Pituitary Function and Immunity

Editor

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PREFACE

Pathologists suspected at the beginning of this century that the thymus might be subject to hormonal regulation. Subsequent observations in animals revealed that the extirpation of some endocrine organs, such as the gonads, induced changes in the size of the thymus and of other lymphoid organs. These findings triggered a series of experiments in the 1930s and 1940s, which were aimed at the elucidation of hormonal influences on lymphoid tissue. At that time, the function of lymphoid organs was unknown and knowledge of the endocrine system was limited, which hampered seriously the development of rational approaches to this problem. This difficulty, coupled with primitive and inefficient methodology, led to confusion and eventual disbelief in hormonal immunoregulation.

Until recently the accumulation of biomedical knowledge was confined within the limits of various disciplines, whereas interdisciplinary research lagged behind. However, it is becoming eminently clear that the creation of disciplines was merely the reflection of our intellectual limitations in understanding biomedicine and that further advancement is possible only through building interdisciplinary bridges, which enable us to view natural phenomena in their true complexity. Thus, it became obvious that neurology and endocrinology examine different facets of the same regulatory mechanism, now frequently referred to as the neuroendocrine system.

The immune system is still regarded by many as autonomous, with an elaborate self-regulatory mechanism, which is influenced only superficially, if at all, by neuroendocrine factors. Presumably, this view stems from the ability of lymphocytes to mount immune reactions in vitro and also to migrate into diseased tissues, or even to mucosal surfaces, and to function in such environments where neurohormonal regulation might be grossly disturbed or nonexistent. Nevertheless, some basic and clinical scientists suspected all along that interaction and coordination must exist between these two systems. Thus, ever since transplantation immunity has been discovered, it was clear that the conceptus in mammals is an allograft equivalent, yet it survives, despite the recognition of paternal antigens of the fetus by the maternal immune system. Also, it has been well known for some time that mammals and birds protect their offspring against environmental pathogens by the transfer of specific antibodies through the egg, placenta and/or milk. This elaborate mechanism, which is vital for the survival of the species, could hardly have evolved without a delicate coordination of reproduction, a neurohormonally regulated function, with the immune system. Clinical observations revealed that certain autoimmune diseases are prevalent in females. Furthermore, some diseases in which psychosomatic factors have been identified, such as rheumatoid arthritis, also have underlying immune abnormalities. These facts point to the inevitable conclusion that interaction between the neuroendocrine and immune systems is a necessity, and that it has to be elucidated, it we are to understand immune function in the context of homeostasis of the organism.

This volume examines the role of the pituitary gland in the regulation of the immune system using an interdisciplinary approach. Introductory chapters are provided for the reader, which are intended to bridge the gaps between disciplines. It is my sincere hope that this book will catalize the reformation of prevailing views about immunoregulation and about the integration of the immune system into the overall function of the body.

I. Berczi

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ABBREVIATIONS

A	—	Adrenalin
ACTH	—	Adrenocorticotropic hormone
ADCC	—	Antibody-dependent cellular cytotoxicity
ADH	—	Antidiuretic hormone
ADP	—	Adenosine diphosphate
Adrx	—	Adrenalectomy
AIPF	—	Anaphylactoid inflammation promoting factor
ATP	—	Adenosine triphosphate
ATS	—	Anti-thymocyte serum
AVP	—	Arginine vasopressin
BCG	—	Bacille Calmette-Guerin
BGG	—	Bovine gammaglobulin
BGH	—	Bovine growth hormone
BPRL	—	Bovine prolactin
BRC	—	Bromocriptine
C_3	—	Component C_3 of complement
cAMP	—	Cyclic 3′, 5′ - adenosine monophosphate
CBG	—	Corticosteroid binding globulin
cGMP	—	Cyclic 3′, 5′ - guanosine monophosphate
CG	—	Chorionic gonadotropin
CH	—	Constant portion of heavy chain
CL	—	Constant portion of light chain
CNS	—	Central nervous system
Con-A	—	Concanavalin A
C. parvum	—	*Corynebacterium parvum*
CRH	—	Corticotropin-releasing hormone
CSF	—	Colony stimulating factor
CTL	—	Cytotoxic T lymphocytes
DES	—	Diethylstilbestrol
2-DG	—	2-Deoxyglucose
DHT	—	Dihydrotestosterone
DLN	—	Draining lymph nodes
DNA	—	Deoxyribonucleic acid
DNCB	—	Dinitrochlorobenzene
DNP	—	Dionitrophenol
DTH	—	Delayed type hypersensitivity
E. coli	—	*Escherichia Coli*
EBV	—	Epstein Barr virus
ECF	—	Eosinophil chemotactic factor
ECF-A	—	Eosinophil chemotactic factor of anaphylaxis
EPF	—	Early pregnancy factor
ESF	—	Erythropoietin stimulating factor
ESP	—	Eosinophil stimulation factor
EV	—	Estradiol valerate
Fc	—	Cristalizing fraction of immunoglobulin
FSH	—	Follicle stimulating hormone
GAF	—	Glucorticoid antagonizing factor
GF	—	Germ-free
GH	—	Growth hormone
GH-RF	—	Growth hormone releasing factor

GH-RIH	—	Growth hormone release-inhibiting hormone
PGE_1	—	Prostaglandin E_1
PHA	—	Phytochaemagglutinin
PIH	—	Prolactin inhibiting hormone
PL	—	Placental lactogen
PNA	—	Peanut agglutinin
poly A:U	—	Polyadenylic-polyuridylic acid
poly I- poly C	—	Polyinosinic-polycytidylic acid
poly I:C	—	Polyinosinic-polycytidylic acid
PPD	—	Purified protein derivative
PRL	—	Prolactin
PTH	—	Parathyroid hormone
PWM	—	Pokeweed mitogen
RES	—	Reticuloendothelial system
RNA	—	Ribonucleic acid
RPRL	—	Rat prolactin
S. aureus	—	*Staphylococcus aureus*
s.c.	—	Subcutaneous
SC	—	Secretory component
20 αSDH	—	20 α Hydroxysterioid dehydrogenase
SLE	—	Systemic lupus erythematosus
Slp	—	Sex-linked protein
S. mansoni	—	*Schistosoma mansoni*
SP	—	Substance P
SPF	—	Specific pathogen-free
SPG	—	Syngeneic pituitary graft
SRBC	—	Sheep red blood cells
SRS-A	—	Slow reactive substance of anaphylaxis
ssDNA	—	Single stranded deoxyribonucleic acid
GIF	—	Glucocorticoid increasing factor
GMP	—	Guanosine monophosphate
GRMF	—	Glucosteroid response modifying factor
GTP	—	Guanosine triphosphate
GVH	—	Graft-vs.-host
GVHR	—	Graft-vs.-host-reaction
H	—	Heavy (chain of immunoglobulin)
^{3}H-DHA	—	^{3}H-dihydroalperenolol
^{3}H-SP	—	^{3}H-spiroperidol
HCG	—	Human chorionic gonadotropin
HGH	—	Human growth hormone
HLA	—	Human histocompatibility antigen
HPL	—	Human placental lactogen
HRBC	—	Horse red blood cells
Hypox	—	Hypophysectomy/ized
^{125}I-HYP	—	^{125}I-hydroxybenzyl pindolol
Ia	—	Immune response associated (antigens)
IGF	—	Insulin-like growth factor
Ig-SC	—	Immunoglobulin secreting cells
IL-1	—	Interleukin 1
IL-2	—	Interleukin 2
i.m.	—	Intramuscular
i.p.	—	Intraperitoneal

Ir	—	Immune response (genes)
ITP	—	Idiopathic thrombocytopenic purpura
K	—	Killer
KLH	—	Keyhole limpet hemocyanin
L	—	Light (chain of immunoglobulin)
LH	—	Luteinizing hormone
LH-RH	—	Lutenizing hormone-releasing hormone
LPH	—	Lipotrophin
LPS	—	Lipopolysaccharide
MBSA	—	Methylated bovine serum albumin
MC	—	Methyl cholanthrene
MCF	—	Macrophage chemotactic factor
MHC	—	Major histocompatibility complex
MIF	—	Macrophage migration inhibitory factor
MLC	—	Mixed lymphocyte culture
MLR	—	Mixed lymphocyte reaction
MMF	—	Macrophage mitogenic factor
MP	—	Methylprednisoline
MSH	—	Melanocyste-stimulating hormone
NA	—	Noradrenaline
NK	—	Natural killer
NTA	—	Natural T cell antibody
NZB	—	New Zealand black
NZW	—	New Zealand white
OV	—	Ovariectomy/ized
PDGF	—	Platelet-drived growth factor
PFC	—	Plaque-forming cells
TA	—	Trimacinolone acetonide
T_3	—	3, 5, 3′ - Triiodo-L-thyronine, triiodothyronine
T_4	—	3, 5, 3′, 5′ - Tetraiodo-L-thyronine, thyroxin
TCGF	—	T cell growth factor
TFM	—	Testicular feminized male mice
TK	—	Thymidine kinase
TL	—	Thymus leukemia antigen
TRH	—	Thyrotropin-releasing hormone
TSH	—	Thyroid-stimulating hormone
VIP	—	Vasoactive intestinal polypeptide

TABLE OF CONTENTS

Chapter 1
The Immune System and its Function 1
Istvan Berczi

Chapter 2
The Pituitary Gland 27
Eva Nagy

Chapter 3
Pituitary Malfunction and Immune Abnormalities 41
Istvan Berczi

Chapter 4
The Influence of Pituitary-Adrenal Axis on the Immune Sytem 49
Istvan Berczi

Chapter 5
The Effects of Growth Hormone and Related Hormones on the Immune System 133
Istvan Berczi

Chapter 6
Prolactin and Other Lactogenic Hormones 161
Istvan Berczi and Eva Nagy

Chapter 7
Gonadotropins and Sex Hormones 185
Istvan Berczi

Chapter 8
The Pituitary Thyoid Axis 213
Istvan Berczi

Chapter 9
The Effect of Miscellaneous Hormones and Neurotransmitters on the Immune System 221
Istvan Berczi

Chapter 10
Immunoregulation by Pituitary Hormones 227
Istvan Berczi

Chapter 11
Regulatory Immune-Neuro-Endocrine Feedback Signals 241
Hugo Besedsovsky, Adriana del Ray, and Ernst Sorkin

Chapter 12
The Central Nervous System and Learning; Feedforward Regulation of Immune Responses 251
Dana Bovbjerg and Robert Ader

Chapter 13
Role of Hormonal Immunoregulation 261
David A. Clark

Chapter 14
The Influence of Hormones on Infectious and Parasitic Disease 273
Istvan Berczi

Chapter 15
Sex Hormones in Autoimmuinity 283
Elizabeth S. Raveche and Alred D. Steinberg

Chapter 16
Pituitary-Neurohormonal Immunoregulation in Cancer 330
Benjamin H. Newberry and Thomas J. Gerstenberger

Index 313

Chapter 1

THE IMMUNE SYSTEM AND ITS FUNCTION

I. Berczi

TABLE OF CONTENTS

I. Introduction 2

II. Cells of the Immune System 3
- A. Development of Immunocytes 3
- B. Lymphocytes 3
  - 1. T Lymphocytes 4
  - 2. B Lymphocytes 5
- C. Macrophages and Monocytes 6
- D. Killer Cells 7
- E. Polymorphonuclear Leukocytes 7
  - 1. Basophilic Leukocytes 8
  - 2. Eosinophilic Leukocytes 8
  - 3. Neutrophil Leukocytes 9
- F. Platelets 9
- G. Other Cells 10
  - 1. Red Blood Cells 10
  - 2. Mucosal and Glandular Epithelial Cells 10
  - 3. Astrocytes, Epidermal, and Endothelial Cells 10

III. Humoral Factors of Immunity 11
- A. Immunoglobulins 11
  - 1. IgA 12
  - 2. IgD 12
  - 3. IgE 12
  - 4. IgG 14
  - 5. IgM 14
  - 6. Antibody Diversity 14
- B. Complement 15
- C. Lymphokines, Interleukins, and Cytokines 16

IV. Antigens 16
- A. Soluble Antigens 17
- B. Histocompatibility Antigens 17

V. The Immune Response 19
- A. Cell Interactions During Immune Reactions 19
- B. Immune Effector Mechanisms 21
  - 1. Antibody-Mediated Mechanisms 21
  - 2. Cell-Mediated Mechanisms 22
- C. The Effect of Immune Mechanisms on Other Systems 22

References 22

I. INTRODUCTION

The science of immunology was founded by Jenner's observations in 1798 on the protection against smallpox by inoculation with cowpox. His experiments were prompted by the widely held impressions that those individuals who had had cowpox, which is a benign disease, were not affected in subsequent smallpox epidemics. To test this belief, he inoculated a boy with pus from a cowpox lesion of a dairy maid. Some weeks later, when the boy was reinoculated with infectious pus from a patient suffering from smallpox, the disease failed to occur. Repetition of the experiment many times led to Jenner's classic report that vaccination (vacca = cow) leads to immunity against smallpox. Jenner's finding was not extended for about 100 years until Pasteur rediscovered the general principles underlying vaccination. During his studies on chicken cholera, Pasteur happened to inoculate some chickens with an old culture of the causative bacterium *(Pasturella aviseptica)*, and these animals failed to develop disease. When the same chickens were reinoculated with a fresh culture, which was known to be pathogenic, they again failed to become ill. These observations were soon applied to many other infectious diseases; various procedures have been used to destroy the viability or to attenuate the virulence of pathogenic organisms for the purpose of vaccination.

Another giant of medical science, Robert Koch, discovered that guinea pigs infected with the tubercle bacillus will display a local reaction if injected intradermally with culture fluids of *Mycobacterium tuberculosis* ("Koch phenomenon"). Chase and Landsteiner showed in 1945 that this type of allergic reaction, classified later as delayed-type hypersensitivity, can only be transferred from one animal to another by living cells (cell-mediated immunity), whereas other immune reactions can be transmitted by serum (humoral immunity).

The ability of responding rapidly to infectious agents, or to other foreign materials (antigens), with the synthesis of specific proteins (antibodies) and/or production of specific effector cells has been encountered only in vertebrates.[1] This adaptive immune response is of vast importance for survival as it constitutes the principal means of defense against pathogenic microorganisms, parasites, and possibly against neoplastic disease.[2] Our knowledge of immunity in invertebrates is rudimentary, but it appears that these animals can also recognize foreign materials. Transplant failures in coelentarates were attributed to the existence of a defense mechanism similar to that of graft rejection in higher animals.[3] Earthworms are able to destroy grafts from donors of the same or different species. This graft rejection is characterized by specificity and anamnesis and can be transferred with immune cells (coelomocytes).[4-6] Insects can also develop immunity rapidly with the appearance of nonprotein antibacterial factors produced by antigenic stimulation, while in general, arthropods fail to recognize tissue grafts as foreign.[7]

Studies on the immune systems of mammals and birds revealed that lymphocytes have the ability to recognize and respond to antigens. There are two major categories of lymphocytes: those that mature in the thymus (T lymphocytes), and those that become immunocompetent in the bursa of Fabricius (birds) or in the bone marrow (mammals, B lymphocytes). All lymphocytes arise from the multipotential stem cells, which reside in the bone marrow.[8] Both T and B lymphocytes can be divided to subsets according to their functions. T lymphocytes can develop into immune effector cells, (e.g., killer T cells and delayed hypersensitive T cells) and also play a fundamental role in the regulation of immune responses (helper and suppressor T cells). The chief function of B lymphocytes is antibody formation. Antibodies are fixed to the surface of all leukocytes (T cells, B cells, monocytes, macrophages, polymorphonuclear leukocytes) via F_c receptors and serve as specific recognition units of the antigen. This amplifica-

tion mechanism permits the recruitment of leukocytes for the defense of the host against intruders as well as being involved in the regulation of immune responses (feedback mechanism). Other soluble mediators derived from lymphoid cells, called lymphokines, also play essential roles in immune defense and immunoregulation. A family of serum proteins belonging to the complement and properdin system is also integrated into immune defense as well as into the regulation of immune reactions. Furthermore, evidence is rapidly increasing that the immune system interacts with a variety of other cells and organs in the body. Of special interest to us is the interactions with the neuroendocrine system.

II. CELLS OF THE IMMUNE SYSTEM

A. Development of Immunocytes

In both birds and mammals, hemopoietic stem cells first appear in the yolk sac. Later in embryonic development, the hemopoietic cells migrate through the blood stream to colonize the liver in mammals and the spleen in both birds and mammals, before they home to their permanent residence in the bone marrow. It was demonstrated[9-11] that the morphologically and functionally very different cells of the erythrocyte, lymphocyte, monocyte-macrophage, and granulocyte series all originate from the same multipotential stem cells. Since all the cells of the blood have finite life spans, some of the small resting stem cells are committed on a regular basis to become progenitors of the various cell types by an unknown mechanism, in order to maintain normal values of blood cells. Progenitor cells are larger than stem cells; they actively synthesize DNA, and they differentiate into mature cells of the lineage they are committed to under the influence of specific hormones and microenvironmental factors. For instance, erythropoietin is known as the major hormone responsible for the generation of red blood cells, colony stimulating factor (CSF), and governs the production of granulocytes and macrophages.

Progenitor cells of the T cell lineage home to the thymus in order to proceed with further differentiation and maturation. The mechanism of homing is not understood in detail, but is presumed to be mediated by cell surface receptors. The stromal framework of the thymus is formed from epithelial cells of the third and fourth pharyngeal pouches during embryonic life. The thymic microenvironment enables the committed stem cells to differentiate into mature T lymphocytes. Hormones secreted by thymic epithelial cells (thymopoietin, thymosine, etc.) as well as cell-to-cell contact appear to play important roles in T cell differentiation.[12,13] A number of thymic hormones and biologically active factors have been described to date awaiting further characterization and determination of biological activity.

In birds, progenitors of B lymphocytes home to the bursa of Fabricius, a pouch that is attached to the intestine near the cloaca. Although much less studied, the maturation of B cells in the bursa appears to follow a similar pattern to that of T cell maturation. Bursopoietin[14] is the presumed hormone having a major regulatory effect. In mammals B lymphocytes differentiate from their progenitors within the bone marrow.

The thymus, bursa, and the bone marrow, which are preoccupied with antigen-independent lymphopoiesis, are known as the primary lymphoid organs. Mature T and B lymphocytes from these organs home to the secondary lymphoid organs, namely the spleen, lymph nodes, and mucosal lymphoid tissues, where some of them will undergo further antigen-driven differentiation, as required.

B. Lymphocytes

B and T lymphocytes cannot be distinguished morphologically in the resting state. Morphological differences will occur, however, after activation. In addition, a number

Table 1
SOME PROPERTIES OF LEUKOCYTES, MAST CELLS AND PLATELETS

Properties	Cell Types							
	T	B	Mf	Ba	Eo	Ne	Ma	Pl
Antigen receptor	+	+	−	−	−	−	−	−
Ig content	−	+	−	−	−	−	−	−
E-rosette	+	−	−	−	−	−	−	−
Differentiation Ag	+	+	+	+	+	+	+	+
Fc receptor	+	+	+	+	+	+	+	+
C′ receptor	±	+	+	+	+	+	+	+[a]
Phagocytosis	−	−	+	+	+	+	−	−
Response to mitogens	+	+	+	−	−	−	−	−
Adherence[b]	−	−	+	+	+	+	+	−

Note: T = T lymphocytes, B = B lymphocytes, Mf = macrophages, Ba = basophilic leukocutes, Eo = eosinophilic leukocytes, Ne = neutrophilic leukocytes, Ma = mast cells, Pl = platelets, Fc = fragment of immunoglobulins, C′ = complement, E = erythrocyte.

[a] Only nonprimate platelets have C′ receptors.
[b] Adherence to glass or plastic under tissue culture conditions.

of other criteria can be used for the detection and separation of lymphocyte subsets as summarized in Table 1.

1. T Lymphocytes

Mature immunocompetent T lymphocytes leave the thymus and settle in the spleen (where approximately 30% of the mononuclear cells are T cells), in the lymph nodes (approximately 60% of mononuclear cells), and also recirculate constantly (about 70% of mononuclear blood cells are T cells). The bone marrow also contains some T cells that are different from T cells of other sources with regard to their response to mitogens and to allogenic cells. When triggered, T cells will initiate DNA synthesis, which results in the accumulation of cytoplasmic RNA that can be stained by pyronin. The uitrastructure of T lymphoblasts is characterized by numerous polyribosomes, smooth endoplasmic reticulum, microfilaments, and microtubules. Activated cells frequently exhibit characteristic protrusions called uropods. T cells in comparison with B lymphocytes contain more lactate dehydrogenase isoenzyme-1, have a higher net negative surface charge, and are more susceptible to freezing and thawing and osmotic damage. They are also less adherent than B lymphocytes to various surfaces in tissue culture. T lymphocytes home specifically to the periarteriolar zone of white pulp in the spleen and to the paracortical area of lymph nodes. Long-lived and short-lived T lymphocytes can be distinguished. T cells lose their recirculating capacity when activated by antigen.

At least four functional classes of T lymphocytes may be distinguished: helper, suppressor, delayed-type hypersensitive, and cytotoxic T cells. Helper T cells are needed for the antigen-driven differentiation of all effector lymphocytes (delayed-type hypersensitive-, killer-, suppressor-T cells, and antibody-secreting B lymphocytes). Suppressor T cells effectively antagonize the initiation of new effector cells during the normal course of immune responses. Delayed-type hypersensitive T cells have the ability to migrate specifically to the sites of minor antigen deposits within the tissues. They secrete lymphokines that attract other mononuclear cells (macrophages) to the site and also activate the recruited cells for the elimination of antigenic microorganisms, or

other antigenic material. Killer (cytotoxic) T cells are able to destroy target cells in an immunologically specific fashion in vitro and are involved in graft and tumor rejection, in defense against viruses, fungi, and certain bacteria, and are also responsible for some autoimmune reactions. In the mouse, these functional subsets of T lymphocytes can be readily distinguished according to their antigenic markers (Lyt and Ia antigens). Recently a series of monoclonal antibodies became available commercially that allow for similar functional distinction of human T lymphocytes on the basis of their specific antigenic surface markers. Monoclonal antibodies capable of distinguishing T cell subsets have also been produced against rat T lymphocytes.

T lymphocytes are able to recognize antigen specifically through their surface receptors. Numerous clones exist within the immune system that are able to recognize a variety of antigen determinants (epitopes). The recognition site of T cell antigen receptors appears to be very similar, if not identical, to the antigen-combining site of corresponding antibodies. However, the rest of the T cell receptors do not seem to be closely related to immunoglobulins. In addition to foreign antigens, some of the helper and suppressor T lymphocytes recognize class II histocompatibility (Ia) antigens, or immunoglobulin isotypes, allotypes, and idiotypes. Most killer T cells recognize class I histocompatibility determinants on their targets.

Regulatory T cells (helper and suppressor) appear to have receptors for the Fc portion of various classes and subclasses of immunoglobulin. Although the function of these receptors has not been fully elucidated, it seems certain that they are involved in immunoregulation. Apparently, some T cells have receptors for complement components as well, especially for C3. The function of complement receptors is largely unknown. A peculiar receptor that is present on most human T cells is the one recognizing sheep erythrocytes (Sheep Red Blood Cells (SRBC), E receptor). Human T cells bind SRBC under proper conditions, which leads to "rosette" formation. This reaction is widely used for the routine discrimination and even for the separation of human T cells from other mononuclear cell types. T cells from other species also bind foreign erythrocytes: marmoset and pig T cells bind to SRBC, guinea pig T cells to rabbit erythrocytes, cat T cells to rodent, dog T cells to human and guinea pig, and rat T cells to guinea pig erythrocytes.

Certain mitogens, such as concanavalin A, or phytohemagglutinin (PHA), stimulate T lymphocytes, whereas some other mitogens, such as pokeweed mitogen, are capable of stimulating both T and B cells. Stimulated cells will transform into blasts, synthesize DNA, divide, and secrete lymphokines. The reactivity of lymphocytes to various mitogens in vitro is used frequently for the evaluation of lymphocyte function, as well as for the generation of a variety of soluble products.

2. B Lymphocytes

In birds, B cells mature in the bursa of Fabricius that contains stem cells, mature B cells, and a small number of T cells. In comparison with mammals, the bursa is regarded as a bone marrow equivalent in birds. Bursal cells are able to respond immunologically when stimulated.

B lymphocytes may be small, medium sized (blasts, proplasmacyte), or large with abundant cytoplasm and characteristically eccentric nucleus (plasma cell). When stimulated, immunoglobulin production may start in association with free ribosomes in the cytoplasm. With continuing stimulation plasmacytes will evolve, which are characterized by a nucleus with coarse chromatin, a well-developed Golgi apparatus, and rough endoplasmic reticulum. Plasma cells secrete large amounts of immunoglobulin and are unable to return to the small lymphocyte stage, but rather, eventually die.

Although B lymphocytes are considered generally as nonadherent, they adhere loosely to nylon wool, which is used routinely for separating from T cells. Adherence

to glass bead column and to acrylic acid polymer also has been reported. Human peripheral B cells form spontaneous rosettes with mouse red blood cells, which may be used as a B lymphocyte marker.

The most important marker of B cells is surface and cytoplasmic immunoglobulin. B cells switch the expression of Ig class during their differentiation: IgD is expressed first, then IgM, which is followed by either IgG or IgA, and perhaps IgE. B lymphocytes may also be classified as long-lived and short-lived.

In the chicken the periellipsoidal lymphoid tissue in the spleen is bursa-dependent. In mammals B cells are localized mainly in the germinal centers of the spleen (in the red pulp) and lymph nodes. Most B lymphocytes producing IgA are located in intimate anatomical relationship to mucous membranes, or glandular tissue. The bone marrow contains 30 to 40% B lymphocytes; in the spleen approximately 60% of the mononuclear cells are B cells, in the lymph nodes around 30%, and in the thymus there are very few B cells, if any (less than 2%).

The most important function of B lymphocytes is antibody formation. Besides antibody formation, B lymphocytes probably perform a number of other functions, which are not studied very well to date. It seems certain, however, that some B cells are able to secrete lymphokines and to trigger immunoregulatory events.

B cell clones recognize specific epitopes on the antigen by their surface immunoglobulin receptors (IgD and/or IgM). After the binding of polyvalent antigen to surface Ig, the complexes are redistributed on the cell surface, a contractile event occurs, and then the complexes are endocytosed and shed from the membrane. Eventually new receptors appear on the cell surface. This in vitro cycle, in the absence of cooperative cell interactions, does not lead to B cell differentiation into secreting plasma cells, whereas it does so when induced in the proper conditions involving helper cells. Virgin precursor cells have antigen receptors of the IgM class, regardless of the class of antibody eventually secreted. Exposure to antigen induces a shift in receptor class from IgM to IgG.

B lymphocytes also have Fc receptors for various immunoglobulin classes and for the C3 complement component. Various polysaccharides, such as lipopolysaccharide (LPS) from Gram-negative bacteria, pneumococcal polysaccharide SIII, levan from *Corynebacterium levaniformis* and dextran, can all function as B lymphocyte mitogens and are able to induce polyclonal antibody synthesis in vitro. These B cell mitogens function also as T-independent antigens, since they are able to initiate specific antibody formation without helper T cells. Pokeweed mitogen is capable of stimulating both B and T lymphocytes, whereas PHA is not mitogenic for B cells.

C. Macrophages and Monocytes

Arising from the bone marrow, monocytes circulate briefly and then, under steady-state conditions, randomly leave the blood stream or attach to the wall of sinusoids. Here they undergo a series of structural and functional alterations, leading to the formation of the tissue macrophage or histiocyte. Their tissue life span is relatively long, and they continue to actively synthesize a variety of macromolecules in response to environmental stimuli.

The nucleus is characteristically round-, or bean-shaped, and for this reason, macrophages and monocytes are often categorized as mononuclear phagocytes. The most characteristic morphological feature of these cells is the abundance of lysosomes in the cytoplasm. In activated macrophages the number of lysosomes, as well as the enzyme content of the lysosomes (acid phosphatase, beta-glucuronidase), is increased. In response to certain stimuli, such as foreign bodies, microbial infections, certain mycoses, parasites (e.g., leishmaniasis), macrophages can transform into multinucleated giant cells that arise through fusion of single cells. The spleen and lymph nodes contain a macrophage-related cell, characterized by cytoplasmic processes and named dendritic