# Hematopoiesis

Handout 4
BIO 329 2004

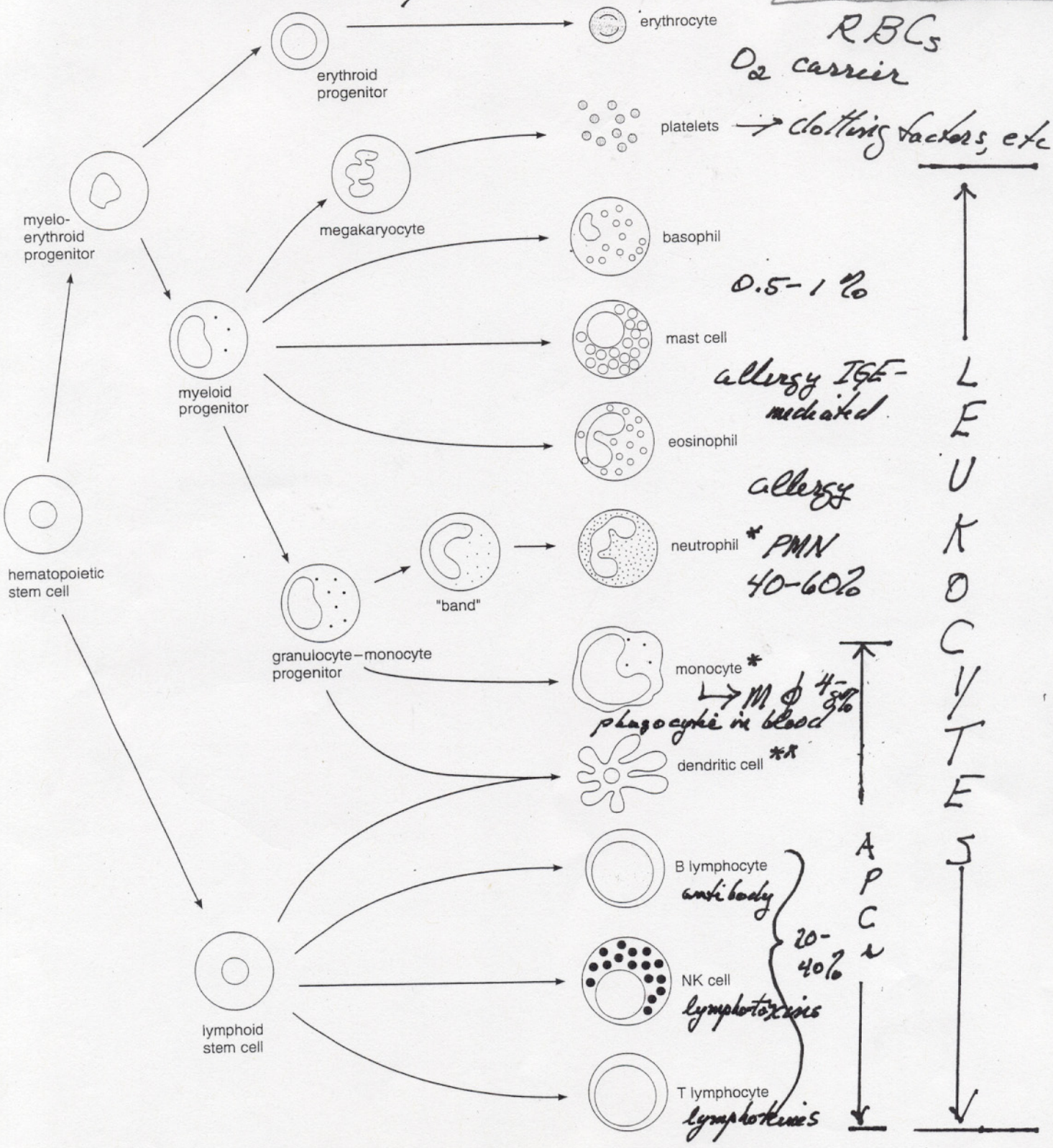



**Figure 1–1.** Schematic overview of hematopoiesis, emphasizing the erythroid, myeloid, and lymphoid pathways. This highly simplified depiction omits many recognized intermediate cell types in each pathway. All of the cells shown here develop to maturity in the bone marrow, except T lymphocytes, which develop from marrow-derived progenitors that migrate to the thymus (see Chapter 3). A common lymphoid stem cell serves as the progenitor of T and B lymphocytes and of natural killer (NK) cells. Dendritic cells arise from both the myeloid and lymphoid lineages.

* The professional phagocytes – mediate innate immunity & adaptive
** APCs that reside in all tissues & initiate most immune responses
*** APCs that mediate specific (acquired) immunity

From Parslow et al., Medical Immunology 10th ed., Lange Publ. NY. 2001

## THE PHAGOCYTES

Although virtually all types of leukocytes contribute to host defense, three types play especially preeminent roles (Table 2–5). Two of these—the **neutrophils** and the **monocyte–macrophage** series—are phagocytic cells, which act primarily by engulfing and digesting bacteria, cellular debris, and other particulate matter. The third group, comprising the **lymphocytes** and their relatives, has little phagocytic capacity but instead carries out a host of other protective reactions that are known collectively as **immune responses.** Lymphocytes are critical for all aspects of acquired immunity, and their properties will be considered at length in later chapters. The phagocytes, on the other hand, may act in cooperation with lymphocytes but also are able to recognize and kill many pathogens directly, and so constitute the most important cellular effectors of the innate immune system.

**Table 2–5.** Properties of three major human cell lineages involved in host defense.[1]

| | Neutrophils | Monocyte–Macrophages | Lymphocytes[2] |
|---|---|---|---|
| Primary effector function | Phagocytosis | Phagocytosis | Varies |
| Cytoplasmic granules | Many | Moderate | Few |
| Can synthesize new membrane or secretory proteins | Very limited | Yes | Yes |
| Terminally differentiated | Yes | Usually | No |
| Principal normal location | Blood and marrow | All tissues | Lymphoid tissues |
| Immunoregulatory cytokine production | No[3] | Yes | Yes |
| Antigen presentation[4] | No | Yes | Yes |

[1] The properties as listed apply to the mature cells of each lineage.
[2] Several distinct subtypes of lymphocytes have been described, and their functional properties differ widely (see Chapter 3). Properties shown are those of B and $\alpha/\beta$ T lymphocytes.
[3] Except certain chemokines (see Chapter 10).
[4] To helper T lymphocytes (see Chapter 4).

# THE TWO PROFESSIONAL PHAGOCYTES: NEUTROPHILS AND MACROPHAGES

| NEUTROPHILS (POLYMORPHONUCLEAR LEUKOCYTES – PMN's) | MACROPHAGES |
|---|---|
| 1. A granulocytic cell which is the predominant cell in peripheral blood; the only granulocytic cell that is phagocytic (other granulocytes include eosinophils and basophils) | A moncytic cell. Monocytes circulate in the peripheral blood and migrate to the tissues to become macrophages; part of the RES system. (Normally unactivated; most efficient at killing when activated.) |
| 2. Huge reserves maintained in the bone marrow which are released into the bloodstream in response to infections; immature forms appear in the bloodstream as "bands"; when band forms are seen in peripheral blood, this is called "a shift to the left" | No large reserves in the bone marrow. |
| 3. Short life span (7-10 days) | Longer life span (months) |
| 4. Expendable "end cells"- delivered to tissues with a brief life span and limited adaptability. They cannot renew their lysosomal granules after use; the entire cell is replaced from bone marrow reserves. | Renewable cells that can undergo profound changes in behavior and biochemical make-up in response to stimuli. They can be stimulated to synthesize large amounts of lysosomal and other enzymes and cytokines. |
| 5. Striking ability to move through tissues | Have a great ability to change shape and outline, but can't move through tissues as well as neutrophils; respond to different chemotactic mediators than neutrophils. |
| 6. Efficient "killers" of bacteria (within minutes) ; weapons include reactive oxygen intermediates, and oxygen independent means – i.e the decreased pH and the contents of the lysosomal granules. | Less efficient killers than neutrophils when unactivated; certain materials degraded slowly or incompletely.<br><br>Contain different lysosomal enzymes, no cationic proteins. Contain defensins but not the same oxygen-dependent system as neutrophils. Activated cells are able to generate reactive nitrogen intermediates. Certain materials degraded slowly or incompletely.<br><br>Serve as the "homes" for intracellular pathogens; must be activated by $T_H$ cells to become efficient killers of intracellular pathogens. |
| 7. Readily adsorb opsonized pathogens: express Fc receptors for IgM and IgG and C3b receptors | Readily adsorb opsonized pathogens: express Fc receptors for IgM and IgG and C3b receptors |
| 8. Cannot serve as antigen presenting cells | Important antigen presenting cells |

Material in this table was adapted from: Mims, C., A. Nash, and J. Stephen. 2001. *Mims' Pathogenesis of Infectious Disease* (5th ed.) Academic Press, San Diego, CA.

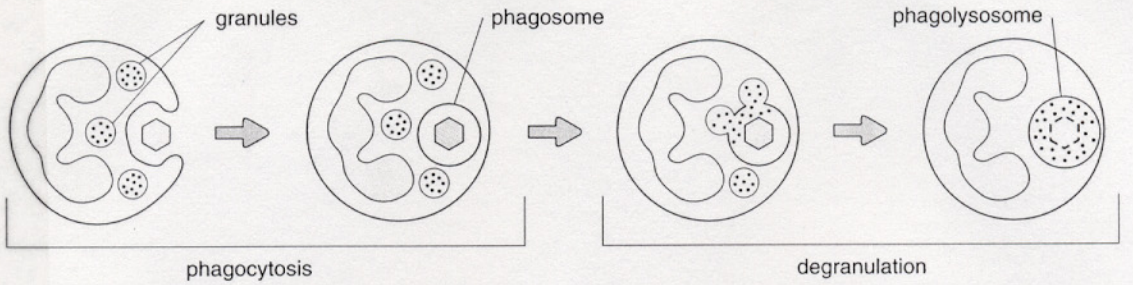



**Figure 2–8.** Engulfment and digestion of a target by a neutrophil. In the process of degranulation, multiple types of cytoplasmic granules may fuse with the phagosome, disgorging their contents into its lumen to inactivate and degrade the target particle.

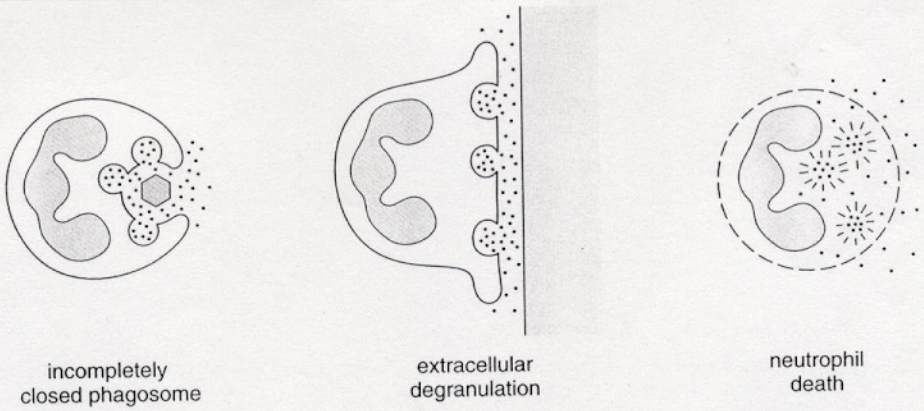


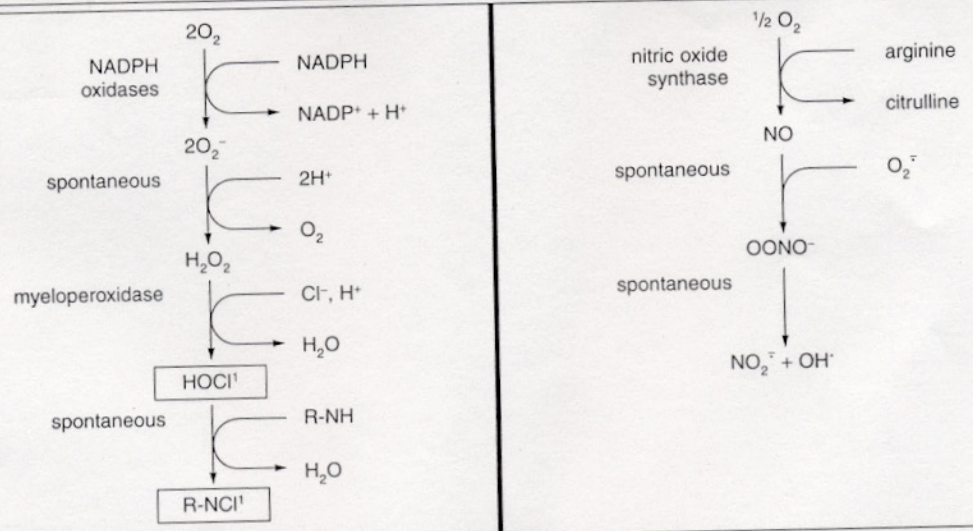

**Figure 2–9.** Some means by which the contents of neutrophil granules may be released into the extracellular milieu. Extracellular degranulation (also called "frustrated phagocytosis") occurs when the cell encounters a target that is too large to engulf. Neutrophil death, and the inadvertent release of granule contents from incompletely closed phagosomes, are common during intense or prolonged neutrophil reactions.

**Table 2–6.** Representative contents of human neutrophil granules.

| | Azurophilic Granules | Specific Granules | Gelatinase Granules |
|---|---|---|---|
| **Soluble Proteins** | | | |
| Microbicidal proteins | Myeloperoxidase<br>Lysozyme<br>Defensins | Lysozyme | |
| Other enzymes | Lysosomal acid hydrolases<br>Elastase<br>Cathepsin G<br>Proteinase 3<br>Azurocidin | Collagenase<br>Gelatinase | Gelatinase |
| Other proteins | | Lactoferrin<br>$\beta_2$-microglobulin<br>Vitamin $B_{12}$-binding protein | |
| **Membrane Proteins** | | | |
| Receptors for: | | Complement proteins (CR3)<br>Chemokines<br>*N*-formyl peptides<br>Laminin<br>Vitronectin | Complement proteins (CR1)<br>Immunoglobulin (FcγRIII) |
| Other proteins | CD63 | Mac-1 (CD11b/CD18) | Mac-1 (CD11b/CD18) |

*Abbreviations:* CR = complement receptor; FcγRIII = type-3 Fc receptor specific for immunoglobulin G (see Chapter 7). Mac-1 is an integrin composed of the CD11b and CD18 chains.

**Table 2–8.** The major oxidative microbicidal pathways in neutrophils.




[1]Hypochlorous acid (HOCl) and organic chloramines (R-NCl) probably account for most of the target oxidation that takes place in vivo. The superoxide ($O_2^-$) and hydrogen peroxide ($H_2O_2$) intermediates in this pathway are also strong oxidizing agents but probably proceed along the pathway too quickly to play a major direct role in attacking target particles. "R-NH" denotes any organic primary or secondary amine.

**Table 2–9.** Cells of the monocyte–macrophage lineage.

| Tissue | Cell Type Designation |
|---|---|
| Blood | Monocytes |
| Bone marrow | Monocytes and monocyte precursors (monoblasts, promonocytes) |
| Any solid tissue | Resident macrophages (histiocytes) and myeloid dendritic cells |
| Skin | Langerhans' cells |
| Liver | Kupffer cells |
| Lung | Alveolar macrophages |
| Bone | Osteoclasts |
| Synovium | Type A synovial cells |
| Central nervous system | Microglia |
| Pleural cavity | Pleural macrophages |
| Peritoneal cavity | Peritoneal macrophages |
| Chronic inflammatory exudate | Exudate macrophages |
| Granuloma | Epithelioid cells, multinucleated |

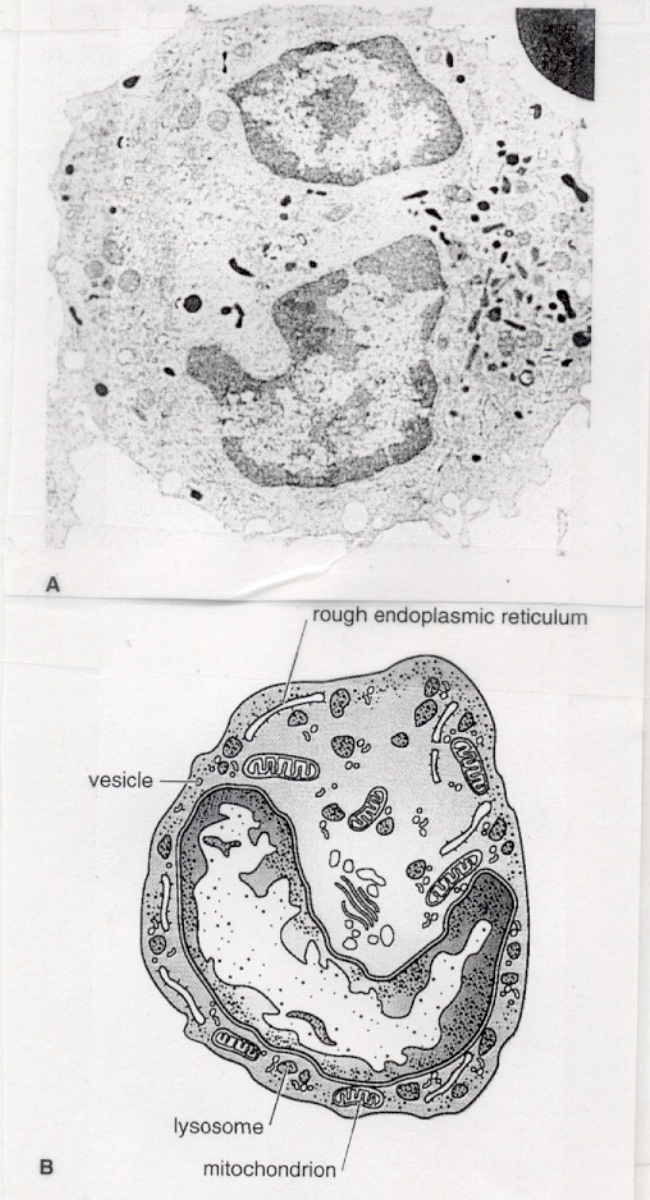



**Figure 2–11. A:** Electron micrograph and **B:** diagram of a human monocyte. Cytoplasmic granules (lysosomes) are present but are much less numerous than in neutrophils. However, the cell retains the abundant Golgi apparatus and rough endoplasmic reticulum needed to synthesize additional granules or secretory proteins as needed.

**Table 2–11.** Secretory products of macrophages.

**Enzymes**
- Lysozyme
- Acid hydrolases (proteases, nucleases, glycosidases, phosphatases, lipases, etc)
- Elastase
- Collagenase
- Plasminogen activator
- Angiotensin-converting enzyme

**Mediators**
- Interferons (IFNα, IFNβ)
- Colony-stimulating factors (GM-CSF, M-CSF, G-CSF, and others)
- Interleukins (IL-1, IL-6, IL-8, IL-10, IL-12)
- Chemokines
- Tumor necrosis factor α (TNFα)
- Platelet-derived growth factor
- Platelet-activating factor (PAF)
- Transforming growth factor β (TGFβ)
- Angiogenesis factors
- Nitric oxide
- Arachidonate derivatives (prostaglandins, leukotrienes)

**Complement components**
- C1–C9
- Properdin
- Factors B, D, I, and H

**Coagulation factors**
- Factors V, VII, IX, and X
- Prothrombin
- Thromboplastin

**Reactive oxygen species**
- Hydrogen peroxide
- Superoxide anion
- Nitric oxide
- Singlet oxygen
- Hydroxyl radicals

**Miscellaneous**
- Glutathione
- Nucleotides (adenosine, thymidine, guanosine, etc)

# Specific Immunity (Acquired Immunity)*

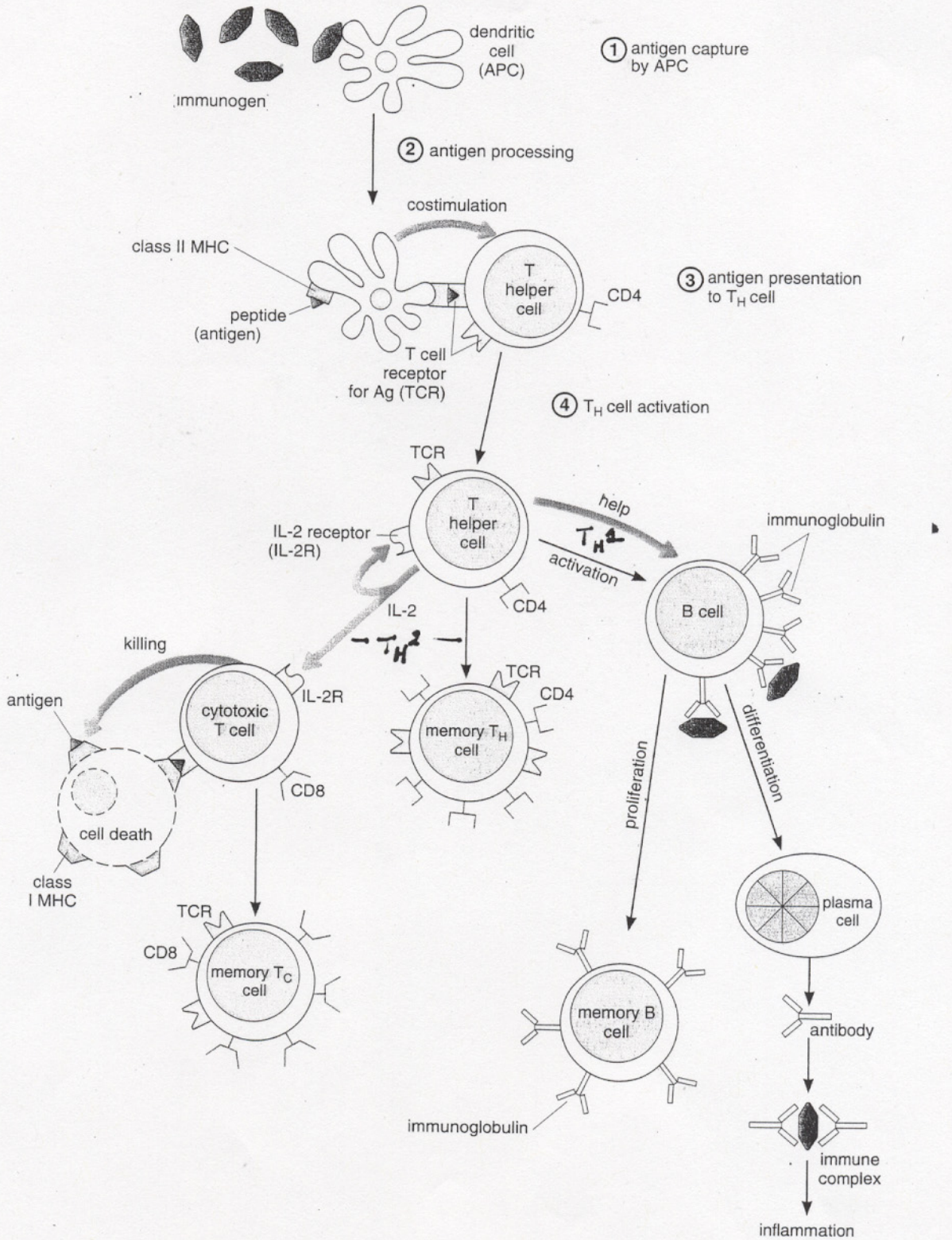


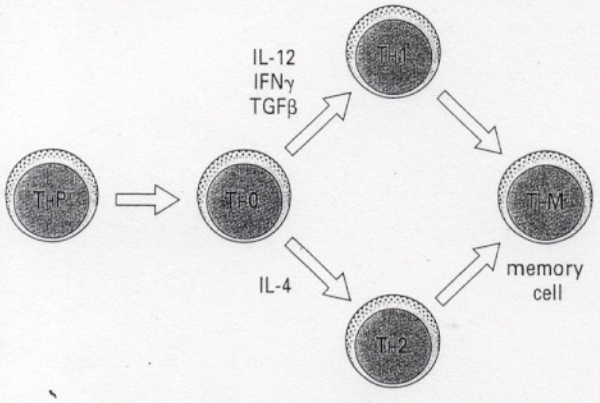

**Figure 4–2.** Sequence of events in a prototypical immune response (see text for details). *Abbreviations:* MHC = major histocompatibility class; APC = antigen-presenting cell; TCR = T-cell receptor.

* adaptive pathways of APCs

From Parslow et al., 2001
Medical Immunology, Lange, N.Y.

TH1 vs TH2

**Differentiation of CD4+ TH cells**




| THP | TH0 | TH1 | TH2 | THM |
|---|---|---|---|---|
| IL-2 | IL-2 | IL-12 | | IL-2 |
| | IFNγ | IFNγ | | |
| | TNFβ | TFNβ | | |
| | IL-3 | IL-3 | | |
| | IL-4 | | IL-4 | |
| | IL-5 | | IL-5 | |
| | IL-6 | | IL-6 | |
| | IL-9 | | IL-9 | |
| | IL-10 | | IL-10 | |
| | IL-13 | | IL-13 | |
| | GM–CSF | GM–CSF | GM–CSF | |
| | TNFα | TNFα | TNFα | |

**Fig. 10.6** The diagram illustrates the differentiation of murine Th cells into subsets with distinctive patterns of cytokine release. IL-12, IFNγ and TGFβ favour differentiation of TH1 cells and IL-4 favours TH2 cells. The cytokine patterns influence the effector functions that are activated.

**Selection of effector mechanisms by TH1 and TH2 cells**

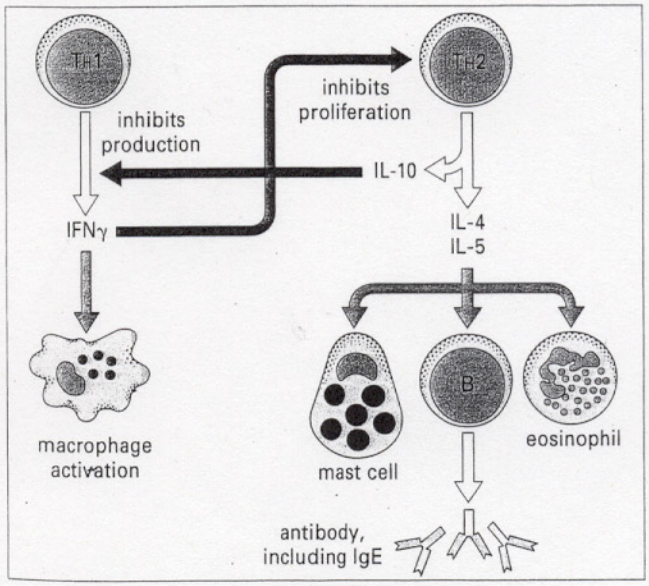



**Fig. 10.7** Not only does their cytokine output drive different effector pathways, but Th1 cells tend to switch off Th2 cells, and *vice versa*.

From Roitt et al., 1998, Immunology, 5th ed. Mosby, London, UK.

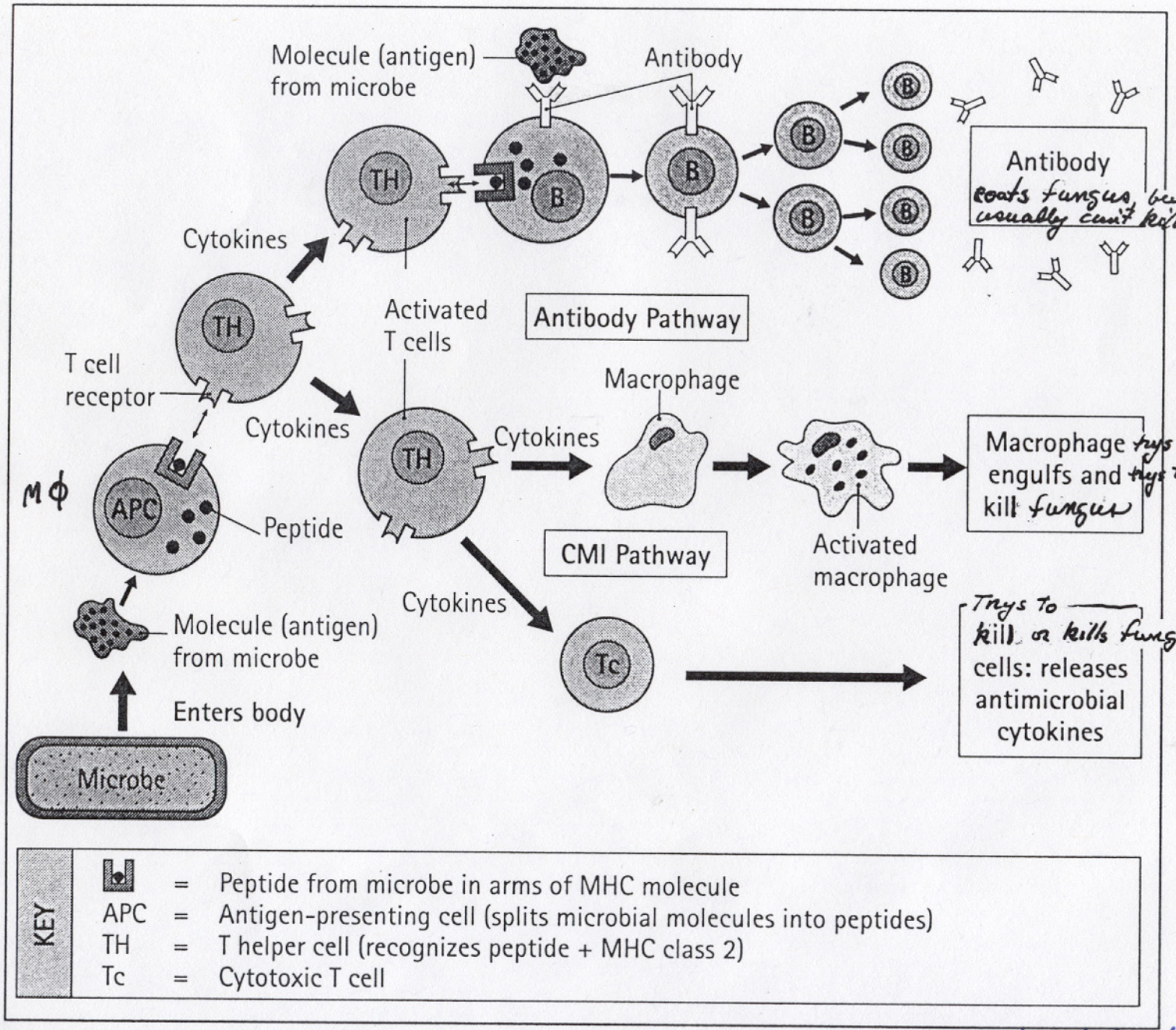



Figure 11 How cells co-operate in an immune response. From Mims (The War Within Us) Academic Press, 2000. pg 50.

**Table 50–3.** Effect of common immunologic abnormalities on disease course of common mycoses.

| Mycosis | Reduction in PMN[1] | Reduction in CMI[2] | Other |
|---|---|---|---|
| **Superficial** | | | |
| Pityriasis (tinea) versicolor | None | None | Lipid hyperalimentation therapy is associated with *Malassezia furfur* and pulmonary vasculitis, especially in infants. |
| *Pityrosporum* folliculitis | None | None | Treatment |
| Tinea nigra | None | None | |
| White piedra | Hematogenous dissemination of *Trichosporon beigelii*[4] | None | |
| Black piedra | None | None | |
| **Cutaneous** | | | |
| Dermatophytosis | None | Increased severity and chronicity of *T rubrum* infection | |
| **Subcutaneous** | | | |
| Chromomycosis | None | None | |
| Mycetoma | None | None | |
| Sporotrichosis | None | Increased in severity and likelihood of dissemination | |
| **Systemic, invasive** | | | |
| Primary pathogens | | | |
| Blastomycosis | None | Increase in severity and likelihood of dissemination | Frequency of meningitis is increased in patients with AIDS. |
| Coccidioidomycosis | None | Definite increase in severity and dissemination | Possible increase in severity and dissemination in second and third trimesters of pregnancy. |
| Histoplasmosis | None | Definite increase in severity and dissemination | |
| Paracoccidioidomycosis | None | Probable increase in severity or likelihood of dissemination | |
| Opportunistic pathogens | | | |
| Candidiasis | Hematogenous dissemination | Increased severity of mucosal disease | |
| Cryptococcosis | None | Definite increase in severity and dissemination | |
| Aspergillosis | Invasive paranasal sinus and respiratory infection, and hematogenous dissemination | Possible increase in severity | |
| Mucormycosis (zygomysosis) | Invasive paranasal sinus and respiratory infection, and hematogenous dissemination | Possible increase in severity | Diabetic ketoacidosis predisposes to invasive paranasal sinus infection. |
| Pneumocystosis | None | Drastic incraese in incidence and severity in AIDS | |
| Phaeohyphomycosis | Invasive paranasal sinus infection and hematogenous dissemination | None | |
| Hyalohyphomycoses | Invasive paranasal sinus infection and hematogenous dissemination | None | |

*Abbreviations:* AIDS = acquired immunodeficiency syndrome; CMI = cell-mediated immunity.
[1] <500 PMN/dL.
[2] Principally AIDS. Histoplasmosis, coccidioidomycosis, and cryptococcosis also occur with increased severity and/or extent of dissemination in patients with other causes of depressed CMI (eg, immunosuppression for organ transplantation).
[3] *Malassezia* is a lipophilic fungus. Lipid hyperalimentation therapy allows them access to the bloodstream. Patients with *Malassezia* fungemia do not have tinea versicolor or folliculitis.
[4] Patients with *Trichosporon beigelii* sepsis do not necessarily have white piedra.

**CHART 2-7. Serologic Tests to Diagnose Various Diseases**

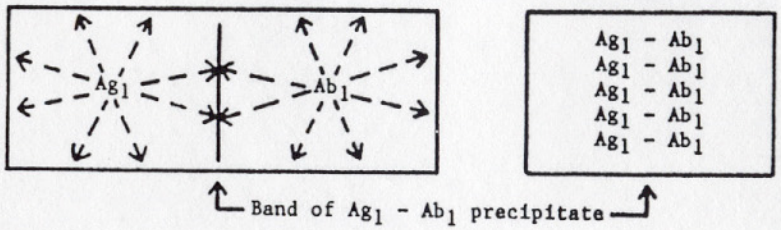
| | HISTOPLASMOSIS | BLASTOMYCOSIS | COCCIDIOI-DOMYCOSIS | PARACOCCIDI-OIDOMYCOSIS | CRYPTO-COCCOSIS | INVASIVE ASPERGILLOSIS | SYSTEMIC CANDI-DOSIS |
|---|---|---|---|---|---|---|---|
| Tests to detect circulating fungal antibodies: | | | | | | | |
| Immunodiffusion | X | X | X | X | | X | X |
| Tube agglutination | | | | | X | | X |
| Latex agglutination | X | | X | | | | X |
| Complement fixation | X | X | X | X | | X | |
| Indirect fluorescent antibody | | | | | X | | |
| Counterimmunoelectrophoresis | X | | X | X | | X | X |
| Tests to detect fungal antigens: | | | | | | | |
| Immunodiffusion | X | X | X | X | | | |
| Latex agglutination | | | | | X | | |
| Direct fluorescent antibody | X | X | X | | X | X | X |

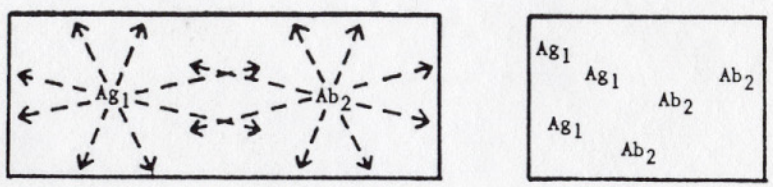
CHART 2-5. Serologic Tests to Detect Patient's Antibodies

POSITIVE TEST

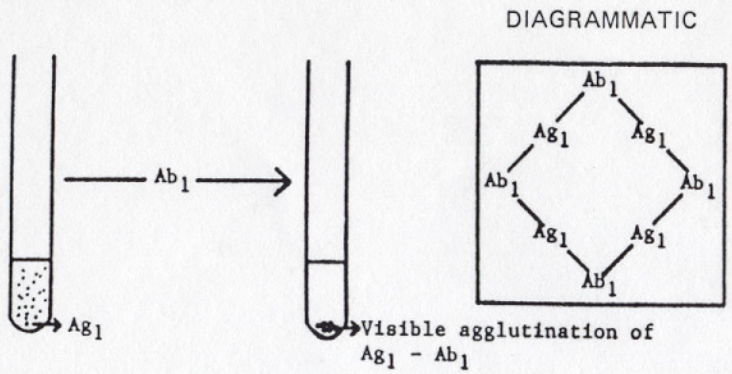
NEGATIVE TEST

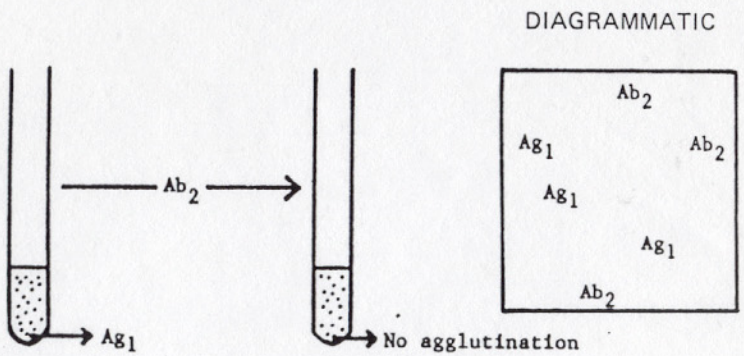
IMMUNODIFFUSION




TUBE AGGLUTINATION



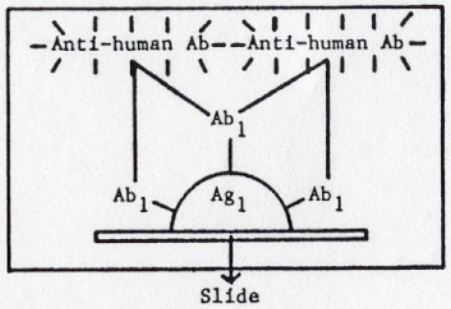



POSITIVE TEST
NEGATIVE TEST
INDIRECT LATEX AGGLUTINATION
DIAGRAMMATIC
Ab1
Ag1 coated latex particles
Visible agglutination of L - Ag1 - Ab1
Ab2
No agglutination
COMPLEMENT FIXATION
RBC, Anti-RBC Ab
Ag1, Ab1, C'
No lysis; RBCs intact; red, smoky solution
Ag1, Ab2, C'
Lysis; no intact RBCs; red, clear solution
RBC
Anti-RBC Ab
C'

POSITIVE TEST

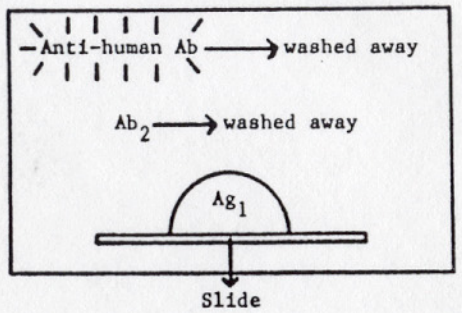
INDIRECT FLUORESCENT ANTIBODY

DIAGRAMMATIC



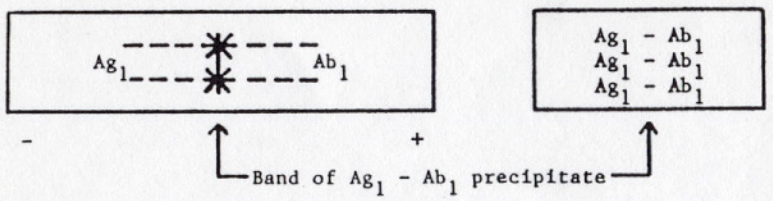

NEGATIVE TEST

DIAGRAMMATIC

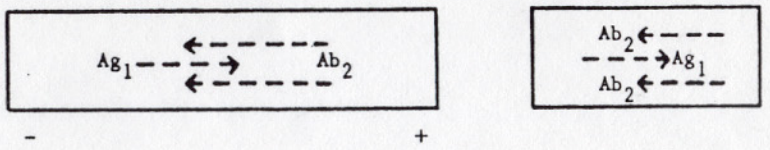



COUNTERIMMUNOELECTROPHORESIS

DIAGRAMMATIC




DIAGRAMMATIC




Key:

Ag = Known fungal antigen

Ab = Patient's unknown antibody

L = Latex particle

RBC = Red blood cell

Anti-RBC Ab = Anti-red blood cell antibody

C′ = Complement

Anti-human Ab = Anti-human antibody

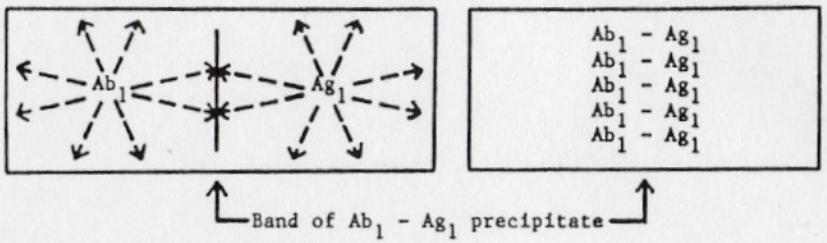
CHART 2-6. Serologic Tests to Detect Fungal Antigens in Patient Specimens

POSITIVE TEST

NEGATIVE TEST

IMMUNODIFFUSION

DIAGRAMMATIC

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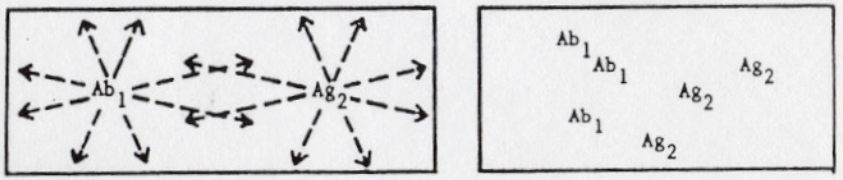
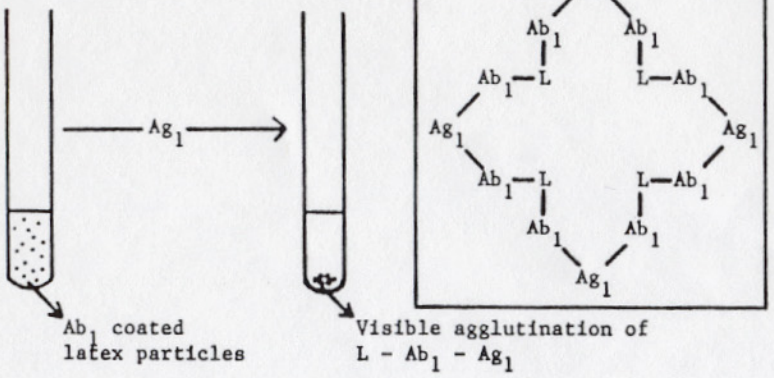



INDIRECT REVERSE LATEX AGGLUTINATION

DIAGRAMMATIC

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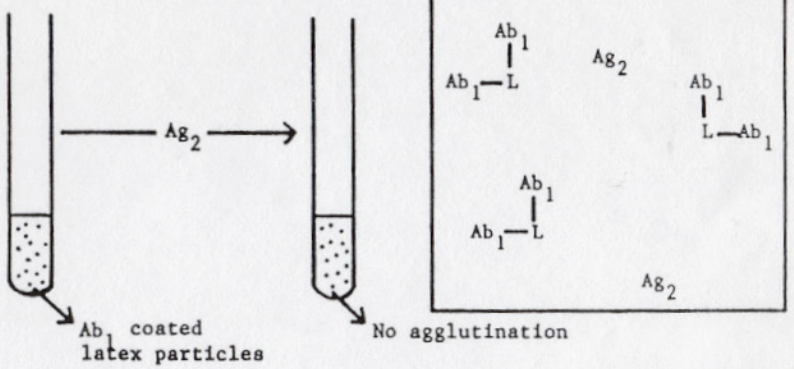
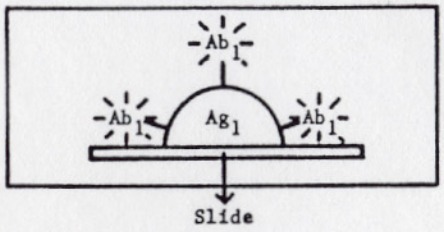


POSITIVE TEST

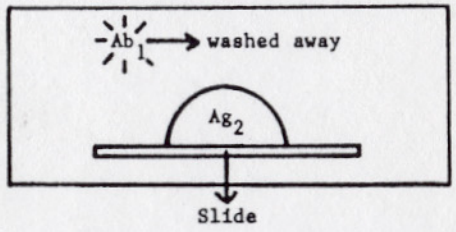
DIRECT FLUORESCENT ANTIBODY

DIAGRAMMATIC




NEGATIVE TEST

DIAGRAMMATIC




Key:

Ag = Patient's unknown fungal antigen

Ab = Known antibody

L = Latex particle

**Table 2** *Tissue Reactions in Fungous Diseases**

Chronic inflammatory reactions
- Lymphocytes, plasma cells, neutrophils, and fibroblasts, occasionally giant cells
- *Rhinosporidium seeberi*
- Entomophthoromycosis

Pyogenic reactions
- Acute or chronic, suppurative neutrophilic infiltrate
- *Actinomyces israelii:* sulphur granules, also lipid-laden peripheral histiocytes
- *Nocardia asteroides*
- Acute aspergillosis
- Acute candidiasis

Mixed pyogenic and granulomatous reactions
- Neutrophilic infiltration and granulomatous reaction, lymphocytes, plasma cells
- *Blastomyces dermatitidis*
- *Paracoccidioides brasiliensis*
- *Coccidioides immitis:* neutrophils, especially at broken spherule
- *Sporothrix schenckii:* organism rarely seen in tissue
- Chromoblastomycosis: chronic pyogenic inflammation; epithelioid cell nodules and giant cells
- Mycetoma; in addition, may be large foamy giant cells similar to xanthoma

Pseudoepitheliomatous hyperplasia
- Following chronic inflammation in skin (hyperplasia of epidermal cells, hyperkeratosis, elongation of rete ridges)
- *Blastomyces dermatitidis*
- *Paracoccidioides brasiliensis*
- Chromoblastomycosis
- *Coccidioides immitis*

Histiocytic granuloma
- Histiocytes frequently with intracellular organisms, sometimes becoming multinucleate giant cells
- *Histoplasma capsulatum*
- Meningeal *Cryptococcus neoformans*

Granuloma with caseation
- Granulomatous reaction, Langhans' giant cells (L.G.C.), central necrosis
- *Histoplasma capsulatum*
- *Coccidioides immitis*

Granuloma "sarcoid" type
- Nonnecrotizing
- *Cryptococcus neoformans*
- Occasionally *Histoplasma capsulatum*

Fibrocaseous pulmonary granuloma; "tuberculoma"
- *Histoplasma capsulatum:* thick fibrous wall surrounding epithelioid and L.G.C. organisms in soft center, often calcification
- *Coccidioides immitis:* Thin fibrous wall, rarely calcified
- *Cryptococcus neoformans:* poorly defined

Thrombotic arteritis
- Thrombosis, purulent coagulative necrosis, invasion of vessels
- Aspergillosis
- Mucormycosis

Fibrosis
- Proliferating fibroblasts, deposition of collagen; may resemble keloid
- *Loboa loboi*

Sclerosing foreign body granuloma
- In paranasal sinuses or following viral infection
- *Aspergillus* sp., bizarre hyphae in giant cells

**Table 1** *Clinical Types of Fungous Infections**

| *Type* | *Disease* | *Causative Organism* |
|---|---|---|
| Superficial infections | Pityriasis versicolor | *Malassezia furfur* |
| | Piedra | *Trichosporon beigelii* (white) |
| | | *Piedraia hortae* (black) |
| | Tinea nigra | Exophiala werneckii |
| Cutaneous infections | Ringworm of scalp, glabrous skin, nails | Dermatophytes (*Microsporum* sp., *Trichophyton* sp., *Epidermophyton* sp.) |
| | Candidiasis of skin, mucous membranes, and nails | *Candida albicans* and related species |
| Subcutaneous infections | Chromoblastomycosis | *Fonsecaea pedrosoi* and related forms |
| | Mycotic mycetoma | *Pseudallescheria boydii. Madurella mycetomatis*, etc. |
| | Entomorphthoromycosis | *Basidiobolus ranarum* |
| | | *Conidiobolus coronatus* |
| | Rhinosporidiosis | *Rhinosporidium seeberi* |
| | Lobomycosis | *Loboa loboi* |
| | Sporotrichosis | *Sporothrix schenckii* |
| Systemic infections | Pathogenic fungous infections | |
| | Histoplasmosis | *Histoplasma capsulatum* |
| | Blastomycosis | *Blastomyces dermatitidis* |
| | Paracoccidioidomycosis | *Paracoccidioides brasiliensis* |
| | Coccidioidomycosis | *Coccidioides immitis* |
| | * Opportunistic fungous infections | |
| | ~~Histoplasmosis~~ Cryptococcosis | *Cryptococcus neoformans* |
| | Aspergillosis | *Aspergillus fumigatus*, etc. |
| | Mucormycosis | *Mucor* sp., *Absidia* sp., *Rhizopus* sp., *Rhizomucor* sp. |
| | Candidiasis (systemic) | *Candida albicans* |
| | Pseudallescheriasis | *Pseudallescheria boydii* |
| Miscellaneous and rare mycoses and algosis | Phaeohyphomycosis | *Wangiella dermatitidis, Phialophora* sp., etc. |
| | Hyphomycosis | |
| | Algosis | *Paecilomyces* sp., *Beauveria* sp., *Scopulariopsis* sp. etc. |
| | Basidiomycosis | *Prototheca* sp. |
| | | *Schizophyllum commune, Coprinus* sp., etc. |