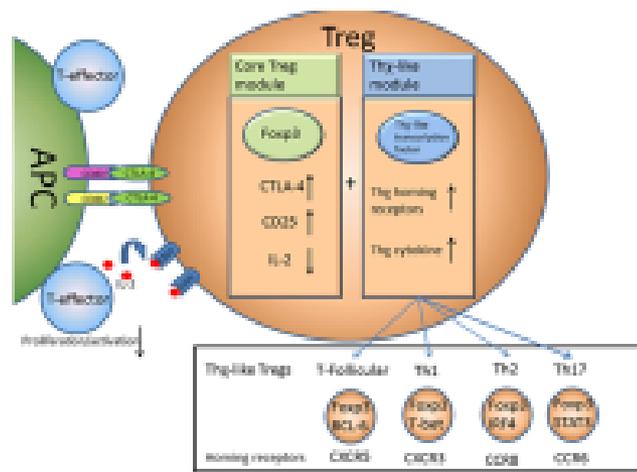


Syncytiotrofoblast ma bezpośrednie kontakty z matczynymi leukocytami krążącymi w przestrzeni międzykosmkowej.
 Syncytiotrofoblast nie wykazuje ekspresji antygenów MHC Klasy I ani klasy II.
 Trofoblast pozakosmkowy ma polimorficzne antygeny HLA-C i monomorficzne antygeny HLA-G, HLA-E i HLA-F, Brak Ekspresji MHC klasy II.
 Matczyne komórki immunokompetentne nie mają kontaktu z komórkami wykazującymi ekspresję ojcowskich alloantygenów.

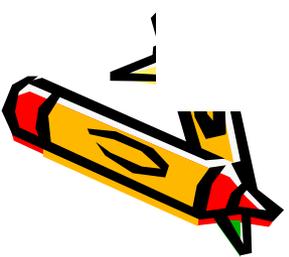
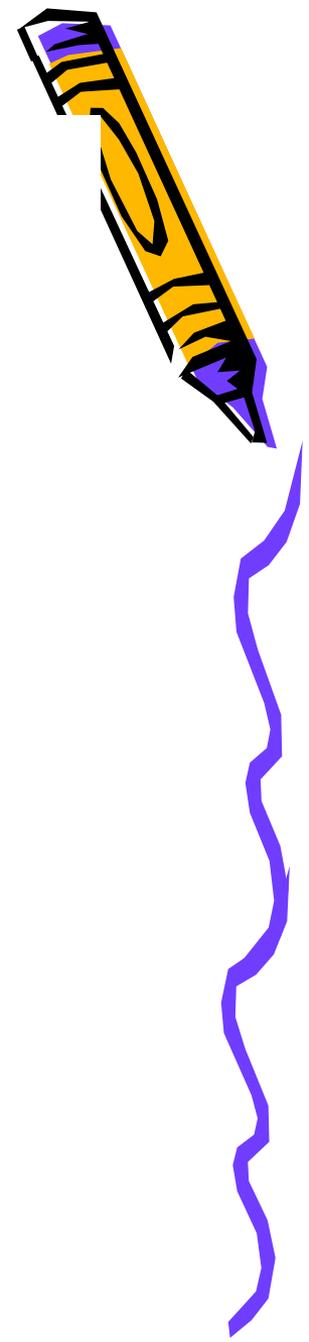


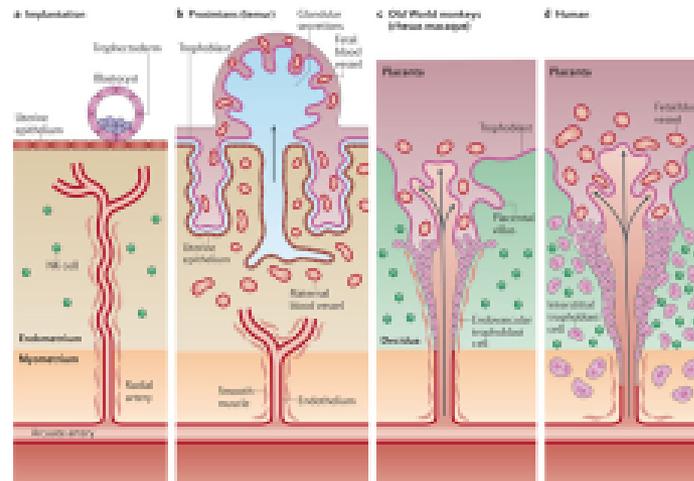


Limfocyty T regulatorowy CD4+/CD25+ (TREG) odgrywają kluczową rolę w rozwoju tolerancji immunologicznej w ciąży pozwalają na rozwój obcoantygennego płodu w łonie matki.

TREG, aktywowane na skutek kontaktu z ojcowskimi antygenami przy współdziałaniu czynników hormonalnych, regulują odpowiedź immunologiczną poprzez bezpośredni kontakt komórka –komórka, a także przez wytwarzanie cytokin.

Populacja TREG rozrasta się w trakcie ciąży, co można stwierdzić zarówno w krążeniu matczynym, jak i doczesnej.

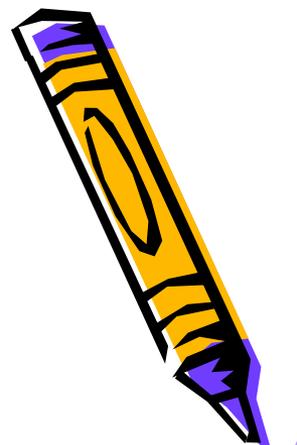


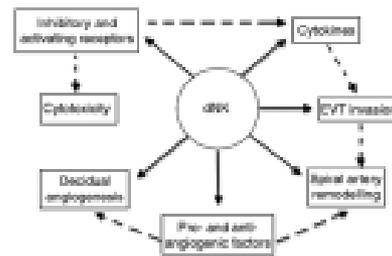


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Wkrótce po implantacji do doczesnej zaczyna dopływać szczególna populacji komórek NK, określonych jako maciczne komórki NK (uteryne NK- uNK).

W doczesnej komórki NK przebywają w dużej liczbie niemal przez cały pierwszy trymestr ciąży, po czym stopniowo znikają.





Najważniejsze cytokiny i czynniki wzrostu wytwarzane przez komórki uNK:

VEGF-C (czynnik wzrostu śródbłonna naczyń) – pobudzenie angiogenezy

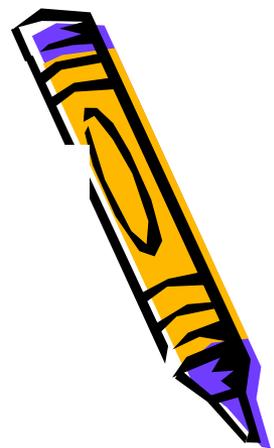
GM-CSF – przyciąganie i aktywacja komórek mieloidalnych wytwarzających czynniki wzrostu dla łożyska

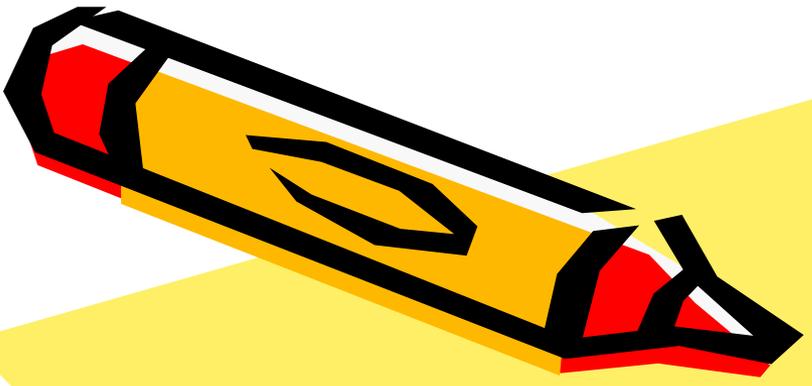
M-CSF – pobudzenie proliferacji komórek trofoblastu

IFN-gamma – indukcja 2,3-dioksygenazy idoloaminy (IDO)

LIF – wpływ na proliferację i różnicowanie blastocysty (cytokina niezbędna do prawidłowej implantacji)

IL-11 – przekształcanie śluzówki macicy w doczesną





Immunofizjologia
męskiego układu rozrodczego

dr Irma Spohr
Centrum Badań Biomedycznych SGGW



Bariera krew- jądro (BTB) jest strukturą istotną dla prawidłowego różnicowania komórek germinalnych, gdyż reguluje przenikanie składników potencjalnie szkodliwych dla spermatogenezy naczyń krwionośnych do przedziału adluminalnego nabłonka plemnikotwórczego. W funkcji barierowej gonady męskiej biorą udział trzy składowe: komórki endotelialne wyściełające naczynia krwionośne zlokalizowane w tkance interstycjalnej, komórki koło kanalikowe (mioidalne) wokół kanalików plemnikotwórczych oraz wyspecjalizowane połączenia międzykomórkowe znajdujące się między sąsiadującymi komórkami Sertoliego.

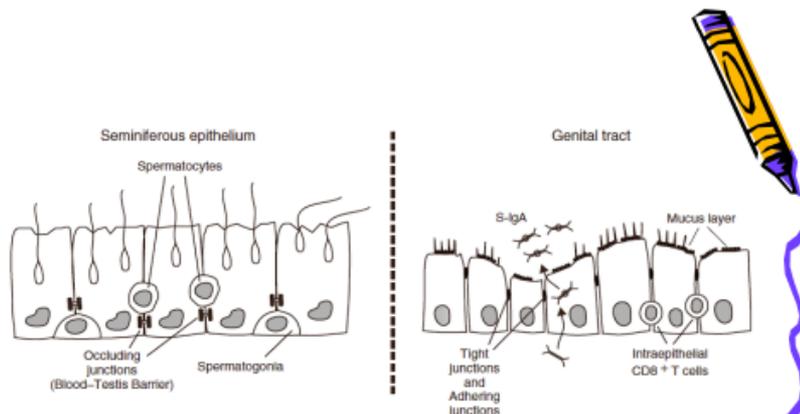
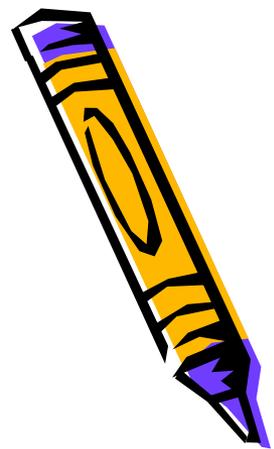
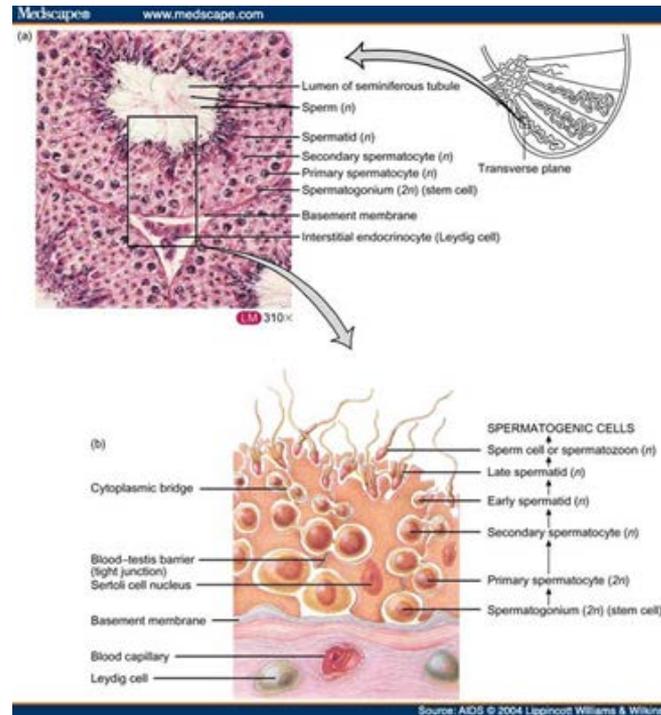
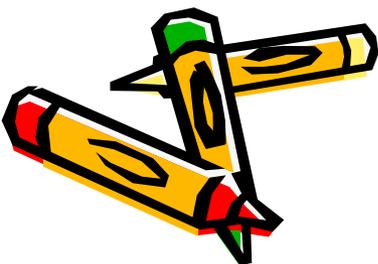
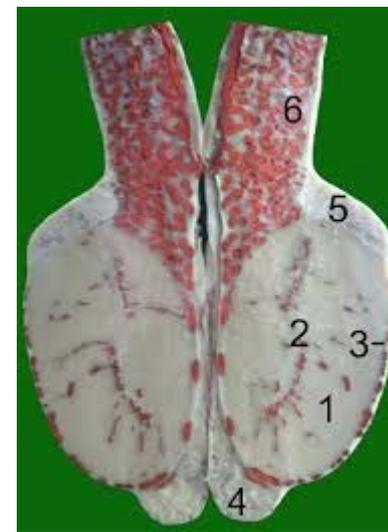
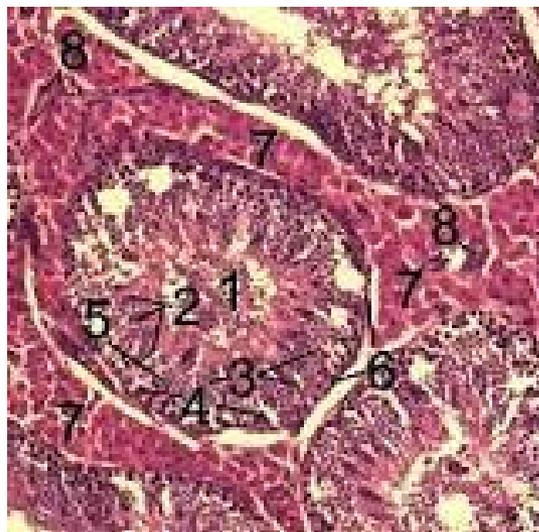
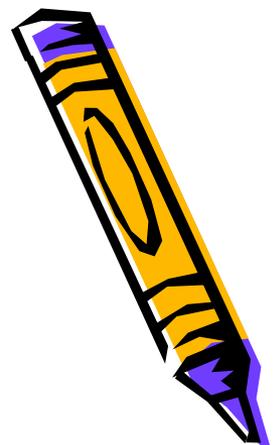


FIG. 9. Comparison of immunoregulation in the testis and male genital tract. Immunoregulation in



Śródmiąższowe naczynia krwionośne jądra zbudowane są z perycytów, błony podstawnej i warstwy komórek endotelialnych z dobrze rozwiniętymi połączeniami zamykającymi. W odróżnieniu od innych gruczołów endokrynnych, endotelium wyściełające naczynia krwionośne gonady męskiej charakteryzuje się ciągłą strukturą bez fenestracji



Najbardziej szczelnym elementem BTB jest kompleks połączeń między komórkami Sertoliego. W kompleksie zidentyfikowano koegzystujące połączenia ściste (zwane również obwódką zamykającą), bazalne specjalizacje powierzchniowe (ES, ectoplasmic specialisations), połączenia szczelinowe (gap junction), i połączenia desmosopodobne (desmosome-like junctions or desmosome-gap junctions), które dzielą nabłonek plemnikotwórczy strukturalnie i funkcjonalnie na dwa przedziały. W przedziale bazalnym (przypodstawnym) znajdują się diploidalne komórki germinalne, natomiast przedział adluminalny (przyśrodkowy) zasiedlony jest przez haploidalne komórki postmeiotyczne. Obecność różnorodnych typów połączeń w miejscu BTB odróżnia ją od barier występujących w innych narządach, jak np. w mózgu.

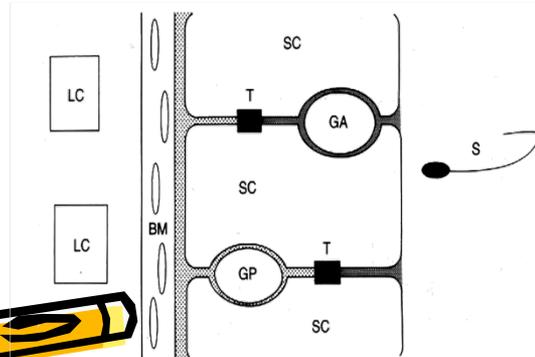
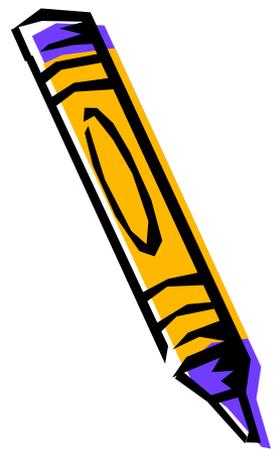
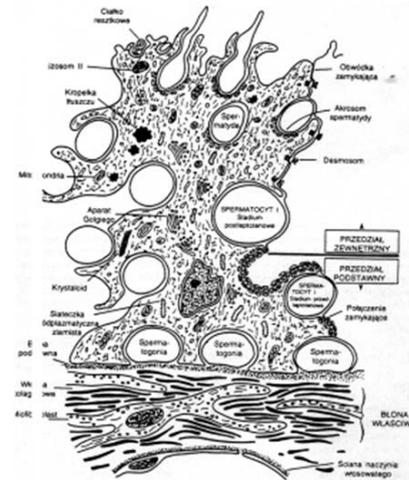


Figure 3.1. Compartmentalization of mammalian testicular tissue. BM, basal membrane; GA, germinal cell in adluminal compartment of seminiferous epithelium; GP, germinal cell in peribasal compartment of seminiferous epithelium; LC, Leydig cell; SC, Sertoli cell; S, spermatozoon; T, tight junction.



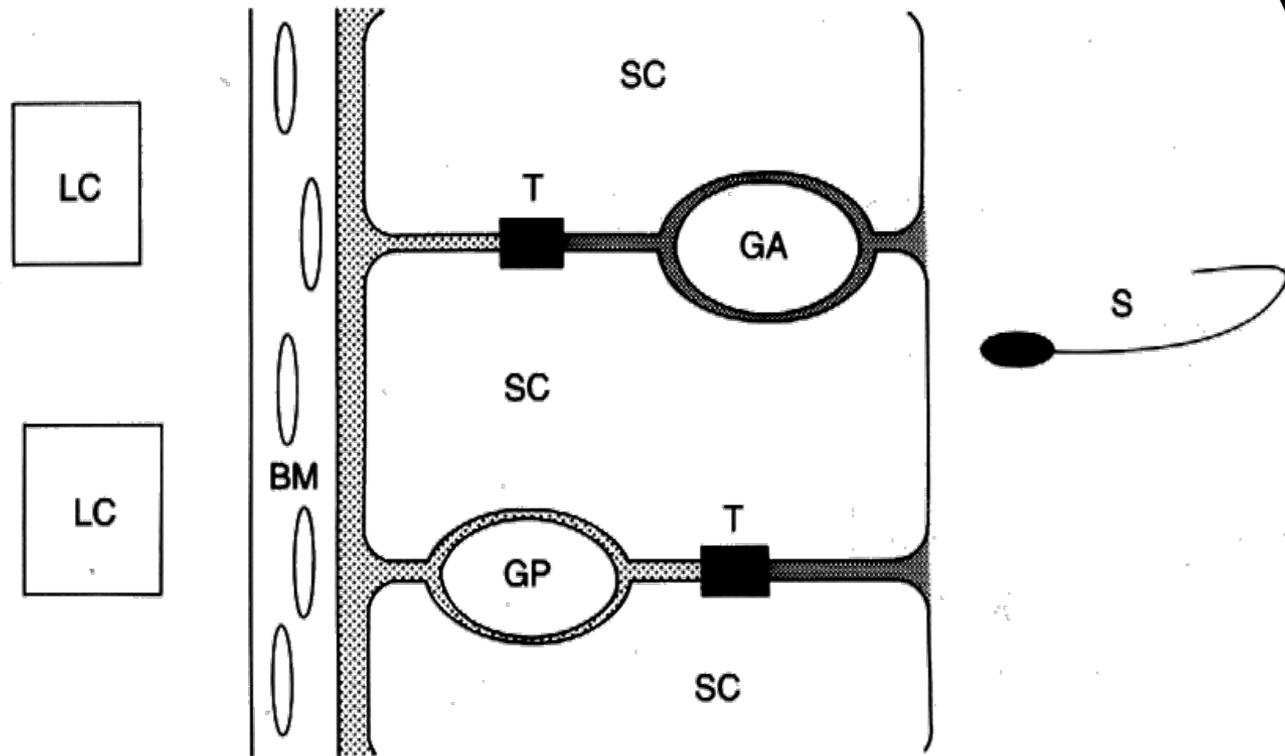
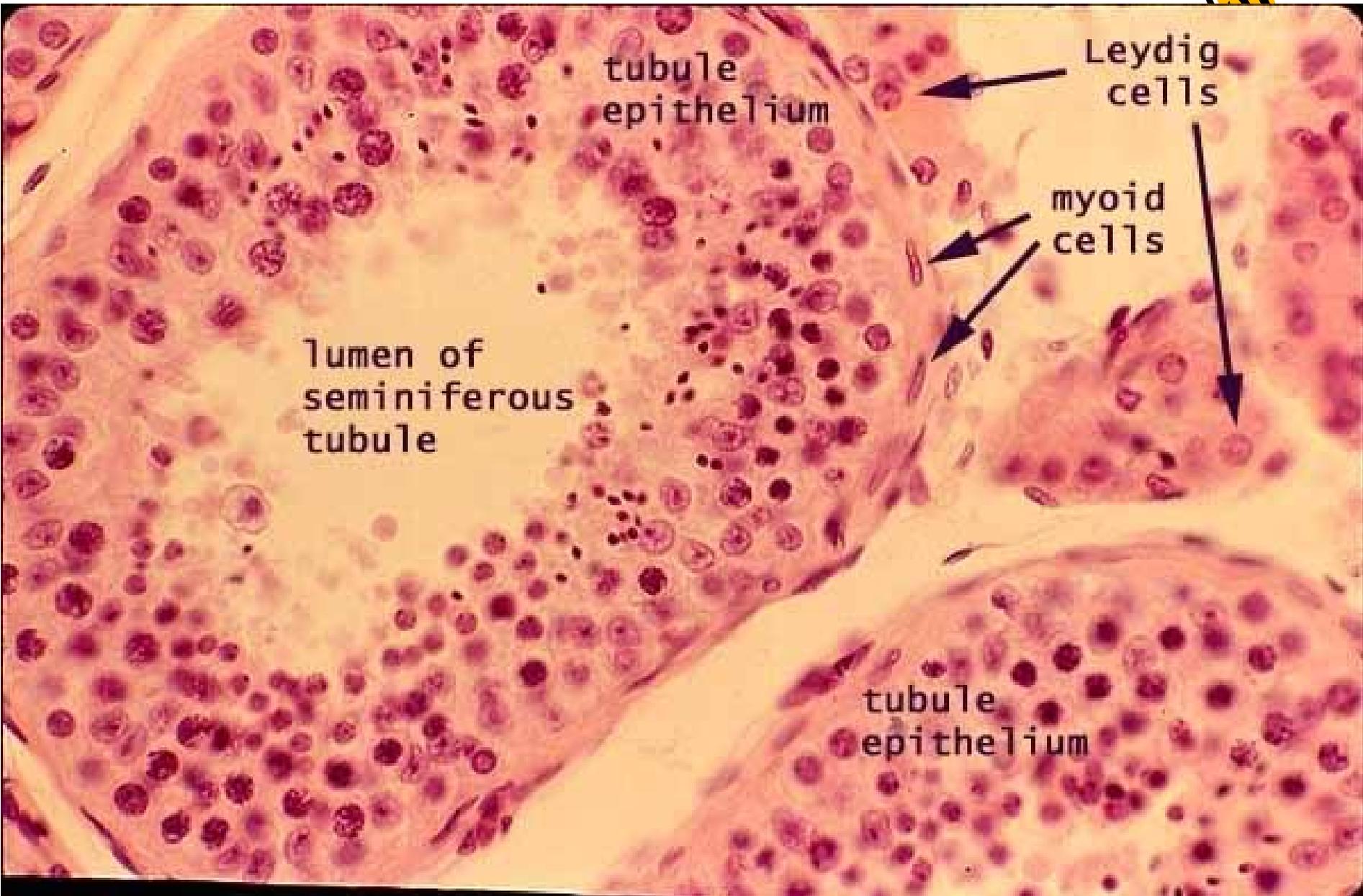


Figure 3.1. Compartmentalization of mammalian testicular tissue. BM, basal membrane; GA, germinal cell in adluminal compartment of seminiferous epithelium; GP, germinal cell in peribasal compartment of seminiferous epithelium; LC, Leydig cell; SC, Sertoli cell; S, spermatozoon; T, tight junction.



tubule
epithelium

Leydig
cells

myoid
cells

lumen of
seminiferous
tubule

tubule
epithelium

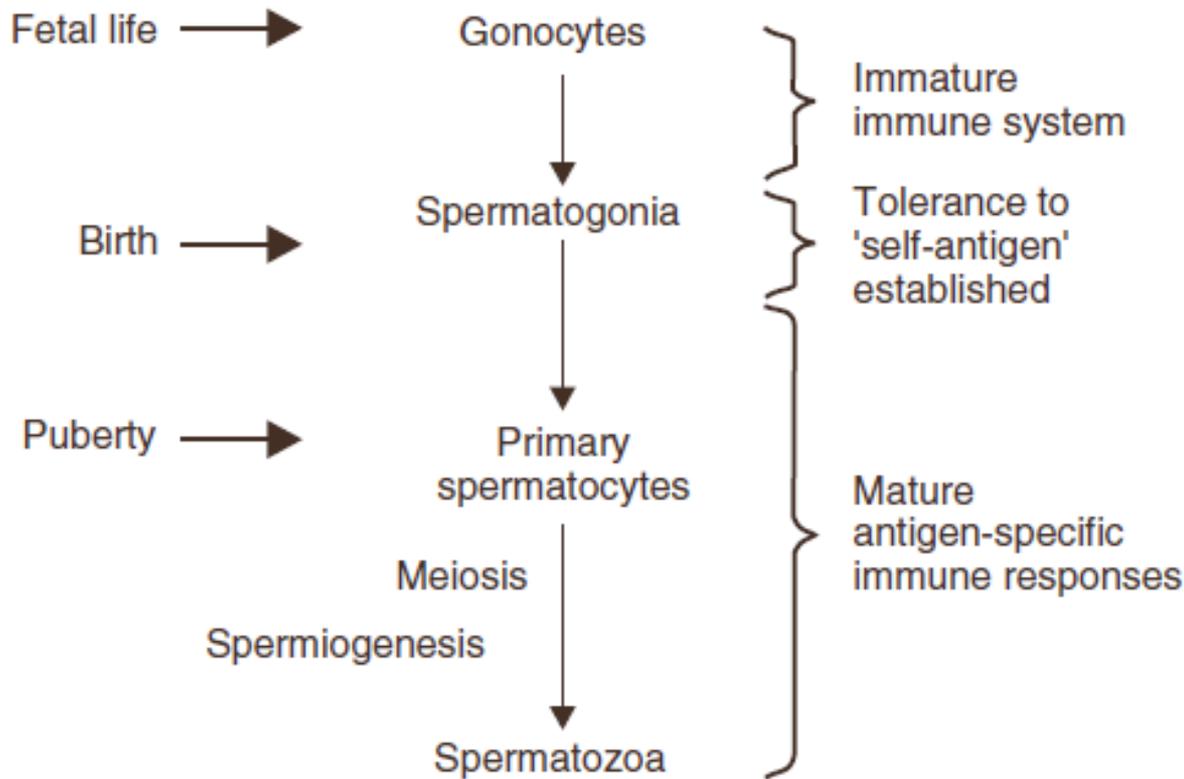


FIG. 1. Developmental time-line of spermatogenesis and the maturation of the immune system. The majority of spermatogenic cells do not appear in the testis until the initiation of meiosis at puberty, whereas tolerance to “self” antigen is largely established at or around the time of birth. Because the development of spermatozoa from the spermatogonial stem cell population involves complex processes of nuclear reorganization (meiosis) and cellular differentiation (spermiogenesis) that are unique to the testis, there exists enormous potential for antigens of spermatogenesis to evade conventional tolerance mechanisms.

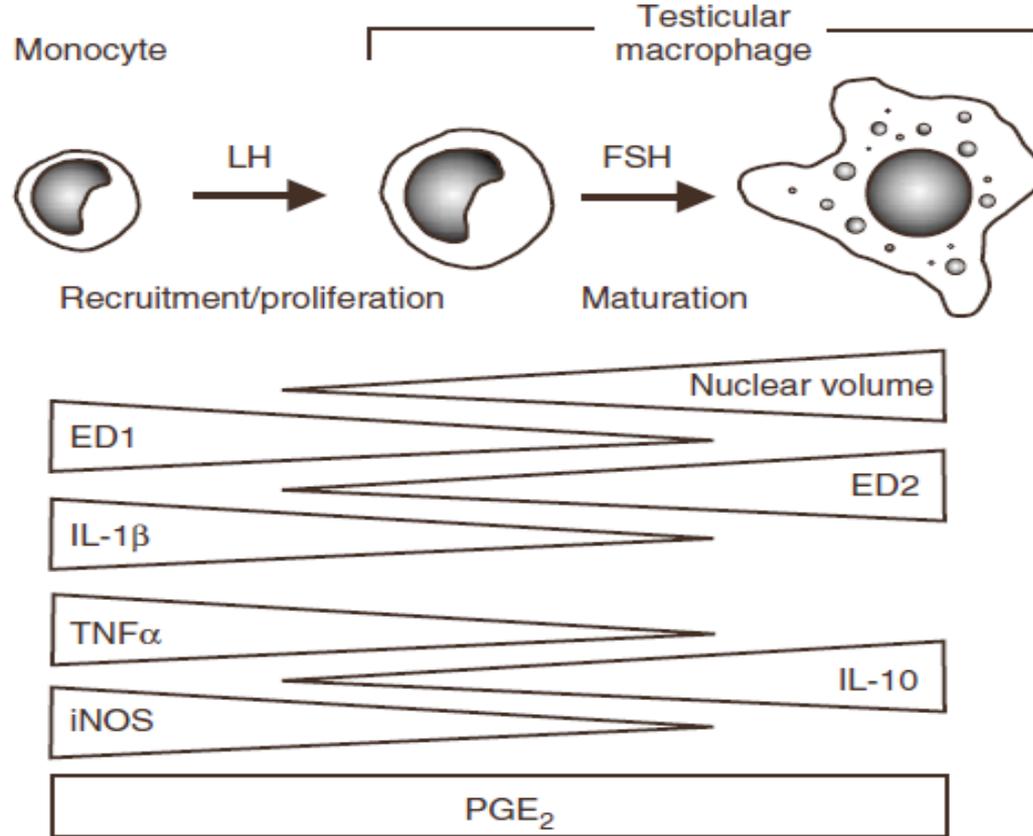


FIG. 8. Maturation of the resident macrophage population of the rat testis. Macrophages in the rat testis are heterogeneous, corresponding to different stages of maturation from circulating monocytes through to a distinct testicular resident macrophage phenotype (378). This testicular phenotype is characterized by an increased nuclear and cytoplasmic volume, loss of the CD68 marker recognized by antibody ED1, upregulation of the resident macrophage surface marker ED2 (CD163), loss of ability to produce several proinflammatory mediators, and upregulation of the ability to produce the immunoregulatory cytokine, interleukin-10. Recruitment of macrophages to the testis is under the control of luteinizing hormone (LH), acting through the Leydig cells (130,397,406,411,412,414), whereas maturation to the mature testicular phenotype appears to be follicle-stimulating hormone (FSH) dependent, indicating regulation by the Sertoli cells (410,413).

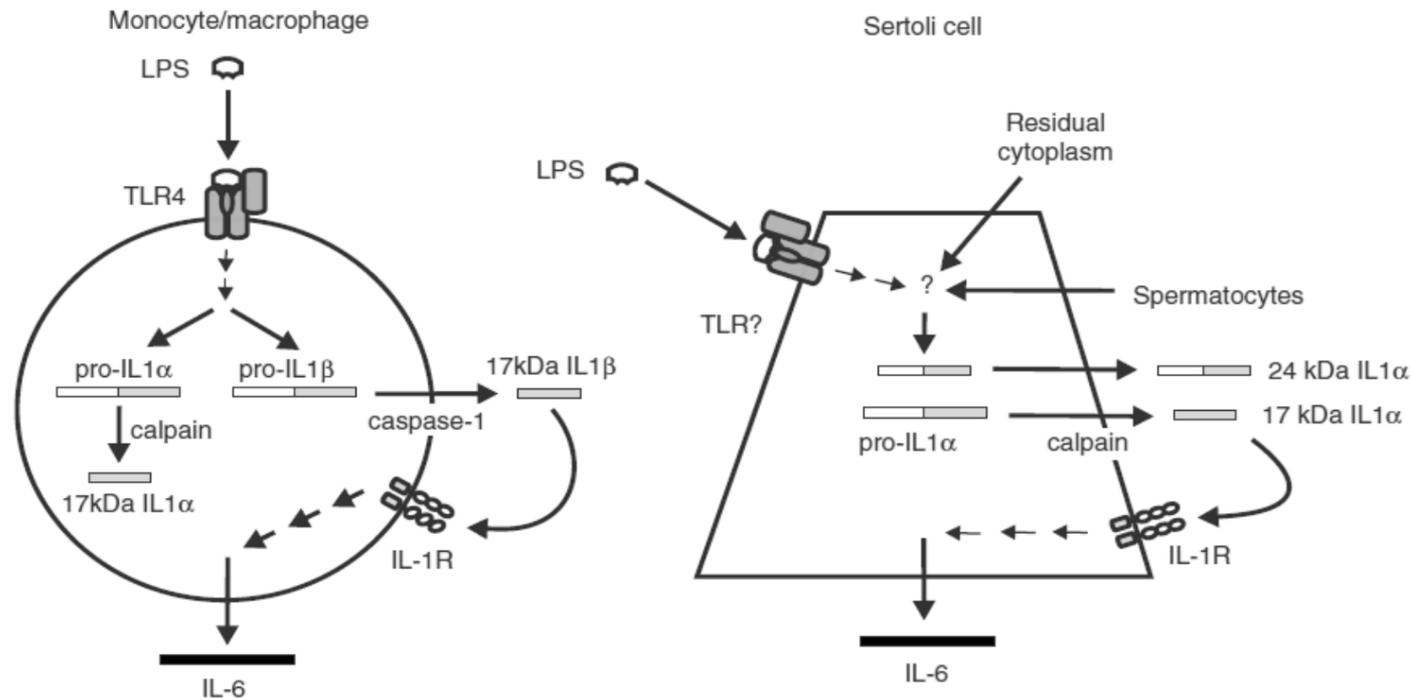
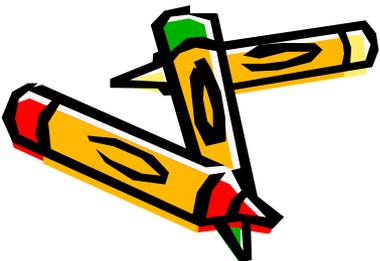
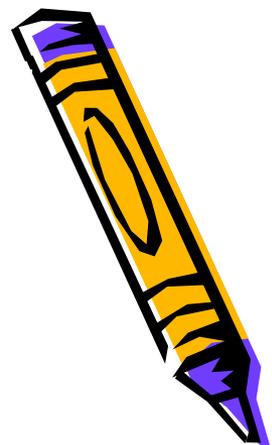
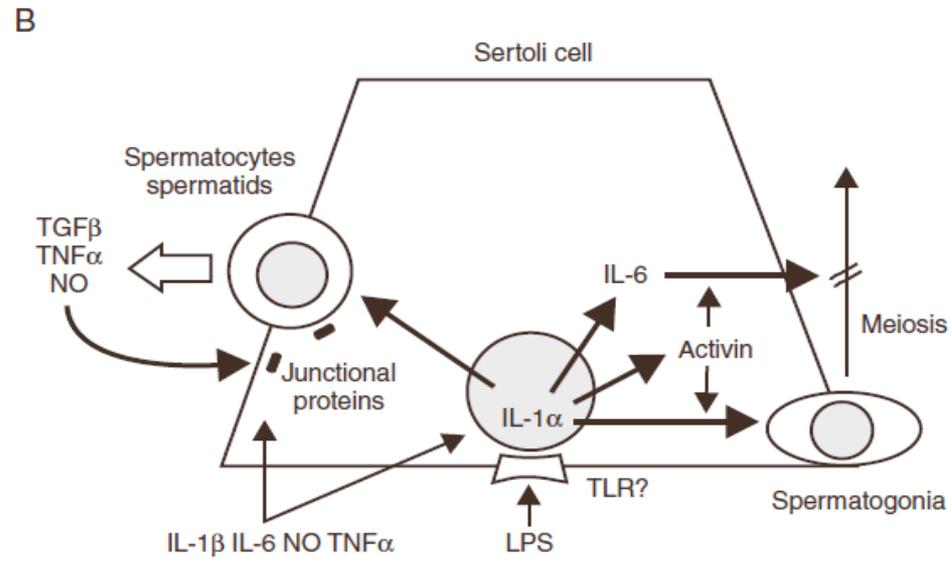
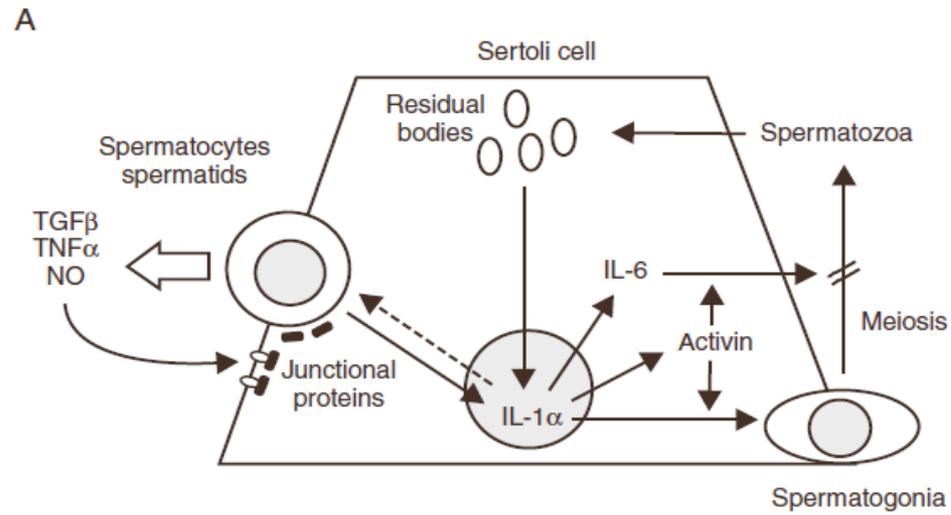


FIG. 10. Differential regulation of interleukin (IL)-1 and IL-6 production and secretion in the monocyte/macrophage and Sertoli cell. Binding of lipopolysaccharide (LPS) to the Toll-like receptor 4 (TLR4) on the surface of the macrophage upregulates expression of both IL-1 α and IL-1 β , which subsequently are processed to their mature bioactive 17-kDa forms by the action of calpain and caspase-1, respectively. IL-1 α tends to remain associated with the cell, but IL-1 β is secreted upon cleavage and binds to the IL-1 receptor (IL-1R) to stimulate production of IL-6 (522). The Sertoli cell also responds to LPS, presumably through TLR4. LPS, spermatocytes, and the residual cytoplasm of released spermatozoa are potent stimulators of IL-1 α (but not IL-1 β) in the Sertoli cell (542,544,545,551,552,556,568). Two alternate transcripts of IL-1 α are produced by the Sertoli cell, including a transcript lacking the calpain cleavage site domain, which encodes a 24-kDa form of IL-1 α (547,548). Both isoforms appear to be secreted by the Sertoli cell and both possess IL-1 bioactivity. IL-1 subsequently signals through the IL-1R to stimulate the production of IL-6 by the Sertoli cell (544,552,568,569).





Junctional disruption

Increased apoptosis

Loss of attachment

Loss of environment

Failure to enter meiosis?

FIG. 14. Cytokine networks in control of Sertoli–germ cell interactions. **A:** Normal interactions in

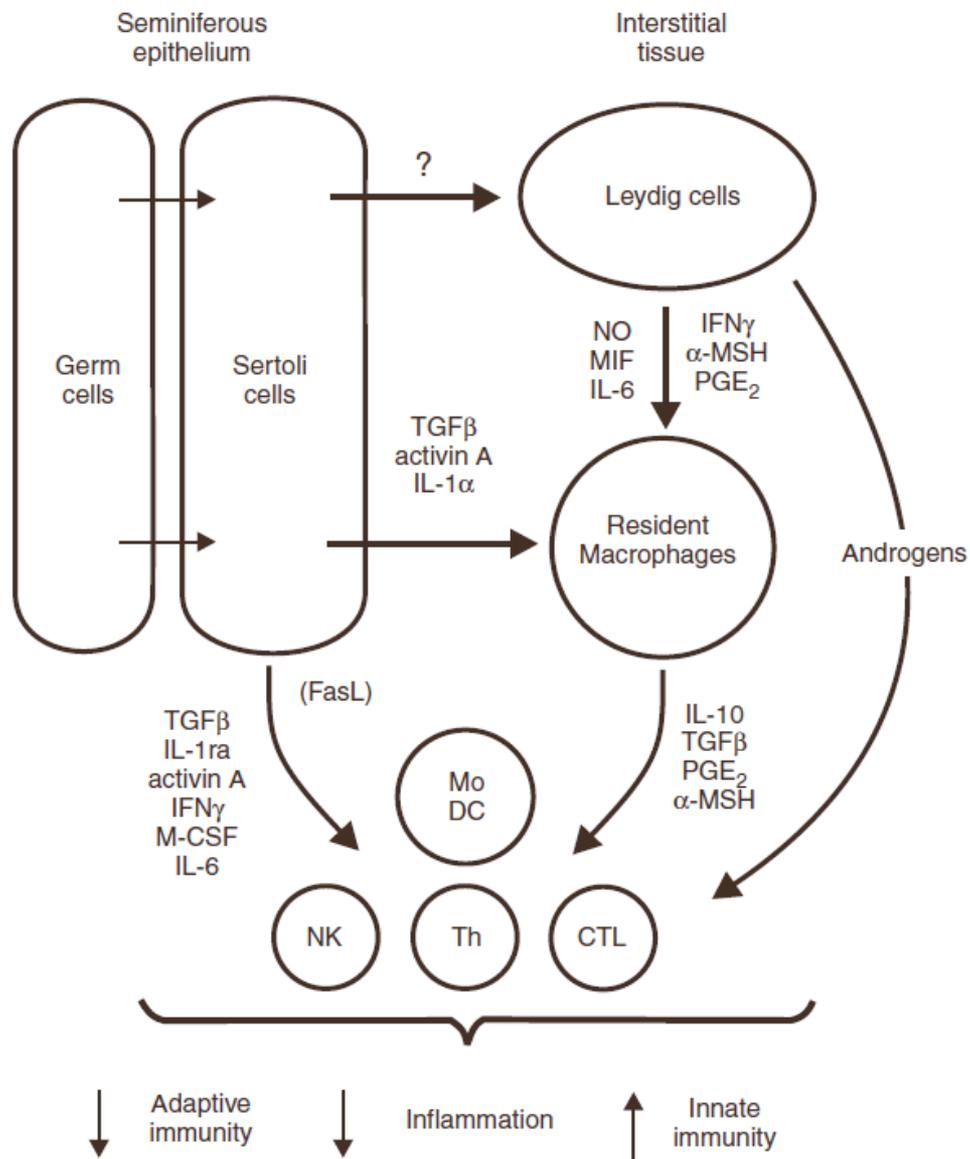
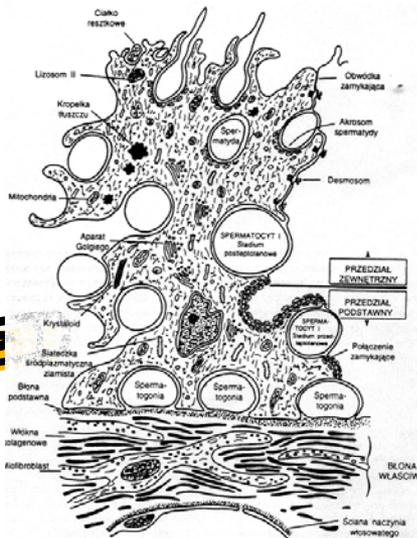


FIG. 17. A paradigm for understanding the intercompartmental interactions regulating immunity in the testis (see text for more details). In the seminiferous epithelium, the Sertoli cell produces a number of

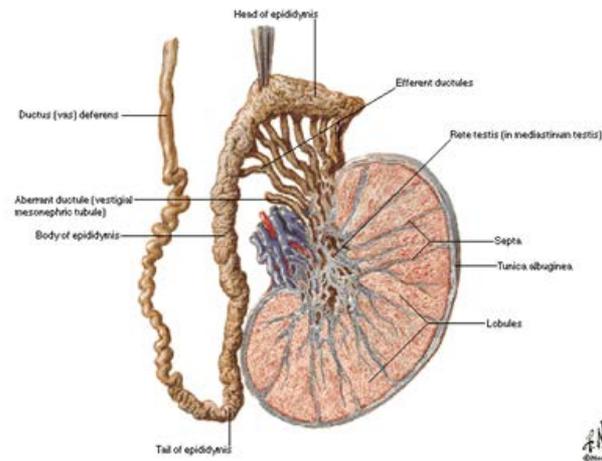
- ❖ Immune cells are found in considerable numbers within the normal, unaffected testes of mammals, including humans.

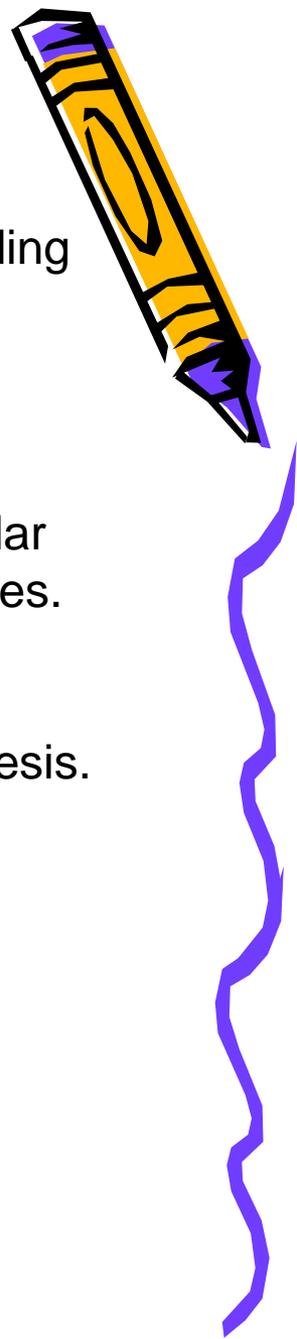
Located in the interstitial compartment, they are implicated in the mechanisms that make the testis an immunologically privileged site where germ cells are protected from autoimmune attack and foreign tissue grafts may survive for extended periods of time

- ❖ With regard to normal development and function of the testis, both pro- and anti-inflammatory cytokines have been shown to play an important regulatory role.
- ❖ The testicular environment. However, does not preclude immune activation resulting in inflammatory reaction and potential damage.

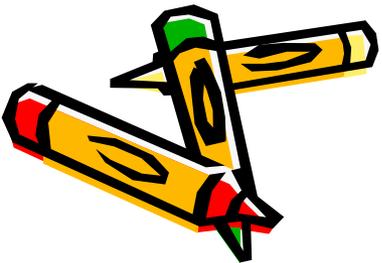


Testis, Epididymis and Ductus Deferens
Frontal Section

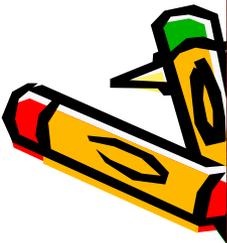
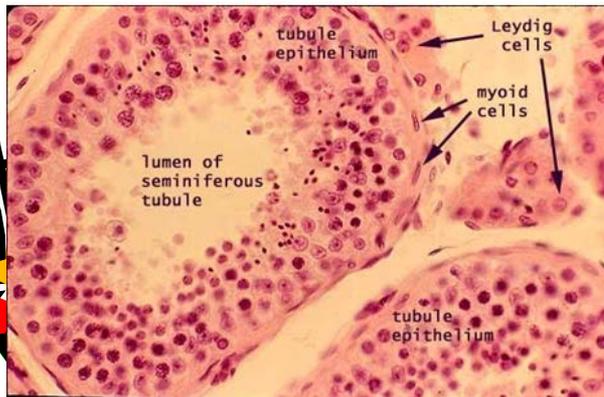
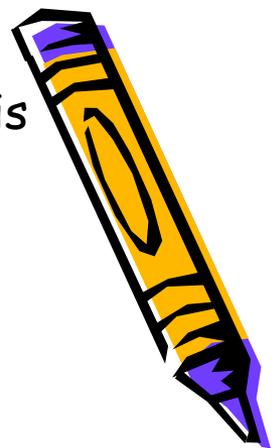




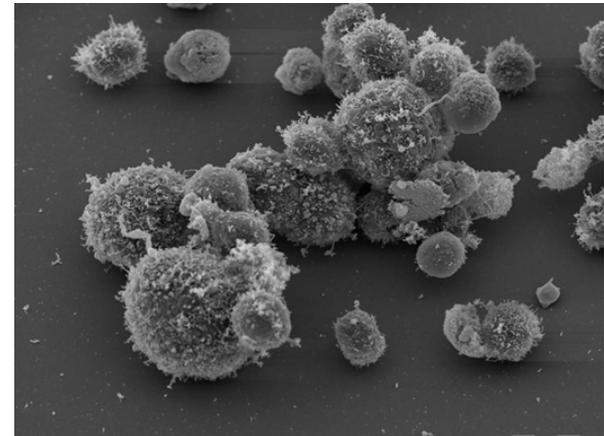
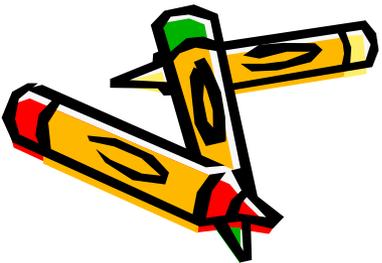
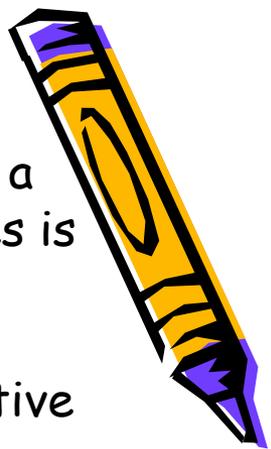
- ❖ In men, infection and inflammation of the reproductive tract including the testes are widely accepted as important etiological factors of infertility.
- ❖ Symptomamatic orchitis due to bacterial or viral infections is considered to be rare, a high prevalence of asymptomatic testicular inflammatory reaction could be demonstrated among infertile males.
- ❖ Despite the patchy distribution of the lesions, inflammation is associated with disruption of testicular function, i.e. spermatogenesis.
- ❖ The pattern of lymphocyte infiltration and concomitant damage of seminiferous tubules supports the concept that activation of autoreactive T cells is involved



- ❖ For many years, research on physiology and pathology of the testis has concentrated on the two major functions: the generation of male gametes and the production and controlled release of sex steroids. Interactions between the male reproductive tract and the immune system have been a source of both considerable curiosity and ignorance.
- ❖ Studies in experimental animals indicate that the testis is one of very few organs of the body capable of sustaining foreign grafts for extended periods of time without evidence of rejection.
- ❖ This 'immunological privilege' of the testis is believed to arise from the need to prevent immune responses against meiotic and haploid germ cells expressing 'nonself' antigens which first appear at the time of puberty, long after the establishment of self-tolerance in the perinatal period.



- ❖ Paradoxically, it is the same antigens that may become targets of a vigorous autoimmune attack if activation of specific T lymphocytes is induced elsewhere in the body.
- ❖ Furthermore, defense mechanisms including both innate and adaptive immunity are not generally impaired in the testis.
- ❖ This is illustrated by the obvious capacity of the testis for inflammatory responses to local and systemic infection.
- ❖ Although the complex mechanisms are not yet completely understood, there is considerable evidence that organ-specific immune regulation plays a key role in testicular function

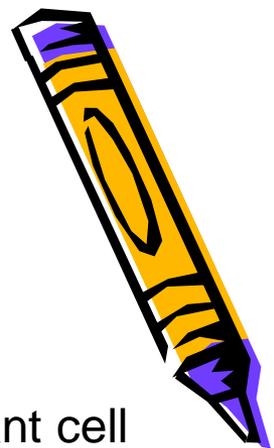
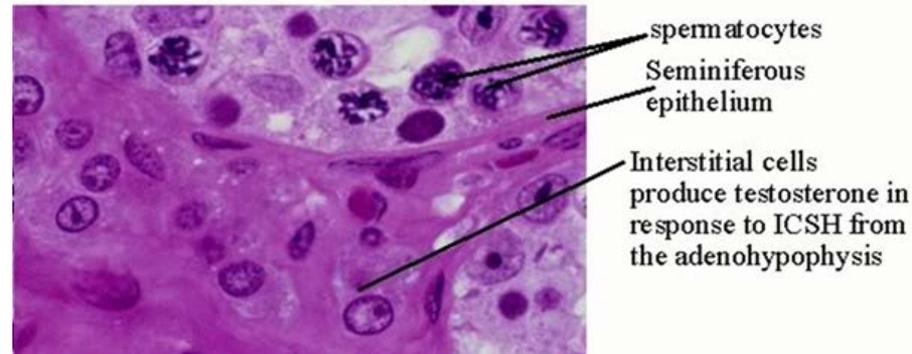


- ❖ Immune cells are found in considerable numbers within the interstitial compartment of the normal unaffected testis of mammals, including humans.

To resident macrophages, which represent the second most abundant cell type next to Leydig cells, mast cells are regular components of the interstitial and peritubular tissue

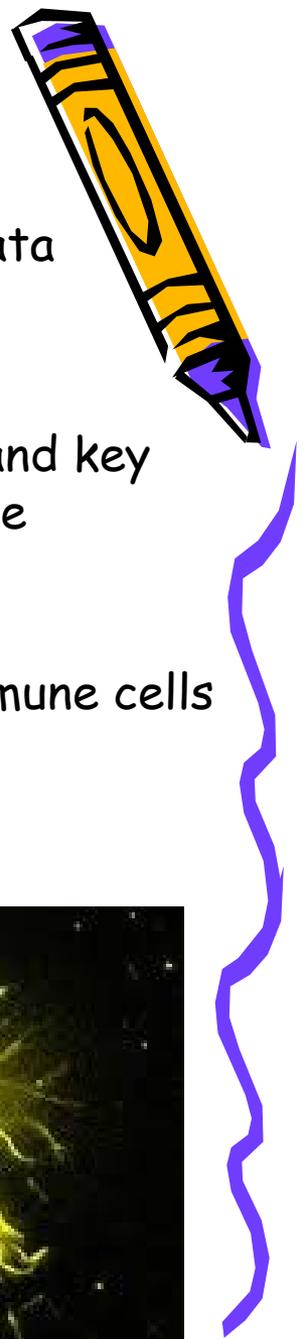
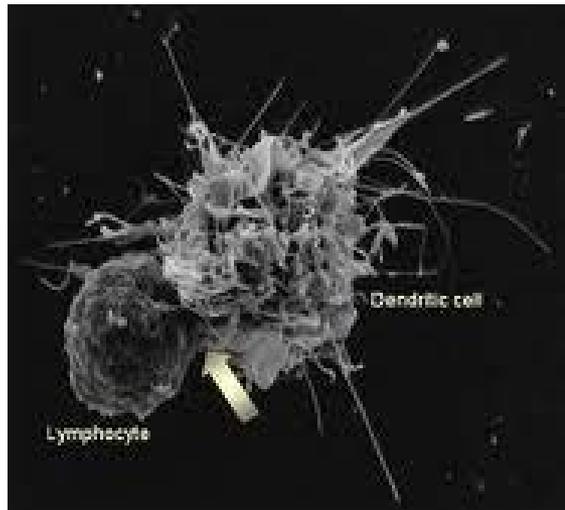
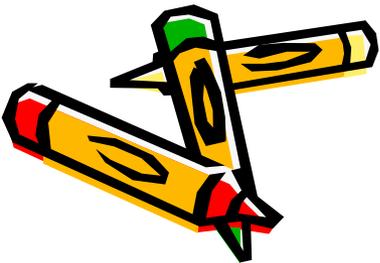
- ❖ Number of lymphocytes in the testis is relatively small, although circulating immune cells have access to the organ and testicular lymphatic vessels allow drainage to regional lymph the testis, in spite of its immunologically privileged status, is not isolated from the immune system.

Interstitial Cells

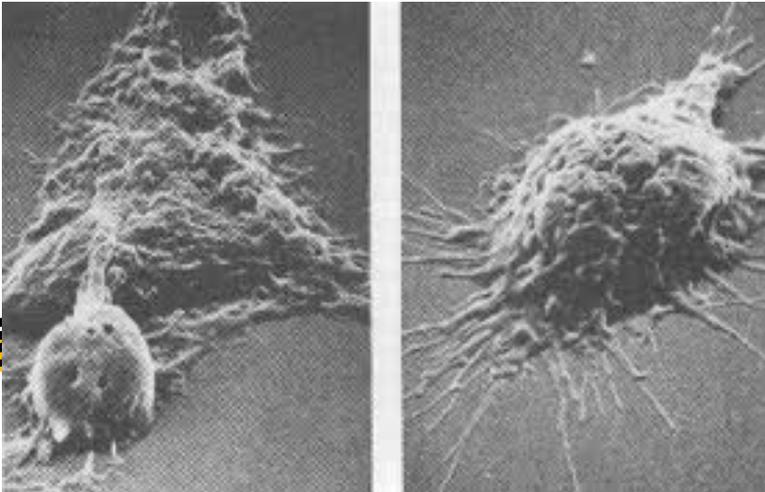


- ❖ The presence of natural killer cells known to be involved in innate immune responses was reported in rodents, whereas consistent data for the human testis are not available.
- ❖ Dendritic cells as potential professional antigen-presenting cells and key players during induction of specific immune responses remain to be identified in the normal testis.

Under physiological conditions, neither resident nor circulating immune cells are found within the seminiferous tubules and polymorphonuclear leukocytes remain completely absent



- ❖ There is substantial evidence that testicular macrophages and their functions are largely determined by the local environment.
- ❖ In the rat testis, two distinct subpopulations of macrophages could be identified by means of the monoclonal antibodies ED1 and ED2, with 85% of the cells revealing the 'resident' phenotype ED1- ED2+.
- ❖ The number of macrophages increases during pubertal development and is partly dependent on interaction with Leydig cells.
- ❖ On the other hand, resident macrophages have a trophic effect on Leydig cells.



Possible Mechanisms of Testicular Immunoregulation

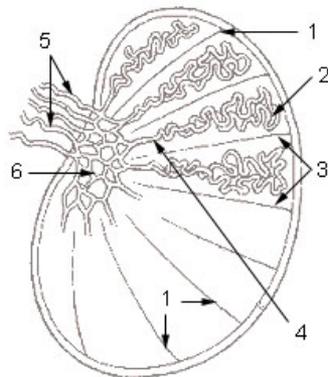
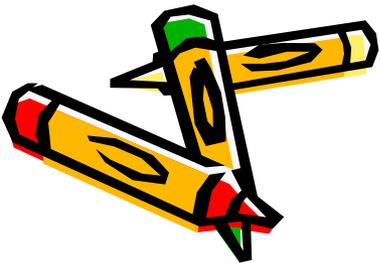


- ❖ Prevention of germ cell-specific autoimmune reactions in the adult testis has long been explained solely on the basis that all germ cell-related autoantigens are segregated within the seminiferous tubules.
- ❖ With the onset of meiosis during puberty, the so-called blood-testis barrier separates the basal compartment of the seminiferous epithelium containing spermatogonia and preleptotene spermatocytes from the adluminal compartment, where meiosis and spermiogenesis occur.
- ❖ Morphologically, Sertoli cells are connected to each other over large areas of their surfaces by 'occluding tight junctions', which render intercellular spaces even impermeable to small molecules.

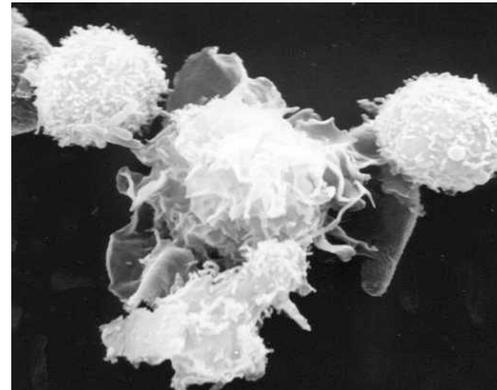
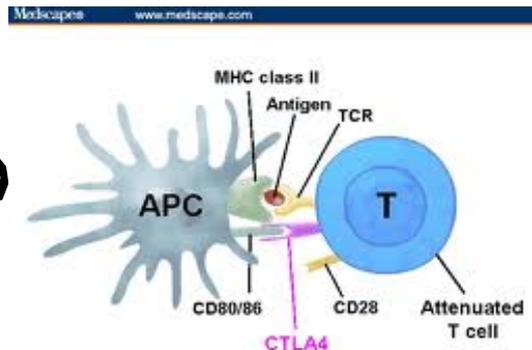


- ❖ The microenvironment of the adluminal compartment is isolated from the vascular system and circulating immune cells.

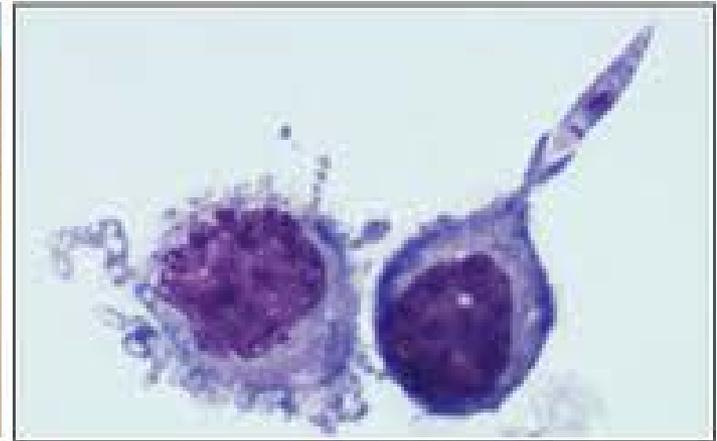
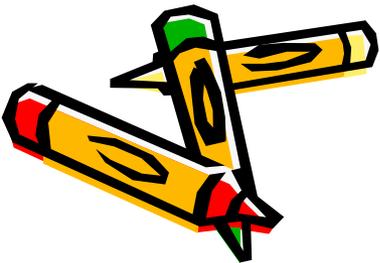
- ❖ Segregation of germ cell-specific autoantigens by the blood-testis barrier is not complete.
- ❖ Autoantigenicity of the basal compartment of the seminiferous epithelium could be demonstrated in rats.
- ❖ Barrier functions are less extensive along the rete testis and excurrent ducts, where T cells are physiologically found within the lining epithelium.
- ❖ Tissue barriers and mechanical sequestration are important but not sufficient to protect male germ cells from autoimmune attack.
- ❖ There is considerable evidence that multiple immunoregulatory mechanisms are involved in maintaining both tolerance towards germ cells and immune privilege within the normal adult testis.

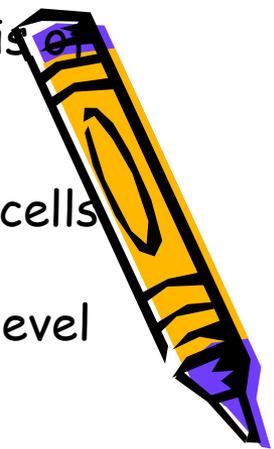


- ❖ Clonal deletion of autoreactive T lymphocytes through thymic selection during perinatal life does not control germ cell-related autoreactivity; mechanisms of peripheral tolerance such as local anergy of T cells have been considered to play a key role.
- ❖ Naive T cells remain refractory to antigen-specific activation when encountering antigenic peptide: MHC complexes without antigen-independent costimulatory signals delivered by the same antigen-presenting cell.
- ❖ Constitutive expression of MHC molecules is found in the interstitial compartment of the testis, whereas costimulatory molecules such as ICAM-1, CD80, and CD86 are absent.
- ❖ Avoidance of deleterious autoimmune responses can also be achieved by active suppression mediated by regulatory T (Treg) cell populations.

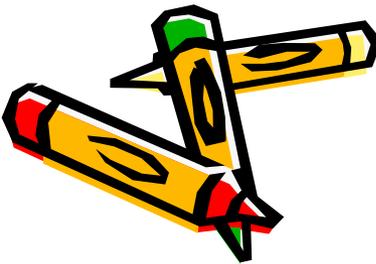
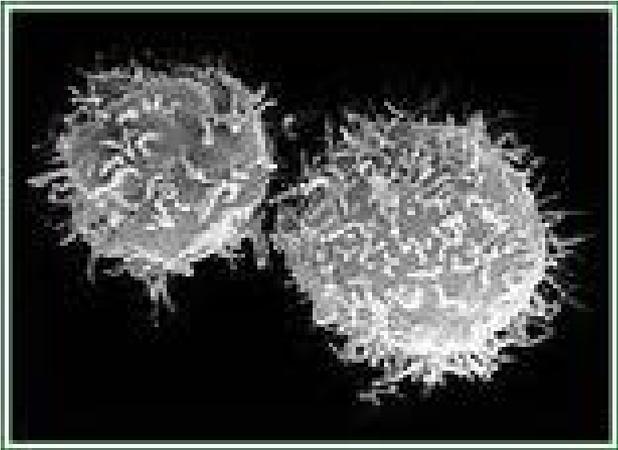
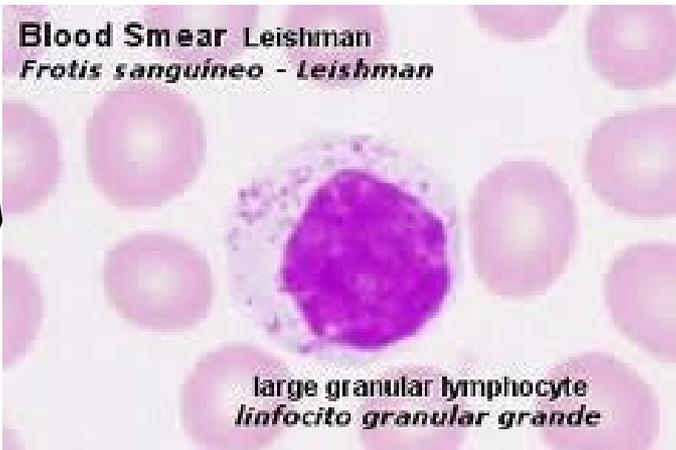


- ❖ Among CD4 effector T cells, the cytokine profile produced by TH2 cells exerts inhibitory effects on TH1 cells which mediate cellular immune responses including organ-specific autoimmunity.
- ❖ Preliminary observations in the normal murine testis suggest functional polarization of T cells towards a TH2 profile.
- ❖ Control of inflammation in vivo has also been attributed to Treg producing IL-10 or transforming growth factor- (TGF-beta).
- ❖ Recent experiments with peripheral blood lymphocytes from healthy donors showed that the expansion of autoreactive T cells directed against a testisrelated antigen can be suppressed by CD4 CD25 Treg.
- ❖ However, the presence and possible role of CD4 CD25Treg in the testis in vivo remains to be elucidated





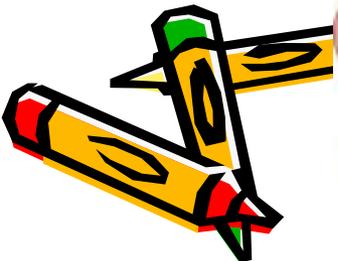
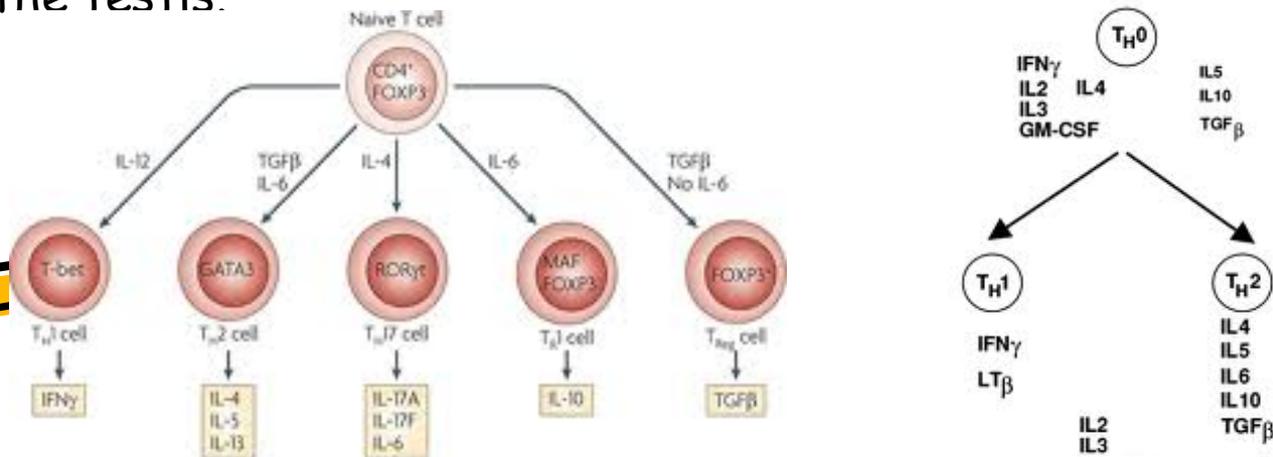
- ❖ A further level of protection represents activation-induced apoptosis of T lymphocytes entering the immunologically privileged testis.
- ❖ Recent data obtained in a mouse model indicate that memory CD8 T cells migrating into the testis are capable to mount an immune response against foreign tissue grafts but undergo apoptosis at an increased level via upregulation of Fas (CD95) and CD30 on their surface.
- ❖ Expression of the ligand of Fas (FasL) by Sertoli cells has been implicated in maintaining testicular immune privilege as well as enhanced survival of allogeneic grafts cotransplanted with testicular tissue into other sites.
- ❖ Immunosuppressive activity has been described in testicular fluids. There is evidence that locally produced mediators, i.e. cytokines, could play a key role in preventing immune activation and subsequent inflammation in the testis

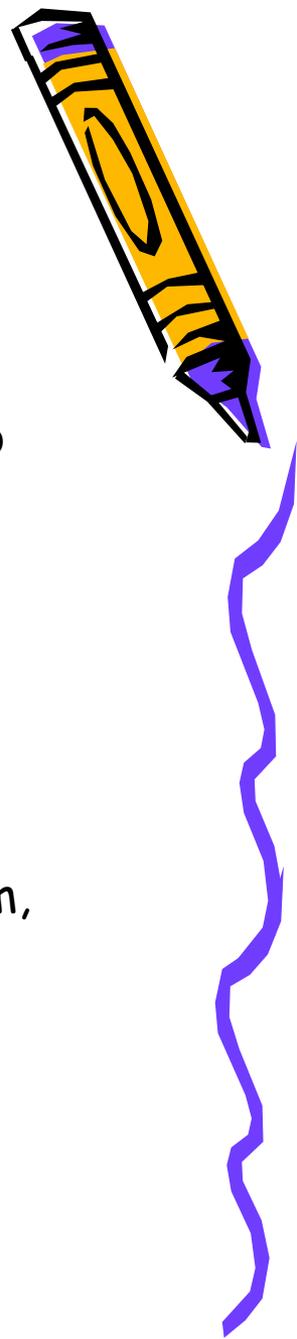


The Dual Role of Cytokines in the Testis

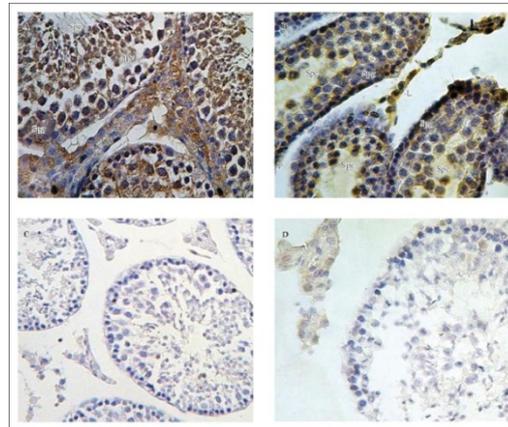
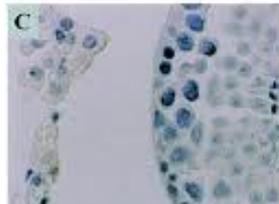
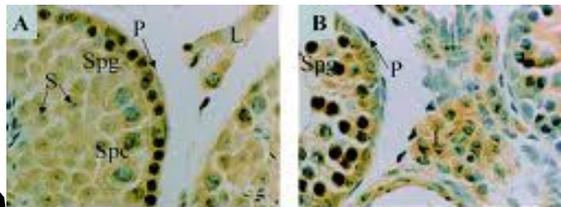


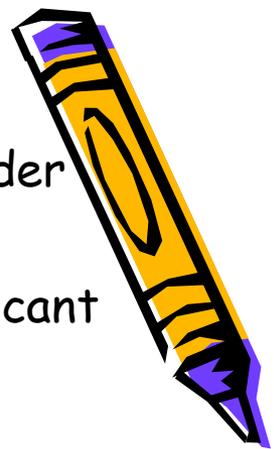
- ❖ Apart from overall hormonal control, precise regulation of spermatogenesis and steroidogenesis within the testis depends on numerous autocrine and paracrine mediators including growth factors and cytokines.
- ❖ Under physiological conditions, resident macrophages as well as nonimmune testicular cells have been shown to produce both pro- and anti-inflammatory cytokines such as IL-1, IL-6, TNF- as well as members of the TGF- family.
- ❖ The apparent overlap between testicular and immune regulatory functions of these cytokines could provide the key to understanding the phenomenon of immune privilege and the processes leading to inflammation-mediated damage in the testis.



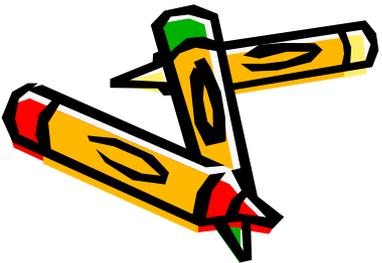
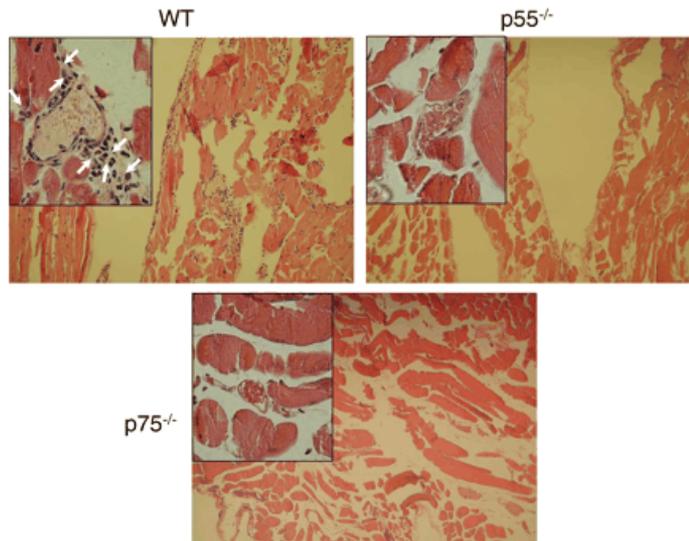


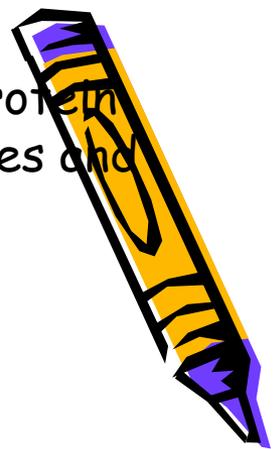
- ❖ The archetypical proinflammatory cytokine IL-1 (occurring as two isoforms: IL-1 α , IL-1 β) is abundantly secreted by activated macrophages, but is also inducible in other cell types.
- ❖ In the rat testis, IL-1 is produced and secreted under physiological conditions by Sertoli cells.
- ❖ There is some evidence that spermatocytes and spermatids may also produce IL-1 constitutively.
- ❖ High-affinity IL-1 binding sites and mRNA for the IL-1 signaling receptor have been found in most cells of the interstitium and seminiferous epithelium.
- ❖ Testicular IL-1 is thought to play an important role in coordinating Sertoli and germ cell development within the seminiferous epithelium, and in controlling steroidogenesis.



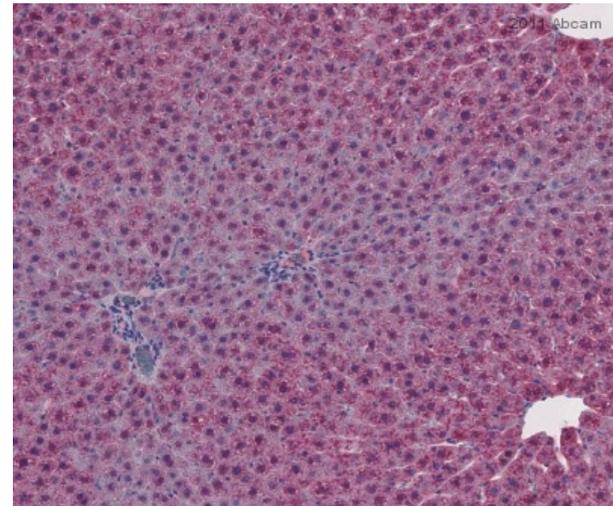
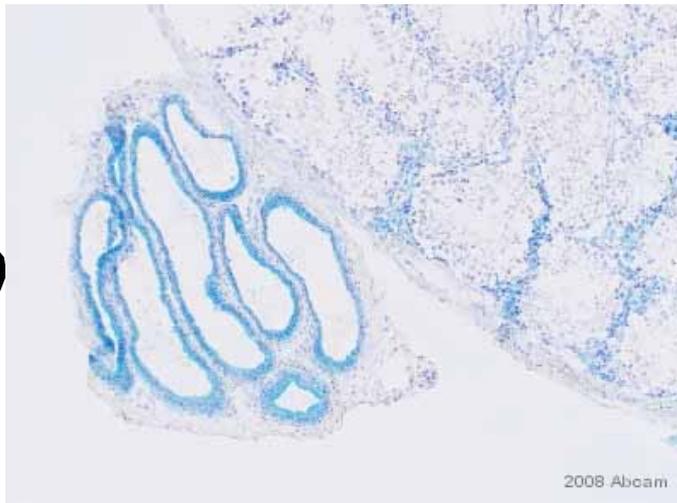
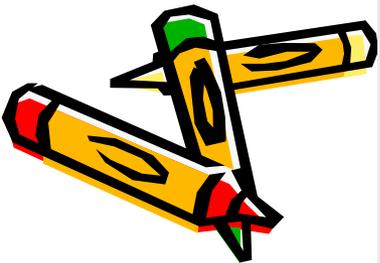


- ❖ Recent data suggest that IL-1 α generally inhibits LH-stimulated testosterone production, but can stimulate basal steroidogenesis under appropriate conditions.
- ❖ In contrast to IL-1 α , IL-1 β does not appear to be produced in significant amounts in the normal testis.
- ❖ TNF- α is produced by activated testicular macrophages in vitro.
- ❖ TNF- α inhibits Leydig cell steroidogenesis, and its localization to the postmeiotic germ cells also indicates possible involvement in the process of spermatogenesis.
- ❖ Observations from the human testis suggest that TNF- α might play a role in controlling the efficiency of spermatogenesis, inhibiting germ cell apoptosis by regulating the level FasL.

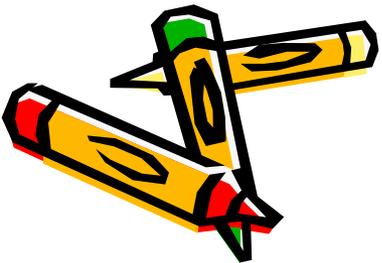
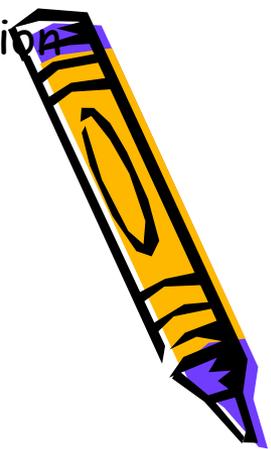




- ❖ The macrophage migration inhibitory factor (MIF) is a pleiotropic protein with a wide tissue distribution participating in inflammatory responses and acting
- ❖ as a counterregulator of glucocorticoid-induced immune suppression.
- ❖ In the rat testis, MIF has been localized to the Leydig cells.
- ❖ MIF has been found to reduce inhibin secretion by Sertoli cells in culture and to evoke a transient increase in calcium levels in peritubular cells.
- ❖ MIF have a role in the paracrine regulation of Leydig cell-seminiferous tubule interactions.
- ❖ MIF has been shown to downregulate TGF-2 secretion in peritubular cells.



- ❖ Upregulation of the proinflammatory cytokine MIF during inflammation can inhibit the immunosuppressive response of the testis.
- ❖ The TGF- family members are dimeric cytokines with predominantly immunosuppressive and anti-inflammatory activities.
- ❖ There are three mammalian TGF- isoforms, which are very highly expressed by Sertoli cells, peritubular cells and Leydig cells in the fetal and immature testis, although production declines dramatically postpuberty.
- ❖ The receptors for TGF- are found in both somatic and germ cells.
- ❖ Consequently, these cytokines have been implicated in controlling both Leydig cell and seminiferous tubule development



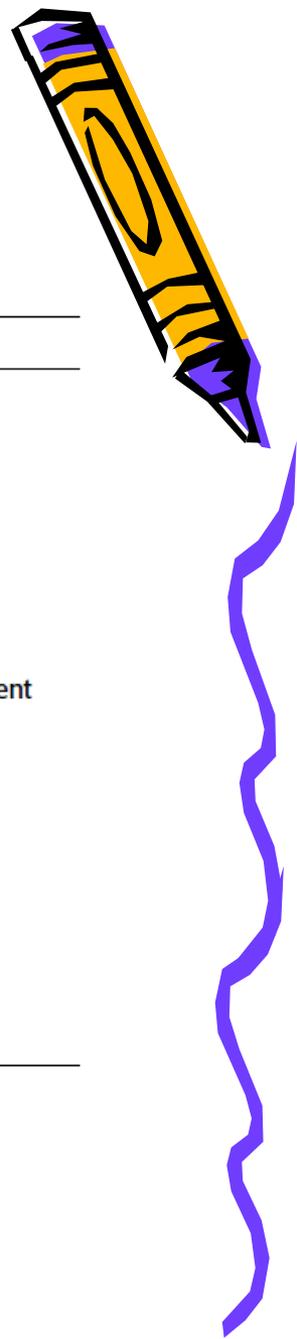


TABLE 5. *Immunoregulatory factors identified in the testis*

Factor	Source	Main immunoregulatory actions
TGF- β	Sertoli cells, peritubular cells, (resident macrophages)	Anti-inflammatory, immunosuppressive Inhibition of T- and B-cell function
Activin A	Sertoli cells, peritubular cells	Anti-inflammatory, immunosuppressive Inhibition of T- and B-cell function
IL-1 α	Sertoli cells, (spermatogenic cells)	Stimulates NO and prostaglandin production Stimulates Th2 responses
α -MSH	Resident macrophages, Leydig cells	Stimulates IL-10 production Inhibits IL-2 responses
M-CSF	not known	Stimulates resident macrophage development
IL-6	Sertoli cells, Leydig cells	Regulates dendritic cell and macrophage development Stimulates Th2 responses
IL-10	Resident macrophages	Th2 cytokine Anti-inflammatory, immunosuppressive
iNOS/NO	Leydig cells, Sertoli cells, spermatocytes	Regulates Th1/Th2 balance Inhibits lymphocyte adhesion Stimulates COX-2 expression
MIF	Leydig cells, (Sertoli cells)	Inhibits T cell and NK cell cytotoxicity
Fas ligand	Spermatogenic cells, (Sertoli cells)	Causes apoptosis of activated T cells
PGE ₂	Resident macrophages, Leydig cells	Modulates inflammatory functions of macrophages
IL-1ra	Sertoli cells	Blocks actions of IL-1
Clusterin	Sertoli cells	Inhibits T cell activation and function

Refer to text for complete names and details.

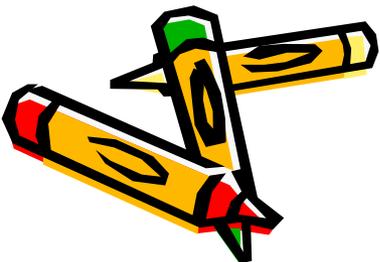


Table 15.3. Possible immunosuppressive factors in seminal plasma

Prostasomes

High molecular weight proteins

e.g. 720 kDa pregnancy-associated protein A-like molecule, 160-kDa complement cytolysis inhibitor, lactoferrin, cross-reacting antibodies

Fc receptor molecules

e.g. FcγRIII, 94-kDa Fc receptor-binding molecule

Fc binding molecules

e.g. 16- and 20-kDa IgG-binding proteins

Cytokines

e.g. TGF-α-like molecule, TGF-β, IL-1β, IL-6, IL-8 and soluble IL-2R

Enzymes

e.g. transglutaminase (alone or in association with uteroglobulin) nucleases and proteases

Other low molecular weight proteins

e.g. 35-kDa protein, β₂-microglobulin

Zn and zinc-binding molecules

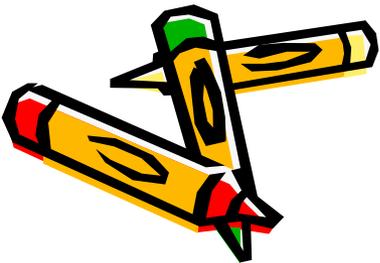
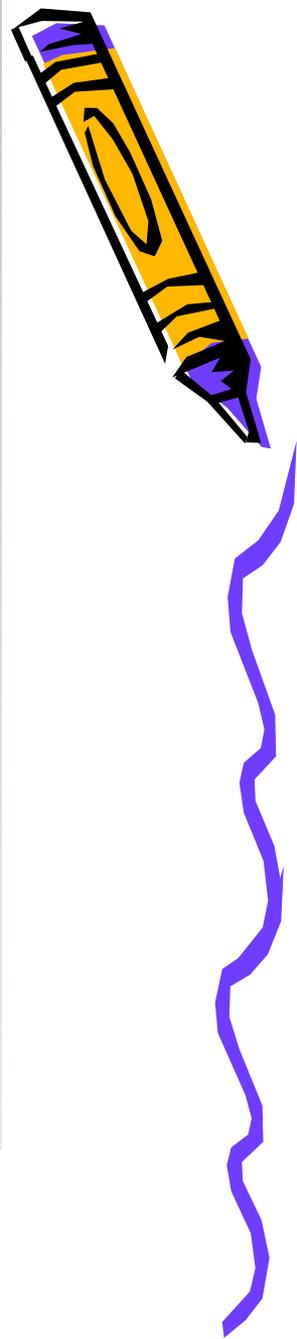
e.g. 5- and 200-kDa molecules

Prostaglandins

e.g. PGE₁, PGE₂, 19-OH PGE₁, 19-OH PGE₂

Polyamines

e.g. spermine and spermidine



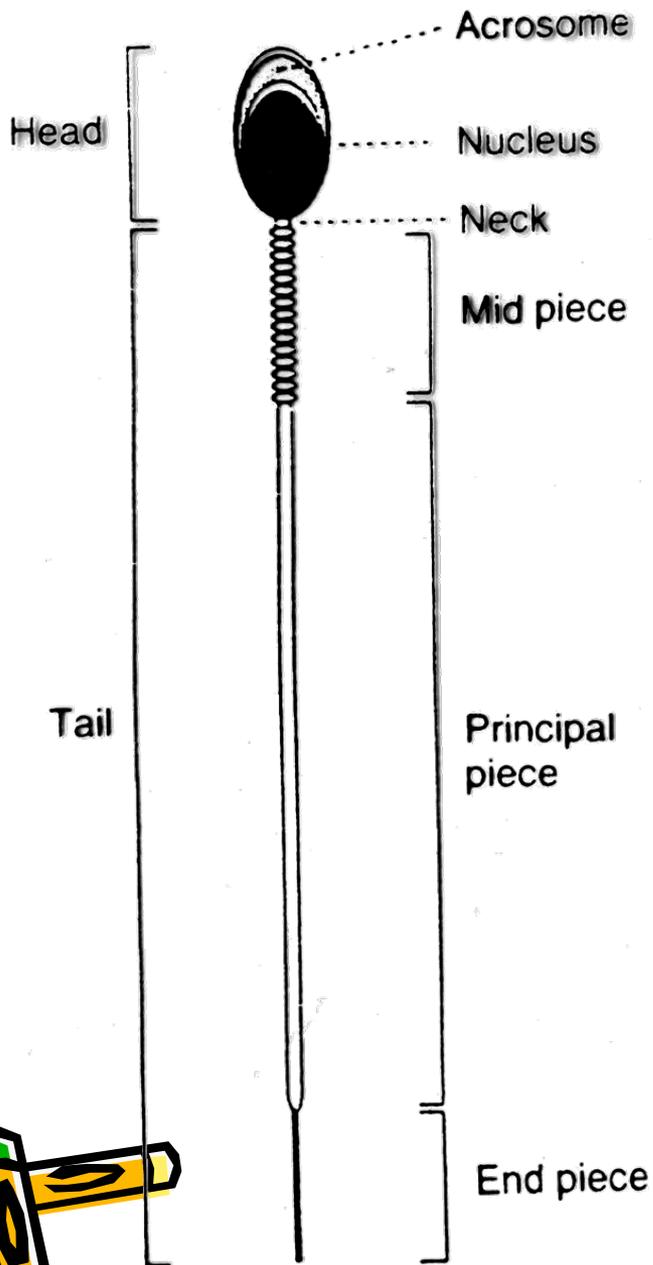


Figure 1.1. Anatomy of mammalian sperm. The sperm head is composed of the nucleus, the acrosome and their surrounding membranes. The sperm flagellum (or tail) is divided into the mid piece (middle piece), principal piece (posterior tail, distal tail) and end piece. The membrane domains of the mid and principal pieces of the tail are divided by the annulus, a cytoskeletal ring associated with the inner surface of the plasma membrane. A mitochondrial sheath surrounds the mid piece and provides the energy necessary for motility. Based on Fawcett (1975) and Eddy and O'Brien (1994).

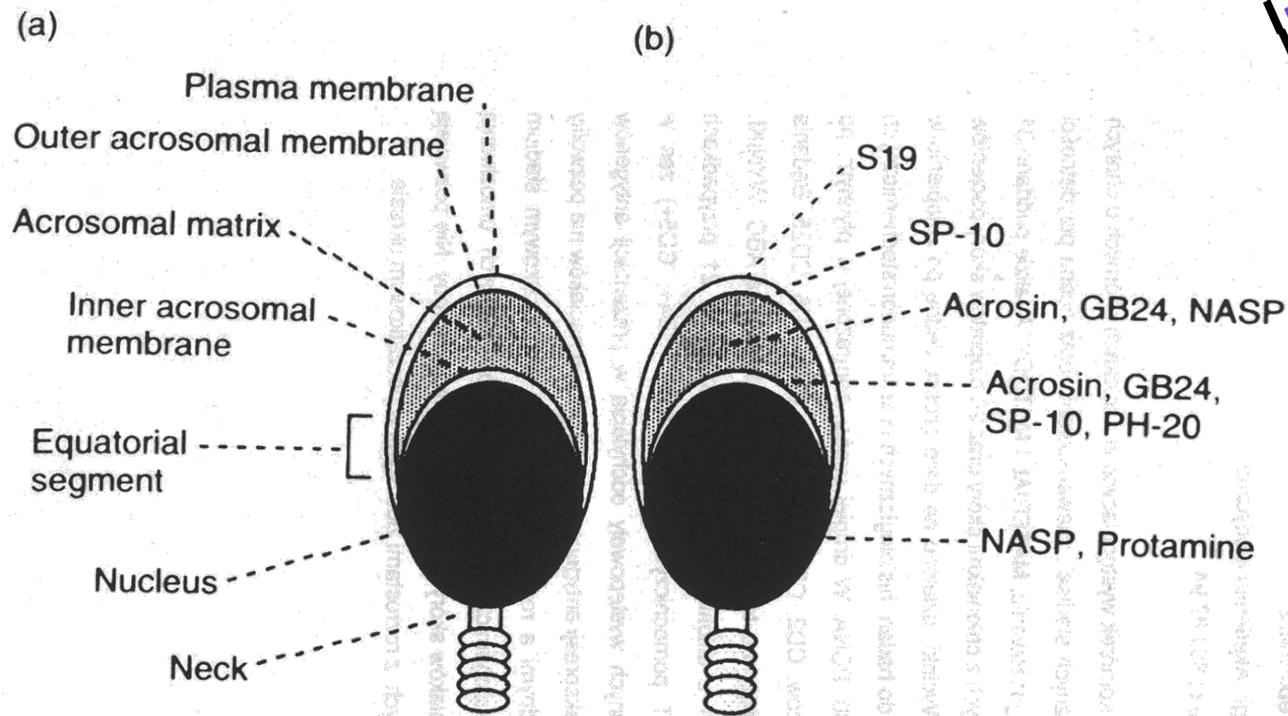


Figure 1.3. Cross-section of the mammalian sperm head. (a) The acrosome is situated in the anterior portion of the head and surrounds the anterior region of the nucleus. The inner acrosomal membrane contours the nuclear envelope while the outer acrosomal membrane underlies the plasma membrane. Lytic enzymes are released from this organelle during the acrosome reaction to facilitate sperm penetration of the zona pellucida. The nucleus, located in the posterior region of the head, contains the highly condensed chromatin of the paternal haploid genome. Based on Fawcett (1975) and Eddy and O'Brien (1994). (b) Localization of nuclear and acrosomal antigens described in the text.

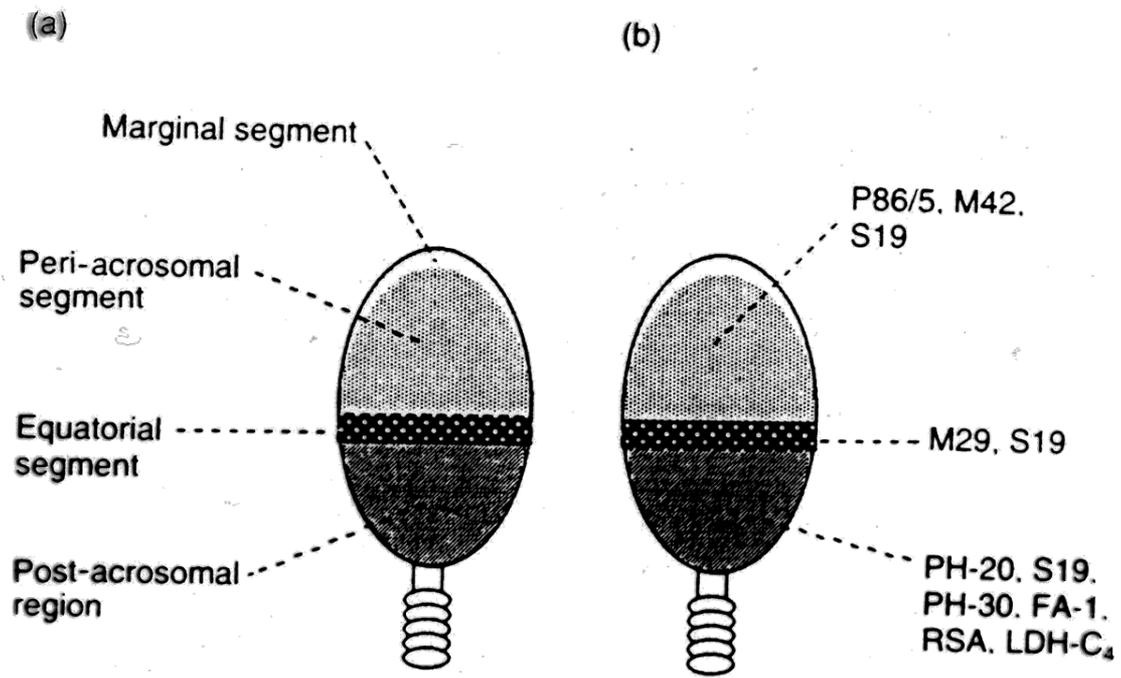
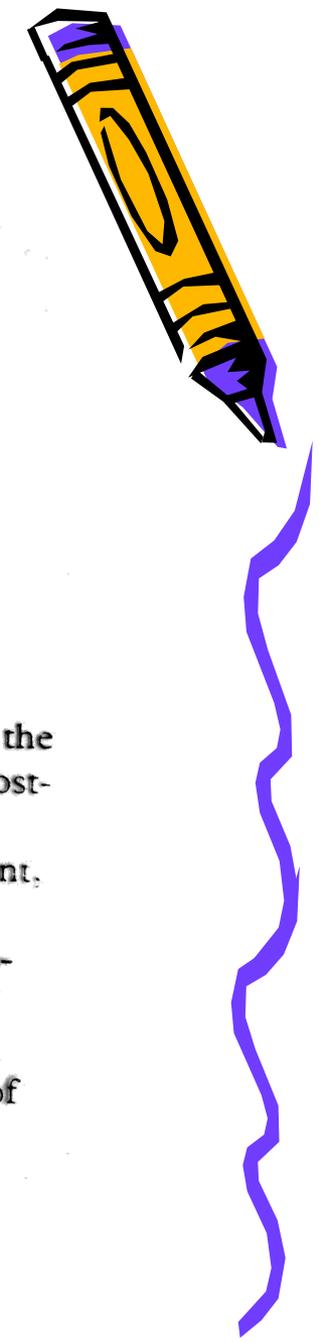


Figure 1.2. Surface of the mammalian sperm head. (a) The plasma membrane of the mammalian sperm head is divided into the acrosomal region (anterior head) and post-acrosomal region (posterior head, post-acrosomal segment). The acrosomal region can be further subdivided into the marginal segment (rostral crescent, apical segment, anterior band, peripheral rim) over the anterior rim of the head, the peri-acrosomal segment (acrosomal segment, principal segment) over the major portion of the acrosome and the equatorial segment (equatorial band) that borders the post-acrosomal region. The post-acrosomal region extends from the equatorial segment to the neck where the posterior ring forms a tight seal between the cytoplasmic compartments of the head and tail. Based on Fawcett (1975) and Eddy and O'Brien (1994). (b) Localization of the described surface antigens of the mammalian sperm head.



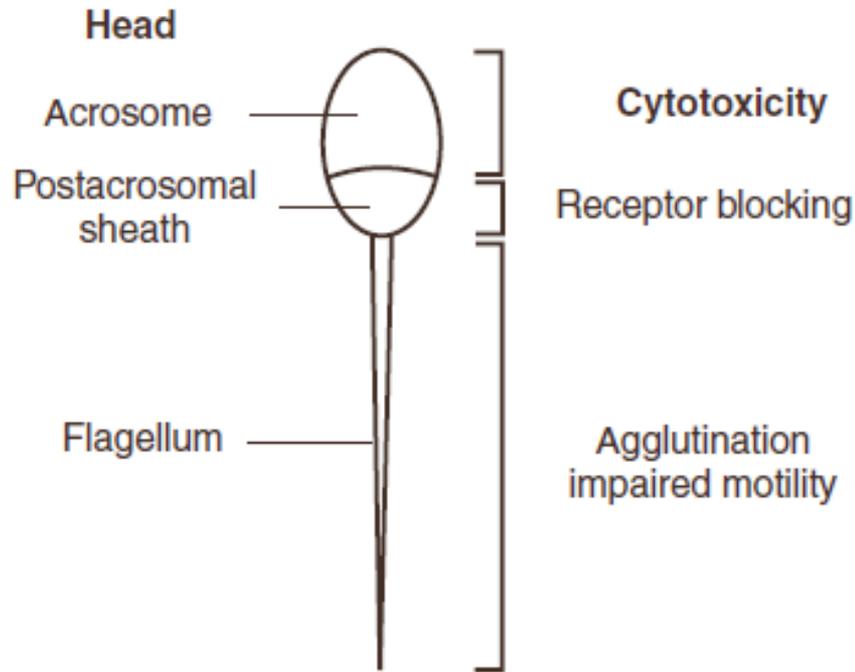
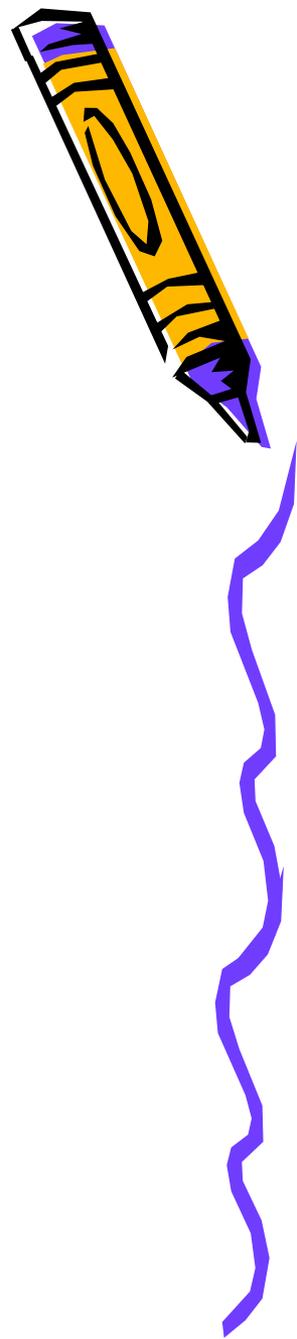
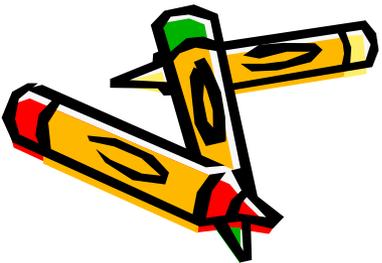
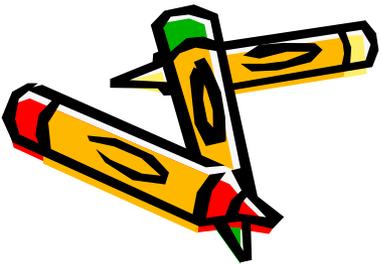
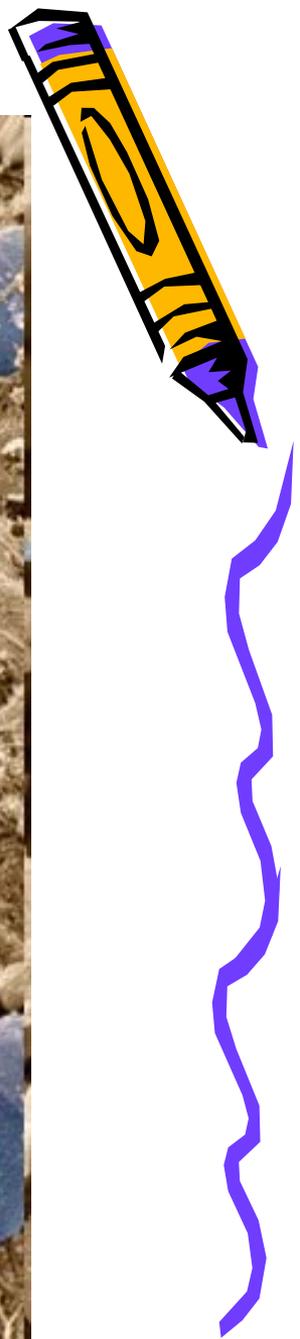
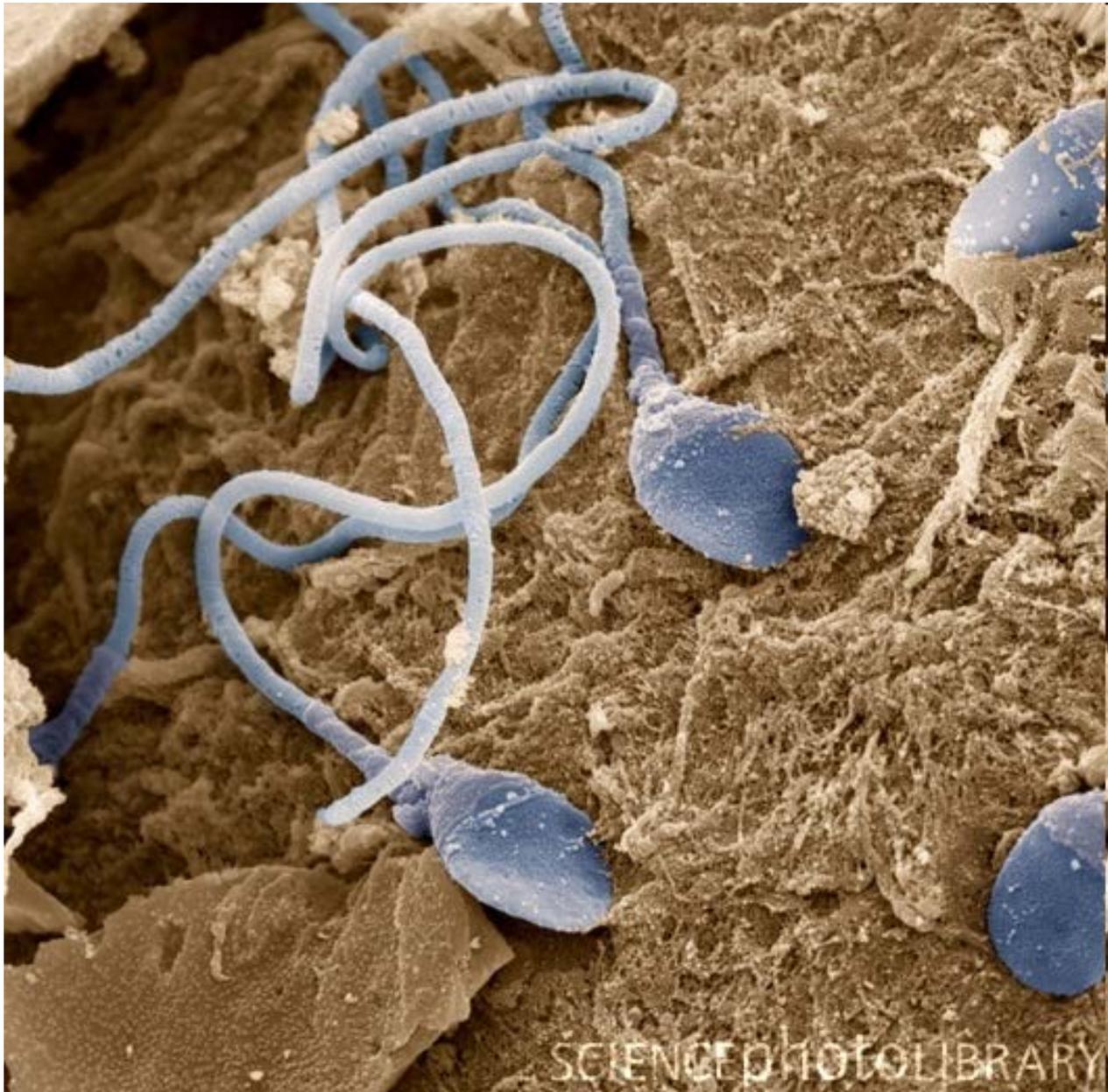
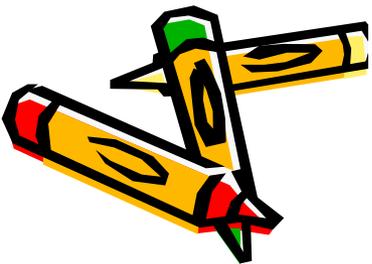
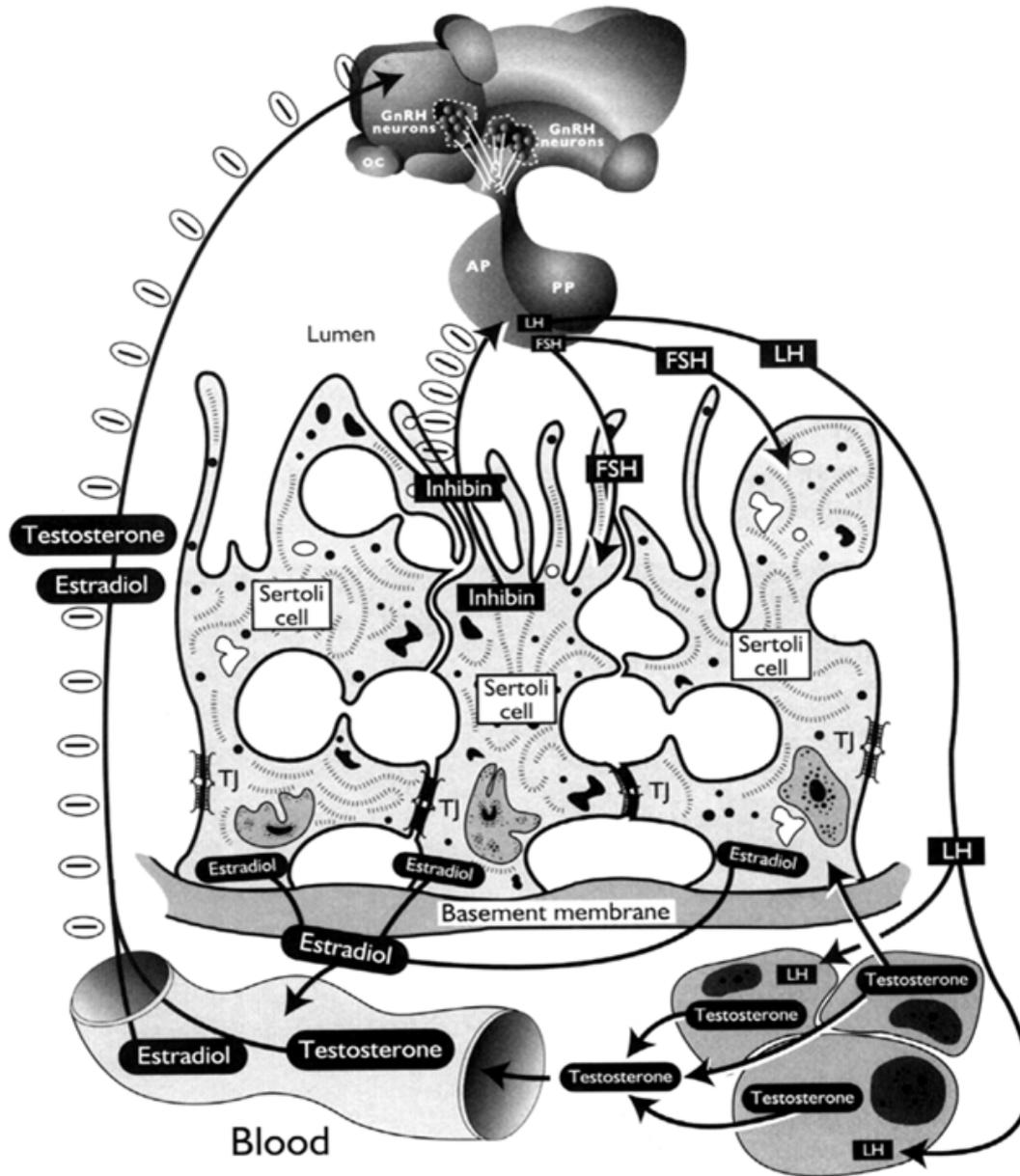


FIG. 15. Sperm antibody binding sites and effects. The principal sequelae of antibody binding to spermatozoa are (a) activation of immune cells against the sperm through complement or through interaction with immunoglobulin Fc receptors on phagocytes leading to cytotoxicity; (b) blocking or interfering with surface recognition molecules, in particular the egg binding receptors in the postacrosomal region; and (c) agglutination caused by cross-linking of sperm by multivalent antibody, which may impede the ability of sperm to swim freely in the female tract.







A

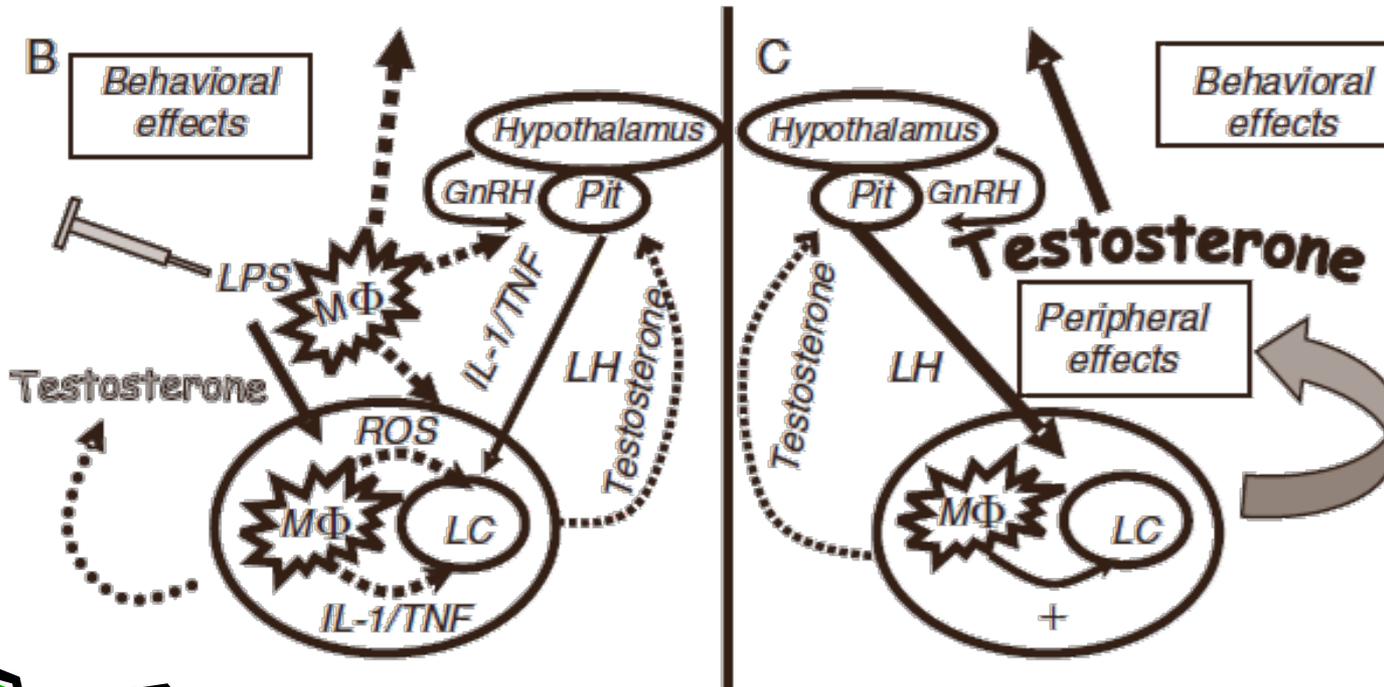
Sickness Behavior

Reduced libido
Anorexia
Decreased aggression



Testosterone Behavior

Libido
Aggression
Well being



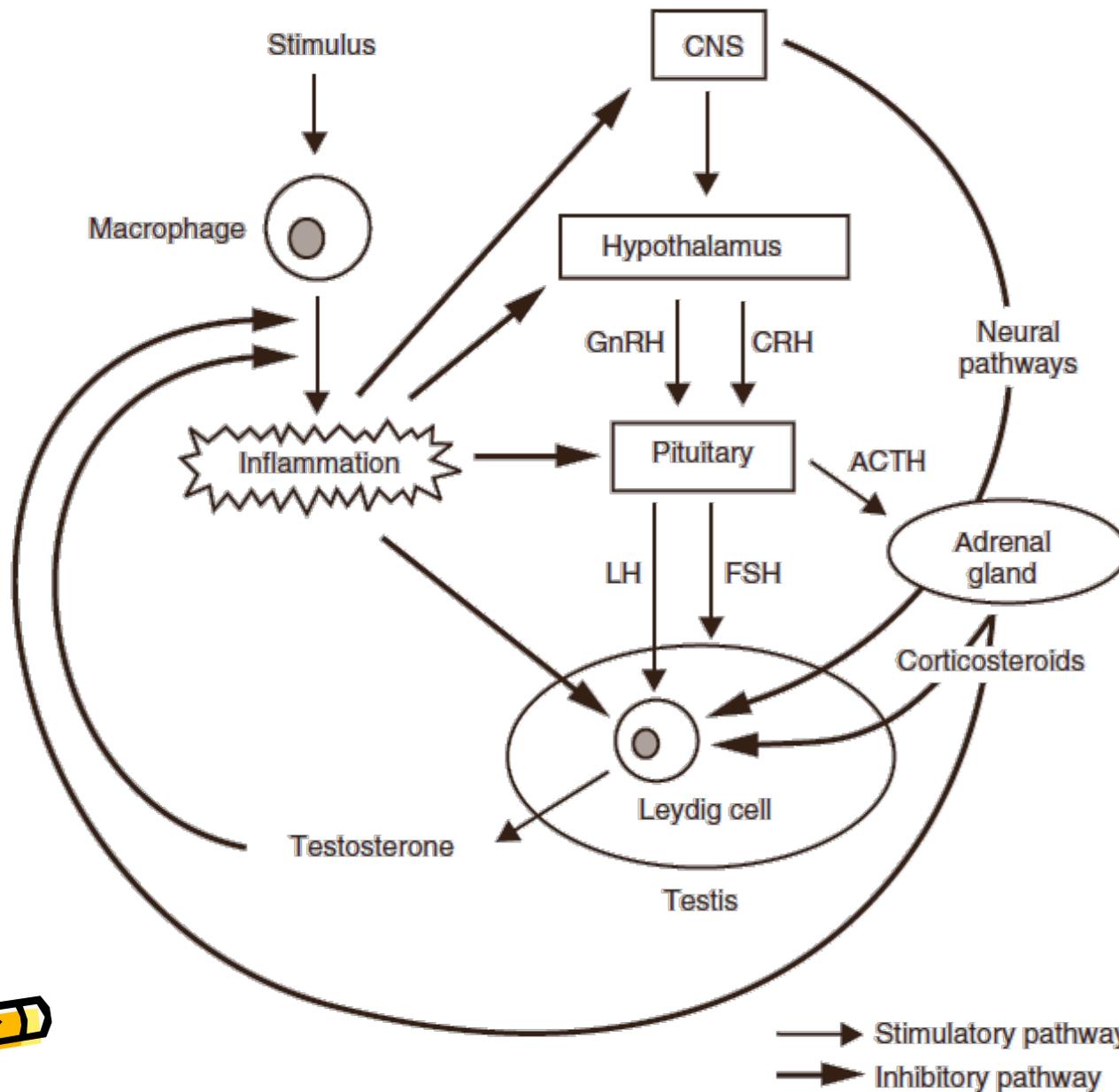


FIG. 4. The interface between the hypothalamic-pituitary-gonadal-adrenal axis and the inflammatory reaction.

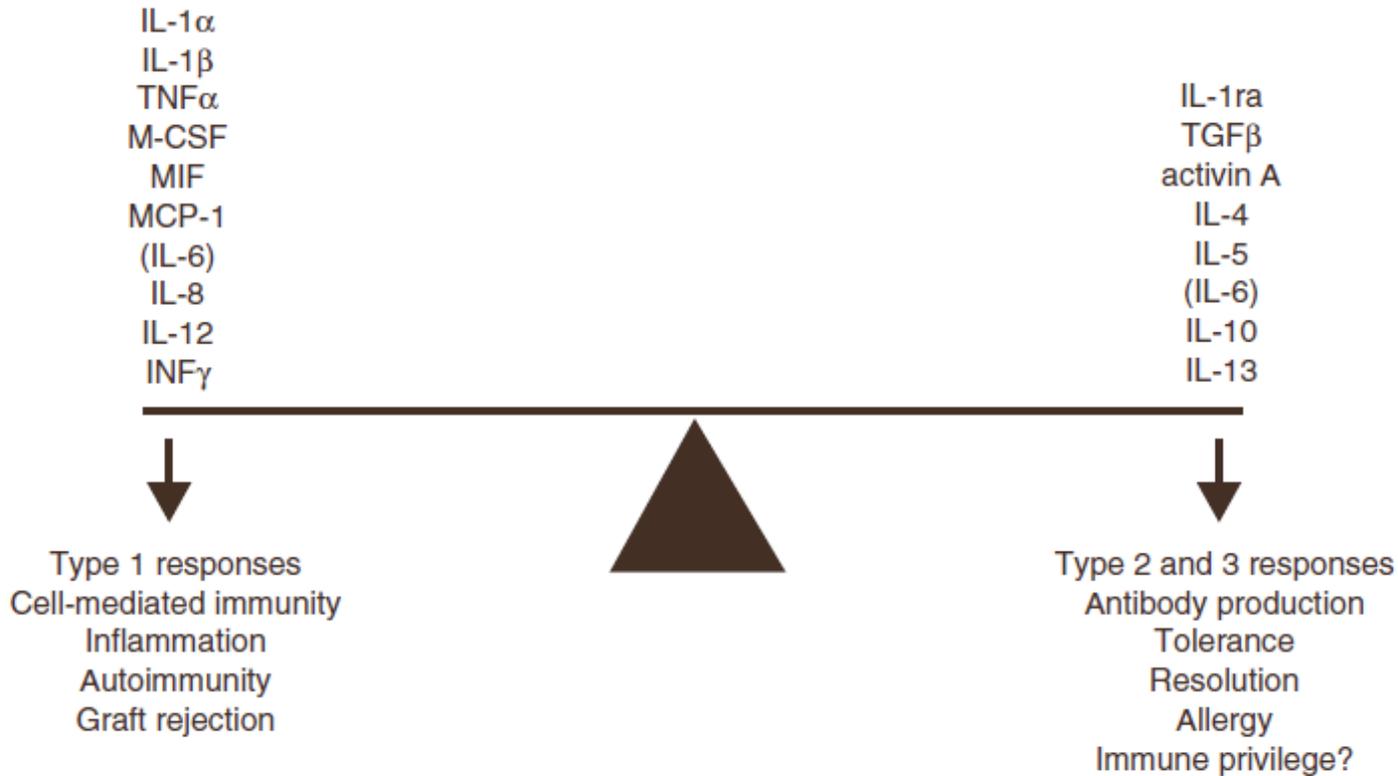
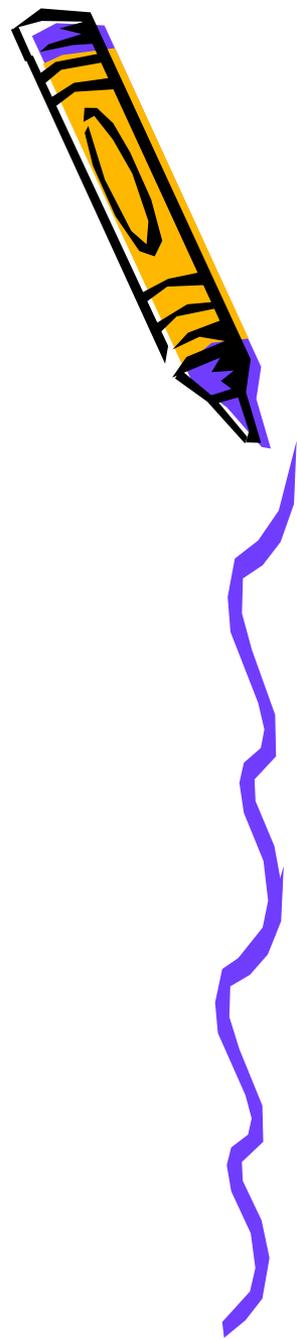
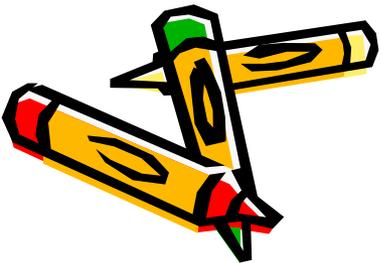


FIG. 6. The cytokine balance. Most cytokines can be designated either proinflammatory or anti-inflammatory/immunoregulatory, depending on their predominant activities. The former group is associated with type 1 responses (cell-mediated immunity, autoimmunity) and the latter with type 2 or type 3 responses (antibody production, allergy, tolerance). Immunological responses involve multiple representatives of one or the other cytokine group, but rarely members of both groups. However, most cytokines, and interleukin-6 in particular, possess both proinflammatory and antiinflammatory properties under different circumstances. (See text for details.)



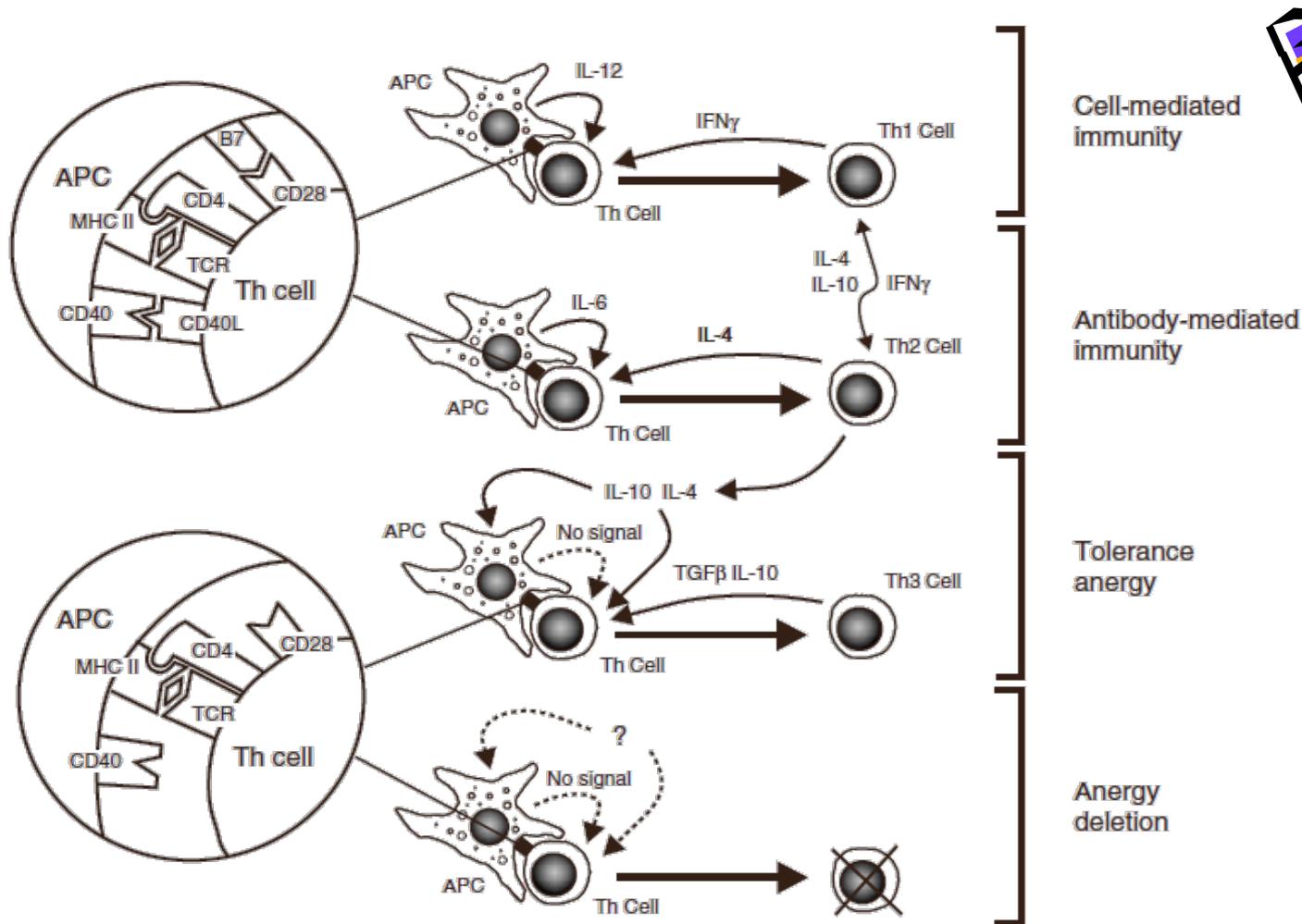


FIG. 7. Activation of the adaptive immune response. Interaction between antigen-presenting cells (APC) and helper T (Th) cells can have different outcomes depending on the cytokine environment and costimulatory surface molecules expressed at the time of interaction. Recognition of the MHC class II–peptide antigen complex by the naive Th cell together with engagement of the B7/CD28 and CD40/CD40L receptor/coreceptor pairs can lead to generation of Th1 cells if type 1 cytokines (interleukin [IL]-12 and interferon [IFN]- γ) are present, or a Th2 response if IL-6 and type 2 cytokines (IL-4 and IL-10) are present (221, 224–226). Presentation of antigen in the absence of costimulation or in the presence of type 2 and “type 3” cytokines such as transforming growth factor (TGF)- β results in a tolerogenic response, involving deletion or inactivation (anergy) of the Th cell, or production of “Th3 cells” producing TGF- β , IL-4, and IL-10 (1161). Similar mechanisms may be responsible for generation of antigen-specific regulatory/suppressor T cells (4,227–229).

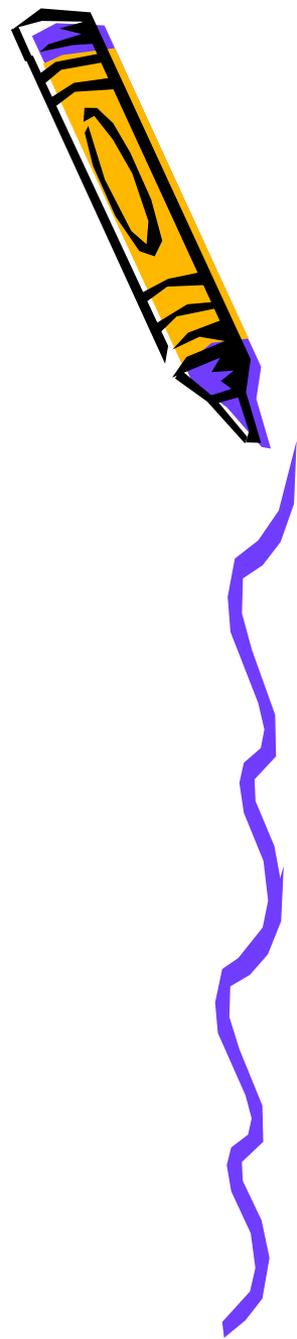
TABLE 3. *Quantification of immune cells in the normal testis of adult rats and humans*

Cell type	Rat testis ($\times 10^6$ /g tissue)	Human testis ($\times 10^6$ /g tissue)
Macrophages	5–10	10–25 ^a
Dendritic cells	0.2–0.3	ND
T cells	1–2	1.4–2.4
CD8 ⁺ T cells	0.6–1.8	ND
CD4 ⁺ T cells	0.2–0.3	ND
NK cells	0.6–1.0	1.0–2.8

ND, no quantitative data available.

Data were largely obtained from stereological analysis of testes from Sprague-Dawley rats (130,131,397,431) and from adult human testes with normal spermatogenesis (M. P. Hedger, unpublished data). The study of Vergouwen and colleagues (357) indicates that adult CBA/P mouse testes contain approximately 2 to 4×10^6 macrophages/g tissue, but there are as yet no definitive quantitative studies of other leukocyte subsets in the mouse testis.

^aUpper limit calculated from data obtained by Frungieri and colleagues (360) using a well-characterized and reliable monoclonal antibody against human CD68. The observation that macrophage numbers in the normal human testis are at least as large, if not larger, than those found in either the rat or mouse testis is consistent with observations in several earlier nonquantitative studies using other macrophage markers (128,388,430,433).



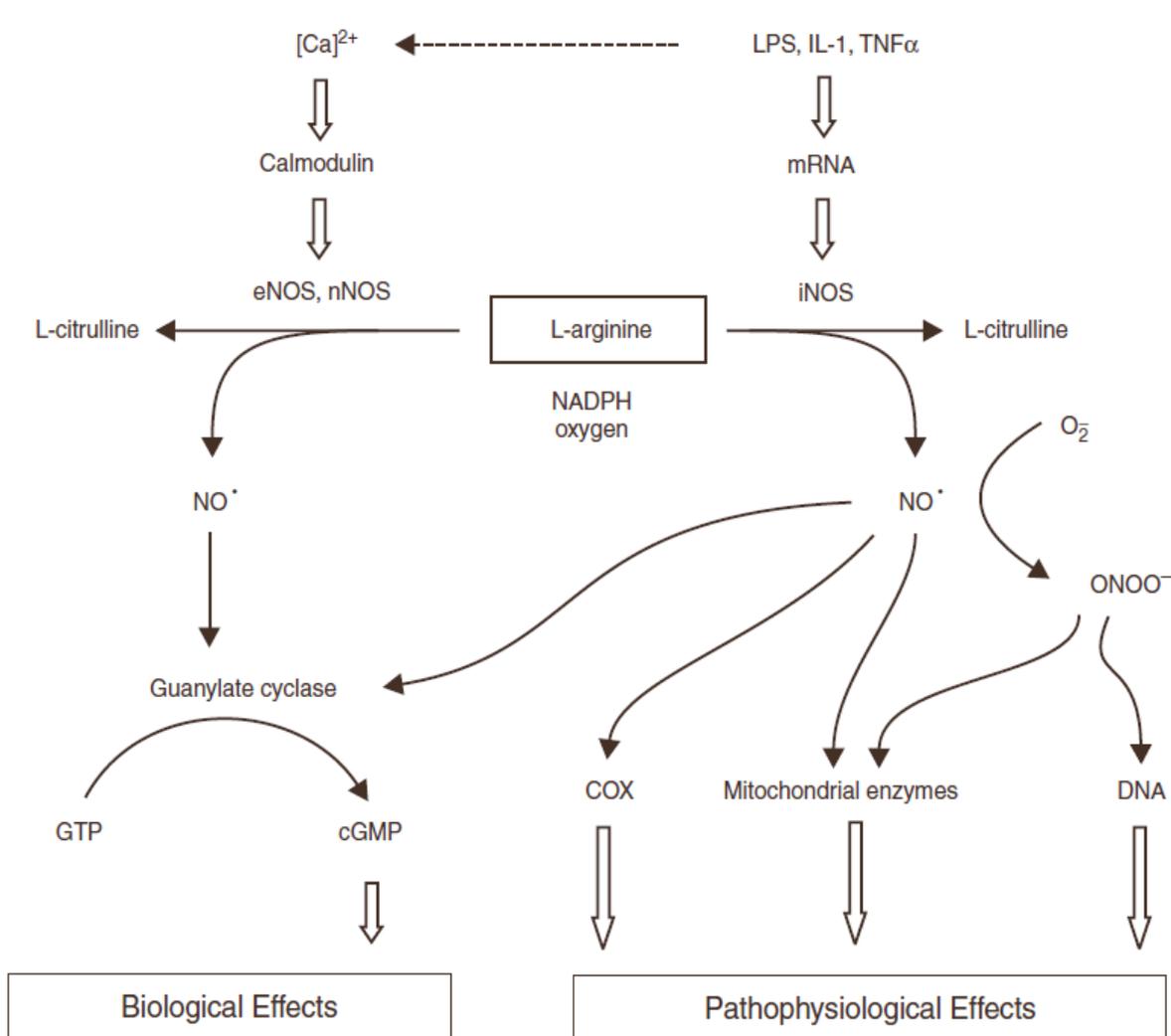


FIG. 13. Regulation and actions of nitric oxide synthase (NOS) and NO production in normal physiology and pathophysiology. NO is produced by enzymic conversion of L-arginine to L-citrulline by NOS, and the freely diffusible NO radical (NO $^{\bullet}$) exerts a variety of physiological functions through regulation of cyclic guanosine monophosphate (cGMP)-dependent protein kinases. The activity of the constitutively expressed isoforms, endothelial NOS (eNOS) and neuronal NOS (nNOS), is regulated through calcium-calmodulin. Synthesis of a constitutively active form of NOS, called inducible NOS (iNOS), is induced by inflammatory mediators and is responsible for the large upregulation of NO production during inflammation. High levels of NO $^{\bullet}$ can be detrimental due because of direct reaction with the heme group of cyclooxygenase (COX), mitochondrial enzymes, and DNA, effects that can be potentiated by interaction with superoxide to produce the extremely reactive peroxynitrite anion (514,751,1284).

