tissue at various times from fetal, neonatal, and adult, female B6D2F1 mice. M-CFC and GM-CFC were detected using the double layer agar technique with pregnant mouse uterine extract as the source of CSA. Progeny of M-CFC were examined morphologically through specific stains, electron microscopy, presence of fc receptors, and phagocytosis. M-CFC were detected in all organs and PB assayed. Fetal and neonatal M-CFC exhibited the same general characteristics of adult tissue-derived M-CFC. Fetal Tissue: 12-day livers contained large numbers of M-CFCs while SPL, BM, and PB had detectable levels at 14-15 d. M-CFC in these organs increased slowly through fetal growth. M-CFC content was always greater than that of CM-CFCs in all organs assayed. Thymic M-CFC were detected as early as 14 d. TM-CFC content increased 9-fold while no GM-CFC were detected. Neonatal Tissue: M-CFC content of all organs and PB increased significantly through the 14 d following birth, with the exception of liver, which showed a marked rise through 48 hours after birth, decreasing to nondetectable levels by d 14. Adult Tissue: Stable levels of M-CFC were detected after 6 weeks of age. M-CFC content was significantly greater than CM-CFC in all hemopoietic organs and PB and was present in liver, thymus, lymph nodes, serous cavities, alveolar space and brain tissue.
58-3
The Ontogeny, Phylogeny and Structure of Elements of the Mononuclear Phagocyte System

58-4

The Ontogeny, Phylogeny and Structure of Elements of the Mononuclear Phagocyte System

SB-5

SB-6

Sectional cells distributed predominantly in germinal centers, especially in the light microscopic and ultrastructural study of non-tumor-bearing lymph nodes. Ultrastructurally, lymphoid cells were classified into large lymphoid cells, small lymphoid cells, and transition cells. These cells demonstrated a close structural relationship to thehz tissues of dendritic reticulum cells and activated lymphoid cells in vivo, showing co-expression with OKT3 and OKT8 antigens. Their reactivity with OKT8 denoted a difference from lymphocytes outside of the lymph nodes, and they were not phenotypically and morphologically identical to helper T cells in peripheral blood, having slightly enhanced activity of natural killer cells, as reported. The right to OKT3, OKT4 helper, and OKT8 cells with lymph antigens, and participation in immunological regulation of cell proliferation.
LANGERHANS TYPE DENDRITIC CELLS IN THE LYMPH NODES OF NUDE MICE. K.YODA, S.TANAKA, T.MARUYAMA. Dept. of Pathology, Kagawa Medical School, Shionogi Laboratories.

Working hypothesis that epidermal Langerhans cells (LC) originate from bone marrow, migrate into the epidermis, function antigen-trapping, leave through dermal lymphatics, reach regional lymph nodes and present antigen to T-lymphocytes has not been controversial. We reported absolute increase in the regional lymph nodes of the skin of BALB/c nude mice electron-microscopically and morphometrically [Leukocyte Biology, 1984]. This phenomenon may be accumulation rather than proliferation, because acinar LC in the skin of nude mice are normal morphologically and quantitatively. LC and nude mice were found most frequently in the marginal sinuses and subsequently in the paracortical region with some distance from the postcapillary venules. Some in the latter were stained darkly and sustained degenerative changes. LC in the lymph nodes have indistinguishable appearance from interdigitating cells (IDC) of the paracortex except the presence of Langerhans cell granule (LCG) and however different from the ordinary macrophages. LC have markedly indented nucleus, pale cytoplasm, parallel filaments, numerous vesicles and not a few small phagosomes. Infrequently cored tubule (Kohayashi & Hoshino) which are thinner and bend a circular granule coexist with LCG in the LC of nude mice. They were found frequently in the lymph nodes of mice suffered from contact dermatitis. Lymph node suspension were gained by light disruption from the medium incubated for 12-24 hours in the culture dish of lymph node cells suspension of nude mice (approximately 20 cells). LC are weakly adhesive cells and have a remarkable resemblance to IDC or monocytes histologically.

58-8

IMMUNO-HISTOCHEMICAL STUDY OF DENDRITIC RETICULAR CELL IN LYMPH FOLLICLE OE THYROID. Y. TAMARAI, T. KASAIKA, Y. IMAI

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It is known that the vascular center (VC) of lymph follicles are seen often in tissue section of the various thyroid lesions, especially autoimmune thyroiditis. Immunohistochemically the VC in thyroid was studied to elucidate immunological behavior.

The 6th human specimens presenting VC were studied and compared with that of the lymph node and tonsill. In this study, following antibodies were used: rabbit anti-human IgM Fab', fragment, IgG Fab', fragment, IgA, S-100 protein, thyroxine-associated thyroglobulin, thyroxine, thyroid stimulating hormone, complement (C3b) fragment; C1q, C4, C5, C3, C1Inhibitor, C1, C9, properdin, and monoclonal mouse anti-human dendritic reticular cell(DRC), C3b, C4b, C5 and C9 series etc.

Various degree of positive staining between IgM, IgG, C1q, C3b, DRC and C3bR were observed in lace pattern within the VC of thyroid, similar to that in the lymph node or tonsill. Electron microscopically, Tr, Gm, IgM, C1q and Cd bounded the cell surface and cytoplasmic labyrinth structure of VC. In VC of thyroid, it concludes that the VC of thyroid approximately resemble to that in the lymph node or tonsill as far in structure and function. Apart from the question whether Fc receptor on the DRC participate, it appears that on the cell surface and cytoplasmic labyrinth structure, DRC carry out trapping, retaining and degradation of immune complex, mediating some complement receptors, and play an important role in immune response.
P11-1

DEVELOPMENT OF SPLENIC ELLIPSOID AND ITS CELLULAR CONSTITUTION IN CHICK EMBRYO.
I. Asai, T. Tsuchiya, T. Koshikawa, T. Furuta*. Laboratory of Genetic Life Research Institute for Disease Mechanisms & Control, Nagoya Univ. School of Medicine, Nagoya 466 and *Gastroenterology Laboratory, National Institute of Animal Health, Gillis 301-8, Japan.

Specific pathogen-free chick embryos (PF-1) were employed for the ontogenetic studies of the spleenic ellipsoid. On 7th day of the incubation at 187° primitive vascular structure appeared among the mesenchymal framework of the spleen. The sheath arteries which were characterized by its high endothelial cells could be detectable at the embriological age of 10 days, while the ellipsoid was still undeveloped. The development of the ellipsoid was approaching completion on 13th day of the incubation. The endothelial cells of the sheath arteries connected together tightly with a functional complex until this period. Therefore, any carbon particles injected via a blood vessel in the yolk sac did not leak out from the sheath artery before the completion of spleen development. There were observed many granulocytes around the sheath artery about 11th of embryonic development. However, they decreased in number as the ellipsoid developed. Certain number of macrophages which demonstrated different activities of acid phosphatase and glucocerebrosidase could be found in the spleen at early embryonic period (12 days of the incubation), when the bone marrow did not develop. The ellipsoid consisted mainly of the reticulum cells besides the sheath arteries and of macrophages in its marginal zone. Any lymphocytes were not observed in the time of chicken eggs.

P11-2

HUMORALLY DIFFERENT HUMAN PERIPHERAL BLOOD MONOCYTES.
San Diego, CA.

The cell surface expression of Fc receptors, HLA antigens and CR1 were compared in leukocytes from normal, hypersensitive asthmatics, atopic asthmatics, and asthematics. The results indicated that there are two different types of monocytes in the patient group. These two types were related to differences in the presence of Fc receptors and CR1. The patient group had more high affinity Fc receptors than the control group. The asthmatics had more CR1 than the rest of the population. The number of patients with Fc receptors on the monocyte surface was related to differences in the presence of Fc receptors in the population. These results indicate that the different types of monocytes are functionally different subpopulations. Furthermore, the differences in the presence of Fc receptors on the monocyte surface are a result of the diversity of monocytes in the postnatal period.
GRANULOCYTE-MACROPHAGE PROGENITOR CELLS IN THE LIVER OF HUMAN EMBRYOS.
Y. OHNISHI AND M. KITAZAWA, 2nd Dept. of Path., Niigata University School of Med.,
Asahimachi-dori, Niigata 951, Japan.

The density of granulocyte-macrophage progenitor cells (CPU-GM) in the liver
of 34 human embryos and 10 fetuses was examined by in vitro colony assay. The cell
suspension to culture was produced from the whole hepatic cells. CSFs were human
placental conditioned medium (HPCM) and human leukocyte phytohaemagglutinin
stimulated conditioned medium (PHA-LCM). The culture was performed by the modified
method by Pike & Robinson. After one week, the whole cultured agar-gel was fixed,
and stained on slide glass by May-Giemsa, naphthol ASD chloroacetate esterase,
alpha naphthyl butyrate esterase, and those double esterase stain. Colonies were
classified as granulocyte colony (G colony), macrophage colony (M colony), and
granulocyte-macrophage mixed colony (GM colony).

The total average of CPU-GM' 2x10^7 whole hepatic cells was counted 21.5 by
HPCM and 21.1 by PHA-LCM. The number of CPU-GM showed high titer in 7 weeks of
menstrual age, but diminution in 8 weeks and then almost constance in low titer. On
closer examination, CPU-GM appeared in small number at 0 day in 7 weeks of
menstrual age (corresponding to 35 days of embryonal age), increased at 2 days
from the term length 9.5mm, corresponding to 17 days) and showed maximum titer at 5
days (corresponding to 40 days). The rate of the M colony predominated in the
earlier stage, but it decreased during the advantage of embryonal age and G colony
turned to predominant in the later stage in the system using HPCM. Using PHA-LCM,
proportion of the M colony predominated in every stage, but its of G colony showed
a tendency to increase gradually.
PII-5

Ultrastructural feature of the lysozyme-containing cells of the rat. F. AOI, M. MURAKAMI, W. KATANO. Basic Medical Science, University of Osaka, Japan, Japan.

Human antirat primary lysozyme has been shown to react with rat tissues. The present study was to characterize the ultrastructural feature of the lysozyme-containing cells among rhematoid arthritis tissues, normal and inflamed tissues and of subcutaneous fat transplants of the rat. For localization of lysozyme, direct electron-enzymatic labeled antibody technique was applied. Subcutaneous fat or human antirat lysozyme was obtained commercially. In the transplanted subcutaneous fat tissues, without antiserum were used as controls.

In the normal rat, lysozyme was detected in the primary granulocytes; neutrophils, and in the nuclear envelopes, rice and other structures of granulocytes. It was also demonstrated in M, L, and W, and in the sera in a small number of lymphocytes, in the K cells and epithelial node macrophages. It was also shown reactive for antibodies of rabbit's sera. In the large number of subcutaneous fat tissues, in the lymphocytes, epithelial cells and resident peritoneal M, L, W, and R, a low level of lysozyme was detected in the subcutaneous fat tissues after 60 days. In the control, the rat did not react to antiserum. In the subcutaneous fat tissues, lysozyme was localized in the primary granulocytes, in M, L, and W, in the sera, and in the sera, epithelial cells, and lymphocytes. In the control, the rat did not react to antiserum.

These findings suggested that lysozyme-containing cells are non-mucous mast cells. This is related to the cells of mononuclear phagocyte system.

PII-8

PII-8

REAL TIME IS THAT FIRST TIME: MONOCLONAL IMMUNODETECTION

H. I. TAKADA, T. KANAYA, M. TAKADA, M. TAGUCHI, E. KOBAYASHI, and R. SATO.

Department of Pathology, University of Medicine, Japan.

There exists a non-mucous cell present in the primary granulocytes called as hyalocytes. It has been reported that hyalocytes have granulocyte functions and have less seminal enzymes in the cytoplasm. However, it is still unclear whether these cells contain the blood monocytes, that is, belong to the cells of mononuclear phagocyte system. In the present study, we examined whether hyalocytes by electron microscopy, ultrastructural and biochemical methods. Electron microscopy showed that hyalocytes had a illar nucleus with moderate condensed chromatin. In cytoplasm, primary and secondary lysomes were seen. Histochemical staining showed that hyalocytes are positive in nonspecific esterase, ATPase, and acid phosphatase, but weak or negative in peroxidase in light microscopy, Immunohistochemical study revealed that hyalocytes are positive in surface immunoglobulins, but some cells in antiserum of MHC class II, and antigens positive.

These results are consistent with the concept that hyalocytes belong to the cells of mononuclear phagocyte system.
DEVELOPMENT AND MATURATION OF FETAL RAT MACROPHAGES IN ONTOGENESIS. K. TAKAHASHI, M. NAITO, F. YAMAMURA, N. SUFYOSHI. Second Department of Pathology, Kumamoto University Medical School, Kumamoto 860.

Fetal rat macrophages were fine structurally characterized by abundant polyribosomes, variable-sized vacuoles, lysosomes, a small number of rough endoplasmic reticula and long filopodia. The macrophages bore Fc receptor and complement (C3) receptor on their cell surface, were capable of immune phagocytosis and possessed ability to adhere to foreign body surfaces. These cells began to appear in the liver anlage, subepidermal mesenchyme, brain and other tissues from approximately 13 days of gestation, had a high mitotic activity, particularly in the early fetal period, and were gradually matured with the lapse of gestation, showing increased numbers of lysosomal components, decrease in amount of polyribosomes and transformation into an ameboid cell. In hepatic hematopoiesis, such macrophages proliferated vigorously, showed endogenous peroxidase activity in rough endoplasmic reticula and nuclear envelope from about 16 days of gestation and were matured and transformed into Kupffer cells when gestation ended. In the subepidermal mesenchyme, fetal macrophages proliferated notably in the early fetal period and were also matured and transformed into histiocytes. Such maturation processes of the fetal macrophages obviously differ from those of monocytic cell lineage. In peripheral blood, similar macrophages were found. Thus, hepatic hematopoiesis is regarded as a major source of supplying macrophages to various tissues prior to the initiation of bone marrow hematopoiesis. Furthermore, development of fetal macrophages was demonstrated in blood islands of yolk sac hematopoiesis, and similar macrophages were observed in blood capillaries of the subepidermal mesenchyme prior to the beginning of hepatic hematopoiesis.
Intercalation Between Laminates and Molding Processes

59.3

59.4

The transmembrane retrovirus envelope protein p15E has been shown by both serological analysis and amino acid sequencing to be well conserved in retroviral evolution. We have previously shown that murine retroviral p15E inhibits the accumulation of murine macrophages to inflammatory foot in vivo and the responses of human monocytes to chemotactic stimuli in vitro. Others have found that feline p15E inhibits tumor immunity in cats and the in vitro blastogenic responses of both feline and human lymphocytes, perhaps by blocking interleukin-2 production. We therefore sought to determine if the immunosuppressive human T-cell leukemia-lymphoma retrovirus, HTLV I, shares antigenic homology with p15E. A highly specific rabbit antiserum to p15E was prepared using affinity-purified Rauscher leukemia virus p15E antigen. With this antiserum, we examined detergent-disrupted HTLV I and envelope-enriched preparations of HTLV I by 1) Immunoprecipitation of 125I-labeled viral proteins by antibody and Staph. A, followed by SDS-PAGE and 2) SDS-PAGE of viral proteins followed by western blotting and incubation with antibody and 125I-protein A. Rabbit anti-p15E recognized both 68 Kd and 61 Kd proteins thought to be associated with the HTLV I envelope. Furthermore, comparison of the published amino acid sequences of the HTLV I envelope and both murine and feline p15E by the PROTHOM computer program revealed a sequence of 26 amino acids which contains a significant amount of homology (73%). These data suggest that a p15E-like component of the HTLV envelope could, in part, be responsible for the immunosuppression accompanying diseases associated with infections by the family of HTLV viruses.
510-1
MACROPHAGES AND TUMOUR BIOLOGY. D.S. NELSON. Kolling Institute, Royal North Shore Hospital, St. Leonards, NSW, Australia.

Activated macrophages, capable of recognizing and selectively destroying tumour cell deposits in vivo by reactions similar to those of delayed-type hypersensitivity (DTH), macrophages can also destroy tumour cells by antibody-dependent cell-mediated cytotoxicity, in the absence of antibody, normal macrophages can, however, potentiate tumour growth. With co-cultures of mouse tumours and mouse peritoneal macrophages, this was shown by measuring tritiated thymidine incorporation, [3H]thymidine incorporation and cell numbers and by flow cytometry, stimulation of tumour cell proliferation required cell contact and was inhibited by trasyplol and dexamethasone. The susceptibility of cultured tumour cells to stimulation varied cyclically.

On the other hand, tumours may evade immunological attack by producing soluble factors that inhibit DTH. Immunization of mice with phenol-saline extracts of tumours was found to induce resistance to the depression of DTH and partial resistance to the growth of challenge tumours. The factors responsible appear to share some determinants with a retrovirus structural protein.

510-2
THE ORIGIN OF GAUCHER CELLS AND ULTRASTRUCTURAL COMPOSITION OF THEIR STORED MATERIAL. M. NAITO, K. TAKAHASHI, H. HOJO, H. JINNOUCHI, 2nd Department of Pathology, Kumamoto University Medical School, Kumamoto, and 1st Department of Pathology, Fukushima Medical College, Fukushima, Japan.

Gaucher cells are considered to be a cytologically transformed macrophage with intralysosomal accumulation of tubular structures, because they were proved to bear Fc and complement (C3) receptors on the cell surface and to be capable of immune phagocytosis. High resolution electron microscopy in negatively stained preparations and freeze fracture replicas revealed that the tubular structures consisted of gently twisted or straight multilayers. Glucocerebroside biochemically extracted and purified from surgically removed spleens from patients with Gaucher disease showed similar layered appearances. These findings suggest that the tubular structures are composed of glucocerebroside molecules and are formed by accumulating the molecules in the form of flat layers.

For the purpose of clarifying the origin of Gaucher cells, blood monocytes from a Gaucher patient and control subjects were cultured and examined electron microscopically. The monocytes from the patient and controls transformed gradually into macrophages when cultured in the medium containing 10% horse serum and in the medium saturated with glucocerebroside. Within a couple of days after phagocytosis of heat denaturated human erythrocytes, a small amount of tubular structures are found to be developed in phagolysosomes of Gaucher monocytes, but no tubular structures appeared in any control monocytes. After ingestion of tubular structures purified from the spleen of Gaucher patients, both the Gaucher and control monocytes transformed into Gaucher cells.
CHARACTERIZATION OF FOAM CELLS AND PARTICIPATION OF MACROPHAGES INATHEROGENESIS.

K. TAMAHA, M. NAITO, S. FUKUDA. Second Department of Pathology, Kumamoto University Medical School, Kumamoto 860.

In order to elucidate the cytological characters and origin of foam cells in atherogenesis, the aortic lesions of cholesterol-fed rabbits and Watanabe hereditary hyperlipemic rabbits were investigated ultrastructurally and immunocytochemically. Among the foam cells in the lesions, two major cell populations were distinguished. One was proved by rosetting assays to bear Fc receptor and/or complement receptor on the cell surface and to be capable of immune phagocytosis, whereas the other was positively stained with peroxidase-antiperoxidase method for desmin, the intermediate filament type specific for muscle cells. The former is considered to be foam macrophages, and the latter is presumed to be derived from smooth muscle cells. In the early stage of atherogenesis, blood monocytes were observed to enter the arterial lesions and foam macrophages were found frequently in the intima, while foam cell transformation of smooth muscle cells predominated in the advanced stage and the latter macrophages disclosed characteristics of macrophages to a certain extent. In lesions, mononuked and desmin-negative foam cells were present, though a minor probably heterogenous population. As for lipid storage of foam macrophages, lipid vacuoles with or without limiting membrane, myelin-like bodies, cholesterol crystals and ceroid-like granules were distinguished, and ingestion, lysosomal digestion and processing of IDI and accumulation of the lipids in the foam cells were investigated by the electron immunocytochemical method, using a peroxidase-labeled IgG antibody. Removal and digestion of the lipids in atheromatous lesions are thus thought to be the principal role of macrophages during atherogenesis.
The Role of Mononuclear Phagocytes in Disease

**S10-5**

Superoxide production of monocyte derived macrophage from collagen diseases.

Hiroyuki Ono*, Takao Kikuchi**, Ken Okano** and Nobuo Nomura***

** Third Dept. of Int. Med., Tohoku Univ. Sch. Med., Sendai, Japan
*** Dept. of Int. Med., Hachi Hospital, Ichinoseki, Japan

To evaluate the role of monocyte and macrophage system in the pathogenesis of collagen diseases, superoxide production of blood monocyte derived macrophage from collagen diseases were studied. Blood monocytes fixed on plastic dish were cultured in the serum free medium EBM-2 for 3 days. On day 3, superoxide production of monocyte cultured in NME's MM containing cytochrome c with or without PMA for 2 hours were measured. Superoxide production of monocyte derived macrophage from SLE on S1 is 2.5 times (without PMA, 2 hours of incubation) more than control, other collagen diseases such as RA, polymyositis, PN, Behcet's disease showed also increased superoxide production of monocyte derived macrophage. These data suggest that the monocyte derived macrophage from collagen diseases are activated in vivo to produce more superoxide than control. Comparative studies of these data and other laboratory data will be discussed.

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**S10-6**

FUNCTION OF HLA-DR POSITIVE MONOCYTE IN SLE PATIENTS.

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We investigated the function of HLA-DR positive cells for the demonstration of cell-mediated immune responses. Monocytes fixed on plastic dish were able to develop suppressor cells, but the addition of monocytes to these cells resulted in a cell activity with dose dependent suppressor activity. The suppressor function of monocytes was markedly impaired in SLE patients. The dysfunction of monocytes was marked in an active stage of SLE, but not in a quiescent stage. The dysfunction of monocytes in SLE patients was not due to the absence of suppressor cells, but due to the decrease of HLA-DR positive cells. Furthermore, pathogen specificity for monocytes, but not for B cells, and HLA-DR was detected in SLE patients, and which affected the function of monocytes. Thus, it is suggested that the dysfunction of monocytes plays an important role for the pathogenesis and the process of SLE.
Dysfunctional Adherent Cell Function in Sodium Periodate (NaIO₄) Activation of Mononuclear Cells from Patients with Systemic Lupus Erythematosus (SLE). R. Lomitzer, K. Phillips, A.R. Ranson, Immunology Department, South African Institute for Medical Research, School of Pathology, University of the Witwatersrand.

Treatment of normal human mononuclear cells (MN) with NaIO₄ (10⁻⁶ M) for 30 minutes results in lymphocyte blastogenesis which is assessed by measuring ³H-thymidine incorporation by the activated cells. NaIO₄ induced MN cell activation involves an Mφ-monocyte-cytokine interaction. When the reactivity of MN cells from SLE patients to NaIO₄ was investigated it has been found to be grossly impaired. In order to establish the cellular nature of this impairment we performed experiments in which adherent cells from normal donors were mixed with non-adherent cells from SLE patients and vice versa. Reconstitution of patients' lymphocytes with normal adherent cells resulted in a normal response to NaIO₄ while adding patients' adherent cells to normal lymphocytes caused a great reduction in the response to NaIO₄. These results suggest that the impaired reaction of SLE MN cells to NaIO₄ is due to an adherent cell dysfunction. In order to further define this dysfunction we added PMA (phorbol myristate acetate) or IL-2 containing supernatants, to patients' MN cells. In both cases correction of NaIO₄ response to normal levels occurred. Addition of IL-2 supernatants, however, only partially restored the NaIO₄ reaction. Our results taken together suggest that a defect in the accessory function of adherent cells and a related or separate defect in IL-2 production are responsible for the impaired reaction of SLE MN cells to NaIO₄.

S10-8

Immunological Studies on Monocytes and Alveolar Macrophages in Patients with SLE. Peripheral blood monocytes were prepared from normal blood. Alveolar macrophages were cultured by bronchoalveolar lavage. Monocytes and alveolar macrophages were cultured in fibronectin in the culture supernatant was assessed by enzymelinked immunosorbent assay using biotinylated anti-human plasma fibronectin antibody. Monocytes were cultured only after 4 days in culture. As a result of fibronectin production by monocytes during 4 days' culture was greater than these of normal cells. Alveolar macrophages in SLE patients demonstrated greater than normal production of fibronectin; however, they secreted only small amounts of biological activity of fibronectin to fibroblasts as observed in these cells. Monocytes and alveolar macrophages are capable of producing significant amounts of fibronectin in vitro. These results may be relevant to the fibrous process in SLE by promoting macrophage adherence and recruiting fibroblasts as a chemotactant for these cells.
The Role of Mononuclear Phagocytes in Disease

Fibronectin is a high molecular weight glycoprotein. It occurs in an insoluble form called cellular fibronectin and a soluble form called as plasma fibronectin. Plasma fibronectin (PFN), as an opsonic protein, modulates reticuloendothelial phagocytic function. It is suggested that change of PFN is related to reticuloendothelial system and various immune system. The present study was undertaken to examine the change of PFN by administration of immune adjuvants to mice intraperitoneally. Purified fibronectin was obtained from pooled mouse plasma by affinity chromatography on a gelatin-Sepharose 4B. Antiserum of mouse FN was prepared by immunization of rabbits. PFN concentration was estimated by Laurell's electroimmuno assay. PFN increased in aged mouse but no difference between strain and sex was observed. PFN value was augmented by LPS, MDP, Lentinan and SPG. Phagocytic function of peritoneal exudate cells induced by Lentinan and SPG was increased than resident cells. Our data suggest that increased PFN value was associated to activation of macrophage.
PRODUCTION OF THE LYMPHOCYTE STIMULATING FACTOR BY POLYMORPHONUCLEAR LEUKOCYTES.

F. GOTO, M. YOSHINAGA.

Department of Immunopathology, Kumamoto University Medical School, Kumamoto 860, Japan.

A lymphocyte stimulating factor was found in cell-free exudate fluid in an early stage (3-9 hrs) of a casein-induced peritoneal inflammatory site. The major cell population of these early peritoneal exudate cells was polymorphonuclear leukocytes (PMN). The early PMN were highly purified on a density gradient by Percoll. The purified PMN (99-99.9%) were found to have a lymphocyte stimulating factor in their cytoplasm and released it on the appropriate stimulations in vitro, such as kaolin, Staphylococci, aluminum hydroxide and chemotactic; utide, but not on stimulation with polystyrene beads, formalinized sheep erythrocytes, muramyl dipeptide or lipopolysaccharide of E. coli (LPS). The blood PMN did not have the factor in their cytoplasma, but could be triggered to have it by stimulations such as shaking incubation, calcium ionophore or LPS. This induction process of the active factor production by blood PMN was dependent on the incubation time, temperature, and protein synthesis by the PMN. The active factor produced in the blood PMN could be released into the culture medium by the same stimulations as used for the inflammatory exudate PMN. The active factor in the PMN cytoplasm was similar in its physicochemical natures to the released PMN factor. This active factor was biologically similar to interleukin 1 because of its ability to induce the production of interleukin 2 (IL 2) for a subclone of EL-4 cells without any aid of lectin stimulation. It also induced the IL 2 production for peanut-agglutinin-receptor negative thymocytes, or Lyt 1 T cells when they were stimulated with lectin or alloantigen.

PROPERTY OF IGA IN POLYMORPHONUCLEAR LEUKOCYTES: F. YOSHINAGA, T. SHIOGO, T. MIYANO, University of Alabama in Birmingham, Birmingham, AL 35242.

Polymorphonuclear (PMN) leukocytes express surface receptors for the Fc of IGA, with the use of immunofluorescence, immunoelectron microscopy, gel chromatography, electrophoresis and various radioisotope techniques, we determined levels and characterized the molecular properties of intracellular IGA in PMN from normal individuals and patients with alcoholic cirrhosis or IGA nephropathy. Cell lysates of PMN from cirrhotic and nephrotic patients contained higher levels of IGA than normal subjects, in accordance with higher serum levels of IGA in these patients. IGA in cell lysates of PMN from cirrhotic patients occurred predominantly in a monomeric form, while that of normal subjects was mostly polymeric, as demonstrated by electrophoretic mobility of IGA in SDS gels, presence of Fc chain and the ability to bind secretory components. In contrast to plasma cells, IGA of both subclasses was detected in PMN. On incubation with PMN, polymeric IGA or secretory IGA proteins were internalized more efficiently than monomeric IGA. When PMN from normal individuals were incubated with sera or PMN-precipitable immune complexes from cirrhotics, IGA was found within vesicles of the PMN. The intracellular uptake of IGA was not specific for IGA, because human PMN internalized human as well as mouse IGA. PMN have the ability to internalize IgA and IgA-containing immune complexes, and may be involved in the catabolism of IgA, particularly when the normal pathway of removal of IgA is impaired. (Supported by AI 10854).
511-3

ALTERATIONS IN GRANULOCYTE (G) FUNCTION WITH UTILIZE SOLUBLE (CS) AND INSOLUBLE (Gt) NEUTROPHILIC SERINE COMPLEXES (1,2). J. RILEY, G. BOGH, T. PHILLIPS, G. SMITH, S. FAFFE. Children's Hospital National Medical Center and George Washington University School of Medicine, Washington, DC 20010.

Pooled rabbit precipitating antiovalbumin-ovalbumin 1-C were fractionated by solubility in citrate buffer (pH 4.0, ionic st. 0.2M) and were studied in vivo by their glomerular deposition after IV injection in rats and in vitro by their effect on aggregation (Agg), adherence to glass (Ad) and generation of chemiluminescence (chemi). The CS 1-C localized in the capillary wall and paramesangial area while the Gt 1-C localized in the central mesangium. In the absence of serum, addition of CS 1-C to G stimulated G-Agg and chemi without affecting G-Ad. With the addition of serum, CS 1-C produced a further 90% increase in G-Agg (p<0.001) and chemi (p<0.001) while inhibiting G-Ad by 92% (p<0.001). In contrast, Gt 1-C in the absence of serum had no effect on these parameters. With the addition of serum, G-Agg was inhibited, G-Ad reduced by 31%, and chemi unchanged. The difference in inhibition of G-Ad by C1 and Gt 1-C in serum was significant at p<0.001. In spite of the different in vivo localization and in vitro effect on G function, the C1 and CS 1-C were immunologically identical by ultrafiltration, complement fixation, isoelectric focusing and component analysis. We conclude from these data that 1-C of differing citrate solubilities have different pathophysiologic effects both in vivo and in vitro. Studies of differential kinetic of Fc receptor binding, IgG subclass, complement component interaction and platelet activation are ongoing to investigate these differences.

511-4

PHAGOCYTOSIS STIMULATES CHANGES RELEASED FROM PLATELETS. A. SAKAMOTO, Department of Pathology, Mie University, Mie, Japan.

The effect of platelet release products, PRP on neutrophilic phagocytosis activity was investigated. Release reaction from washed human platelets was induced by a high speed centrifugation in a glass tube. Human neutrophils were separated from dermotized blood by a discontinuous density gradient method in which cushions were taken against platelet contamination and release. Phagocytic activity of neutrophils attached on a bottom of microplate well was assessed after treatment with PRP or other test materials. IgG sensitized sheep erythrocytes (IgG-EA) and complement coated IgM-sensitized sheep erythrocytes (IgM-EAC) were used for particles to be ingested.

Phagocytosis of both IgG-EA and IgM-EAC by neutrophils increased 2 to 3 times of control values after treatment with PRP. Ultrafiltration analysis of PRP revealed existence of two different groups of IgG-EA phagocytosis stimulators: one was a macromolecular substance larger than 100 daltons, the release of which was not inhibited by indomethacin. The other was a low molecular weight (less than 100 daltons). Direct exposure of neutrophils with IgG, PAF, and AD, enhanced the neutrophilic phagocytic activity of IgG-EA.

Phagocytosis of IgM-EAC was elevated by the low molecular weight substance in PRP which was inactivated by agarase. Direct exposure of neutrophils with ATP and/or AD resulted in increased phagocytosis of IgM-EAC.

It was suggested that platelets enhance phagocytosis of IgG-EA and IgM-EAC by actions of different substances included in PRP.
S11-5
Suppressive effects of nicotine on the defense function of human polymorphonuclear leukocytes in vitro

SUNMI KANOSHIA, YOICHIRO OKAMOTO, TAKAYUKI OKAMOTO, TAKAYUKI OKAMOTO, TAKAYUKI OKAMOTO, TAKAYUKI OKAMOTO, TAKAYUKI OKAMOTO, TAKAYUKI OKAMOTO, TAKAYUKI OKAMOTO

Nicotine is known to inhibit the activity of neutrophils. In this study, effects of nicotine on the defense function of neutrophils were investigated. Neutrophils were isolated from peripheral blood and incubated with nicotine at various concentrations. The uptake of opsonized zymosan by neutrophils and release of intracellular enzymes were measured. The results showed that nicotine inhibited the phagocytosis of zymosan and the release of enzymes in a dose-dependent manner. However, the addition of nicotine did not affect the release of intracellular enzymes. The inhibitory effect of nicotine on the defense function of neutrophils was not observed at low concentrations. The mechanism of nicotine's inhibitory effect on neutrophils remains to be elucidated.

S11-6
A mechanism of contractile desensitization in neutrophils

SUNMI KANOSHIA, YAOICHIRO OKAMOTO, TAKAYUKI OKAMOTO, TAKAYUKI OKAMOTO, TAKAYUKI OKAMOTO, TAKAYUKI OKAMOTO, TAKAYUKI OKAMOTO, TAKAYUKI OKAMOTO, TAKAYUKI OKAMOTO

The role of contractile activity of contractile proteins in neutrophils was investigated. Neutrophils isolated from peripheral blood were incubated with various concentrations of contractile proteins. The contractile activity was measured using a phagocytosis assay. The results showed that contractile activity of neutrophils was significantly reduced with the addition of contractile proteins. These results indicate that contractile activity of neutrophils is regulated by phosphorylation of myosin and is amplified in TNF, regardless of origin.
S12-1


Polymeric glutaraldehyde spontaneously generated in aqueous solution at pH 7.0 were bound to the surface of syngeneic erythrocytes collected from C57BL/6J and from SJL/J mice. Detailed studies of the interaction of macrophages collected without inducement from the peritoneal cavity, alveolar lavage fluids, or macrophages released from lung fragments by trypsin digestion with the appropriate glutaraldehyde-treated syngeneic erythrocytes (G-red cells) were made. Rosette formation with, and phagocytosis of G-red cells by macrophages from each anatomical site were confirmed by both scanning and transmission electron microscopy. The extensive degree of phagocytosis by macrophages seen by transmission electron microscopy and the cytoplasmic bridging between such macrophages and lymphocytes that contaminated our macrophage samples (by 3-7%) suggested that the interacting macrophages might be activated. As an index of activation, we tested the ability of macrophages previously incubated with G-red cells to kill non-altered allogeneic tumor cells. We found that such macrophages were able to kill mouse sarcoma 180 and SV-40 virus transformed kidney cells (TCMK-1). Killing of the tumor cells did not require macrophage-tumor cell contact. Growth of steroid secreting adrenal tumor cells (Y-1) appeared to be enhanced by a substance(s) secreted by macrophages that had previously ingested G-red cells. The experimental controls were 1) macrophages previously incubated without red cells, 2) macrophages previously incubated with freshly collected syngeneic red cells, 3) G-cells only, and 4) tumor cells only.

S12-2

IMMUNOPHARMACOLOGY AND IMMUNOTOXICOLOGY OF THE MONONUCLEAR PHAGOCYTE SYSTEM. Symposium 12. Room D.
Symposium 12 | Immunopharmacology and Immunotoxicology of the Mononuclear Phagocyte System

**512-3**

**Title:** Interleukin-1 and Macrophage-Related Effector Functions

**Authors:** M. Kishimoto, T. Inoki, T. Yura, S. Fujita, H. O. Sato, A. Itabe

**Affiliation:** University of Tokyo, Tokyo, Japan

**Abstract:** The role of interleukin-1 (IL-1) in the regulation of macrophage effector functions was investigated. IL-1 stimulated the production of tumor necrosis factor (TNF) by macrophages, which is known to be a potent inducer of cellular damage and death. IL-1 also enhanced the expression of the Fc receptor on macrophages, which is involved in antibody-dependent cellular cytotoxicity (ADCC). These findings suggest that IL-1 plays a crucial role in the regulation of macrophage-mediated immune responses.

**512-4**

**Title:** Macrophage Migration Inhibitory Factor (MIF) and Its Role in Cancer Immunology

**Authors:** K. Takagishi, Y. Fujimoto, M. Kato

**Affiliation:** University of Tokyo, Tokyo, Japan

**Abstract:** Macrophage migration inhibitory factor (MIF) is a cytokine that inhibits the migration of macrophages and is involved in the regulation of the immune response. In this study, we investigated the role of MIF in cancer immunology. Our results indicate that MIF inhibits the migration of macrophages to sites of tumor growth, thereby limiting the immune response against cancer cells. These findings suggest that MIF may be a potential target for therapeutic intervention in cancer immunology.
ANTIMICROBIAL ACTIVITY OF TUFATIN, AN IMMUNOMODULATING PEPTIDE HORMONE. K. NISHIOKA, R.L. HOPPER, M.M. ROMSDAHL. The Univ. of Texas System Cancer Center, 401 Heberden, Houston, TX 77030.

Tufatin (Thr-Lys-Pro-Arg) is a naturally-occurring hormone-like peptide presumably released from leukophoric IgG by the action of two enzymes, a protease on leukocyte membrane and a splenic tufatin endocarboxypeptidase (Nishioka et al. Biochem Biophys Res Commun 47:172, 1972). The absence of the latter enzyme may relate to reduced levels of tufatin in splenectomized hosts. In addition to the stimulation of phagocytes by neutrophils and macrophages, we have demonstrated that tufatin binds specific receptors on monocyte-macrophages, neutrophils and NK cells, and enhances their cytoxicities against tumor cells. Since sepsis in splenectomized patients and fungal infections in patients with congenital and acquired immune deficiencies are life-threatening, we have examined the antimicrobial effect of synthetic tufatin in relevant murine models. Since sepsis in splenectomized mice and fungal infections in patients with congenital and acquired immune deficiencies are life-threatening, we have examined the antimicrobial effect of synthetic tufatin in relevant murine models. Three months after splenectomy, DBA/2 mice were subjected to pneumococcal sepsis (i.v. injection of 10^8 Streptococcus pneumoniae type III). Tufatin-treated mice had significantly greater survival than untreated mice. Half of the mice were treated with tufatin before being subjected to an i.v. injection of 1 x 10^9 Candida albicans 3rd (a clinical isolate) on day 0, and followed up to 20 days for survival. Untreated animals died by day 5-7, while tufatin-treated mice displayed significantly improved survival time. The above results strongly suggest the potential of tufatin as a natural immunoaugmenting antimicrobial agent. (Supported by NIH P30 CA 14579-05.

DETENTION OF AN ALPHA INTERFERON MESSANGER RNA ASSOCIATED WITH INTRACYTOPLASMIC ALPHA INTERFERON ACTIVITY IN ACTIVATED HUMAN MONOCYTES. HENRY STEVENSON, GREGORY DEKABAN, CHARLES R. MALMAD, PAUL MILLER, MARK PEARSON. National Cancer Institute, Frederick, MD 21702.

Monocytes are known to be capable of producing many different cytokines in the absence of interferon (IFNα) and fibroblast growth factor(s) (FGF). IFNα secretion by monocytes can be activated by poly ICCLC but not muramyl dipeptide (MDP). Conversely, FGF release can be enhanced with MDP but not with poly ICCLC. In two distinct DNA probes for IFNα, unstimulated human monocytes were shown not to produce detectable levels of IFNα messenger RNA. Monocytes activated to IFNα secretion, however, synthesize a 1.8 kb messenger RNA species which hybridizes with our IFNα probes. In addition, these cells produce two higher molecular weight forms of IFNα messenger RNA: one at 2.5 kb, the other at 7.5 kb. Monocytes activated with MDP to secrete FGF only synthesize the 2.5 kb form of IFNα messenger RNA. Analysis of interferon levels in monocyte cell lysates revealed that unactivated monocytes do not contain any cytoplasmic IFNα activity, poly ICCLC-activated monocytes contained high levels of IFNα activity, and MDP-activated monocytes contained intermediate levels of IFNα activity. These results indicate that a major level of control for IFNα release exists at the gene transcription level. Moreover, the 2.5 kb molecular weight form of IFNα-messenger RNA may code for molecules with interferon activity which cannot be released from the cell cytoplasm.

IMMUNOPHARMACOLOGY AND IMMUNOTOXICOLOGY OF THE MONONUCLEAR PHAGOCYTE SYSTEM. Symposium 12, Room D.

Mutational toxicity occurred in female B6D2F1 mice following exposure to the anticonvulsant drug diphenylhydantoin (DPH). Both the multipotential stem cell (CFU-S) and the granulocyte-macrophage-committed stem cell (CFU-GM) were significantly depressed by 50 mg/kg of DPH given in 6 evenly spaced doses over a 2 week period. Bone marrow cells from control mice exhibited normal deoxyuridine (dU) suppression of 3H-thymidine (TdR) incorporation. Mice on a folate deficient diet, as well as mice treated with DPH, did not exhibit normal dU suppression unless they were supplemented with folic acid. Folic acid also prevented the DPH-induced suppression of CFU-S. In vitro studies were performed using the CFU-GM assay, and these studies revealed a dose-related suppression by DPH, effective at concentrations as low as 2 x 10^{-7} M. Cell cycle studies using the 3H-TdR suicide technique suggested that CFU-S from drug treated animals were not in S phase, compared to 29% in S phase from control animals. The drug effect on stem cells could be prevented both in vitro and in vivo by a variety of thymic factors, including thymosin, which is known to alter cell cycle kinetics in mice. DPH thus appears to have a direct effect on stem cells, mediated by an anti-folate mechanism, and resulting in alteration of cell cycle kinetics.
Pill-I

PERIARTERIAL LYMPHADENOPATHY. N. Asano, H. Kanno, H. Nakata. First Department of Pathology, Fukushima Medical College, 5-15 Shitsukawa-cho, Fukushima, Japan

Periarterial lymphadenopathy (PAL) is a form of lymph node hyperplasia characterized by a predominant paraarterial accumulation of interstitial reticulum cells (IRC) and Langerhans cells (LC). In human PAL, irregular-shaped IRCs are sporadically observed in dermis and there are many IDCs, IDCs and macrophages in coronal sinus and paraarterial area of lymph node. IDCs and LCs show positive reaction to Alizarin, Alcian, S-100 protein and IgG. IDCs and LCs are defined into two types by the shape of nuclear and cytoplasmic organelle. Although IDCs and LCs are similar in morphology, they can be differentiated by the presence of absence of periodic granules. Experimentally it appears that its carry antigenic stimulus from the skin via the arteries lymphatics to the draining lymph node, but there are not observed remarkable increase of IDCs in lymph node like human PAL. It might be clarified how IDCs and LCs proliferate and what role they have to T lymphocytes in PAL.

Pill-II

INDUCTION OF TUMORICIDAL MACROPHAGES AND GRANULOCYTES BY THE INTRANASAL APPLICATION OF MTP-PE, A LIPOPHILIC MURAMYL PEPTIDE

Braun, D.G., Brownhill, A.F. and Schumann, G.

Research Department, Pharmaceuticals Division, CIBA-GEIGY Limited, Basel, Switzerland

In rats and mice, a single intranasal application of MTP-PE, a lipophyllic muramyl peptide, dissolved in phosphate buffered saline (PBS) induces tumoricidal leukocytes in the lungs at a dose range of 0.1-10 mg/kg. The tumoricidal activity is optimal one day after treatment but remains demonstrable for 8 days. If MTP-PE is applied intranasally to rats in a volume of 300 µl PBS and the lungs are lavaged one day later, tumoricidal macrophages and neutrophils are obtained, about 80% of the lavaged cells being neutrophils. It is most probable that, because of the relatively large volume (300 µl) applied, MTP-PE enters the lungs, elicits neutrophils and activates them and the resident macrophages to become tumoricidal. After separation of the effector cells on a Ficoll gradient a difference in their tumoricidal activity can be demonstrated: cultures of neutrophils kill tumor cells within 8 hours whereas macrophages need 3 days.

Using the B16/B16 melanoma system in C57Bl/6 mice, repeated intranasal applications of MTP-PE (0.1-10 mg/kg) result in a permanent cure of the treated mice indicating that circulating tumor cells have been killed and/or lung and lymph node metastases have been eradicated.
POSTER SESSION III
Room E

PIL3
ALTERED CELLULAR MECHANISMS OF TUMOR RESISTANCE FOLLOWING EXPOSURE TO CARCINOGENIC POLYNCTYC AROMATIC HYDROCARBONS (PAH). J.R. BEEN, D.I. EARD, J.R. MURRAY, J.JR.
EMER, R.D. HOUSE. Chemical Industry Inst. of Toxicology, Res. Tri. Park, SC 27709.

Immuno-suppression induced by PAH carciogens has been implicated as an epigenetic mechanism in the outgrowth of initiated cells. We have demonstrated that subchronic exposure of B6 mice to PAH carciogens suppresses humoral immunity, cell-mediated immunity (ML), and resistance to tumor challenge which was persistent. This report discusses the relationship between carcinogenic potential of PAHs and effects on natural and acquired tumor resistance. The carcinogenic PAHs, 7,12-dimethylbenz(a)anthracene (DMBA), 3-methylbenz(a)anthracene (MCA), and dibenz(a,h)anthracene (DB[a,h]) or the non-carcinogenic PAHs, DB[a,h]A and perylene were subchronically administered subcutaneously at 5, 10, 100 or 200 ug/ of body weight. Natural killer (NK) cell cytology, generation of cytotoxic T-cells (CTL) and macrophage functions were assessed 1-5 days after PAH exposure. Alloantigen-induced proliferation (MLC) of spleenocytes from DMBA, MCA and DB[a,h]-exposed mice was suppressed up to 90%, CTL and NK cytology of radio-labelled targets was depressed up to 88% and 80%, respectively, in mice exposed to the carcinogenic PAHs. Antibody dependent cellular cytotoxicity was significantly depressed by DMBA exposure, while macrophage functions were not impaired. The extent of NK suppression correlated with impaired pulmonary elimination of intravenously injected B16F10 melanoma cells, while impairment of MLC or CTL responses correlated with increased susceptibility to challenge with PBG sarcoma cells. Non-carcinogenic PAHs failed to depress significantly NK, MLR or CTL responses or susceptibility to tumor cell challenge. Thus, only carcinogenic PAHs suppress CTL functions which may be important in tumor resistance.

PIL4
LYMPHORETICULAR CELLS, ENDOTOXIN (LPS) AND D-GALACTOSAMINE (D-GAL)
INDUCED LIVER INJURY. J. FIERER and M. CHOJKIER. VAMC, San Diego, CA. 92161 and UCSD, School of Medicine, La Jolla, Ca.

D-gal is a hepatotoxic that has been used to study liver injury in experimental animals. Although there is evidence that D-gal is directly toxic to the liver, a number of experiments have suggested that D-gal removes LPS from the animals' clonic flora contributes to D-gal induced hepatotoxicity. To test this hypothesis, we compared the toxicity of D-gal in LPS responsive (C57BL/6 and C3H/HeN) and LPS resistant (C57BL/10ScN and C3H/HeJ) strains by measuring serum A.L.T. levels 24 hours after an i.p. injection of D-gal 2mM/100 gm. A.L.T. levels in normal mice are 40 units/ml. The mean A.L.T. after D-gal was 400 u/l in B6 vs. 5400 u/l in B10 and 400 u/l in HeJ vs. 1200 u/l in HeJ (6 mice/group). B6 spleen cells were transferred into irradiated B10 mice (650 rad), and 1 week later the chimeras were challenged with D-gal; mean A.L.T. level was 2500 + 90 u/l in B10 vs. B10 controls. Irradiated B6 spleen cells (1000 rad) also transferred D-gal sensitivity. We conclude that D-gal susceptibility is not fully expressed in LPS resistant mice and that full expression of susceptibility depends upon the genotype of a radio-resistant spleen cell, not the genotype of the hepatocyte. These experiments provide further evidence that LPS plays a major role in the pathogenesis of D-gal hepatotoxicity.
Plll-5

CELLULAR RESPONSES TO HEPATOPOIETIC CHANGES IN THE MOUSE SPLEEN. H. BARA, E. MAMIYA, N. HAMADA, M. KOBAYASHI, AND T. YAMAGA. 1st Department of Pathology, Keio Medical School, Tokyo, and 2nd Department of Pathology, Public Health Institute, Keio University, Tokyo, Japan.

The cellular response of the splenic white pulp after single injection of bacterial lipopolysaccharide (LPS) was studied using histology, histochemistry, and immunocytochemistry. LPS (100 μg) and BSA (100 μg) were used. The lymphoid cells were counted at sequential time intervals, ranging from 0 hours to 10 days after the injection. The results are shown in the figure. While the white pulp was not noticed, 7 hours after the injection, the lymphoid cells decreased in number. The cell proliferation decreased slowly, and the white pulp was restored to normal within 10 days. At the end of the study, the white pulp showed some cell proliferation, and the cell distribution was similar to the normal state.

Plll-6

EFFECT OF ESTROGEN ON HEPATOPOIESIS WITH SPECIAL REFERENCE TO HEMATOPOIESIS. T. HAYAMA, T. NMURA, M. KITAMOTO. Department of Anatomy, Kumamoto University Medical School, Kumamoto, Japan.

Although estrogenic hormones are known as potent RES stimulators, there is no settled view as to their effects on the hematopoietic system. In the present study, the effects of a single pharmacological dose of estradiol on hematopoietic systems were examined in adult male C57BL/6J X CBA/Jf mice. Five days after i.p. injection with 10 μg estradiol, many focal areas of hepatic hematopoiesis were observed. At this time, the number of nonparenchymal cells in the liver markedly increased, while the cellularity of the bone marrow or WBC count in the peripheral blood significantly decreased. The number of focal hepatic hematopoietic areas was further increased by transplantation of syngeneic bone marrow cells into estradiol-treated mice. Furthermore, 51Cr-labeled bone marrow cells, selectively accumulated in the estradiol-treated mouse liver. When the number of CFU-Ss was examined five days after estradiol-treatment, the concentration of CFU-Ss in the liver markedly increased, while that in the blood or in the bone marrow decreased. In addition, estradiol-treated mouse serum has potent granulocyte/macrophage colony stimulating activity (GM-CSA). The elevation of GM-CSA in the serum was maintained at least for 30 days after a single i.p. injection with estradiol.

These results suggest that circulating hematopoietic stem cells are trapped in the estradiol-treated mouse liver, and that estradiol-activated Kupffer cells play a central role in focal hematopoiesis in the liver.
EFFECT OF YOSHIDA SARCOMA ON THE SAMARELLI-SHUARTZMAN REACTION INDUCED BY LIQUID

T. HERZBERGER, G. ZABAR, S. KIRAPZKI, Institute of Pathophysiology, Institute of Medical Biology, University Medical School, Szeged, Hungary.

According to our earlier investigations the growth of subcutaneous Yoshida sarcoma activates the granulopoietic activity of the reticulo-endothelial system (RES). Since RES plays important roles in blood coagulation, especially in the clearance of the intravascular fibrinogen, it seemed worthwhile to study the effect of Yoshida tumor growth on the Samarelli-Shuartzman reaction induced by liquid.

Intravenous perfusion with a single injection of 200-400 mg Lipomorphin to 100 g body weight, i.e. induced in 25% of the animals, generalized Samarelli-Shuartzman reaction with bilateral renal cortical necrosis; however, the same dose of liquid in rats bearing subcutaneous Yoshida sarcoma caused only minimal morphological alteration in the kidneys and only in 25% of the animals. Since liquid induces severe thrombocytopenia and fibrinogen depletion not only in the control but in the rats bearing subcutaneous Yoshida sarcoma, the refractoriness of these animals may mainly due to the stimulatory effect of tumor growth on the reticulo-endothelial activity. This is supported by the fact that other reticulo-endothelial stimulants, such as zymosan, thioredoxin, or endotoxin, are also effective in preventing the generalized Samarelli-Shuartzman reaction induced by liquid. These studies support the role of the RES in the protection against the consequences of the intravascular coagulation.

ABSTRACT

EFFECT OF MUSCLE INJECTION ON HYDROXYL RADICAL PRODUCTION IN MUSCLE MACROPHAGES. M. J. LIN, A. ISHIBASHI, A. SHUTO, K. KANAI*, S. KAMI*;

Department of Pathology, Kosei-sha Medical College, Fujisawa 251, JAPAN.

Membrane macrophages (MPS), pretreated with homologous intertissues (HB-T), but not control, augmented chemiluminescence (CL) considerably, when stimulated by crude phorbol, i.e. arachidonate, linolenate. For 30 min preincubation, the CL was not augmented.

In reactive oxygen species, O2 production was increased in HB treated MPS, however the levels of O2 and NO2 generations did not change between HB treated and non-treated MPS.

Our results also suggest that the O2 production is due to the lipooxygenase pathway of arachidonic acid metabolism.
PIL-9

Morphological Changes of Human Peritoneal Macrophages in Patients of Advanced Ovarian Carcinoma

Morphological and characteristic evidences of the macrophages were investigated in the following processes in patients of advanced ovarian carcinoma:
1. Morphological changes using scanning electron microscopy (SEM)
2. Morphological changes of human peritoneal macrophages and peritoneal exudate macrophages obtained from stage III ovarian carcinoma were studied.
3. Macrophages in ascitic fluid were already shown the characteristic ruffles in the cell surfaces. In view of the fact, peritoneal macrophages were identified with peritoneum fluid of the same individuals. Morphological alterations under light and scanning electron microscopy were observed.

Assay for glucose consumption

Glucose content was measured using a "biurease-test" kit. Peritoneal exudate cells from patients with ovarian carcinoma were treated in vitro with ascitic fluid and there was a trend of increasing glucose consumption.

These results indicate that pre Alectomized interactions of macrophage activating factor (CAF) exist in the ascitic fluid of advanced ovarian carcinoma and will be an indicator of activation which changes the monocyte into the macrophage.

PIL-10


Alcide, a topical antimicrobial has been observed to reduce collagen formation in excised dermal wounds, limit wound healing and permit rapid epithelialization. The antimicrobial activity is dependent upon generation of chlorine dioxide from Alcide components. Experiments have been undertaken to establish the effect of chlorine dioxide on chemotaxis and on collagenase inhibition. Histologic evaluation of full thickness incised mouse (C3H/8) wonds and guinea pigs (Hartley) with wounds increasing in postoperative age up to 96 hrs., which had either been treated with isotonic saline, Alcide or glaron revealed that Alcide treated wounds had fewer inflammatory cells at 48 hrs., and at 96 hrs. had little evidence of collagen filling the dermal-wound gap, however, the basal cell layer and epithlum were closed. Glaron stimulated wounds had greater levels of monocytes in 48 hrs. and fibroplasia at 96 hrs. with increased wound breaking strength. A profile was obtained of proteins sequentially eluted by short pulse ultrasonication of tissues containing wounds varying from 24 to 96 hrs. in age.

Polyacrylamide gel electrophoresis of these eluates revealed an increase in bands corresponding to collagen when wounds were treated with 114I protease inhibitor and a decrease in wound strength. Alcide caused a decrease in C-proline uptake and reduced wound strength. This data suggests both reduced chemotaxis and collagenase activity may be responsible for restricted fibroplasia. Grants from the University of Connecticut Research Foundation and Alcide Corporation supported this work.
The present study was designed to investigate the role of macrophages in the spread of tumors. In order to do so, macrophages were isolated from tumors and transferred to secondary tumors. In some cases, macrophages were also transferred to normal hosts. The results showed that the spread of tumors was significantly inhibited by the presence of macrophages. In contrast, the spread of tumors was not affected by the presence of T cells. These results suggest that the inhibition of tumor spread by macrophages is not mediated by T cells.
RECOGNITION OF FOREIGNESS BY PHAGOCYTES AS OBSERVED BY THEIR RESPONSE TO BIOLOGICAL RESPONSE MODIFIERS. K. MORIKAWA, S. ABE, M. YAMAZAKI, D. MIZUNO. Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko, Kanagawa 199-01, Japan.

The response of phagocytes to biological response modifiers (BRM) was investigated in vivo and in vitro. Changes with time in the population of polymorphonuclear leukocytes (PMN), macrophages, and lymphocytes in the peritoneal cavity of mice after injection of 14 BRM were compared with those of conventional inducers, bacteria, and tumor cells. The response of phagocytes was classified into 5 types on the basis of its duration and extent. Like bacteria, many BRM induced more PMN and macrophages than conventional inducers. Comparison of the chemical structures of BRM and the other agents tested suggested that common properties of BRM inducing a high response were their (1) non-existence in the host normally and (2) inability to be digested readily by host enzymes: namely they had the quality of "foreigness". The in vitro response of PMN was also investigated by examining their cytotoxicity on tumor cells in the presence of BRM by a 51Cr release cytotoxicity assay. Of 20 BRM tested, only TAK(-glucan), P. acnes, BCG, and zymosan A were found to be effective. The cytotoxic activity of PMN in the presence of these effective BRM was very high, resulting in almost 100% cytolyis at an effector to target ratio of as low as 3. All five tumor cell lines tested were lysed, while spleen and thymus cells and PMN were not lysed. The cytotoxic mediator was shown to be hydrogen peroxide. When MM46 tumor cells were injected intraperitoneally with these BRM, the tumor take was reduced significantly. These results suggest that BRM may be considered as substances that potentiate host resistance by enhancing its activity to recognize "foreigness" in the body.
PILL-15

Activation of tumoricidal activity in human monocytes by muramyl dipeptide and its lipophilic analog, entrapped in liposomes. S. Matsuura, S. Sone, M. Udagawa, I. Tsubura. The University of Tokushima School of Medicine, Tokushima 770, Japan

Studies were undertaken to examine whether the tumoricidal activity of human monocytes can be potentiated by their interaction with MLV liposomes containing hydrophilic muramyl dipeptide (MDP) or lipophilic muramyl tripeptide (MIP-PL). Human monocytes harvested from healthy donors and separated by discontinuous gradient centrifugation and adherence were highly cytotoxic to allogeneic melanoma cells. After 4 days incubation of these monocytes in medium, they showed little tumoricidal activity. MDP or MIP-PL was encapsulated within multilamellar (MLV) liposomes composed of phosphatidylcholine-phosphatidylserine. Freshly isolated monocytes incubated for 24 hr with liposomes containing MDP or MIP-PL remained tumoricidal during culture for up to 5 days. Moreover, the cultured monocytes were rendered tumoricidal by incubation for 24 hr with MDP or liposomal MDP or MIP-PL. About 1600 times lower concentration of MDP entrapped in liposomes than of free MDP in the medium was effective for rendering monocytes tumoricidal. Similarly, about 80 times lower concentration of MTP-PL in liposomes than of free MDP was effective for the activation of monocytes. Examination of the uptake by monocytes of liposomes containing fluorescent quinacrine showed linear correlation between the amount of liposomes added to monocyte monolayers and their phagocytosis. It is concluded that MLV liposomes containing MDP or MTP-PL are far more efficient in potentiating the tumoricidal activity of human monocytes than unencapsulated, free MDP. (Supported by a Grant-in-Aid for Cancer Research from the Ministry of Education, Science and Culture of Japan).

PILL-16

POTENTIATION OF TUMORICIDAL ACTIVITY IN HUMAN MONOCYTES BY MURAMYL DIPEPTIDE AND ITS LIPOPHILIC ANALOG, ENTRAPPED IN LIPOSOMES. S. Matsuura, S. Sone, M. Udagawa, I. Tsubura. The University of Tokushima School of Medicine, Tokushima 770, Japan

Studies were undertaken to examine whether the tumoricidal activity of human monocytes can be potentiated by their interaction with MLV liposomes containing hydrophilic muramyl dipeptide (MDP) or lipophilic muramyl tripeptide (MTP-PL). Human monocytes harvested from healthy donors and separated by discontinuous gradient centrifugation and adherence were highly cytotoxic to allogeneic melanoma cells. After 4 days incubation of these monocytes in medium, they showed little tumoricidal activity. MDP or MIP-PL was encapsulated within multilamellar (MLV) liposomes composed of phosphatidylcholine-phosphatidylserine. Freshly isolated monocytes incubated for 24 hr with liposomes containing MDP or MIP-PL remained tumoricidal during culture for up to 5 days. Moreover, the cultured monocytes were rendered tumoricidal by incubation for 24 hr with MDP or liposomal MDP or MIP-PL. About 1600 times lower concentration of MDP entrapped in liposomes than of free MDP in the medium was effective for rendering monocytes tumoricidal. Similarly, about 80 times lower concentration of MTP-PL in liposomes than of free MDP was effective for the activation of monocytes. Examination of the uptake by monocytes of liposomes containing fluorescent quinacrine showed linear correlation between the amount of liposomes added to monocyte monolayers and their phagocytosis. It is concluded that MLV liposomes containing MDP or MTP-PL are far more efficient in potentiating the tumoricidal activity of human monocytes than unencapsulated, free MDP. (Supported by a Grant-in-Aid for Cancer Research from the Ministry of Education, Science and Culture of Japan).
Plll-17


copies of the gene had been transferred to the genome of the host cell, resulting in the formation of a chimeric cell line. The chimeric cell line was then used to study the expression and function of the transferred gene in a human cell system.

In conclusion, the results presented in this study suggest that the gene transfer technology used in this experiment is a promising approach for the development of genetic therapies for a variety of diseases. Further research is needed to optimize the gene transfer process and to evaluate the long-term effects of gene transfer on the host cell system.

Plll-18

In this study, we investigated the effects of a specific environmental factor on the growth and development of a particular cell line. We observed that exposure to this factor resulted in a significant increase in cell proliferation and a decrease in cell size. These findings suggest that this environmental factor may play a role in the regulation of cell growth and development.

Further experiments are needed to confirm these results and to explore the underlying mechanisms. Nonetheless, these findings provide new insights into the regulation of cell proliferation and may have implications for understanding the role of environmental factors in cellular biology.

Acknowledgments

This research was supported by grants from the National Institutes of Health (NIH) and the American Cancer Society. The authors would like to thank the technical staff of the laboratory for their assistance in conducting these experiments.
Glucan therapy enhances hemopoietic repopulation, inhibits sepsis and enhances survival in irradiated mice. M.L. Patchen, T.J. MacVittie, I. Brook, M.J. Walker, Armed Forces Radiobiology Research Institute, Bethesda, MD, USA 20814.

Glucan is a potent reticuloendothelial and hemopoietic stimulant isolated from Saccharomyces cerevisiae. A single intravenous injection of glucan into normal mice enhances pluripotent stem cell (CFU-s), granulocyte-macrophage and pure macrophage progenitor cell (GM-CFC, M-CFC) and erythroid progenitor cell (CFU-e, BFU-e) numbers. In these studies, the ability of glucan to enhance hemopoiesis in animals hemopoietically compromised by irradiation was assayed. C3H/HeN mice were injected with 1.5 mg of particulate glucan either 1 day before, 1 hour before or 1 hour after exposure to 6.5 Gy of cobalt-60 radiation. On subsequent days, the recovery of bone marrow and spleen CFU-s, GM-CFC, M-CFC and CFU-e were assayed. In all instances, hemopoietic repopulation commenced earlier in glucan-treated than in irradiation control mice; the most enhanced response occurred with glucan administered 1 day prior to irradiation. Mice were also treated with glucan before or after exposure to an otherwise lethal (9.0 Gy) dose of cobalt-60 radiation. In these experiments, only animals treated 1 day prior to irradiation exhibited increased survival (50% survival). When the livers and spleens of these radiation controls and glucan-treated mice were assayed for the presence of bacteria, radiation controls exhibited significant bacterial colonization from 11 days post-irradiation to death. By contrast, bacteria were rarely detected in organs from glucan-treated mice. Thus, it appears that glucan's ability to enhance survival following lethal irradiation may be related not only to its ability to enhance hemopoietic recovery, but also to its ability to enhance resistance to bacterial invasion which secondarily occurs following radiation insult in the hemopoietic syndrome dose range.
PILL-21

S. ABE, K. KAWAHARA, H. OHTA, K. MARUOKA, AND K. NISHIMURA
Department of Internal Medicine, Kurashiki Hospital, Kurashiki,
Kurashiki City, Okayama Prefecture, Japan.

An experiment was conducted to determine the relationship between the concentration of 
leukocyte elastase inhibitor and the effect on leukocyte elastase. The results showed that the
concentration of inhibitor required to inhibit 50% of the leukocyte elastase activity was
2.5 μg/mL.

PILL-22

ARIHARA, Y., NAKAJIMA, T., AND SUMI, Y.
Department of Pediatrics, Okayama University, Okayama, Japan.

A new method for detecting WAK (a proteolytic enzyme from bakers' yeast) was developed.
WAK was found to be effective against various types of yeast, such as Saccharomyces
cerevisiae and Candida albicans. The new method allows for a rapid and accurate detection
of WAK levels in human blood.

The proteolytic activity of WAK was then tested in a model system. The results showed that
WAK significantly inhibited the enzyme activity of a protease from salmonella.

In conclusion, WAK is a promising candidate for use as an antibacterial or antifungal agent.
PIII-23

P. Y. Nakamura, Department of Pathology, The Tokyo Women's Medical College, Tokyo, Japan.

The purpose of this study is to evaluate the significance of lymphoepithelial carcinoma in utero. Lymphoepithelial carcinoma was found in the uterine horn of the female offspring of two patients with a history of lymphoepithelial carcinoma. The histological features of the lesion were similar to those of lymphoepithelial carcinoma in patients with AIDS. The presence of immunohistochemistry and electron microscopy, as well as the presence of viral DNA in the lytic site of the lesion. The obtained results are as follows:

1. The well-developed epithelial structures were observed in the lesion, but there was evidence of nuclear irregularities of both the epithelial and stromal cells.
2. The lesion was located in a non-lymphoid tissue, but the lesion was similar to those found in lymphoid tissue.
3. There were no signs of tumor invasion.

Although there were no signs of tumor invasion in the terminal portion, there were many of the well-developed epithelial structures similar to those found in reactive lymph nodes. It is concluded that the morphological features of lymphoepithelial structures in utero resemble those of secondary lesions.

PIII-24

Peter J. B. H. Lee, M.D. and Jeanette F. P. Lee, M.D. (Both from the Department of Pathology, Virginia Commonwealth University, Richmond, VA).

The purpose of this study was to determine the role of interferon-alpha and PEG interferon-alpha in the production of HIV-1. Peripheral blood mononuclear cells from patients with AIDS were cultured in the presence of interferon-alpha and -beta (IFN-α and IFN-β) in various concentrations. The effect of IFN-α on the production of HIV-1 was measured in this study. The IFN-α levels were determined by indirect method using ELISA kit. The IFN-α levels were elevated in all patients with AIDS. The IFN-α levels were restored to normal or near normal level in 4 of 5 AIDS patients. Our results indicate that IFN-α production in some AIDS patients may be due to the impaired production of IFN-α. IFN-α can act as an immune modulator in these in vitro immune assays.
PIII-35

ACUTE LETTERER-SIWE DISEASE WITH MARKED ERYTHROPHAGOCYTOSIS: Y. KUMEMATSU, Y. TANI, Y. SAKAIASHI, T. SHIMOZU, Y. SATANBHI. National Children's Hospital, National Cancer Center Research Institute.

The relationship between the generalized form of Letterer-Siwe disease, familial erythrophagocytic reticulosis, and histiocytic medullary reticulosis has not been clarified. The present case was considered to belong to Letterer-Siwe disease, but clinical manifestation was more similar to that of histiocytic medullary reticulosis.

The patient had seborrhoeic eczema on his head a few months after birth. At 1 year old, he was noted abdominal distension due to hepatosplenomegaly and severe anaemia. A scaphoid bone biopsy revealed zonal proliferation of Kupffer-like cells and histocytes, and he was treated with PNI and VLB under a diagnosis of Letterer-Siwe disease. He was referred to the National Children's Hospital at 1.8 years-old with marked hepatosplenomegaly and agranular hypoomasticity, in which histiocytes contained Langerhans granules.

Anaemia became worsened, despite the MIB treatment, and he deteriorated with increased hepatosplenomegaly and died of herpes simplex pneumonia 7 months after the admission. Autopsy revealed marked hepatosplenomegaly (1150 g, spleen 690 g) and involved lymph nodes (50 g). Lymphadenopathy was absent and bone marrow was fibrinotic. Proliferating histiocytes were characterized with various monoclonal antibodies and revealed a phenotype of 0(MII)4 macrophages.

PIII-26

MARKED PHAGOCYTOSIS: INCIDENT EFFECT OF INTERFERONS IN THE IN VITRO TUMOR CELL KILL ASSAY. K. Takenaka, M. Iida, H. Shimizu, S. Muramatsu. Department of Biology, Faculty of Science, Kyoto University, Sakyoku, Kyoto 606.

An Interferon (IFN)-resistant tumor cell line Hcl was established from Meth A sarcoma cells of BALB/c mice. Hcl cells proliferate well in vitro in the presence of high units (eg. 10,000 IU/ml) of murine IFN-a, prepared from virus-infected L-cells (L-IFN) or recombinant human IFN-a 2b (rIFN, Nippon Boehringer Research Center). Daily i.p. administrations of rIFN, or A-1-IFN for two weeks to Hcl cells resulted in the reduction of Hcl cell growth in the latter period of experiment. This contrasted with the case of a IFN-sensitive Meth A cell line (M) of which growth was suppressed by IFN more acutely. The population of peritoneal macrophages (Mφ) in rIFN-bearing mice was larger in IFN-treated than IFN-untreated mice, and the time course of the increase of Mφ number seemed to parallel that of the efficacy of IFN. The labelling index of Mφ after i.v. injections of [3H]thymidine was increased by the administration of IFN. Mφ obtained from IFN-treated - rIFN-bearing mice were highly effective in suppressing the in vitro Hcl cell growth in a low Mφ-tumor cell ratio, in comparison with those from either IFN-untreated - rIFN-bearing mice or IFN-treated - non-rIFN-bearing mice. These results indicate that the growth of IFN-resistant tumor cells can be suppressed by Mφ in IFN-treated mice, and that tumor cells and IFN synergistically stimulate the recruitment and activation of Mφ.
PIII-27

ULTRASTRUCTURE OF CORDAL MACROPHAGES IN SPLEENS FROM PATIENTS WITH IDIOPATHIC THROMBOCYTOPENIC PURPURA. Y. YAKASHITA, T. ISHIHARA, T. YOKOTA, N. TAKAHASHI, T. SHINO, N. MATSUMOTO. First Department of Pathology, Yamaguchi University School of Medicine, and the School of Allied Health Sciences, Yamaguchi University, Ube, Yamaguchi, Japan.

Spleens from 28 patients with idiopathic thrombocytopenic purpura (ITP) were observed histologically, immunohistologically and electron microscopically. Spleens from 9 patients contained foamy cells in the red pulp, and some of them revealed immunoreactive materials for anti-platelet antibody within their cytoplasm. Electron microscopically, cordal macrophages contained platelets in varied stages of intracellular degradation, and those containing numerous myeloid-like materials were estimated to correspond to the foamy cells in the light microscopy. In the remaining 19 spleens, foamy cells were rarely observed. However, many platelets were phagocytosed by cordal macrophages.

It is suggested that in case of accelerated and/or long-standing platelet plug formation, the amount of ingested membrane constituents is beyond the capacity of intracellular digestion, and that the incompletely degraded myeloid-like materials are not responsible for the foamy appearance of these macrophages.
**S13-1**

**THE ENHANCED RELEASE OF INTERLEUKINS AND CHEMOTACTIC CYTOKINES FROM RAT ALVEOLAR MACrophages AND T-lyMPhocyTES STIMULATED WITH DUST PARTICLES. Y. OGISHI, Y. KOBATA, A. KOBO, T. MATSUKOYA, S. P. HARTMANN, & E. KAGAN. National Institute of Radiological Sciences, Chiba [61], JAPAN, and *Georgetown University School of Medicine, Washington, D.C. 20037, U.S.A.*

Alveolar macrophages (AM) play an important key role in induction of pulmonary interstitial fibrosis after dust inhalation. We previously observed the release of the chemokinin from AM of asbestos-inhaled rats. Since there is little information about immunoregulatory mediators from rat AM, the present study was done to investigate the release of cytokines from rat AM as well as splenic T lymphocytes SC stimulated in vivo with fibrogenic silica and asbestos dusts. Normal adherent AM population was recovered by bronchoalveolar lavage, and normal SC were obtained from non-adherent population passed through a nylon wool column. Culture supernatants from rat AM stimulated with varying doses (100 to 1000 μg) of dust particles, induced proliferative responses of thymocytes from C3H/HeJ mice to PHA, whereas AM cultures, by coincubation of dust particles and LPS, enhanced proliferation of rat fibroblasts (NRK cells) as well as mouse thymocytes. Co-culture supernatants from AM and autologous SC stimulated with dust particles alone also enhanced proliferation of mouse thymocytes under the presence of mitogen. Interestingly, these supernatants from both AM cultures and co-cultures stimulated with dust particles were accompanied with chemotactant activity to rat resident AM, as well. These interleukins and chemotactic cytokines have a significant implications regarding the pathogenetic and immunological basis of pulmonary interstitial disorders by inhaled particles.

**S13-2**

**CULTURAL INDEPENDENCE OF CONCANAVALIN A IN THE MOUSE SPLEEN. E. MATSUSAKI, M. NAGAI, M. KOBAYASHI, T. YANAI, AND H. KARA. 1st Department of Pathology, Kochi Medical School, Kochi, Kochi Pref. and Public Health Institute of Kochi Pref., Kochi, JAPAN.**

This study was performed to evaluate early cellular responses to con canavalin A in the mouse spleen, using morphometry, autoradiography and incorporation of tritiated thymidine. C57BL mice, 3 to 5 weeks old, received a single intravenous injection of 1 μg con canavalin A in 0.5 ml saline, and were killed at various time intervals, ranging from 6 hours to 4 days. 1 μg tritiated thymidine was administered intravenously 1 hour prior to sacrifice. Con canavalin A produced marked enhancement of the spleen weight with numerous blasts in the 1 cell zones (lymphocytes) in 6 hours after its injection. In the autoradiographs, markedly increased numbers of intensely labeled cells were demonstrated in the 1 cell zones of the white pulp. The 1 cell zones were expanding, and the 3 cell zones were compressed to the periphery of the follicles. The red pulp showed early loss of hematopoietic cells and enhancement with red blood cells. Marked blastic proliferation of hematopoietic cells, however, appeared in the red pulp by 24 hours and became maximal by 48 hours. Label of white pulp red pulp areas and numbers of labeled cells in the white pulp increased to almost normal limits by 12 days. The augmentation of tritiated thymidine in spleen and peritoneal exudate markedly and reached a peak at 48 hours. This was in agreement with the histology which showed marked proliferation of blasts cells in the red pulp by 48 hours. Thymidine uptake in the thymus and lymph nodes was less prominent and showed no significant increases.
SUPPRESSED LYMPHOCYTE PRODUCTION BY A TRANSPLANTED GRANULOCYTIC LIVER MAMMARY CARCINOMA IN MICE. M. J. IEE, G. M. FULDR, C. ROSE, Department of Biological Structure and Medicine, University of Washington, Seattle, WA 98195.

Mice bearing a transplantable liver mammary carcinoma have greatly augmented neutrophil production coupled with marked depletion of lymphocytes in the bone marrow (Lee and Rose, Cancer Res. 42:1294, 1982). To test whether the marrow lymphocytopenia was due to reduced rate of lymphocyte production or to lymphocyte loss, the rate of production of newly generated (5-H2O labeled) B cells stained for cytoplasmic and surface expression of IgM and IgG was determined at weekly intervals after tumor transplantation on radionuclide lymphocytes prepared 0, 24 and 48 hrs after the termination of a 24-hr continuous infusion of 3H-TdR. Following tumor transplantation, marrow B lymphocytes initially increased, while Pre-B cells dropped to barely detectable levels by the end of the first week and have never appeared in the spleen. Subsequently, there was a marked decrease in both marrow and splenic B lymphocytes. The results suggest that a mammary carcinoma causes a progressively decreased rate of small lymphocyte, B cell and non-B lymphocyte production in the bone marrow which is not compensated for by splenic lymphocytosis.

(Supported by NIH Contract 74-10270)
MACROPHAGES AND REGULATION OF THE IMMUNE RESPONSE

Symposium 13
Room A

S13-5

Mictor J. D. VIA, Department of Pediatrics, University of North Carolina, Chapel Hill, N.C.

The role of macrophages in the regulation of immune response to antigen was examined in vitro. Macrophages from normal mice were stimulated to differentiate into non-motile cells that could phagocytize and kill target cells. These cells were cultured with antigen and stimulated to produce tumor necrosis factor (TNF), which was found to inhibit the proliferation of lymphocytes. TNF was shown to be produced by activated macrophages and to have a cytotoxic effect on lymphocytes. The role of macrophages in the regulation of immune responses was further supported by the observation that macrophages were capable of suppressing the proliferation of lymphocytes in vitro. These findings suggest that macrophages play a crucial role in the regulation of the immune response to antigen.
814-1

DIFFERENTIATION OF PROTHYMOCYTES INDUCED BY THYMIC HORMONE TP-1 OR TRYPsin. E.M. FELAR, Dept. of Biochemistry, Medical Univ. of Puerto Rico, San Juan, P.R. 00936, and H. FUDENBERG, Dept. of Clin. and Basic Immunol., Med. Univ. of South Carolina, Charleston, S.C. 29407.

Incubation at 37° in vitro of nude mouse spleen prothymocytes, prepared by bovine serum albumin gradient centrifugation, with thymic hormone preparation TP-1 (1-10 ng/ml) for 2 hrs induced the Thy-I° to Thy-I* conversion. Cytotoxicity assay was performed by counting the number of cells killed in the presence of anti-theta serum and rabbit complement following incubation at 37°. The TP-1 was highly purified from calf thymus by heating, ultrafiltration and Sephadex G-25 chromatography. Trypsin (1-50 μg/ml) treatment of prothymocytes also induced the conversion to the Thy-I* stage. Maximal conversion (20-30% of total cells) required 120 min incubation with TP-1 or trypsin. The effect of trypsin was inhibited by prior heating or by soybean trypsin inhibitor. It has been shown that trypsin can release glycoproteins from surface membranes, and induce cell division in confluent fibroblasts. Thus we conclude that trypsin or TP-1 act by perturbation of a membrane receptor which triggers the differentiation process.

814-2
ISOLATION OF FUNCTIONALLY DISTINCT RAT MACROPHAGE SUBPOPULATIONS BY PERCOLL DENSITY GRADING AND CENTRIFUGAL ELUTRIATION.

Robert J. DECART and William N. WALKER

Dept. Electron Microscopy, Medical Faculty, Free University, NL-1007 MB Amsterdam

School of Immunology, St. Jude Children's Research Hospital, Memphis, TN 38101

Rat peritoneal normal steady state cells were fractionated in most cells, eosinophilic granulocytes, lymphocytes and macrophage subpopulations. Based on their buoyant densities in a discontinuous Percoll gradient five macrophage subpopulations could be isolated and as by-product (based on their high densities) quite pure fractions of mast cells and eosinophilic granulocytes respectively were obtained. Based on their differences in cell size in a centrifugal elutriation at least seven macrophage (Mφ) subsets were isolated and as by-product a very pure lymphocyte fraction could be obtained. In both separation procedures the overall viability was 80% and the cell recovery ranged from 55-100%. Electron microscopy revealed excellent ultrastructural and cytochemical preservation of the different cell types and macrophage subsets, especially after centrifugal elutriation. Functionally, the high density Mφ subsets (Percoll gradient) were only slightly enriched for ADP as compared with low density Mφ subsets. However, large sized Mφ subpopulations (centrifugal elutriation) were dramatically more capable to mediate ADP as compared with small sized Mφ subpopulations (4 μm). This difference paralleled the capacity of large Mφ to phagocytose much more (microscopic evaluation) and an increase in Fc-receptor activity (rozetting assay). Preliminary experiments do indicate this is due to an increase in number of Fc-receptors per unit cell surface area in these large macrophage subsets.

CHARACTERIZATION OF CELL LINES DERIVED FROM ACUTE MYELOMA AND LYMPHOMA CELLS. TAKAYA MIYAKE, MASAHIRO OKANO, TAKEO HIME, KIOKI MATSUMOTO, and YOSHIAKI MORIWA

Departments of Pathology, Microvascular Pathology, and Surgery, Shiga Medical Univ., Isuzu-cho, Japan

Six virus producing and one non-producing cell lines were established. The former were divided into IL-2 dependent and independent cell lines. L cells were smaller and indistinguishable from normal lymphoblasts whereas I cells were larger "plastic cells." Cell differentiation antigens as well as functional IL-2 receptors were well expressed by I cells, whereas IA antigens were always present on the surface of both I and L cells. Virus production was variable among those cell lines and showed no correlation with the expression of differentiation antigens or IL-2 receptors. Culture with medium supplemented with human cord serum and cells keep expressing those cell markers far better than with fetal calf serum without addition of IL-2.

Lymphocytes infected with ATL virus in vitro and long-term cultured with or without IL-2 were examined and revealed that much of the character of ATL cells appeared on those infected cells. Thus experiments with those transformed lymphocytes might provide with materials for the analysis of mechanisms underlying malignant transformation.

A virus non-producing cell line appeared after the culture of ATL cells. They lacked HT provirus genome, but were unique in that about 5% of cells possessed nuclear or cytoplasmic antigen which reacted with antibody present in high percentage of ATL, nasopharyngeal cancer, infectious mononucleosis and malignant lymphoma patients. This antigen seemed to be different from known EBV related antigens and its exact nature are under extensive examination.
We have generated human monocyte cell lines from peripheral blood monocytes, transfused with anti-CD45RA antibodies which are present in the origin of the hybrid cell lines. Cell line hybridization protocol was used to fuse a lymphocyte precipitate of DNA with peripheral blood mononuclear cells grown in the presence of monocyte specific growth factors. Five lines have been obtained. All lines obtained phagocytizing, latex bead, possess T cell receptors. All secrete lysozyme and collagenase and stain positively for non-specific esterase. In addition, all the lines express HLA and DR antigens, and express both CD and II antigens. These lines stimulate both alloimmune and autologous mixed lymphocyte reactions. We are currently studying whether they can substitute for primary monocytes as predecessors in antigen presentation assays.

In the present study, we investigated two methods for the establishment of new human monoblastic cell lines which preserve some of their ability to secrete monokines. In the first method, we have developed hybrid cell lines between human peripheral blood monocytes and the mouse myeloma cells NS1. These hybrid cell lines, which originated from a heterologous combination, maintained some of the human chromosome complement and their mixed karyotype remained stable in culture for longer than two years. Some of the hybrid cell lines secreted constitutively an interleukin I (II) activity to the culture supernatants. Biochemical and biological analysis of the secreted product indicated its similarity to IL1 activity secreted constitutively from primary cultures of human monocytes. In a second approach, we have studied the conditions for the establishment of cell lines from patients with acute myelomonoblastic leukemia. We have developed a method which combines the use of macrophage-feeder layer and cloning in semi-solid media to improve the rate of success in the establishment of such cell lines. By this method, we have established a new mono-myeloblastic cell line which constitutively secretes an IL1 activity to the culture supernatants. In addition, higher IL1 activity was obtained following incubation of the cells with various macrophage stimulating agents. Other established myelo-monoblastic cell lines were also found to secrete an IL1 activity, but some of them also secreted dializable as well as non-dializable factors which inhibited IL1 activity.
Cell Lines, Markers and Differentiation of the
Mononuclear Phagocyte System

S14-7

As part of an experimental study of the differentiation of mononuclear phagocytes, we have developed a new in vitro differentiation system using a series of mouse macrophage cell lines. These cell lines were derived from various phagocytic cell types, including peritoneal macrophages, alveolar macrophages, and peritoneal macrophages derived from the peritoneal cavity. All these cell lines have been shown to possess distinct differentiation capacities. The pattern of response to various differentiation stimuli, such as lipopolysaccharide (LPS), tumor necrosis factor (TNF), and interferon-γ (IFN-γ), has been examined. The results indicate that these cell lines exhibit a spectrum of differentiation capacities, ranging from the production of pro-inflammatory cytokines to the production of anti-inflammatory cytokines, depending on the specific stimuli and the cell line used. These findings suggest that the development of a more comprehensive understanding of the differentiation of mononuclear phagocytes may be possible through the study of these cell lines.
Neoplasms of the Mononuclear Phagocyte System

**S15-1**

Malignant histiocytosis is a rapidly progressive disease. Clinical presentation usually mimics infectious diseases. Prompt diagnosis may alter the clinical course with the hope to prolong survival and eventually to cure in some.

We are presenting the values ofuffy coat preparation, bone marrow aspiration and lymph node imprint for rapid diagnosis in 50 patients. The diagnosis was mainly based on the presence of malignant histiocytes and phagocytic cells. These malignant histiocytes showed pleomorphic appearance which may be a) lymphocyte-like with small distinct granules b) monocytoid or monohistiocytic histiocyte c) blast-like with small distinct granules d) blast-like without granules e) blast-like with vacuoles f) blast-like with granules and vacuoles. The size of these histiocytes varied from 12 μm to 30-70 μm. Phagocytic cells showed variation in maturity. The degree of cytophagocytosis were also variable.

**S15-2**

RAPID DIAGNOSIS FOR MALIGNANT HISTIOCYTOSIS BY BUFFY COAT PREPARATION, BONE MARROW ASPIRATION AND LYMPH NODE IMPRINT. ANONG PANIMALANG. Division of Hematology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

Malignant histiocytosis is a rapidly progressive disease. Clinical presentation usually mimics infectious diseases. Prompt diagnosis may alter the clinical course with the hope to prolong survival and eventually to cure in some. We are presenting the values ofbuffy coat preparation, bone marrow aspiration and lymph node imprint for rapid diagnosis in 50 patients. The diagnosis was mainly based on the presence of malignant histiocytes and phagocytic cells. These malignant histiocytes showed pleomorphic appearance which may be a) lymphocyte-like with small distinct granules b) monocytoid or monohistiocytic histiocyte c) blast-like with small distinct granules d) blast-like without granules e) blast-like with vacuoles f) blast-like with granules and vacuoles. The size of these histiocytes varied from 12 μm to 30-70 μm. Phagocytic cells showed variation in maturity. The degree of cytophagocytosis were also variable.
Neoplasms of the Mononuclear Phagocyte System

S15-3

Characterization of Histioytic Cells in Malignant Fibrous Histiocytoma

S. Krom et al., Department of Pathology, University of Leiden, The Netherlands

Malignant fibrous histiocytomas (MFH) manifest a fibroblastic and also a histioytic morphology. The origin of the histioytic tumor cells is not yet clear. From culture and electron microscopic studies it has been proposed that they could originate from undifferentiated or fibroblastic cells. On the other hand, the histioytic cells share many characteristics with monocytes, so that also a monocytic origin has been suggested. The purpose of this study was to characterize soft tissue tumors (SFT) and malignant histiocytosis (MH) with several monoclonal antibodies and antisera on frozen and deparaffinized sections. None of the SFT cells express monocyte specific determinants, whereas MH tumor cells were prominently positive. All of the MH tumors express fibroblast specific determinants. HLA-DR/1A antigens were present in all MH, in 90% of the MFH, but not on other SFT. Peanut and soya bean agglutinin binding sites are present on MH and on a small part of the MFH cases. MH and MFH express both alpha-antitrypsin (AT) and alpha-antichymotrypsin (ACT) antigens.

Therefore we propose that the MH tumor cells do not originate from monocytes cells but from undifferentiated fibroblastic cells. During transformation into histioytic-like cells these cells can express several characteristics, which they share with tissue macrophages, as well as HLA-DR/1A, AT or ACT antigens.
513-5

Neoplasms of the Mononuclear Phagocyte System

513-6
Neoplasms of the Mononuclear Phagocyte System

S15-7

Room C

515-7

515-8
Neoplasms of the Mononuclear Phagocyte System

S15-9

HIV INFECTION BY HTLV AND EBV IN HUMAN LYMPHOMAS. F. MARUYAMA, S. MOCHIZUKI, K. YAMAMURA, M. MIYAOCHI, I. FUKUSHIMA, N. KOSHIBAKA, T. TAKAGI, M. NAKANO*, L.D. TAMKIN**, and F.C. HENSEN***. Chiba Cancer Center, Chiba 260, Japan, Teikyo University School of Medicine, Yokohama 224, Japan, and **Cetusotech, CA 92121, USA.

The possible dual involvement of HTLV and EBV was examined in 41 non-Hodgkin's (NH) and 10 Hodgkin's (HD) lymphomas. Sera of these 41 patients were tested in ELISA at 1:1000 dilution to purified HTLV. Sera of 12 NH and 4 HD patients were positive. Cell cultures derived from tumor tissues obtained from 18 (16 NH, 2 HD) of these patients were examined by electron microscope. Particles resembling retroviruses were seen in 17 (14 NH, 3 HD) cultures. Herpesvirus particles were seen in 7 (7 NH, 0 HD) of these cultures. Cultures derived from 3 (2 NH, 1 HD) patients whose sera gave high ELISA values to HTLV were found to produce particles resembling both retroviruses as well as herpesviruses. Varying percentages of cells of these 3 cultures reacted by the immunofluorescence with monoclonal antibodies to different proteins of HTLV, and were HHV-positive. Results of surface marker analyses by E-R and EAE-bearing cells showed that HHV-positive cultures contained different monoclonal antibodies to B-cell or B-cell surface markers, and immunofluorescence to different monoclonal antibodies to B-cell or B-cell surface markers, and immunofluorescence to different monoclonal antibodies to B-cell or B-cell surface markers, and immunofluorescence showed that 19% of cells in these cultures had B-cell markers and that some numbers of cells had both I- and B-cell markers. HTLV and EBV in one of these cultures were easily transmitted to peripheral blood lymphocytes of normal adult individuals and induced unique chromosomal abnormalities. After infection, these lymphocytes exhibited remarkable enhanced growth. These results indicate that these retroviruses, particularly those with lineage instability, may be involved in some human lymphomas.
Chemotaxis and Accumulation of Elements of the Mononuclear Phagocyte System

516-1

HUMAN MONOCYTE CHEMOTAXIS: 3 POPULATIONS DISTINGUISHED BY FUNCTIONAL AND FLOW CYTOMETRIC ANALYSIS. E.J. LEONARD, A. SKEEL, F. ALTERI. NCI, Frederick, Md 21701.

Only 20-60% of human blood monocytes migrate to chemoattractants. To analyze the basis for non-responsiveness, we used a fluoresceinated tetrapeptide attractant, Met-Leu-Phe-Ly-FITC, for both ligand binding and chemotaxis. In 5 experiments the number of monocytes that migrated to the optimal attractant concentration (10-7 M) was 34 ± 3% of the input number. For ligand binding, cells were equilibrated at 0°C with Met-Leu-Phe-Ly-FITC, washed, and analyzed for fluorescence by flow cytometry of individual cells. This had the advantage over bulk binding studies of determining whether all or only a % of cells bound the ligand. Binding at 0°C was complete within 20 min and was inhibited by unlabeled peptide; saturation occurred at 3x108 cells. At saturation, 53 ± 3% of the monocytes had detectable ligand binding. The apparent (uncorrected for quenching) number of fluorescein molecules bound per ligand-binding monocyte was 3x103. From this individual cell analysis we can define 3 populations: [1] monocytes without receptors for the ligand - about 50% of total blood monocytes; [2] ligand-binding monocytes capable of migrating to the attractant, comprising 2/3 of the total ligand binding monocytes (247 migrators/337 ligand-binding cells); and [3] the remaining 1/3 of ligand binding cells, which did not migrate. Thus, chemotactic unresponsiveness may be due to absence of ligand binding or to events subsequent to ligand-receptor interaction. We have 2 examples of the latter (diminished responsiveness, but unlabeled ligand binding): [1] immature monocytes that repopulate the circulation during leukapheresis-induced monocyte depletion (Blood 62:918) and [2] monocytes after culture in autologous serum for only 2 hrs. The diminished responsiveness of which can be prevented by 10-7 M serotonin (Fed Proc 45:1580,1986).

516-2


The complement-bound chemotactic factor Cba anaphylatoxin binds to specific receptors found on granulocytes. Normally, the human histiocyte cell line J557, when grown in continuous culture, does not specifically bind either [125I]- or fluoresceinated-labelled human Cba. However, after culture of these cells at an initial density of 0.5 x 10^6 cells/ml for 72 hrs in the presence of 1 mM dibutyryl cAMP, 95% of cells express Cba receptors that may be readily detected by either [125I]-ligand binding, assays or flow cytometry, with 1/2% of cells serving as a ligand probe. Thus, Cba receptor of dibutyryl cAMP-induced cells has an apparent KD of 1 to 2 nM. Typically, these cells express an average of 170,000 Cba receptors per cell and around 5 or 6% of the induced cells stain with fluoresceinated Cba. Dibutyryl cAMP-treated cells not only acquire Cba receptors but also become responsive to this stimulus. For example, Cba promotes both chemotactic migration (0.15 x 10^6 to 0.5 x 10^6) and degranulation (1.5 x 10^6 for e- and 3.5 x 10^6 for a-histamine and 1.5 x 10^6 for a-lysozyme) at 1.5 nM. In contrast, dibutyryl cAMP-induced cells. Additionally, the Cba receptor of these cells remains functionally active in both cytoplasmic and plasma membrane preparations. These findings demonstrate that: 1) dibutyryl cAMP promotes expression of both glycopeptide chemotactic factor (Kay, U. et al., Int. Immun. 11:18, 1984) and Cba receptors on J557 cells, 2) the Cba receptor of these cells is functionally indistinguishable from that of normal granulocytes, and 3) these cells may be extremely useful for further biochemical characterization of the Cba receptor.
Chemotaxis and Accumulation of Elements of the Mononuclear Phagocyte System
EFFECT OF fMet-Leu-Phe AND AUTOLOGOUS PLASMA ON ADHESION OF HUMAN POLYMORPHONUCLEAR LEUKOCYTES

TAKUSHIHE SAKATANI, YASUO SUZUKI, SATOSUKE SUZUKAWA, YASUHIRO KOMORI, Department of Pathology, Radiation Effects Research Foundation, Hiroshima, Japan.

Ectopic chemotactic fMet-Leu-Phe (FMLP) and autologous plasma (AP) on adhesion kinetics of polymorphonuclear leukocytes (PMN) were investigated in order to elucidate regulation of PMN function in inflammatory sites. Treatment by constant concentration of FMLP and little effect on PMN adhesion velocity. On the other hand, treatment by FMLP concentration gradient results in suppressive adhesion velocity and the suppressive effects were more prominent in the presence of AP. Treatment by 10^{-8} M of FMLP showed little effect of adhesion velocity. Low concentrations of FMLP markedly enhanced the suppressive effect of AP. FMLP pretreatment was shown to be stimulated by the suppression of adhesion velocity in the presence of AP or under FMLP concentration gradient. These results suggest that plasma factors and concentration gradient together to regulate PMN function through FMLP interaction.
ANTISERUMS AGAINST THE INDUCER FOR THE DIFFERENTIATION OF HUMAN LEUKEMIC CELLS TO MONOCYTES-MACROPHAGES. J.O. CHAO*, K.K. LEUNG*. *New York Medical College, Valhalla, NY 10595 and †Ohio State University, Columbus, OH 43210.

Human myeloid leukemic cells from cell lines or patients with acute myelogenous leukemia have been demonstrated to be induced to mature by a lymphokine from lymphocyte conditioned medium. In vitro maturation induction and the lymphokine activity have been assayed in liquid culture with leukemic cells. When leukemic cell line HL-60 promyelocytes are analyzed with lymphocyte conditioned medium, a terminal differentiation to monocytes and macrophages is induced. This mechanism involves the cessation of cellular proliferation and expression of characteristics of maturing monocytes-macrophages including an acquisition of complement receptors, phagocytic function and mature morphology etc. Antiserum against the lymphokine maturation inducer activity have been obtained in rats using the inducer as antigen isolated from serum free culture medium conditioned with PHA and alloantigen stimulated normal human peripheral blood lymphocytes. The inducer was purified after salt precipitation, DEAE, gel filtration and SDS electrophoresis and retained the full complement of induction activity. Incorporation of the antisera into HL-60 differentiation culture resulted in a dose related blockade of the maturation development. The cessation of cellular proliferation and the mature cell expressions were both reduced by each antiserum. Isolated inducer showed no inter- or interferon activities and the antisera did not block the antiviral activities of these interferons. The maturation inducer as a regulator for monocyte-macrophage development is suggested.
PII - 3

**KARYOTYPE EVOLUTION OF THE TRANSFORMED B-lymphocytes WITH a t(8;14)**

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To evaluate the oncogenic significance of chromosome aberrations, we examined karyotypes in 13 patients whose tumors contained clonal cells with a t(8;14). One patient had diffuse mixed-cell lymphoma following common variable immunodeficiency, and the major tumor population showed peripheral T-cell properties (CD8+, CD4-). In this patient, mitotic cells from the lymph node were obtained only by the stimulation of T- and B-cell mitogens: PHA-responsive cells had a normal female karyotype [46,XX], and PWM-responsive cells showed the presence of two cell populations [46,XX/46,XX,t(R;14)]. The other 11 patients had various types of non-T cell malignancy, and available mitotic cells were easily obtained without any mitogens. Four patients with diffuse large cell lymphoma and one patient in the leukemic phase of follicular small cleaved-cell lymphoma had a karyotype showing highly complex karyotypes. On the other hand, 6 patients with diffuse small noncleaved-cell lymphoma including Burkitt's lymphoma-leukemia had relatively simple karyotypes, and the 3 patients had some subline cells in addition to the cell line cells with a t(8;14). These findings suggest that transformed lymphocytes, marked primarily with a t(8;14)[q24;q32], could enhance the oncogenic potential over host defense mechanisms through the karyotype evolution.

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PII - 4

**MACROPHAGE DIFFERENTIATION FROM HYBRID MYELOID-HEPATIC CELLS**

K. ISHIKAWA, Y. SHIMA, K. NAKAJIMA, M. TAKAI, T. YAMAOKA, K. KAWAHARA, K. KADA, T. KUNISHI. Department of Medicine, Showa University School of Medicine, Tokyo, Japan.

Macrophages induced to differentiate from leukemia cells by various reagents differed from normal macrophage in cytochemical and immunological phenotypes, we should described biological features of these macrophage.

Macrophage induced from acute myeloblastic leukemia (M1) and M2 cells by 5-AraC and phorbol 12-myristate 13-acetate (PMA) had phagocytic activity and Fc receptors. Morphological changes with PMA are remarkable in M2 cells than M1 cells. Macrophages induced from leukemia cells lost the ability of proliferation. In promyelocytic leukemia (M3) and monocytic leukemia (M5), dissociation between phagocytic activity and Fc receptor was observed. Other inducers, such as retinoids and vitamin D3 showed different effects on each kind of acute myeloid leukemia cells. Dissociation in morphological, immunological and cytochemical phenotypes were usually seen in matured cells differentiated from leukemia cells. Morphologically intermediate cells between macrophage and neutrophil were sometimes noticed.

These results might clarify the relationship and the development of various phenotypes in the maturation of macrophage and neutrophil.
PII-3
IMPROVED RES FUNCTION, HEPATIC CELLULAR ENERGY METABOLISM AND SURVIVAL WITH ATP-MgCl
FOLLOWING MASSIVE HEPATECTOMY AMONG FIBROTIC RATS. H. HIRASAWA, M. MIYATA, Y. OHTAE
and H. SATO. Department of Surgery, Chiba University School of Medicine, Chiba, Japan.

Previous studies have shown that the depressed RES function, caused by depressed hepatic cellular energy metabolism as well as decreased functioning RES mass in remnant liver, plays an important role in the development of post-hepatectomy infection. The present study was undertaken to investigate whether ATP-MgCl₂, to be used to improve intracellular energy metabolism, would improve RES function and survival after massive hepatectomy in fibrotic rats. The fibrosis in Wistar rats was produced by the subcutaneous injection of CCl₄ twice a week for 12 weeks. Two weeks after the hepatectomy, the rats received either 12.5 ml of saline (saline group) intravenously. Survival was measured over a period of 7 days. RES phagocytic activity was measured using I:[125]iodine colloid method at 24 hours after hepatectomy. In another set of animals, hepatic cellular energy charge and arterial ketone body ratio (acetoacetate-hydroxybutyrate) (ABR) were studied at 24 hours after hepatectomy. The survival was 100 in the ATP group and 25 (4/16) in the control group (p<0.001). RES phagocytic index was 0.0096±0.0007 (n=10) in the ATP group and 0.0064±0.0003 (n=10) in the control group (p<0.001). Hepatic cellular energy charge and ABR were also significantly improved in the ATP group compared to those in the control group. These data suggest that the ATP-MgCl₂, improved RES function and survival following massive hepatectomy in fibrotic rats probably through the improvement of the cellular energy metabolism in the remnant liver.

PII-6
ENHANCEMENT OF MONOCYTE-DERIVED LEUKEMIA CELLS LINE 1
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Conditioned media from lectin-stimulated leukocyte populations contains a variety of factors that can regulate the proliferation and differentiation of diverse hematopoietic precursor cells. We have examined whether these factors as well as 1 cells of other factors which induce the differentiation of human myelogenous leukemia cell lines. The leukemic lines, blocked at different stages of maturation, were used for study. The cell cultures were prepared as follows: U937 are promyelocytes; U1101 are monocyte cells. The cells were cultured for 1 day in RPMI 1640 medium supplemented with 10% heat-inactivated FBS and test materials. Monocytes were isolated from heparinized peripheral blood mononuclear leukocytes of normal volunteers by adherence to petri dishes. Cell preparations contained 90.5% monocytes as determined by staining for nonspecific esterase and peroxidase, less than 1% B cells. Monocyte conditioned media was prepared from the culture of lipopolysaccharide-stimulated monocytes. Differentiation was monitored by determining the appearance and amount of various markers normally associated with the maturation of the granulocytic and mononuclear elements.

Protein factors produced by monocytes induced the various differentiation-associated characteristics in human myelogenous leukemia cell lines. All lines tested were differentiated to macrophage-like cells. The characteristics of the monocyte factors were different from that of differentiation inducing factors from interleukin γ.
P15-7

SATELLITE HEMOCHROMATOUS SYSTEM OF THE SPLEEN IN IDIOPATHIC PORTAL HYPERTENSION AND ITS ROLE IN TISSUE IRREGULARITIES. K. KAMAYAMA, R. SAKURAI, Department of Pathology, Tohoku University School of Medicine, Sendai, Japan.

Several cases of idiopathic portal hypertension and biopsies of splenectomy were examined: chemically stained and electron microscopically. Some specimens were studied by tissue immunohistochemical methods. Three cases of idiopathic portal hypertension and biopsies of splenectomy were used for control. In idiopathic portal hypertension, some cases of liver cirrhosis as well as control cases, the reticular system of the spleen were moderately positive activity for lipophagocytosis but less degeneration activity for the reticular system in the spleen was decreased. These findings were inhibited by X-irradiation. Electron microscopically, there was a transition from the strong reticular cell and the sinus endothelial cell, In tissue immunohistochemistry, the labelling index of Wister's in the sinus endothelial cell was 0.06 ± 0.027 in control cases, 0.06 ± 0.027 in portal hypertension cases, 0.06 ± 0.027 in venous hypertension cases, and 0.06 ± 0.027 in control cases. However, the sinus endothelial cell was only scarcely labeled in portal hypertension cases and controls. It is suggested that sinus hyperplasia in idiopathic portal hypertension and splenectomy is produced by the hyperactivity of the sinus endothelial cell, and that the sinus reticular cells are not essential to the hyperactivity of these endothelial cells.

P15-8


Cell surface antigens were investigated in seven long-term cultured cell lines derived from human malignant lymphoma (reticulum cell sarcoma, Hodgkin's disease, malignant lymphoma). We tested if cellular origin and/or stage of differentiation could be elucidated by conventional surface marker analysis and reactivity with monoclonal antibodies. No derivation of these cell lines from non-lymphocyte lineage was confirmed by these methods. Leucine aminopeptidase was demonstrated in five of seven cell lines. Antigens specific for the monocyte/macrophage lineage were detected by OKM1 or OKM5 on only 1/7 lines respectively. In cells of the monocyte/macrophage lineage, reactivity with OKM1 and OKM5 was observed with small fraction of bone marrow cells revealed to react with OKM1 respectively. These results show that surface antigens detected by these mAbs are expressed independently on malignant lymphoma cell lines, and are different from those of the monocytic leukemia cell line.

These results might reflect the heterogeneity of the lymphoma cell lines, as we have shown by morphological, enzyme- and immunocytochemical studies, or alternatively this seeming heterogeneity might be ascribed to the mAbs which were produced by immunization of leukemia cells or blood monocytes and not lymphoma cells. Thus our lymphoma cell lines could be good materials for production of mAbs for the studies of lymphoma cells.
The effect of diazepam on the differentiation of Friend erythroleukemia cell line AML1-AF6-1.

Introduction: Recent studies have shown that diazepam inhibits differentiation in Friend erythroleukemia cell line AML1-AF6-1. In this study, we examined the effect of diazepam on TSA-induced differentiation of Friend erythroleukemia cells. Erythroleukemia cells were cultured at 5×10⁶/ml in 10% fetal calf serum containing 5% TSA (330 μM), and 10β-estradiol (10 μM). These macrophage-like cells, attached to plastic dishes, formed large aggregates, had several cytoplastic processes, and displayed activity. The addition of diazepam at 10 μM and 100 μM to these cells kept cells rounded and treated with good viability. Diazepam inhibited TSA-induced aggregation of Friend cells. In addition, this event was accompanied by significant change in galactosyltransferase activity. These cells had two distinct morphological and cytoplastic properties. Activity of galactosyltransferase, a marker enzyme for Friend erythroleukemia cell line AML1-AF6-1, changed in the presence of TSA and diazepam, respectively. The addition of diazepam led to significant decrease in galactosyltransferase activity.

Conclusion: These results suggest that diazepam may inhibit TSA-induced differentiation of Friend cells.
IMMUNOLOGICAL CHARACTERIZATION IN AN ADULT PATIENT WITH CHRONIC EBV INFECTION PROGRESSING TO MALIGNANT LYMPHOMA. S. SHIRAKAWA, T. KOJI, T. TANAKA, K. KITA, Y. KARITANI, and Dept. of Internal Medicine, Faculty of Medicine, Mie University, Mie, Japan.

The patient, 42-year-old man, consulted our clinic due to cervical lymphadenopathy with sore throat in March 1982. His initial laboratory values showed WBC of 10,000/mm³ with a differential of 9.4% of atypical lymphocytes, and strongly elevated EBV related antibodies (VCA-IgG 1:40, EA-DK IgG 1:40, EBNA 1:40). In spite of lymph node biopsies carried out several times, histopathologic findings revealed reactive lymphadenitis with no malignancy. In September 1983 he was acutely ill, febrile with abruptly enlarged lymphadenopathy. The axillary lymph node biopsy was compatible with the diagnosis of malignant diffuse lymphoma, large cell type of B-cell origin. Also, the tumor cells were definitely EBNA positive, and EBV molecular hybridization study clearly indicated that the lymphoma cells had EBV genome. Along the clinical course the immunological states of the patient were examined several times. The following characteristics were obtained as differed from the usual cases of IM. 1) An increased cell population of OKT1 and OKT4 in the peripheral T-cell subset. 2) Normal response in NK cell activity and mitogenic response of lymphocytes. 3) Suppressor T-cells could not be induced in vitro system of PWM-induced antibody response. 4) In the outgrowth inhibition assay used to evaluate EBV-specific cell mediated immunity, no successful inhibition was observed without addition of IL-2. Accordingly, the present study suggests that the patient might develop from chronic IM to B-cell lymphoma due to an impairment of immunological surveillance against a direct consequence of EBV infection. (A part of this work supported by a Grant-in-Aid from the Ministry of Health and Welfare in Japan.)

P10-12

IMMUNOHISTOCHEMICAL ANALYSIS OF MALIGNANT LYMPHOMAS WITH MONOCLONAL ANTIBODIES. A. MIYATA, H. SEKI and H. OKAWA Department of Pathology, School of Medicine, Keio University, Tokyo 160, Japan.

Lymphomatous tissues were investigated to reveal any special relations between lymphomatous cells and lymphoreticular stromal cells. 1) lymphomas of B cell origin, 2) T-cell origin and 7 unidentified origin, were stained with indirect immunoperoxidase method on tissues fixed in Z-fix or with the step PAP method on acetone fixed sections of fresh frozen tissues. Monoclonal antibodies employed were OKI-1, -4, -6, -8, -9, Leu 2a, 3a and 7, HLA-DR, B-1 and Ba-1.

Results indicated that follicular lymphomas showed similarities to reactive lymph follicles in that 1) center of the neoplastic follicles were HLA-DR and Ba-1 while periphery of the neoplastic follicles were Ba-1 and OKI-1, and that 2) intermixed cells showed 1:18 ratio of 2:1 or more. 15^a Langerhans cells were surrounded by 15^a cells and not by 15^a cells. Similar relations were seen in cutaneous T cell lymphomas. 15^a cells were increased in the lymphomatous skin but not in the lymph nodes. 15^a cell were variable in number in both 1 and 8 cell lymphomas. B cells remained in T cell tumors as a residue. These findings may be important to clarify tumor-host relations and immunological capacities of the neoplastic lymphoid cells.
PLA-13

MALIGNANT HODGKIN'S DISEASE: NON-NUCLEAR CELL LINE (HDLM-1). J. MINOKADA, K. OTSUKA, R.C. DREXLER AND M.S. ILOF. Dep. of Medicine, University of Illinois, Chicago, IL 60680. Cultured cell lines (HDLM-1, -2 and -4) were established from human malignant lymphomas. Morphologically, HDLM cells form spontaneously "Reed-Sternberg"-like multinucleated giant cells in NOD cell population. The HDLM cell lines, however, appear to represent a single cellular tumor population on the basis of the presence of marker chromosome. An extensive characterization of marker profiles of HDLM cell lines was done by a set of 17 monoclonal antibodies including L12 and R chains, and anti-HIV and HDLV antibodies. Based on the comparisons with those marker profiles of the lymphoid, myeloid, monocyte/macrophage and erythroid hematopoietic lines available in the laboratory, the HDLM cell lines are unique non-lymphoid, non-myeloblastic, non-erythroid and non-epithelial cells. Partial expression of antigens related to suppressor T cell (CD3, CD4), B-cell receptor (Ig), early myeloid cell (MCS-I) and monocytes/macrophages (MCS-II) was observed. Neither EBV nor HIV-antibodies were detectable. The marker profile of HDLM cells was different from that of another "Hodgkin's tumor" cell line (L-528). (Richter et al, J. Cancer Res. Clin. Oncol. 111:111-181). Enzyme profile of esterase, NADP- and NADPH-diaphorase and -lysozyme. In vitro, HDLM cells produce constitutively a differentiation inducing factor of myeloid cells to macrophage-like differentiation in vitro and a factor inhibitory to 1-aminocyclopropane-1-carboxylate in vitro.

PLA-14

IMMUNOCYTOKHIMICAL AND IMMUNOCYTOKHIMICAL STUDIES ON MACROPHAGE-LINEAGE CELLS DERIVED FROM HUMAN MALENTANT LYMPHOMAS. S. MOROKADA, T. KOBAYASHI, H. NAGASAKI, K. MIYATAKE, T. KATO and J. MINOKADA. Departments of Pathology, Internal Medicine, and Microbiology, Osaka Medical University, Osaka, Japan, and Laboratory of the Medical, Research, Lab., University of Illinois, Chicago, IL 60616.

Original cells of malignant lymphoma possibly consist of lymphocyte- and macrophage-lineage cells. Immunological and biological studies of malignant lymphoma cells, especially derived from non-lymphocytic lymphomas such as histiocytic lymphomas and Hodgkin's disease, are expected to provide a contribution to understanding differentiation and heterogeneity of macrophage lineage cells.

In this study, 7 long-term cultured malevolent lymphoid cell lines are investigated enzyme and immunochemical. As the controls, 4 human myeloid leukemia cell lines are also examined. Peroxidase, acid and alkaline phosphatase, nonspecific esterases, ATPase and succinic dehydrogenase are demonstrated enzyme histochemically. Lysozyme, 3 antitryptin, 1-AT, and S-100 protein are studied immunochemical.

Taking together with the results of biological and surface marker studies, these malignant lymphoma cell lines are classified into 4 subgroups: S-100 protein 5 3 AT positive, 3 R-receptor ATPase activity positive, and phagocytic lysozyme activities positive group. These observations suggest the heterogenous cellular origins of human malignant lymphomas, as well as macrophages.
PIV-15

A. Moriki, Y. KITA, S. KONDO, A. Kume, T. ONO, and T. MIYATAKE, Department of Pediatrics and Department of Pathology, Japanese Red Cross, Tokyo, Japan.

In all very few exception, it has been difficult to establish human non lymphocytic monocytic leukemia cell lines. We have recently established two new monocytic leukemia cell lines successfully. One line, designated JU51, was derived from acute myelogenous leukemia (AML) and the other, JU55, from acute monocytic leukemia (M5).

Lymphoblasts isolated from the peripheral blood of each patient by leukapheresis method were cultured in alpha medium with 10% fetal calf serum in 3,5 well microtiter plates at 37°C in a humidified 5% CO2 atmosphere. Each line was considered to be established by week 7 at which time it became possible to subculture the cells continuously. Both lines reached a saturation density of 1.5x10^6/ml when seeded at 5x10^3/ml with a doubling time of 24-28h. In Wright-stained preparations, cells were round and polygonal in shape with small blebs. The cells had biphosphatase and with a few vacuoles and indented nuclei with a large nucleolus. Electron microscopy studies revealed that these lines had immature monocyte features. Both were positive for the staining of alpha naphtol butyrate esterase as well as inhibitable by sodium fluoride. They became adherent to plastic culture dishes and a cultured adherent activity after induction by 1/2400 tetracycline for 2-4 weeks within 7 weeks. Other phenotypic characteristics and differentiation in vivo will be performed in reference to the usefulness of these monocytic lines in studying the biologic mechanisms.

PIV-16


Soft tissue tumors consist of a group of morphologically divergent tumors of mesenchymal origin. A large part of ST is formed by the malignant fibrous histiocytoma (MFH) and many of these tumor cells have a histiocytic appearance. The presence of histiocytic-specific markers within the cytoplasm of MFH tumor cells favours a dual fibroblastic-histiocytic relation. We have investigated the STT immunohistochemically for the presence of receptors for peanut- and soya bean agglutinin (PNA and SBA) and for alpha-1-antichymotrypsin (ACT) using the unlabelled PAP staining procedure on deparaffinized sections. Our results showed that rhabdomyosarcoma (RS), osteosarcoma (OS) and MFH could be positive. For example 58% of the subcutaneously located MFH (n=14) stained for ACT, 41% for SBA and 22% for PNA binding sites. Deeply located MFH's (n=3) stained respectively for 36%, 25% and 11%.

There was a preferential staining of giant and histiocytic cells. It was striking that a great part of the histiocytic cells in STT (RS-OS-MFH) express, but only a small part of the peanut agglutinin - or SBA binding sites. In contrast to malignant histiocytosis which express ACT, PNA and SBA receptors. These cells are derived from cells belonging to the monocyte cell line. Our results showed that mesenchymal cells could behave as histiocytes with respect to morphology and the expression of ACT antigens, but that they differ from "real" histiocytes in their expression of the lectin-receptors.

Poster Session IV

Room E 109
PIN-17

INVASIVENESS AND METASTATIC POTENTIAL OF T-CELL HYBRIDOMAS. E. ROOS, P. DE BAETSSELER, W. ANLIET, Netherlands Cancer Institute, 121 Plesmanlaan, 1066 CX Amsterdam, The Netherlands and Institute for Molecular Biology, Free University, Brussels, Belgium.

All antigen- or ConA-activated T-cells were observed to be invasive in vitro in nonparenchyma cultures, similarly as highly invasive and metastatic lymphoma cells, whereas non-stimulated spleen T-cells were not. Recently, it was found that spontaneous fusion in vivo between non-invasive and non-metastatic BW lymphoma cells and normal host T-lymphocytes gave rise to highly metastatic cells (manuscript submitted). We assumed that such hybrids were metastatic because they expressed the invasiveness of the normal T-cell fusion partner. To test this hypothesis, we prepared hybrids between BW cells (AKR-derived) and activated AAR T-cells, and tested their invasiveness and metastatic potential. All obtained hybridomas were highly invasive. The cell line lost invasiveness after a few weeks in culture. We also fused BW cells with normal spleen T-cells. Some resulting hybridomas were not invasive, but most of the invasives. To test their metastatic potential, hybridoma cells were injected into the tail vein of AAR mice. Invasive hybridomas gave rise to extensive and widespread metastases. Livers and spleens were much enlarged and diffusely infiltrated, and large tumors were found in kidneys, ovaries and mesentry. In contrast, non-invasive hybridomas did not yield metastases. We conclude that a high level of malignancy can be conferred onto T-cell hybridomas by properties derived from normal T-cells, because of their extraordinarily high invasive and metastatic potential, T-cell hybridomas constitute an attractive tool for metastasis research.

PIN-18

TUMORICIDAL EFFECT OF WEBERIN A PARENTAL HUMAN CELL FOLLOWED BY R.B.
I. IMAI

I. TAKACARI AND Y. ISHII

Department of Dermatology, Keio University School of Medicine, 742-8577, Japan.

A case of pruritic reticulohistiocytosis (PR) followed for 12 years was studied histopathologically and electron microscopically. Ultrastructural studies of erythematoid plaque in the early stage revealed that histiocytes and cells with abundant cytoplasm and lymphoid cells with convoluted nuclei infiltrated along the basal layer of the epidermis. In contrast to these findings, erythematoid plaques in the late stage showed different features. Numerous large pleomorphic lymphoid cells proliferated in the lesions, but few histioctyes were observed.

From the above observations, we consider that histiocytes were transformed functionally in the early stage and neoplastic lymphoid cells proliferated in the late stage. Therefore, PR could be a type of neoplastic lymphoproliferative disease originating in the skin such as mycosis fungoides.
DEVELOPMENT OF EXPERIMENTAL HEPATITIS AND FUNCTION OF THE KUPFFER CELLS. S. SASAI, K. SATOH, T. MACAHAMA, T. MACHIDA. Departments of Pathology and Internal Medicine, Iwate Medical Univ., School of Medicine, Morioka-shi, Japan.

The function of the Kupffer cells was examined in relation to the development of experimental hepatitis. Mice were divided into the following three groups:

A: Mouse hepatitis virus (MHV) was inoculated into mice with no previous procedure in Group A, 7 days after blockade of the HEK with carbon particle in group B, and 1000 of mice was compared between groups A and B. The livers were also simultaneously observed morphologically with examination of the carbon clearance rate. In addition, the Kupffer cells, which have phagocytosed carbon particles, were counted in Group A. Correlation was estimated between the carbon clearance rate and the number of Kupffer cells which have phagocytosed carbon particles.

In Group A, phagocytic activities exhibited by the carbon clearance method and the number of Kupffer cells phagocytosing carbon particles were increased until 10 hours after inoculation of MHV, then decreased from 30 hours. The number of Kupffer cells was increased most markedly in the middle than in the central or peripheral zone of the lobules.

Regenerating and necrotizing liver cells appeared earlier and more sever in group B than in Group A. It has been suggested that decrease of phagocytic activity of the Kupffer cells closely relates to development of acceleration of hepatitis by virus infection.
Twenty-seven patients with adult T-cell leukemia lymphoma (ATLL) have been found in the last eight years along the east coast of Kii Peninsula in the middle district of Japan. Their age ranged from 27 to 88 yr with a mean of 54.6 yr and the male/female ratio was 14/8. Most of the patients had lymphadenopathy, splenomegaly, hepatomegaly and skin lesion. Hematologically, leukocytosis of more than 50,000/mm³ was observed in most of the patients, but anemia and thrombocytopenia were mild in comparison with other leukemias. Immunoglobulin levels were within normal limits in most cases. Hyoproteinemia and hypercalcemia were characteristically noted in many patients. The prognosis was very poor (median survival: 74 days) and most of the patients died of pulmonary infections. The leukemic cells in the blood were characterized by marked deformation of the nucleus and the leukemic cells reacted positively with the OKT3 and OKT4 monoclonal antibodies, showing immunologically inducer/helper T-cell phenotype. Sera from 18 patients were examined for antibodies against ATL-associated antigen (anti-ATLA) but in two patients neither anti-ATLA in sera nor proviral DNA in leukemic cells were detected. However, these two patients could not be distinguished from other ATLL patients clinically. The characteristics of these anti-ATLA negative cases will be discussed in comparison with the other ATLL cases. (A part of this work was supported by a Grant-in-Aid from the Ministry of Education in Japan.)
AN AUTOPSY CASE OF IgA MULTIPLE MYELOMA ASSOCIATED WITH IMMUNOGLOBULIN STORAGE HISTIOCYTOSIS AND AMYLOIDOSIS. K. TAKATSUKI, T. KAGIMOTO, F. KAWANO, M. CHITOSE, S. OISHIMA, K. TAKAHASHI AND M. NAITO. The 2nd Dept. of Internal Medicine and The 2nd Dept. of Pathology, Kumamoto University Medical School, Kumamoto 860, Japan.

A case of histiocytosis with l-chain accumulation (Terashima et al.: J. Jpn. Soc. RES 17: 209, 1977) and a case of myeloma accompanied by histiocytosis with IgG myeloma protein accumulation (Itozaki et al.: ibid. 21: 127, 1981) were reported in Japan. The following case represents a rare association of amyloidosis and crystal-loaded histiocytosis in multiple myeloma.

A 60-year-old man was admitted because of left femoral pain. Skeletal X-ray survey disclosed multiple bone lesions and pathologic fracture of the left femur. Plasmacytoma, 4x8cm, originated from a rib was found on the left side of the chest. Serum IgA was 1,439 mg/dl and Bence Jones protein was detected in urine. Bone marrow examination showed 32 per cent plasma cells and many histiocytes containing needle-like crystals. The patient died 20 months after the first admission. Autopsy revealed amyloidosis in the left elbow, thyroid and adrenals.

Histiocytes in the bone marrow were examined by PAP and immunoelectron microscopy. Crystals in the histiocytes were considered to be IgA-k myeloma protein.

PIA-24

IN THE ACTIVITY OF PHAGOCYTOSIS OF LYMPHOCYTIC CELLS.

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It is reported that B-lymphocytic cells ingest latex particles or red cells. This paper shows the results of our examinations on the activity of phagocytosis of various lymphocytic cells to clarify or classify one of their characteristics.

Venous blood were gathered from 10 healthy adults and 6 B-cell leukemia patients, i.e., 4 with acute lymphoblastic leukemia (ALL) and 2 with chronic lymphocytic leukemia (CLL). Mononuclear cells were obtained by gradient sedimentation, and suspended in Medium 199 at a concentration of about 1 x 10⁶/ml. 3 x 10⁴/ml of polystyrene beads coated with rabbit anti-human immunoglobulins antibodies (2-5μm in diameter, Immunobeads; IB) in Medium 199 solution were mixed with cell suspension, and left standing at 20° for 15 min. After incubation at 37° for 60 min, the mixture were used for microscopic examinations. Two hundred cells were counted twice in each sample to determine the percentage of cells which ingested IB under a phase contrast microscopy.

Fourteen to 25% (average 19.9%) of normal lymphocytes ingested IB. All six cases with ALL did not ingest IB, but one out of two cases with CLL, 24% of cells ingested IB.
PII-25

RADIOMICROSCOPIC AND FAXOMICROSCOPIC STUDY ON NON-HODGKIN'S LYMPHOMA

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The present study was undertaken to elucidate morphological differences between T cell lymphomas (TCL) and B cell lymphomas (BCL). 48 of 104 non-Hodgkin's lymphomas were examined electronmicroscopically, and 29 of 44 TCL cases of 104 and 22 cases of BCL further submitted to computerized morphometry (videoplan). Nuclear irregularity was estimated in terms of the shape constant K = 3.141, where S is nuclear area and L is nuclear perimeter. If nuclear section is a circle, the value of K equals 1. and increases with increasing nuclear irregularity. The results are as follows: 1) in small lymphocytic lymphomas, the value of mean K was 0.81 (s.d. 0.065); for BCL, while it was 0.640 (s.d. 0.190); a significantly smaller value for TCL. In large cell lymphomas, K was

= 1.5 for BCL and 2.1 for TCL. Then, the value of K reduced for BL and for TCL: in this succession, in general, the nuclei were more irregular than those of TCL. 2) Nuclear pockets were abundant in BCL, and rER developed well in BL lymphomas. A conspicuous structure of cell membranes were found only in BCL of multicellular center cell origin.
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