МИНИСТЕРСТВО ОБРАЗОВАНИЯ И НАУКИ КЫРГЫЗСКОЙ РЕСПУБЛИКИ
УЧРЕЖДЕНИЕ «САЛЫМБЕКОВ УНИВЕРСИТЕТ»
МЕЖДУНАРОДНЫЙ ФАКУЛЬТЕТ МЕДИЦИНЫ

Кафедра Естественно-гуманитарных дисциплин

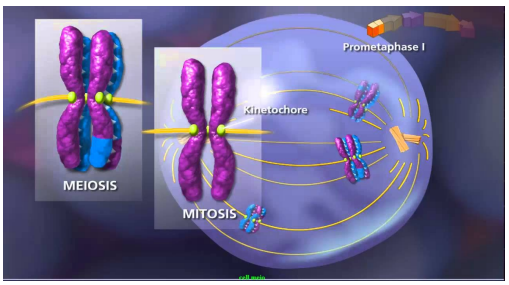
СОГЛАСОВАНО
Заведующий кафедрой
Естетсвенно-гуманитарных
дисциплин
_____Касымалиева К.К.
«_____» _____20____г.

УТВЕРЖДЕНО
Ректор Учреждения
«Салымбеков Университет»
_____Жумадилов Э.Ж.
«____» _____20____г.

Учебно-методический комплекс дисциплины

ГИСТОЛОГИЯ, ЦИТОЛОГИЯ, ЭМБРИОЛОГИЯ

основной образовательной программы по направлению подготовки «Лечебное дело»



Составитель (и): преподаватель Князев И.А.

Бишкек

МИНИСТЕРСТВО ОБРАЗОВАНИЯ И НАУКИ КЫРГЫЗСКОЙ РЕСПУБЛИКИ
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МЕЖДУНАРОДНЫЙ ФАКУЛЬТЕТ МЕДИЦИНЫ

Факультет *Лечебный*

Кафедра *Естественно-гуманитарных дисциплин*

Название дисциплины *Гистология, Цитология, Эмбриология*

Учебно-методический комплекс дисциплины *Гистология, Цитология, Эмбриология*

Название и код направления подготовки *«Лечебное дело»*

Квалификация выпускника *Врач*

Форма обучения *Очная*

Составитель(и): преподаватель **Князев Игорь Алексеевич**

Рабочая программа рассмотрена и одобрена на заседании УМС
Учреждения «Салымбеков Университет»
№_____ от_____20_____

Рабочая программа рассмотрена и одобрена на заседании кафедры ЕГД
Учреждения «Салымбеков Университет»
№_____ от_____20_____

зав. УМО
Акматова А.Т. _____

Заведующий кафедрой ЕГД
Касымалиева К.К._____

Составитель
Преподаватель Князев И.А. _____

ОГЛАВЛЕНИЕ

МИНИСТЕРСТВО ОБРАЗОВАНИЯ И НАУКИ КЫРГЫЗСКОЙ РЕСПУБЛИКИ
УЧРЕЖДЕНИЕ "САЛЫМБЕКОВ УНИВЕРСИТЕТ"
МЕЖДУНАРОДНЫЙ ФАКУЛЬТЕТ МЕДИЦИНЫ

Кафедра Естественно-гуманитарных дисциплин

РАБОЧАЯ УЧЕБНАЯ ПРОГРАММА

по дисциплине «Гистология, Цитология, Эмбриология»

Тип дисциплины Профессиональный цикл

Направление подготовки Лечебное дело

Курс 1

Семестр 1, 2

Количество учебных недель в семестре 20

Число кредитов 4

Всего часов по учебному плану 120

Из них:

Лекции _____32_____

Практические (семинарские)_____52_____

СРС_____36_____

СРСП_____25,2_____

Рабочая программа составлена в соответствии с требованиями Государственного образовательного стандарта по специальности «Лечебное дело»

Разработчики рабочей программы:

преподаватель Князев Игорь Алексеевич _____

Рабочая программа рассмотрена и одобрена на заседании кафедры_____ЕГД_____

Протокол №_____ от «_____»_____20_____г.

Согласовано с Учебно-методическим советом Учреждения «Салымбеков Университет»

Протокол №_____ от «_____»_____20____г. _____

Зав. Каф. ЕГД _____ _____

Бишкек

Раздел 1.

ОБЩИЕ ПОЛОЖЕНИЯ

1.1. Аннотация дисциплины

Гистология, Цитология, эмбриология – один из базовых медицинских предметов, позволяющих студентам рассмотреть строение человеческого организма на микроскопическом уровне, оценить свойства клеток и тканей на надмолекулярном, клеточном и тканевом уровне. Включение в состав данного предмета Эмбриологии также позволяет студентам проследить развитие организма на уровне внутриутробного процесса..

Таким образом, предмет Гистология, Цитология, Эмбриология является связующим звеном в глубоком осмыслении функционирования организма между молекулярным уровнем (что изучают на предметах Биохимия и Молекулярная Биология), и органным уровнем (что изучают на предметах Нормальная анатомия и Нормальная Физиология).

Цель преподавания дисциплины

Целью предмета является установление студентам принципов клеточного уровня организации человеческого тела, его неотъемлемой связи с животными клетками, а также подготовить к изучению таких предметов как Патологическая Анатомия и Патологическая Физиология, так как данные предметы базируются на глубоком понимании нормы.

К тому же в процессе обучения на данном предмете используется применение микроскопической техники исследования, что позволяет студентам освоить один из самых достоверных способов проведения клинических исследований организма как гистологическое исследование биоптата.

1.2. Задачи преподавания дисциплины

Основными задачами предмета является постижение студентами глубокой взаимосвязи структуры и функции тканей в живом организме, освоение основных принципов гистологического исследования, понять границы возможностей современной науки при гистологическом исследовании. Формируются навыки интерпретации данных гистологического исследования с функциями организма.

Узнать строение тканей организма, различтаь гистологические препараты на ультраструктурном уровне, понять нормальное строение тканей и органов, чтобы отличать здоровые ткани от поврежденный при патогистологическом исследовании.

1.3. Место дисциплины (модулей) в структуре ООП ВПО

Перед изучением предмета Гистология, Цитология, Эмбриология студент должен обладать базовыми познаниями школьных предметов, обладать знанием примерного расположения органов, функции основных систем человеческого организма, устройства

биологических систем, а также понимать основные принципы взаимоотношение микромира и макромира.

Пререквизиты: Общая биология, Общая химия, Органическая химия, Нормальная анатомия

Постреквезиты: Нормальная физиология, Патологическая Анатомия, Патологическая Физиология, Мед.генетика, Внутренние болезни, Онкология

1.4. Формируемые компетенции, а также перечень планируемых результатов обучения по дисциплине (знания, умения, владения), сформулированные в компетентностном формате

В соответствии с ГОС ВПО КР по соответствующему направлению выписываются все компетенции, формирование которых полностью или частично осуществляется при изучении данной дисциплины.

а) универсальные:

- (ОК-1); способностью к абстрактному мышлению, анализу, синтезу;
- (ОК-2); способностью использовать основы философских знаний для формирования мировоззренческой позиции;
- (ОК-5); готовностью к саморазвитию, самореализации, самообразованию, использованию творческого потенциала;
- (ОК-8); готовностью к работе в коллективе, толерантному восприятию социальных, этнических, конфессиональных и культурных различий.

— (ОПК-1); готовностью решать стандартные задачи профессиональной деятельности с использованием информационных, библиографических ресурсов, медико-биологической терминологии, информационно-коммуникационных технологий и учетом основных требований информационной безопасности;

— (ОПК-7); готовностью к использованию основных физико-химических, математических и иных естественнонаучных понятий, и методов при решении профессиональных задач;

— (ОПК-9); способностью к оценке морфофункциональных, физиологических состояний и патологических процессов в организме человека для решения профессиональных задач;

б) профессиональные (ПК)*:*

- (ПК-1); способностью и готовностью к осуществлению комплекса мероприятий, направленных на сохранение и укрепление здоровья детей и включающих в себя формирование здорового образа жизни, предупреждение возникновения и (или) распространения заболеваний, их раннюю диагностику, выявление причин и условий их

возникновения и развития, а также направленных на устранение вредного влияния на здоровье детей факторов среды их обитания;

- (ПК-20); готовностью к анализу и публичному представлению медицинской информации на основе доказательной медицины;
- (ПК-21); способностью к участию в проведении научных исследований;
- (ПК-22); готовностью к участию во внедрении новых методов и методик, направленных на охрану здоровья граждан.

15. Требования к уровню подготовки студента, завершившего программу изучения данной дисциплины.

В результате изучения базовой части цикла:

Студент должен знать:

- Структуру живой клетки человека
- Клеточные процессы функционирования человеческого тела
- Строение организма на клеточном и тканевом уровне организации
- Основные этапы развития органов и систем организма

Студент должен уметь:

- Формулировать знания по строению клетки, процесса деления и размножения, а также развития организма
- Давать гистологическое описание тканей организма
- Использовать современную литературу для изучения предмета
- Использовать микроскопическое исследование

Студент должен владеть:

- Методами подготовки тканей организма для гистологического исследования
- Методами микроскопического исследования тканей человека

Раздел 2.

СОДЕРЖАНИЕ И ТРУДОЁМКОСТЬ

В соответствии с учебным планом Учреждения «Салымбеков Университет» лечебного факультета предмет Гистология, Цитология, Эмбриология преподаётся в следующем объеме: всего 4 кредита на 1, 2 семестре.. Количество часов всего: 120 из них лекционных занятий 16 часов в 1 семестре и 16 часов во 2 семестре, Практических занятий 26 часов в 1

№	Темы модулей	Количество академических часов			Количество СРС		ВСЕГО
		Лек.	Пр. (сем)	Лаб.	СРС	СРСП	
1.	1,2 семестр						
2.	Cytology	8	10		6	2	24
3.	Sexual reproduction	4	8		3	2	15
4.	Embryogenesis	4	8		9	3	21
5.	Epithelial tissues	4	4		3	4	11
6.	Connective tissues	8	14		9	4	31
7.	Muscular tissue	2	4		3	4	9
8.	Nervous tissue	2	4		6	4	12
Общий объем учебной нагрузки (в часах):		**32**	**52**		**36**	**25,2**	120
Всего часов по учебному плану:		120					

семестре и 26 часов во 2 семестре, СРС в 1 семестре 18 часов, во 2 семестре 18 часов.

Раздел 3.

ТЕМАТИЧЕСКИЙ ПЛАН ПО МОДУЛЯМ (1 СЕМЕСТР)

3.1. Тематический план лекционных занятий на 1 семестр

№		Themes	hour
1.	Microscopy. Histological sample preparation	Explain the microscopy method of examination. Define types of microscopy, way to use compound microscope. Histological sample preparation technic. Staining methods	2
2.	Cell membrane	Define the structure and function of cell membrane. Membrane transport and vesicular transport	2
3.	Cytoplasm	Cytoplasm components. Role of membranous and non-membranous organelles in a normal cell live.	2
4.	Nucleus, Cell division	Structure of nucleus, components and functioning. Cell cycle in interphase and M phase. Detailed process of cell division.	2
5.	Meiosis. Spermatogenesis	Detailed process of meiosis. Role of meiosis in living organism. Detailed process of spermatogenesis in male's body	2
6.	Oogenesis. Fertilization	Detailed process of oogenesis in female reproductive system. Fertilization male's and female's events. Zygote formation.	2
7.	First week of embryo development. Preimplantation, Implantation	The process of early embryogenesis starting from cleavage until gastrulation process. Attachment of embryo to endometrial wall.	2
8.	Second – third week of embryo development. Gastrulation, notochord development, neurulation, body cavities formation	The process of 3 germ layer development. Axis organs formation. Neural plate folding and followed embryo folding process, leading to form body cavities.	2

3.2. Тематический план практических (семинарских) занятий на 1 семестр

№	Наименование занятия	Краткое содержание	Кол-во часов
1.	Microscopy. Histological sample preparation	Explain the microscopy method of examination. Define types of microscopy, way to use compound microscope. Histological sample preparation technic. Staining methods	2
2.	Cell membrane	Define the structure and function of cell membrane. Membrane transport and vesicular transport	2
3.	Cytoplasm	Cytoplasm components. Role of membranous and non-membranous organelles in a normal cell live.	2
4.	Nucleus, Cell division	Structure of nucleus, components and functioning. Cell cycle in interphase and M phase. Detailed process of cell division.	2
5.	Mitosis	Cytology control work	2
6.	Meiosis.	Detailed process of meiosis. Role of meiosis in living organism.	2
7.	Spermatogenesis	Detailed process of spermatogenesis in male's body	2
8.	Oogenesis.	Detailed process of oogenesis in female reproductive system.	2
9.	Fertilization	Fertilization male's and female's events. Zygote formation.	2
10.	First week of embryo development. Preimplantation, Implantation.	The process of early embryogenesis starting from cleavage until gastrulation process. Attachment of embryo to endometrial wall.	2
11.	Second – third week of embryo development. Gastrulation, notochord development.	The process of 3 germ layer development. Axis organs formation. Primary mesoderm differentiation	2

12.	Neurulation, body cavities formation	Neural plate folding and followed embryo folding process, leading to form body cavities.	2
13.	Third to eight week of embryonic development	General process of organ and system primordium formation.	2

3.4. Самостоятельная работа студентов (СРС)

№	Перечень тем и разделов	Кол-во часов	Форма отчетности (предлагаемые)
1.	Biochemical structure of cell membrane	3	Report
2.	Expression of genetic information	3	Report
3.	Regulatory mechanism of cell division	3	Report
4.	Epithelio-mesenchymal and mesenchymo-epithelial transition	3	Report
5.	Mesenchymal cells structure and further development	3	Report
6.	Neural crest cell function	3	Report

3.1. Тематический план лекционных занятий на 2 семестр

№	Наименование занятия	Краткое содержание	Кол-во часов
1.	Types of tissues. Epithelial tissue	Short introduction to different types of tissues. Detailed explanation of epithelial tissue structure	2
2.	Glandular epithelium	Glands as a special type of epithelia. Exocrine gland classification. Serous and mucous secretion. Merocrine, apocrine, holocrine mechanisms of secretion	2
3.	Blood	Components of blood. Structure and function of blood plasma. Cells of blood count and structure	2
4.	Connective tissue	Components of connective tissue. Fibers, ground substance, cells of connective tissue	2

5.	Cartilages	Structure of cartilage. Process of cartilage growth. Classification of cartilages and their location	2
6.	Bones, osteogenesis	Structure of bones. Extracellular and cellular composition. Process of bone growth and renewal	2
7.	Skeletal muscles. Cardiac muscle. Smooth muscle	Classification of muscles. Skeletal muscle structure. Difference between skeletal and cardiac muscles. Smooth muscle structure	2
8.	Nervous tissue	Cells of nervous tissue. Neurons and neuroglial cells. Classification and general structure.	2

3.2. Тематический план практических (семинарских) занятий на 2 семестр

№	Наименование занятия	Краткое содержание	Кол-во часов
1.	Epithelial tissue	Short introduction to different types of tissues. Detailed explanation of epithelial tissue structure	2
2.	Glandular epithelium	Glands as a special type of epithelia. Exocrine gland classification. Serous and mucous secretion. Merocrine, apocrine, holocrine mechanisms of secretion	2
3.	Blood	Components of blood. Structure and function of blood plasma. Cells of blood count and structure	2
4.	White blood cells	WBC classification and functioning	2
5.	Connective tissue. Extracellular matrix	Fibers and ground substance of connective tissue	2
6.	Connective tissue. Cells of connective tissue. Types of connective tissue	Residence and migratory cells classification and functioning. Differentiation of dense and loose connective tissue	2
7.	Cartilages	Structure of cartilage. Process of cartilage growth. Classification of cartilages and their location	2

8.	Bones	Structure of bones. Extracellular and cellular composition.	2
9.	Osteogenesis	Process of bone growth and renewal	2
10.	Skeletal muscles.	Classification of muscles. Skeletal muscle structure.	2
11.	Cardiac muscle. Smooth muscle	Difference between skeletal and cardiac muscles. Smooth muscle structure	2
12.	Nervous tissue	Cells of nervous tissue. Neurons classification	2
13.	Nervous tissue	Neuroglial cell classification and function	2

3.4. Самостоятельная работа студентов (СРС)

№	Перечень тем и разделов	Кол-во часов	Форма отчетности (предлагаемые)
1.	Blood formation. Stem cell theory	3	Report
2.	Macrophages role in immunity	3	Report
3.	Healing of fractured bones	3	Report
4.	Differentiation of mesemchymal cells	3	Report
5.	Conductive cardiac muscle cells	3	Report
6.	Degenerative brain disorders	3	Report

Раздел 4.
ФОНД ОЦЕНОЧНЫХ СРЕДСТВ ДЛЯ ТЕКУЩЕГО, РУБЕЖНОГО И ИТОГОВОГО КОНТРОЛЕЙ ПО ИТОГАМ ОСВОЕНИЯ ДИСЦИПЛИНЫ

Учебные достижения - результаты обучения студентов оцениваются по 100-балльной шкале, соотносятся с пятибалльной системой, и могут соотносится с системой ECTS **(табл.1)**.

Итоговая модульно-рейтинговая оценка по дисциплине выставляется по результатам двух модулей и итогового контроля знаний.

Распределение баллов рейтинговой оценки между видами контроля устанавливается в следующем соотношении:

Форма промежуточной аттестации	Количество баллов			
	Текущий контроль	Рубежный контроль	Итоговый контроль	Сумма баллов
Экзамен	40	40	20	100
Дифференцированный зачет	40	40	20	100

Таблица 1

Рейтинговая оценка (%)	5-ти балльная оценка	Оценка ECTS	Определение ECTS
85-100	5 – отлично	A	Отличный результат с минимальными ошибками
81-84	4 – хорошо	B	Вышесредний результат с некоторыми ошибками
70-80		C	Средний результат с заметными ошибками
60-69	3 – удовлетворительно	D	Слабый результат со значительными недостатками
55-59		E	Посредственный результат
0-54	2 – неудовлетворительно	F	Необходимо пересдать весь пройденный материал

Самостоятельная работа студента (СРС) состоит из двух частей:

- первая часть включает самостоятельную работу с участием преподавателя (СРП).
- вторая часть основана на выполнение индивидуальной самостоятельной работы (ИСР). Следовательно, **СРС = СРП + ИСР**.

Задание на СРС студенты должны получить в начале семестра.

Итоговая оценка знаний студентов слагается из трех составляющих:

- текущий контроль (ТК);
- рубежный контроль (РК), т.е. результатов модульной работы;
- самостоятельной работы студента СРС).

Следовательно, **ИК=ТК+РК+СРС**

№ п/п	Наименование раздела	Виды учебной работы	Формируемые компетенции (указывается код компетенции)	Информационные и образовательные технологии
1	2	3	4	5
1.	Cytology	Лекция 1-4 Семинар 1-5 Самостоятельная работа	ОК-1, ПК-1, ПК-2. ОК-3, ПК-2, ПК-5. ПК-1, ПК-2,	Вводная лекция с использованием видеоматериалов Устный и письменный опрос, выполнение упражнений, решение ситуационных задач и тестов Консультирование и проверка домашних заданий.
2.	Sexual reproduction	Лекция 5-6. Семинар 6-9. Самостоятельная работа	ОК-1, ПК-2, ПК-3. ОК-3, ПК-2, ПК-5 ОК-1, ПК-2,	Лекция-визуализация с применением слайд-проектора Устный и письменный опрос, выполнение упражнений, решение ситуационных задач и тестов Консультирование и проверка домашних заданий.

3	Embryogenesis	Лекция 7-8. Семинар 10-13. Самостоятельная работа	ОК-1, ПК-2, ПК-3. ОК-3, ПК-2, ПК-5 ОК-1, ПК-2,	Лекция-визуализация с применением слайд-проектора Устный и письменный опрос, выполнение упражнений, решение ситуационных задач и тестов Консультирование и проверка домашних заданий
4	Epithelial tissues	Лекция 9-10 Семинар 14-15 Самостоятельная работа	ОК-1, ПК-2, ПК-3. ОК-3, ПК-2, ПК-5 ОК-1, ПК-2,	Лекция-визуализация с применением слайд-проектора Устный и письменный опрос, выполнение упражнений, решение ситуационных задач и тестов Консультирование и проверка домашних заданий
5	Connective tissues	Лекция 11-14 Семинар 16-22 Самостоятельная работа	ОК-1, ПК-2, ПК-3. ОК-3, ПК-2, ПК-5 ОК-1, ПК-2,	Лекция-визуализация с применением слайд-проектора Устный и письменный опрос, выполнение упражнений, решение ситуационных задач и тестов Консультирование и проверка домашних заданий
6	Muscular tissue	Лекция 15	ОК-1, ПК-2, ПК-3.	Лекция-визуализация с применением слайд-

		Семинар 23-24 Самостоятельная работа	ОК-3, ПК-2, ПК-5 ОК-1, ПК-2,	проектора Устный и письменный опрос, выполнение упражнений, решение ситуационных задач и тестов Консультирование и проверка домашних заданий
7	Nervous tissue	Лекция 16 Семинар 25-26 Самостоятельная работа	ОК-1, ПК-2, ПК-3. ОК-3, ПК-2, ПК-5 ОК-1, ПК-2,	Лекция-визуализация с применением слайд-проектора Устный и письменный опрос, выполнение упражнений, решение ситуационных задач и тестов Консультирование и проверка домашних заданий

4.1. Методические материалы, определяющие процедуры оценивания знаний, умений навыков и (или) опыта деятельности

- **Контрольные вопросы и задания для проведения текущего контроля (в течение семестра по темам и модулям)**

1. Neural plate cells are not responsible for:

a) Medulla of adrenal gland development
b) Spinal cord development
c) Liver development
d) Brain development

2. Name of embryonic cell mass responsible for somite formation?

a) Lateral mesoderm

b) Neural tube

c) Paraxial mesoderm

d) Neural plate

3. Somites are:

a) Medial part of mesoderm responsible for urinary tract development

b) Peripheral part of mesoderm, responsible for body cavity formation

c) Medial part of mesoderm responsible for axial skeleton development

d) Intermediate part of mesoderm, responsible for digestive tract development

4. What is the role of lacunae in syncitiotrophoblast?

a) Containing enzymes to dissolve endometrium

b) Defense against maternal antibodies

c) Establishment of blood circulation in embryo

d) Allows movement of embryo deep in endometrium

5. What assists to zygote and early embryo in travelling along the fallopian tube?

a) Fimbria actively push the embryo toward uterus

b) Corona radiata uses its flagella to commit transportation

c) Epithelium of Fallopian tube which is covered by cilia

d) Zona pellucida uses it's cilia for active transportation

6. Gastrulation is:

a) Formation of extraembryonic mesoderm

b) Migration of hypoblast cells to epiblast to replace them

c) Folding of trophoblast to form endoderm

d) Bilaminar to trilaminar disc transformation

7. Septum transversum is responsible for:

a) Atrium formation

b) Ascending aorta formation

c) Formation of part of diaphragm

d) Heart ventricles formation

8. Name the process when secondary oocyte enveloped by zona pellucida and corona radiata cells sheds out from ovary

a) Meiosis 2

b) Ovulation

c) Meiosis 1

d) Luteinization

9. Roles of syncitiotrophoblast is NOT:

a) Destroys the components of endometrium

b) Invade embryo deep in endometrium

c) Rupturing of zona pellucida

d) Invasion of myometrium of uterus

10. What happens due to capacitation of sperm?

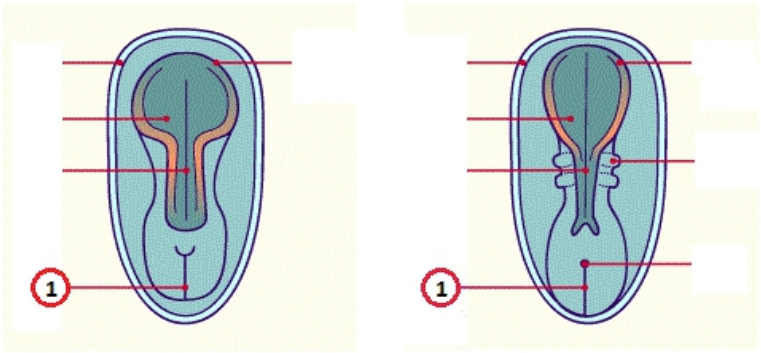
a) Motility of flagella decreased

b) Acrosome collects more enzymes

c) Acrosome gets ready for acrosome reaction

d) Acrosome ruptures

11. What is marked by #1 in diagram?



a) Somite

b) Rostral neuropore

c) Primitive groove

d) Neural plate

12. Which changes ARE NOT normally happened with the embryo in uterus?

a) Shedding of zona pellucida

b) Hatching

c) Blastocyst formation

d) Meiotic division

13. Characteristic of which embryonic structure is: "mesenchymal cells which aggregate near the axial organs of embryo"?

a) Lateral mesoderm
b) Paraxial mesoderm
c) Endoderm
d) Intermediate mesoderm

14. Notochord growth goes:

a) Toward the lateral part of embryo
b) Toward the cranial part of embryo
c) Toward the caudal part of embryo
d) Toward the yolk sac region

15. Which protein of zona pellucida plays the role of trigger in acrosome reaction

a) Acrosin
b) Zona protein 3
c) proteolytic enzymes
d) Hyaluronidase

16. What is the first phase when embryo touches the endometrium?

a) Invasion
b) Adplantation
c) Penetration
d) Sticking

17. This step of fertilization takes place during spermatozoa stay in the female genital tract, especially during the ascension towards the ovary through the uterus and fallopian tube.

a) Ejaculation
b) acrosome reaction
c) capacitation
d) Activation

18. Primitive yolk sac is formed of:

a) Hypoblast

b) Syncitiotrophoblast
c) Epiblast
d) Zona pellucida

19. Between which stages of embryogenesis embryo entered into the uterus?
a) Zygote to two cell stage
b) two cell stage to four cells stage
c) Four cells stage to eight cell stage
d) morula to blastocyst stage

20. What is termed as a polarity of embryo?
a) Presence of positive charge on the surface of embryonic cell
b) Place of hatching determines the polarity
c) Location of embryoblast on the one pole of embryo
d) Presence of negative charge on the surface of embryo cells

21. Chorionic cavity is lined up by:
a) Cytotrophoblast
b) Extraembryonic mesoderm
c) Amnion cells
d) Epiblast cells

22. Notochord tube temporary (for 24 hours) fuses with this cell layer
a) Exocoelomic membrane
b) Neural plate
c) Endoderm
d) Mesoderm

23. One of layer of bilaminar disc is made up of:
a) Hypoblast
b) Amnion
c) Exocoelomic membrane
d) Extraembryonic mesoderm

24. One of layer of bilaminar disc is made up of:

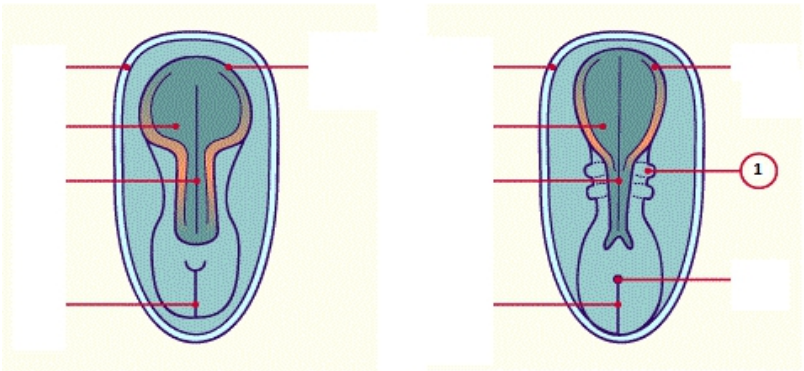
a) Epiblast
b) Extraembryonic mesoderm
c) Endoderm
d) Ectoderm

25. Neurenteric canal connects amniotic cavity with:
a) Uterine cavity
b) Chorionic cavity
c) Oral cavity
d) Yolk sac

26. What of these is component of chorion?
a) intraembryonic mesoderm
b) Extraembryonic mesoderm
c) Epiblast
d) Hypoblast

27. In which part of embryo precardial plate (primordium of the heart) is located before the folding?
a) Paraxial mesoderm
b) Cranial end mesoderm
c) Caudal end mesoderm
d) Lateral plate mesoderm

28. What is marked by #1 in diagram?



a) Cranial neuropore
b) Primitive streak
c) Somite

d) Caudal neuropore

29. Mark the true statement about the cleavage.

a) Polar bodies emerge from embryo in that stage

b) Made by mitotic division only

c) Zona pellucida ruptures after the first cell division

d) after the cleavage period blastocyst occurs

30. How many sperms usually reach the ovum right before the fertilization?

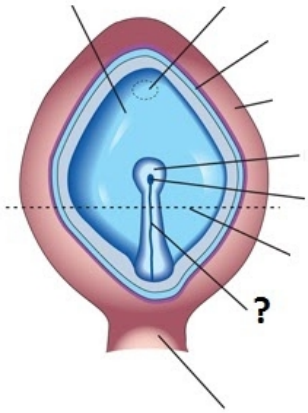
a) 10-20 thousands

b) 100-300

c) 1-2 million

d) 1

31. What is shown in the diagram by "?" sign?



a) Primitive node

b) Endoderm

c) Primitive pit

d) Primitive groove

32. Amniotic cavity is formed by:

a) Syncytiotrophoblast

b) Zona pellucida

c) Hypoblast

d) Epiblast

33. Cortical vesicles' primary and most important function is

a) submission of polar bodies

b) feeding of the sperm

c) Polyspermy block

d) assistance in impregnation

34. Which cell population appears peripherally to the embryo shortly before the contact with endometrium?

a) Epiblast

b) Cytotrophoblast

c) Syncitiotrophoblast

d) Embryoblast

35. What happens to sperm cell when it touches the surface of zona pellucida?

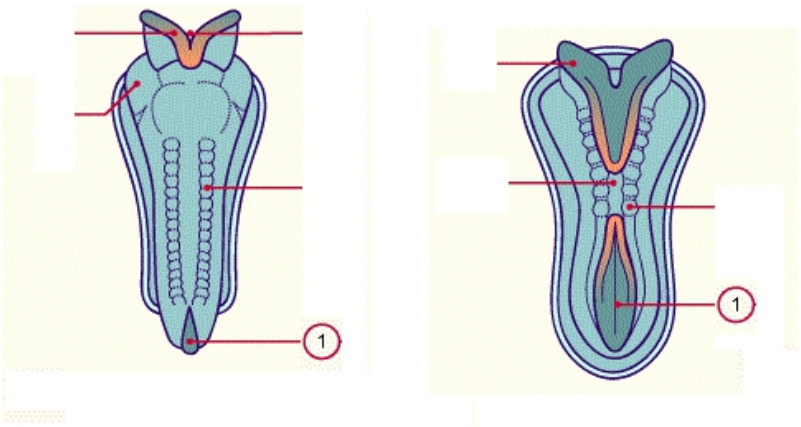
a) Acrosome reaction

b) Capacitation

c) Fertilization

d) Fusion with ovum

36. What is marked by #1 in diagram?



a) Somites

b) Neural crest cells

c) Caudal neuropore

d) Rostral neuropore

37. Second polar body forms:

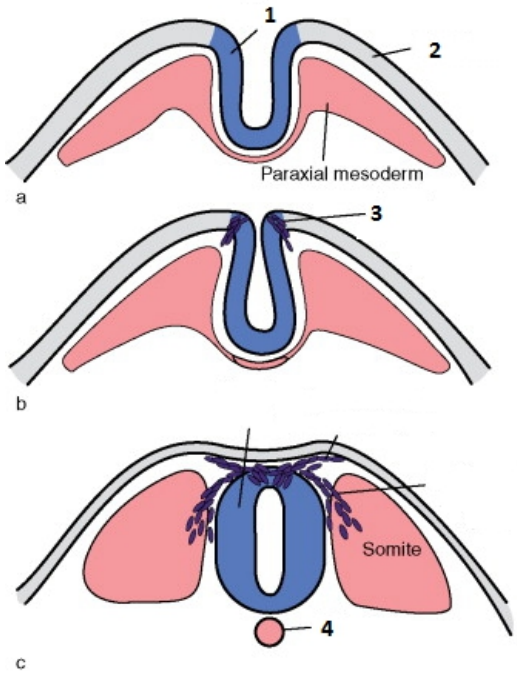
a) After the 1 meiosis

b) After the puberty

c) after the fertilization of secondary oocyte

d) after the menopause

38. Show the location of future neural crest cells on this diagram



a) 1

b) 2

c) 3

d) 4

39. Extraembryonic mesoderm is appeared between:

a) Yolk sac and amnion

b) Yolk sac and Syncitiotrophoblast

c) Yolk sac and cytotrophoblast

d) Cytotrophoblast and syncitiotrophoblast

1. What type of tissue lines the bladder?
2. What type of tissue lines most ducts?
3. What type of epithelium is associated with goblet cells?
4. What type of epithelial cells are as tall as they are wide?
5. What do you call the simple squamous epithelium that lines the blood vessels?
6. What cell type makes up the mucosa of the gallbladder?

7. Which of the following is lined by a serosa?
8. What type of gland secretes its product through a duct or tube?
9. What is a gland called if the secretory portion is flask shaped?
10. What forms the brush border?
11. What type of epithelium forms the epidermis?
12. What type of tissue lines most of the gastrointestinal tract?
13. What type of tissue forms the alveoli in the lung?
14. What type of epithelium is composed of flat cells?
15. What do you call the simple squamous epithelium that lines the abdominal cavity?
16. What type of epithelium is composed of cells which all touch the basement membrane and is only one cell layer thick?
17. Which of the following is NOT lined by a mucosa?
18. What is a gland called if it has an branched duct?
19. What are finger like projections on the surface of some cells called?
20. What cell surface modification is made of microtubules?
21. Which of the following is NOT primarily composed of connective tissue?
22. Which of the following is NOT a fiber found in connective tissue?
23. Which connective tissue cell type contains properties of smooth muscle cells?
24. Which cell is a connective tissue macrophage?
25. Which of the following can be classified as "specialized connective tissue"?
26. Which of the following can be classified as "embryonic connective tissue"?
27. What type of tissue makes up the dermis of the skin?
28. What type of adipose tissue tends to increase as humans age?
29. Which of the following would be best suited to differentiate collagen fibers from other fibers?
30. What type of epithelium forms the epidermis?
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32. What type of tissue forms the alveoli in the lung?
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45. Which of the following can be classified as "embryonic connective tissue"?
46. What type of tissue makes up the dermis of the skin?
47. What type of adipose tissue tends to increase as humans age?
48. Which of the following would be best suited to differentiate collagen fibers from other fibers?
49. Which of the following is NOT primarily composed of connective tissue?
50. Which one of these cells is not a cell type routinely found in loose connective tissue?
51. Which connective tissue cell is a tissue macrophage?
52. Which of the following can be classified as "specialized connective tissue"?
53. Which of the following can be classified as "connective tissue proper"?
54. What type of tissue is Wharton's jelly?
55. What type of tissue is a tendon composed of?
56. What does connective tissue develop from?
57. What color do elastic fibers stain with Verhoeff Elastic stain?
58. Which of the following is a component of the ground substance?
59. Which of the following is NOT primarily composed of connective tissue?

Which connective tissue cell type produces the ground substance in connective tissue?

- **Контрольные вопросы семестрового (итогового) контроля**

(по итогам изучения дисциплины)

1. Epithelial tissue. Functions. Special features. Location of epithelium in different body organs.
2. Epithelial cell. Polarity of the epithelial cell. Structure, features and function of basal and lateral domains. Basement membrane
3. Epithelial cell. Polarity of the epithelial cell. Apical domain. Apical domain modification
4. Classification of epithelial tissue. Simple squamous epithelia. Simple cuboidal epithelium. Structure, location of appearance.
5. Classification of epithelia. Simple columnar epithelia. Pseudostratified epithelium. Structure, location of appearance.
6. Classification of epithelial tissue. Transitional epithelia. Stratified Squamous epithelia. Structure, location of appearance.

7. Glandular epithelium. Exocrine and endocrine glands. Define differences, show examples of endocrine and exocrine gland. Composition and function of its secretion.
8. Classification of exocrine glands. Simple tubular, Simple coiled tubular, branched tubular glands. Their structure, location of appearance.
9. Classification of exocrine glands. Simple acinar, branched acinar glands. Their structure, location of appearance.
10. Classification of exocrine glands. Comopound tubular, compound acinar, compound tubulo-acinar glands. Their structure, location of appearance.
11. Merocrine mechanism of secretion. Explain mechanism. Show location
12. Apocrine mechanism of secretion. Explain mechanism. Show location
13. Holocrine mechanism of secretion. Explain mechanism. Show location
14. Plasma of blood. Plasma proteins. Define difference between plasma and serum
15. Plasma of blood. Organic and inorganic components. Composition. Function.
16. Erythrocyte's function, structure and recycling
17. Granulocytes. Neutrophils. Morphology. Functions. Composition of granules
18. Granulocytes. Basophils. Morphology. Functions. Composition of granules
19. Granulocytes. Eosinophils. Morphology. Functions. Composition of granules
20. Agranulocytes. Monocytes. Morphology. Functions. Development
21. Agranulocytes. Lymphocytes. Morphology. Functions. Development
22. Three phases of blood formation. Yolk sac phase.
23. Three phases of blood formation. Fetal and bone marrow phase
24. Monophyletic theory of hemopoiesis. Name main branches of hemopoiesis
25. Lymphoid branch of hemopoiesis. Maturation of lymphocytes.
26. Myeloid branch of hemopoiesis. CFU-GM. Granulocyte maturation
27. Myeloid branch of hemopoiesis. MEP. Erythropoiesis. Developmental stages from proerythroblast until erythrocyte
28. Myeloid branch of hemopoiesis. MEP. Thrombopoiesis
29. Regulation of hemopoiesis.
30. Connective tissue proper. Composition. Classification.
31. Connective tissue proper. Fibers of connective tissue. Elastic and reticular fibers.
32. Connective tissue proper. Fibers of connective tissue. Collagen fibers.
33. Cells of connective tissue. Residence cells. Morphology, function and location of fibroblast
34. Cells of connective tissue. Residence cells. Classification, morphology, function and location of adipocytes.

35. Cells of connective tissue. Migratory cells. Classification, morphology and function of mast cell. Function of eosinophils in connective tissue
36. Cells of connective tissue. Migratory cells. Classification, morphology and function of macrophage and lymphocytes. Cellular immunity
37. Cells of connective tissue. Migratory cells. Classification, morphology, function and development of plasma cell. Humoral immunity
38. Cartilages. Composition of cartilages. Classification.
39. Hyaline cartilage. Structure, special features, appearance.
40. Hyaline cartilage. Articular surface, epiphyseal plate, correlated diseases
41. Elastic cartilage. Structure, special features, appearance, location
42. Fibrous cartilage. Structure, special features, appearance, location
43. Structures of cartilage. Perichondrium. Lacunae. Isogenous group.
44. Chondrogenesis. Types of cartilage growth.
45. Bone. Woven and lamellar bone structure. Structure of osteon
46. Cells of bone. Explain function of every cell of the bone
47. Bone's extracellular matrix. Structure, formation.
48. Haversian system of bone. Compact and spongy bone
49. Bone growth in epiphyseal plate. Show and explain zones. Explain functions.
50. Types of ossification. Intramembranous and endochondral ossification
51. Structure of striated muscles. Define filaments, fibrils, fibers, fascicles. Name their coverings.
52. Structure of striated muscle fibrils. Explain process of muscle contraction according to changes in muscle fiber.
53. Explain neuromuscular junction. Structure and role of triads in muscle excitement
54. Cardiac muscle structure. Define differences between cardiac and skeletal muscles.
55. Cardiac muscle structure. Intercalated disc. Define differences between cardiac and smooth muscles.
56. Smooth muscle structure. Location. Regulation of the smooth muscle contraction.
57. Nervous tissue. Structure of neuron. Classification of neurons.
58. Synapse. Classification of synapses. Explain the synaptic signal transmission.
59. Classification of neuroglial cells. Explain location and function of every glial cell you know.
60. Connective tissue investments of nervous tissue. Connective tissue in CNS, connective tissue in PNS.

Раздел 5.

СРЕДСТВА И МАТЕРИАЛЬНО–ТЕХНИЧЕСКОЕ ОБЕСПЕЧЕНИЕ ДИСЦИПЛИНЫ

Лекционный зал укомплектовано комплектом электропитания ЩЭ, специализированной мебелью и оргсредствами (доска аудиторная, стойка-кафедра, стол лектора, стул-кресло, столы аудиторные, стул аудиторный, а также техническими средствами обучения (экран настенный с электроприводом и дистанционным управлением, мультимедиа проектор с ноутбуком в стационаре).

При изучении дисциплины используется:

1. Технические средства: компьютер, проектор.
2. Наглядные пособия, стенды, таблицы и.т.д.
3. Компьютерные программы, презентации, видеолекции и.т.д.

Лабораторное оборудование:

сушильный шкаф, дозиметры, рефрактометр, вытяжной шкаф, микроскоп и т.п.

Лабораторные животные, биоматериалы, препараты по всем темам.

Раздел 6

УЧЕБНО-МЕТОДИЧЕСКИЕ И ИНФОРМАЦИОННОЕ ОБЕСПЕЧЕНИЕ ДИСЦИПЛИНЫ

6.1. Основная литература

1. Laiq Hussain Siddiqui. Histology. 9-th edition
2. Medical Embryology Langman’s 12-th edition T.W. Sandler
3. Histology text and atlas with correlated molecular biology 7-th edition

6.2. Дополнительная литература

1. Netter’s histology flash cards Updated edition William K. Ovalle, Patrick C. Nahirney
2. Atlas of histology with functional correlations. Eleventh edition. Victor P. Eroschenko

6.3. Перечень ресурсов информационно-телекоммукационной сети «Интернет» необходимый для освоения дисциплины

1. ***https://www.embryology.ch***
2. https://www.ncbi.nlm.nih.gov/

МИНИСТЕРСТВО ОБРАЗОВАНИЯ И НАУКИ КЫРГЫЗСКОЙ РЕСПУБЛИКИ

7. ПЕРЕЧЕНЬ МЕТОДИЧЕСКИХ УКАЗАНИЙ ДЛЯ ОБУЧАЮЩИХСЯ ПО ОСВОЕНИЮ ДИСЦИПЛИНЫ.

Самостоятельная работа при изучении дисциплин включает:

- чтение студентами рекомендованной литературы и усвоение теоретического материала дисциплины;
- знакомство с Интернет-источниками;
- подготовку к различным формам контроля (тесты, контрольные работы);
- подготовку и написание рефератов;
- выполнение контрольных работ;

Материал, законспектированный на лекциях, необходимо регулярно прорабатывать и дополнять сведениями из других источников литературы, представленных не только в программе дисциплины, но и в периодических изданиях.

При изучении дисциплины сначала необходимо по каждой теме прочитать рекомендованную литературу и составить краткий конспект основных положений, терминов, сведений, требующих запоминания и являющихся основополагающими в этой теме для освоения последующих тем курса. Для расширения знания по дисциплине рекомендуется использовать Интернет-ресурсы; проводить поиски в различных системах и использовать материалы сайтов, рекомендованных преподавателем.

7.1. Методические рекомендации к практическим и лекционным занятиям

Лабораторная работа - это проведение студентами по заданию преподавателя или по инструкции опытов с использованием приборов, применением инструментов и других технических приспособлений, т.е. это изучение каких-либо объектов, явлений с помощью специального оборудования.

Практическая работа проводятся после лекций, и носят разъясняющий, обобщающий и закрепляющий характер. Они могут проводиться не только в аудитории, но и за пределами учебного заведения.

В ходе лабораторно-практических работ студенты воспринимают и осмысливают новый учебный материал. Практические занятия носят систематический характер, регулярно следуя за каждой лекцией или двумя-тремя лекциями.

Лабораторно-практические работы выполняются согласно графика учебного процесса и самостоятельной работы студентов по дисциплинам. К лабораторно-практическим работам студент допускается только после инструктажа по технике

безопасности. Положения техники безопасности изложены в инструкциях, которые должны находиться на видном месте в лаборатории.

При подготовке к лабораторным занятиям необходимо заранее изучить методические рекомендации по его проведению. Обратить внимание на цель занятия, на основные вопросы для подготовки к занятию, на содержание темы занятия.

Каждый студент ведет рабочую тетрадь, оформление которой должно отвечать требованиям, основные из которых следующие:

- на титульном листе указывают предмет, курс, группу, фамилию, имя, отчество студента;
- каждую работу нумеруют в соответствии с методическими указаниями, указывают дату выполнения работы;
- полностью записывают название работы, цель и принцип метода, кратко характеризуют ход эксперимента и объект исследования;
- при необходимости приводят рисунок установки; результаты опытов фиксируют в виде рисунков с обязательными подписями к ним, а также таблицы или описывают словесно (характер оформления работы обычно указан в методических указаниях к самостоятельным работам);
- в конце каждой работы делают вывод или заключение, которые обсуждаются при подведении итогов занятия.

Все первичные записи необходимо делать в тетради по ходу эксперимента.

Проведение лабораторно-практических работ включает в себя следующие этапы:

- постановку темы занятий и определение задач лабораторно-практической работы;
- определение порядка лабораторно-практической работы или отдельных ее этапов;
- непосредственное выполнение лабораторной/практической работы студентами и
- контроль за ходом занятий и соблюдением техники безопасности;
- подведение итогов лабораторно-практической работы и формулирование основных выводов.

Для проверки академической активности и качества работы студента рабочую тетрадь периодически проверяет преподаватель.

7.2. Методические рекомендации по подготовке письменных работ

Реферат – краткое изложение в письменном виде содержания научного труда по предоставленной теме. Это самостоятельная научно-исследовательская работа, где студент раскрывает суть исследуемой проблемы с элементами анализа по теме реферата.

Приводит различные точки зрения, а также собственные взгляды на проблемы темы реферата. Содержание реферата должно быть логичным, изложение материала носить проблемно-тематический характер.

Требования к оформлению реферата:

Объем реферата может колебаться в пределах 5-7 печатных страниц.

Основные разделы: оглавление (план), введение, основное содержание, заключение, список литературы.

Текст реферата должен содержать следующие разделы:

- титульный лист с указанием: названия ВУЗа, кафедры, темы реферата, ФИО автора и ФИО преподавателя

- введение, актуальность темы.
- основной раздел.
- заключение (анализ результатов литературного поиска); выводы.
- список литературных источников должен иметь не менее 10 библиографических названий, включая сетевые ресурсы.

Текстовая часть реферата оформляется на листе следующего формата:

- отступ сверху – 2 см; отступ слева – 3 см; отступ справа – 1,5 см; отступ снизу – 2,5 см;
- шрифт текста: Times New Roman, высота шрифта – 14, пробел – 1,5;
- нумерация страниц – снизу листа. На первой странице номер не ставится.

Реферат должен быть выполнен грамотно с соблюдением культуры изложения. Обязательно должны иметься ссылки на используемую литературу, включая периодическую литературу за последние 5 лет.

Критерии оценки реферата:

- актуальность темы исследования;
- соответствие содержания теме;
- глубина проработки материала;
- правильность и полнота разработки поставленных вопросов;
- значимость выводов для дальнейшей практической деятельности;
- правильность и полнота использования литературы;
- соответствие оформления реферата стандарту;
- качество сообщения и ответов на вопросы при защите реферата.

7.3. Методические рекомендации по подготовке самостоятельных работ

Самостоятельная работа студентов направлена на решение следующих задач:

- выработка навыков восприятия и анализа профессиональной информации;
- развитие и совершенствование способностей к принятию решений и их реализации;
- развитие и совершенствование творческих способностей при самостоятельном изучении профессиональных проблем.

Для решения первой задачи студентам предлагаются к прочтению и содержательному анализу монографии и научные статьи по проблемам биохимии человека. Результаты работы с текстами обсуждаются на семинарских занятиях и коллоквиумах.

Для развития навыков самостоятельной работы студенты выполняют задания, самостоятельно обращаясь к учебной, справочной и научно-методической литературе. Проверка выполнения заданий осуществляется как на семинарских занятиях с помощью устных выступлений студентов и их коллективного обсуждения, так и с помощью письменных самостоятельных работ.

Для развития и совершенствования коммуникативных способностей студентов организуются специальные учебные занятия в виде «диспутов» или «конференций», при подготовке к которым студенты заранее распределяются по группам, отстаивающим ту или иную точку зрения по обсуждаемой проблеме.

8. ИНФОРМАЦИОННЫЕ И ОБРАЗОВАТЕЛЬНЫЕ ТЕХНОЛОГИИ

Образовательная технология – упорядоченная система действий, выполнение которых приводит к достижению поставленных целей и образовательная технология – конструирование учебного процесса с гарантированным достижением целей. Образовательные технологии обучения как обобщенная универсальная система, которая органично и оптимально интегрирует многие технологии, необходимые для достижения конкретных образовательных и развивающих целей и которая как целостное единство содержания и технологии его изучения реализуется через комплекс технологий:

Используемые интерактивные формы и методы обучения по дисциплине

Лекция – форма организации учебного процесса, при котором преподаватель передает большой объем систематизированной информации как ориентировочной основы для самостоятельной работы студентов.

Общий структурный каркас любой лекции – это формулировка темы, сообщение плана и рекомендуемой литературы для самостоятельной работы, а затем – строгое следование плану предложенной работы.

Виды лекций

1. *Вводная лекция* дает первое целостное представление об учебном предмете и ориентирует студента в системе работы по данному курсу. Лектор знакомит студентов с назначением и задачами курса, его ролью и местом в системе учебных дисциплин и в системе подготовки специалиста. На этой лекции высказываются методические и организационные особенности работы в рамках курса, а также дается анализ учебно-методической литературы, рекомендуемой студентами, уточняются сроки и формы отчетности.

2. *Лекция-информация.* Ориентирована на изложение и объяснение студентам научной информации, подлежащей осмыслению и запоминанию. Это самый традиционный тип лекций в практике высшей школы.

3. *Обзорная лекция* — это систематизация научных знаний на высоком уровне, допускающая большое число ассоциативных связей в процессе осмысления информации, излагаемой при раскрытии внутри предметной и меж предметной связи, исключая детализацию и конкретизацию. Как правило, стержень излагаемых теоретических положений составляет научно-понятийная и концептуальная основа всего курса или крупных его разделов.

4. *Лекция-визуализация* представляет собой визуальную форму подачи лекционного материала средствами ТСО или аудиовидеотехники. Чтение такой лекции сводится к развернутому или краткому комментированию просматриваемых визуальных материалов.

5. *Бинарная лекция* – это разновидность чтения лекции в форме двух преподавателей (либо как представителей двух научных школ, либо как ученого и практика, преподавателя и студента).

6. *Лекция-конференция* проводится как научно-практическое занятие, с заранее поставленной проблемой и системой докладов, длительностью 5-10 минут. Каждое выступление представляет собой логически законченный текст, заранее подготовленный в рамках предложенной преподавателем программы.

Методы и приемы интерактивного обучения практических занятий

- *Мозговой штурм* — поток вопросов и ответов, или предложений и идей по заданной теме, при котором анализ правильности/неправильности производится после проведения штурма. Читайте подробнее о мозговом штурме на уроках.
- *Кластеры*, сравнительные диаграммы, пазлы — поиск ключевых слов и проблем по определенной мини-теме.

- *Интерактивный урок* с применением аудио- и видеоматериалов, ИКТ. Например, тесты в режиме онлайн, работа с электронными учебниками, обучающими программами, учебными сайтами.
- *Круглый стол* (дискуссия, дебаты) — групповой вид метода, которые предполагает коллективное обсуждение учащимися проблемы, предложений, идей, мнений и совместный поиск решения.
- *Метод проектов* — самостоятельная разработка учащимися проекта по теме и его защита.

№ п/п	**Наименование раздела**	**Виды учебной работы**	**Формируемые компетенции (указывается код компетенции)**	**Информационные и образовательные технологии**
1	**2**	**3**	**4**	**5**
1.	Cytology	Лекция 1-4 Семинар 1-5 Самостоятельная работа	ОК-1, ПК-1, ПК-2. ОК-3, ПК-2, ПК-5. ПК-1, ПК-2,	Вводная лекция с использованием видеоматериалов Устный и письменный опрос, выполнение упражнений, решение ситуационных задач и тестов Консультирование и проверка домашних заданий.
2.	Sexual reproduction	Лекция 5-6. Семинар 6-9. Самостоятельная работа	ОК-1, ПК-2, ПК-3. ОК-3, ПК-2, ПК-5 ОК-1, ПК-2,	Лекция-визуализация с применением слайд-проектора Устный и письменный опрос, выполнение упражнений, решение ситуационных задач и тестов Консультирование и проверка домашних заданий.
3	Embryogenesis	Лекция 7-8. Семинар 10-13. Самостоятельная	ОК-1, ПК-2, ПК-3. ОК-3, ПК-2, ПК-5	Лекция-визуализация с применением слайд-проектора Устный и письменный опрос, выполнение упражнений, решение ситуационных задач и тестов

		работа	ОК-1, ПК-2,	Консультирование и проверка домашних заданий
4	Epithelial tissues	Лекция 9-10 Семинар 14-15 Самостоятельная работа	ОК-1, ПК-2, ПК-3. ОК-3, ПК-2, ПК-5 ОК-1, ПК-2,	Лекция-визуализация с применением слайд-проектора Устный и письменный опрос, выполнение упражнений, решение ситуационных задач и тестов Консультирование и проверка домашних заданий
5	Connective tissues	Лекция 11-14 Семинар 16-22 Самостоятельная работа	ОК-1, ПК-2, ПК-3. ОК-3, ПК-2, ПК-5 ОК-1, ПК-2,	Лекция-визуализация с применением слайд-проектора Устный и письменный опрос, выполнение упражнений, решение ситуационных задач и тестов Консультирование и проверка домашних заданий
6	Muscular tissue	Лекция 15 Семинар 23-24 Самостоятельная работа	ОК-1, ПК-2, ПК-3. ОК-3, ПК-2, ПК-5 ОК-1, ПК-2,	Лекция-визуализация с применением слайд-проектора Устный и письменный опрос, выполнение упражнений, решение ситуационных задач и тестов Консультирование и проверка домашних заданий
7	Nervous tissue	Лекция 16 Семинар 25-26 Самостоятельная работа	ОК-1, ПК-2, ПК-3. ОК-3, ПК-2, ПК-5 ОК-1, ПК-2,	Лекция-визуализация с применением слайд-проектора Устный и письменный опрос, выполнение упражнений, решение ситуационных задач и тестов Консультирование и проверка домашних заданий

9. МАТЕРИАЛЬНО-ТЕХНИЧЕСКОЕ ОБЕСПЕЧЕНИЕ ДИСЦИПЛИНЫ

Методы изучения дисциплины

1. Лекционный материал

2. Самостоятельная работа

3. Теоретическое обоснование

4. Групповое обсуждение

5. Визуализация

6. Работа с микроскопом

Информационно-техническое обеспечение

1. Книги и атласы по гистологии
2. Описания препаратов

Технические средства обучения

1. Проекционная компьютерная установка

2. ПК

3. Микроскопы

4. Слайды с препаратами по всем темам

10. КОНСПЕКТ ЗАНЯТИЙ

1. Tissue Preparation and Microscopy

General Considerations

Biological tissues must undergo a series of treatments to be observed with light and electron microscopes. The process begins by stabilization of the tissue with chemical fixatives. Next, the tissue is made rigid to allow sectioning. Finally, it is stained to provide contrast for visualization in the microscope.

Steps in tissue preparation

Fixation

Dehydration

Infiltration and embedding

Sectioning

Staining

Chemical Fixation

Preserves cellular structure and maintains the distribution of organelles.

Formaldehyde and **glutaraldehyde** are the most commonly used **chemical fixatives**. They stabilize protein by forming cross-links between primary amino groups. Formaldehyde in solution is referred to as formalin.

Osmium tetraoxide is a fixative used to preserve lipids, which aldehydes cannot do. Osmium combines with and stabilizes lipid and, in addition, also adds a **brown color** (light microscopy)

or **electron density** (electron microscopy) at the site of the lipid. Osmium fixation is required for electron microscopy, especially to preserve the lipid in membranes.

Dehydration, Infiltration, and Embedding

Tissue water is not miscible with the embedding solutions and must be **replaced** using a **series of alcohols** at increasingly higher concentrations. This step is followed by alcohol **replacement** with an intermediate solvent that is miscible with both alcohol and the embedding solutions.

Infiltration and embedding. The liquid form of the embedding compound, for example, **paraffin wax** or **epoxy plastic**, replaces the intermediate solvent. The liquid embedding medium is allowed to solidify, thereby providing rigidity to the tissue for sectioning.

Sectioning

The embedded tissue is cut thin enough to allow a beam of light or electrons to pass through.

Section thickness

Light microscopy. 1–20 microns

Electron microscopy. 60–100 nanometers

Section planes

Cross-section (cs) or transverse section (ts) is a section that passed perpendicular to the long axis of a structure.

Longitudinal section (ls) is a section that passed parallel to the long axis of a structure.

Oblique (tangential) section is any section other than a cross- or longitudinal section.

Staining

Most tissues have no inherent contrast; thus, stains must be applied to visualize structures.

Conventional staining. Relies mostly on charge interactions.

Light microscopy staining

Hematoxylin and eosin (H&E). These two dyes are the most commonly used stains in routine **histology and pathology slides**. Most conventional stains bind to tissue elements based on charge interactions, that is, positive charge attraction for a negatively charged structure. **Hematoxylin binds to negatively charged components of tissue**, the most prominent being **nucleic acids**. Hematoxylin imparts a **purple/blue** color to structures and, therefore, the **nucleus** and accumulations of **rough endoplasmic reticulum** in the cytoplasm, which contains large amounts of **nucleic acid**, appear blue or purple in sections.

Structures, like the **nucleus** and **rough endoplasmic reticulum** that stain with hematoxylin, are referred to as **basophilic** or “base loving.” The term basophilia, refers to the property of a structure or region that stains with a basic dye, such as **hematoxylin**.

Structures that stain with eosin, for example, the **cytoplasm of most cells** and **collagen fibers**, appear **pink** or **orange** and are referred to as **eosinophilic**.

Electron microscopy

Images in the electron microscope are produced by passing a **beam of electrons** through the tissue that has been "stained" with salts of heavy metals, usually lead (**lead citrate**) and uranium (**uranyl acetate**). These metals bind to areas of negative charge and block the passage of the electrons through the section, resulting in a dark area in the electron micrograph. Electron density is also achieved using **osmium tetroxide**, which also serves as a lipid fixative.

Areas or structures in tissue that bind the metals are referred to as **electron dense**. Areas where the metals do not bind appear light and are referred to **electron lucent.**

Histochemical staining. Localizes chemical groups

Osmium tetroxide. Stains lipids

Periodic acid–Schiff stain (PAS). Stains carbohydrates

Immunocytochemistry

Localization of specific antigens in cells using labeled antibodies

In situ hybridization

Detection of messenger RNA or genomic DNA sequences using labeled nucleotide probes

Artifact

The term artifact is used to refer to any feature of a tissue section that is present as a result of the tissue processing. These include tears and folds, shrinkage, spaces resulting from extracted cellular contents (e.g., lipid, precipitates), and redistributed organelles.

Microscopy

Properties

Resolution is the smallest degree of separation at which two objects can still be distinguished as separate objects and is based on the wavelength of the illumination.

Light microscopy. Approximately 200nm

Electron microscopy. Approximately 1nm

Magnification. Enlargement of the image

Bright field microscope

An image is formed by passing a **beam of light** through the specimen and then focusing the beam using glass lenses.

The bright field microscope is called a compound microscope because it uses two lenses, objective and ocular, to form and magnify the image. The compound microscope typically has a total magnification range of 40–1000 times.

Electron microscope

Transmission electron microscope (TEM)

An image is formed by passing a **beam of electrons** through the specimen and focusing the beam using electromagnetic lenses.

Similar arrangement of lenses is used as with optical microscopy; magnification is up to 400,000 times, which is sufficient to visualize macromolecules (e.g., antibodies and DNA).

Scanning electron microscope (SEM).

The image is formed by **electrons** that **are reflected off** the surface of a specimen, providing a **three-dimensional** image; magnification ranges from 1–1000 times.

Freeze fracture technique

This technique is used to examine the number, size, and distribution of membrane proteins.

A tissue is frozen and mechanically fractured; the exposed membrane surface is coated with a thin metal film called a "replica."

The replica is viewed by TEM. Membrane proteins appear either as bumps or pits in the replica.

Section Interpretation

In histology, three-dimensional tissues are viewed in two dimensions; therefore, it is extremely important to learn to visualize the three dimensional structure from the two-dimensional image. For example, a cross-section through a tubular structure appears as a ring, whereas a longitudinal section appears as two parallel bands. As an added challenge, most sections pass obliquely to these perpendicular axes and, thus, require further "mental gymnastics."

- The plasma membrane is a lipid-bilayered structure visible with transmission electron microscopy. The plasma membrane (cell membrane, plasmalemma) is a dynamic structure that actively participates in many physiologic and biochemical activities essential to cell function and survival. When the plasma membrane is properly fixed, sectioned, stained, and viewed on edge with the transmission electron microscope (TEM), it appears as two electron-dense layers separated by an intermediate, electron-lucent (nonstaining) layer. The total thickness of the plasma membrane is about 8 to 10 nm.

2. Cell membrane

The plasma membrane is composed of an amphipathic lipid layer containing embedded integral membrane proteins with peripheral membrane proteins attached to its surfaces. The current interpretation of the molecular organization of the plasma membrane is referred to as the modified fluid-mosaic model. The membrane consists primarily of phospholipid, cholesterol, and protein molecules. The lipid molecules form a lipid bilayer with an amphipathic character (it is both hydrophobic and hydrophilic). The fatty-acid chains of the lipid molecules face each other, making the inner portion of the membrane hydrophobic (i.e., having no affinity for water). The surfaces of the membrane are formed by the polar head groups of the lipid molecules, thereby

making the surfaces hydrophilic (i.e., they have an affinity for water). Lipids are distributed asymmetrically between the inner and outer leaflets of the lipid bilayer, and their composition varies considerably among different biologic membranes.

In most plasma membranes, protein molecules constitute approximately half of the total membrane mass. Most of the proteins are embedded within the lipid bilayer or pass through the lipid bilayer completely. These proteins are called integral membrane proteins. The other types of protein— peripheral membrane proteins —are not embedded within the lipid bilayer. They are associated with the plasma membrane by strong ionic interactions, mainly with integral proteins on both the extracellular and intracellular surfaces of the membrane. In addition, on the extracellular surface of the plasma membrane, carbohydrates may be attached to proteins, thereby forming glycoproteins; or to lipids of the bilayer, thereby forming glycolipids. These surface molecules constitute a layer at the surface of the cell, referred to as the cell coat or glycocalyx. They help establish extracellular microenvironments at the membrane surface that have specific functions in metabolism, cell recognition, and cell association and serve as receptor sites for hormones.

Integral membrane proteins

Have important functions in **cell metabolism**, **regulation**, **integration**, and **cell signaling**.

Six broad categories of membrane proteins have been defined in terms of their function: **pumps**, **channels**, **receptors**, **linkers**, **enzymes**, and **structural proteins**. The categories are not mutually exclusive (e.g., a structural membrane protein may simultaneously serve as a receptor, an enzyme, a pump, or any combination of these functions).

Pumps

serve to transport certain ions, such as Na+, actively across membranes. Pumps also transport metabolic precursors of macromolecules, such as amino acids and sugars, across membranes, either by themselves or linked to the Na+ pump.

Channels

allow the passage of small ions, molecules, and water across the plasma membrane in either direction (i.e., passive diffusion). Gap junctions formed by aligned channels in the membranes of adjacent cells permit passage of ions and small molecules involved in signaling pathways from the cytoplasm of one cell to the cytoplasm of the adjacent cells.

Receptor proteins

allow recognition and localized binding of ligands (molecules that bind to the extracellular surface of the plasma membrane) in processes such as hormonal stimulation, coated-vesicle endocytosis, and antibody reactions. Receptors that bind to signaling molecules transmit the

signal through a sequence of molecular switches (i.e., second messengers) to the cell's internal signaling pathways, thereby initiating a physiological response.

Linker proteins

anchor the intracellular cytoskeleton to the extracellular matrix. Examples of linker proteins include the family of integrins that link cytoplasm actin filaments to an extracellular matrix protein (fibronectin).

Enzymes

have a variety of roles. ATPases have specific roles in ion pumping: ATP synthase is the major protein of the inner mitochondrial membrane, and digestive enzymes such as disaccharidases and dipeptidases are integral membrane proteins.

Structural proteins

are visualized by the freeze fracture method, especially where they form junctions with neighboring cells. Often, certain proteins and lipids are concentrated in localized regions of the plasma membrane to carry out specific functions. Examples of such regions can be recognized in polarized cells such as epithelial cells.

Cell signaling

is the process by which extracellular stimuli are received, processed, and conveyed by the cell to regulate its own physiological responses. A single cell may receive many different signals at the same time, and it needs to integrate all information into a **unified action plan**. Signaling processes often are involved in regulation of **gene expression, exocytosis, endocytosis, differentiation, cell growth and death, cytoskeletal reorganization, movement, contraction, and/or cell relaxation.** Individual cells also send out signaling molecules to other cells both near (e.g., neurotransmitters in nerve synapses) and far away (e.g., hormones acting on distant cells).

Internal membrane proteins such as cell surface receptors and channels are involved in cell signaling processes.

Membrane Transport and Vesicular Transport

Some substances (fat-soluble and small, uncharged molecules) cross the plasma membrane by **simple diffusion** down their concentration gradient. All other molecules require membrane transport proteins to provide them with individual passage across the plasma membrane.

There are generally two classes of transport proteins: **Carrier protein** and **channel protein**

Carrier proteins

Transfer small, water-soluble molecules. They are **highly selective**, often transporting only one type of molecule. After binding to a molecule designated for transport, the carrier protein undergoes a series of conformational changes and releases the molecule on the other side of the membrane. Some carrier proteins, such as the **Na+/K+ pump** or **H+ pump**, require **energy** for

active transport of molecules **against** their concentration gradient. Other carrier proteins, such as glucose carriers, do not require energy and participate in **passive transport**.

Channel proteins

also transfer small, **water-soluble molecules**. In general, channels are made of transmembrane proteins with several membrane-spanning domains that create hydrophilic channels through the plasma membrane. Usually, channel proteins contain a pore domain that partially penetrates the membrane bilayer and serves as the **ion-selectivity filter**. The pore domain is responsible for exquisite ion selectivity, which is achieved by regulation of its three-dimensional structure. Channels are ion-selective and are regulated on the basis of the cell's needs. Channel protein transport can be regulated by **membrane potentials** (e.g., voltage-gated ion channels in neurons), **neurotransmitters** (e.g., ligand-gated ion channels such as acetylcholine receptors in muscle cells), or **mechanical stress** (e.g., mechanically gated ion channels in the internal ear).

Vesicular transport

maintains the **integrity** of the plasma membrane and also provides for the transfer of molecules between different cellular compartments.

Some substances enter and leave cells by vesicular transport, a process that involves configurational changes in the plasma membrane at localized sites and subsequent formation of vesicles from the membrane or fusion of vesicles with the membrane

The major mechanism by which large molecules enter, leave, and move within the cell is called **vesicle budding**.

Vesicles formed by budding from the plasma membrane of one compartment fuse with the plasma membrane of another compartment. Within the cell, this process ensures **intercompartmental transfer** of the vesicle contents.

Vesicular transport

Vesicular transport involving the cell membrane may also be described in more specific terms:

Endocytosis is the general term for processes of vesicular transport in which substances enter the cell. In general, endocytosis controls the composition of the plasma membrane and the cellular response to changes in the external environment. It also plays key roles in nutrient uptake, cell signaling, and cell shape changes.

Exocytosis is the general term for processes of vesicular transport in which substances leave the cell.

Endocytosis

Uptake of fluid and macromolecules during endocytosis depends in general on three different mechanisms. Some of the endocytotic mechanisms require special proteins during vesicle formation. The best known protein that interacts with the plasma membrane in vesicle formation

is **clathrin**. Although the presence of **clathrin** is certainly important for endocytic vesicle formation, many vesicles are formed in a **clathrin-independent** manner utilizing different proteins (i.e., caveolins or flotillins). Therefore, endocytosis can be classified as either clathrin-dependent or clathrin-independent. In general, three mechanisms of endocytosis are recognized in the cell:

1. Pinocytosis
2. Phagocytosis
3. Receptor-mediated endocytosis

- Pinocytosis
- [Gr., cell drinking] clathrin-independent endocytosis. It is the nonspecific ingestion of fluid and small protein molecules via small vesicles, usually smaller than 150 nm in diameter. Pinocytosis is performed by virtually every cell in the organism, and it is constitutive (i.e., it involves a continuous dynamic formation of small vesicles at the cell surface). The mechanism proposed for **vesicle formation** in pinocytosis is associated with the presence of **caveolin** and **flotillin** proteins that are found in lipid rafts.
- Phagocytosis
- [Gr., cell eating] **clathrin independent** but **actin-dependent** endocytosis is the ingestion of large particles such as cell debris, bacteria, and other foreign materials. In this nonselective process, plasma membrane sends out pseudopodia to engulf phagocytosed particles into large vesicles (larger than approximately 250 nm in diameter) called **phagosomes**. Phagocytosis is performed mainly by a specialized group of cells belonging to the mononuclear phagocytotic system (MPS). Phagocytosis is generally a receptor-mediated process in which receptors on the cell surface recognize **non—antigen-binding domains (Fc fragments) of antibodies** coating the surface of an invading microorganism or cell.
- Receptor-mediated endocytosis
- Is the clathrin-dependent endocytosis which allows entry of **specific molecules** into the cell. In this mechanism, receptors for specific molecules, called **cargo receptors**, accumulate in well-defined regions of the cell membrane. These regions, which are represented by the lipid rafts in the plasma membrane, eventually become **coated pits**. Cargo receptors recognize and bind to specific molecules that come in contact with the plasma membrane. Clathrin molecules then assemble into a basket-like cage that helps change the shape of the plasma membrane into a **vesicle-like invagination**
- Exocytosis

- Exocytosis is the process by which a vesicle moves from the cytoplasm to the plasma membrane, where it discharges its contents to the extracellular space.
- A variety of molecules produced by the cell for export are initially delivered from the site of their formation to the Golgi apparatus. The next step involves sorting and packaging the secretory product into transport vesicles that are destined to fuse with the plasma membrane in a process known as exocytosis.

There are two general pathways of exocytosis:

- In the **constitutive pathway**, substances designated for **export** are continuously delivered in **transport vesicles** to the **plasma membrane**. Proteins that leave the cell by this process are secreted immediately after their synthesis and exit from the Golgi apparatus, as seen in the secretion of immunoglobulins by plasma cells and of procollagen by fibroblasts. This pathway is present to some degree in all cells. The TEM reveals that these cells lack secretory granules.
- In the **regulated secretory pathway**, specialized cells, such as endocrine and exocrine cells and neurons, concentrate secretory proteins and transiently store them in secretory vesicles within the cytoplasm. In this case, a regulatory event (hormonal or neural stimulus) must be **activated for secretion to occur**, as in the release of secretory vesicles by chief cells of the gastric mucosa and by acinar cells of the pancreas. The signaling stimulus causes a transient **influx of Ca2+** into the cytoplasm, which in turn stimulates secretory vesicles to fuse with the plasma membrane and discharge their contents. In the past, secretory vesicles containing inactive precursor (zymogen) were called *zymogen granules.*

3. Cytoplasm

Endosomes

- The TEM reveals the presence in the cytoplasm of membrane-enclosed compartments associated with all the endocytotic pathways described in previous lecture. These compartments, called **early endosomes**, are restricted to a portion of the cytoplasm near the cell membrane where vesicles originating from the cell membrane fuse. From here, many vesicles return to the plasma membrane. However, large numbers of vesicles originating in early endosomes travel to deeper structures in the cytoplasm called **late endosomes**. The latter typically **mature into lysosomes**.
- Early and late endosomes differ in their cellular localization, morphology, and state of acidification and function. **Early** and **late endosomes** are localized in different areas of the cell. Early endosomes can be found in the **more peripheral cytoplasm**, whereas late endosomes are often positioned **near the Golgi apparatus** and the **nucleus**. An early

endosome has a tubulovesicular structure: The lumen is subdivided into cisternae that are separated by invagination of its membrane. It exhibits only a **slightly more acidic environment** (pH 6.2 to 6.5) than the cytoplasm of the cell. In contrast, late endosomes have a more complex structure and often exhibit onion-like internal membranes. Their pH is more acidic, averaging 5.5. TEM studies reveal specific vesicles that transport substances between early and late endosomes. These vesicles, called multivesicular bodies (MVBs), are highly selective transporters. Within early endosomes, proteins destined to be transported to late endosomes are sorted and separated from proteins destined for recycling and packaging into MVBs. In general, substances transported to late endosomes are eventually degraded in lysosomes in a default process that does not require any additional signals. Because late endosomes mature into lysosomes, they are also called prelysosomes. Late lysosomes may fuse with each other or with mature lysosomes.

- **Lysosomes**
- Lysosomes are digestive organelles that were recognized only after histochemical procedures were used to demonstrate lysosomal enzymes.
- Lysosomes are organelles rich in hydrolytic enzymes such as **proteases**, **nucleases**, **glycosidases**, **lipases**, and **phospholipases**. A lysosome represents a major digestive compartment in the cell that degrades macromolecules derived from endocytotic pathways as well as from the cell itself in a process known as autophagy (removal of cytoplasmic components, particularly membrane-bounded organelles, by digesting them within lysosomes).
- Previously it was postulated that lysosomes arise as complete and functional organelles budding from the Golgi apparatus. These newly formed lysosomes were termed **primary lysosomes** in contrast to **secondary lysosomes**, which had already fused with incoming endosomes. However, the primary and secondary lysosome hypothesis has proved to have little validity as new research data allow a better understanding of the details of protein secretory pathways and the fate of **endocytotic vesicles**. It is now widely accepted that lysosomes are formed in a complex series of pathways that converge at the late endosomes, transforming them into lysosomes. These pathways are responsible for a targeted delivery of newly synthesized lysosomal enzymes and structural lysosomal membrane proteins into the late endosomes. As stated earlier, lysosomal enzymes are synthesized in the rER and sorted in the Golgi apparatus
- Three different pathways deliver material for intracellular digestion in lysosomes.

- **Extracellular large particles** such as bacteria, cell debris, and other foreign materials are engulfed in the process of phagocytosis. A phagosome, formed as the material is internalized within the cytoplasm, subsequently receives hydrolytic enzymes to become a late endosome, which matures into a lysosome.
- **Extracellular small particles** such as extracellular proteins, plasma-membrane proteins, and ligand-receptor complexes are internalized by pinocytosis and receptor-mediated endocytosis. These particles follow the endocytotic pathway through early and late endosomal compartments and are finally degraded in lysosomes.
- **Intracellular particles** such as entire organelles, cytoplasmic proteins, and other cellular components are isolated from the cytoplasmic matrix by endoplasmic reticulum membranes, transported to lysosomes, and degraded. This process is called **autophagy**
- Rough-Surfaced Endoplasmic Reticulum
- The protein synthetic system of the cell consists of the rough endoplasmic reticulum and **ribosomes**.
- The cytoplasm of a variety of cells engaged chiefly in protein synthesis stains intensely with basic dyes. The basophilic staining is caused by the presence of RNA. That portion of the cytoplasm that stains with the basic dye is called **ergastoplasm**. The ergastoplasm in secretory cells (e.g., pancreatic acinar cells) is the light microscopic image of the organelle called the **rough endoplasmic reticulum** (rER).
- The rER is most highly developed in active secretory cells. The rER is particularly well developed in those cells that synthesize proteins destined to leave the cell (secretory cells) as well as in cells with large amounts of plasma membrane, such as neurons. Secretory cells include glandular cells, activated fibroblasts, plasma cells, odontoblasts, ameloblasts, and osteoblasts. The rER is not limited, however, to secretory cells and neurons. Virtually, every cell of the body contains profiles of rER. However, they may be few in number, a reflection of the amount of protein secretion, and dispersed so that in the light microscope they are not evident as areas of basophilia. The rER is most highly developed in active secretory cells because **secretory proteins** are synthesized **exclusively by the ribosomes of the rER**. In all cells, however, the ribosomes of the rER also synthesize proteins that are to become pe**rmanent components of the lysosomes**, **Golgi apparatus**, **rER**, or **nuclear envelope** or **integral components of the plasma membrane**.
- Ribosomes
- Ribosomes, are attached to the membrane of the rER by ribosomal docking proteins. Ribosomes measure 15 to 20 nm in diameter and consist of a small and large subunit. Each subunit contains ribosomal RNA (rRNA) of different length as well as numerous

different proteins. In many instances, the rER is continuous with the outer membrane of the nuclear envelope (see the next section). Groups of ribosomes form short spiral arrays called polyribosomes or polysomes

- Protein synthesis involves transcription and translation.
- The production of proteins by the cell begins within the nucleus with **transcription**, in which the genetic code for a protein is transcribed **from DNA to pre-mRNA**. Transcription is followed by translation in which the coded message contained in the mRNA is read by ribosomal complexes to form a polypeptide. A typical single cytoplasmic mRNA molecule binds to many ribosomes spaced as close as 80 nucleotides apart, thus forming a polyribosome complex, or polysome. A polysome attached to the cytoplasmic surface of the rER can translate a single mRNA molecule and simultaneously produce many copies of a particular protein. In contrast, free ribosomes reside within the cytoplasm. They are not associated with any intracellular membranes and are structurally and functionally identical to polysomes of the rER.
- "Free" ribosomes
- synthesize proteins that will remain in the cell as cytoplasmic structural or functional elements. Proteins targeted to the nucleus, mitochondria, or peroxisomes are synthesized on free ribosomes and then released into the cytosol. In the absence of a signal sequence, proteins that are synthesized on free ribosomes remain in the cytosol.
- **Cytoplasmic basophilia** is associated with cells that produce **large amounts of protein** that will **remain in the cell**. Such cells and their products include developing red blood cells (hemoglobin), developing muscle cells (the contractile proteins actin and myosin), nerve cells (neurofilaments), and keratinocytes of the skin (keratin). In addition, most enzymes of the mitochondrion are synthesized by free polysomes and transferred into that organelle.
- **Basophilia** in these cells was formerly called **ergastoplasm** and is caused by the presence of large amounts of RNA. In this case, the ribosomes and polysomes are free in the cytoplasm (i.e., they are not attached to membranes of the endoplasmic reticulum). The large basophilic bodies of nerve cells, which are called **Nissl bodies**, consist of both rER and large numbers of free ribosomes. All ribosomes contain RNA; it is the phosphate groups of the RNA of the ribosomes, not the membranous component of the endoplasmic reticulum, that account for basophilic staining of the cytoplasm.

Nissl bodies in neuron

- Smooth-Surfaced Endoplasmic Reticulum

- The sER consists of short anastomosing tubules that are not associated with ribosomes. Cells with large amounts of smooth-surfaced endoplasmic reticulum may exhibit distinct cytoplasmic **eosinophilia** (**acidophilia**) when viewed in the light microscope. The sER is structurally similar to the rER but **lacks the ribosome-docking proteins**. It tends to be tubular rather than sheet-like, and it may be separate from the rER or an extension of it. The sER is abundant in cells that function in **lipid metabolism** (i.e., cells that synthesize fatty acids and phospholipids), and it proliferates in hepatocytes when animals are challenged with lipophilic drugs. The sER is well developed in cells that synthesize and secrete **steroids** such as adrenocortical cells and testicular Leydig (interstitial) cells
- **Golgi Apparatus**
- The Golgi apparatus is well developed in secretory cells and does not stain with hematoxylin or eosin.
- The Golgi apparatus was described more than 100 years ago by histologist Camillo Golgi. It is active both in cells that secrete protein by exocytosis and in cells that synthesize large amounts of membrane and membrane-associated proteins such as nerve cells. In the light microscope, secretory cells that have a large Golgi apparatus (e.g., plasma cells, osteoblasts, and cells of the epididymis) typically exhibit a clear area partially surrounded by **ergastoplasm**
- **Golgi Apparatus**
- In EM, the Golgi apparatus appears as a series of stacked, flattened, membrane-limited sacs or cisternae and tubular extensions embedded in a network of microtubules near the microtubule-organizing center.
- The Golgi apparatus is polarized both morphologically and functionally. The flattened cisternae located closest to the rER represent the forming face, or the **cis-Golgi network** (CGN); the cisternae located away from the rER represent the maturing face, or the **trans-Golgi network** (TGN). The cisternae located between the TGN and CGN are commonly referred as the medial-Golgi network.
- **The Golgi apparatus functions in the posttranslational modification, sorting, and packaging of proteins.**
- Mitochondria
- Mitochondria are abundant in cells that generate and expend large amounts of energy.
- It is now evident that mitochondria increase in number by division throughout interphase, and their divisions are not synchronized with the cell cycle. Videomicroscopy confirms that mitochondria can both change their location and undergo transient changes in shape. They may therefore be compared to mobile power generators as they migrate from one

area of the cell to another to supply needed energy. Because mitochondria **generate ATP**, they are more numerous in cells that use large amounts of energy such as striated muscle cells and cells engaged in fluid and electrolyte transport.

- **Mitochondria evolved from aerobic bacteria that were engulfed by eukaryotic cells.**

Structure of mitochondrion

Mitochondria contain the enzyme system that generates ATP by means of the citric acid cycle and oxidative phosphorylation.

- Peroxisomes (Microbodies)
- Peroxisomes are single membrane-bounded organelles containing oxidative enzymes.
- Peroxisomes (microbodies) are small (0.5 μm in diameter), membrane-limited spherical organelles that contain oxidative enzymes, particularly catalase and other peroxidases. Virtually all oxidative enzymes produce (H_2O_2) as a product of the oxidation reaction.
- Hydrogen peroxide is a toxic substance. The catalase universally present in peroxisomes carefully regulates the cellular hydrogen peroxide content by breaking down hydrogen peroxide, thus protecting the cell.
- NONMEMBRANOUS ORGANELLES
  Microtubules
- Microtubules are nonbranching and rigid hollow tubes of polymerized protein that can rapidly assemble and equally rapidly disassemble. In general, micro tubules are found in the cytoplasm, where they originate from the MTOC. They grow from the MTOC located near the nucleus and extend toward the cell periphery. Microtubules are also present in cilia and flagella, where they form the axoneme and its anchoring basal body; in centrioles and the mitotic spindle; and in elongating processes of the cell, such as those in growing axons.
- Microtubules are involved in numerous essential cellular functions:
- **Intracellular vesicular transport** (i.e., movement of secretory vesicles, endosomes, and lysosomes). Microtubules create a system of connections within the cell, frequently compared with railroad tracks originating from the grand central station, along which vesicular movement occurs.
- **Movement of cilia and flagella**
- Attachment of chromosomes to the **mitotic spindle** and their movement during **mitosis** and **meiosis**
- **Cell elongation** and movement (migration)
- **Maintenance of cell shape**, particularly its asymmetry
- Actin Filaments

- Actin filaments are present in virtually all cell types.
- Actin molecules (42 kDa) are abundant and may constitute as much as 20 % of the total protein of some nonmuscle cells. Similar to the tubulin in micro tubules, actin molecules also assemble spontaneously by polymerization into a linear helical array to form filaments 6 to 8 nm in diameter. **They are thinner, shorter, and more flexible than microtubules**. Free actin molecules in the cytoplasm are referred to as **G-actin** (globular actin), in contrast to the polymerized actin of the filament, which is called **F-actin** (filamentous actin). An actin filament or microfilament is a polarized structure; its fast-growing end is referred to as the **plus** (barbed) end, and its slow-growing end is referred to as the minus (pointed) end.

  Actin filaments participate in a variety of cell functions. Actin filaments are often grouped in bundles close to the plasma membrane. Functions of these membrane-associated actin filaments include the following.
- **Anchorage and movement of membrane protein**. Actin filaments are distributed in three-dimensional networks throughout the cell and are used as anchors within specialized cell junctions such as focal adhesions.
- **Formation of the structural core of microvilli** on absorptive epithelial cells. Actin filaments may also help maintain the shape of the apical cell surface (e.g., the apical terminal web of actin filaments serves as a set of tension cables under the cell surface).
- **Locomotion of cells**. Locomotion is achieved by the force exerted by actin filaments by polymerization at their growing ends. This mechanism is used in many migrating cells—in particular, on transformed cells of invasive tumors. As a result of actin polymerization at their leading edge, cells extend processes from their surface by pushing the plasma membrane ahead of the growing actin filaments. The leading-edge extensions of a crawling cell are called lamellipodia; they contain elongating organized bundles of actin filaments with their plus ends directed toward the plasma membrane.
- **Extension of cell processes**. These processes can be observed in many other cells that exhibit small protrusions
- Intermediate Filaments
- Intermediate filaments play a **supporting** or **general structural** role. These rope-like filaments are called intermediate because their diameter of 8 to 10 nm is between those of actin filaments and microtubules. Nearly all intermediate filaments consist of subunits with a molecular weight of about 50 kDa. Some evidence suggests that many of the stable structural proteins in intermediate filaments evolved from highly conserved

enzymes, with only minor genetic modification. Intermediate filaments are formed from nonpolar and highly variable intermediate filament subunits.

- Unlike those of microfilaments and microtubules, the protein subunits of intermediate filaments show considerable diversity and tissue specificity. In addition, they do not possess enzymatic activity and form nonpolar filaments. Intermediate filaments also do not typically disappear and re-form in the continuous manner characteristic of most microtubules and actin filaments. For these reasons, intermediate filaments are believed to play a primarily structural role within the cell and to compose the cytoplasmic link of a tissue-wide continuum of cytoplasmic, nuclear, and extracellular filaments
- Centrioles and Microtubule-Organizing Centers
- Centrioles represent the focal point around which the MTOC assembles.
- Centrioles, visible in the light microscope, are paired, short, rod-like cytoplasmic cylinders built from nine microtubule triplets. In resting cells, centrioles have an orthogonal orientation: One centriole in the pair is arrayed at a right angle to the other. Centrioles are usually found close to the nucleus, often partially surrounded by the Golgi apparatus, and associated with a zone of amorphous, dense pericentriolar material. The region of the cell containing the centrioles and pericentriolar material is called the microtubule-organizing center or centrosome. The MTOC is the region where most microtubules are formed and from which they are then directed to specific destinations within the cell. Therefore, the MTOC controls the number, polarity, direction, orientation, and organization of microtubules formed during the interphase of the cell cycle. During mitosis, duplicated MTOCs serve as mitotic spindle poles. Development of the MTOC itself depends solely on the presence of centrioles. When centrioles are missing, the MTOCs disappear, and formation of microtubules is severely impaired. The pericentriolar matrix of MTOC contains numerous ring-shaped structures that initiate microtubule formation.
- Centrioles provide basal bodies for cilia and flagella and align the mitotic spindle during cell division.

4. The Cell Nucleus

- OVERVIEW OF THE NUCLEUS
- The nucleus is a membrane-limited compartment that contains the **genome** (genetic information) in eukaryotic cells. The nucleus contains genetic information, together with the machinery for **DNA replication and RNA transcription and processing**. The

nucleus of a nondividing cell, also called an interphase cell, consists of the following components:

- **Chromatin** is nuclear material organized as **euchromatin** or **heterochromatin**. It contains DNA associated with roughly an equal mass of various nuclear proteins (e.g., **histones**) that are necessary for DNA to function.
- The **nucleolus** (pi., nucleoli) is a small area within the nucleus that contains DNA in the form of transcriptionally active ribosomal RNA (**rRNA**) genes, RNA, and proteins. The nucleolus is the site of rRNA synthesis and contains regulatory cell-cycle proteins.
- The **nuclear envelope** is a double membrane system that surrounds the nucleus of the cell. It consists of an inner and an outer membrane separated by a **perinuclear cisternal space** and perforated by **nuclear pores**. The outer membrane of the nuclear envelope is continuous with that of the rough-surfaced endoplasmic reticulum (rER) and is often studded with ribosomes.
- The **nucleoplasm** is nuclear content other than the **chromatin** and **nucleolus**.
- NUCLEAR COMPONENTS. Chromatin
- Chromatin, a complex of DNA and proteins, is responsible for the characteristic basophilia of the nucleus. Each eukaryotic cell contains about 6 billion bits of information encoded in DNA structure, which has a total length of about 1.8 m. The length of the DNA molecule is 100,000 times longer than the nuclear diameter. Therefore, the DNA must be highly folded and tightly packed in the cell nucleus. This is accomplished by the formation of a unique nucleoprotein complex called **chromatin**. The chromatin complex consists of DNA and structural proteins. Further folding of chromatin, such as that which occurs **during mitosis**, produces structures called **chromosomes**. Each human cell contains 46 chromosomes. Chromatin proteins include five basic proteins called **histones** along with other nonhistone proteins. A unique feature of chromatin packaging is that it permits the transcriptional machinery
- **In general, two forms of chromatin are found in the nucleus: a condensed form called heterochromatin and a dispersed form called euchromatin.**
- In most cells, chromatin does not have a homogeneous appearance; rather, clumps of densely staining chromatin are embedded in a more lightly staining background. The densely staining material is highly condensed chromatin called **heterochromatin**, and the lightly staining material (where most transcribed genes are located) is a dispersed form called **euchromatin**. It is the phosphate groups of the chromatin DNA that are responsible for the characteristic **basophilia** of chromatin
- Nucleosomes

- The smallest units of chromatin structure are macromolecular complexes of **DNA** and **histones** called **nucleosomes**.
- They are found in both euchromatin and heterochromatin and in chromosomes. These 10-nm-diameter particles represent the first level of chromatin folding and are formed by the coiling of the DNA molecule around a protein core.
- This step shortens the DNA molecule by approximately sevenfold relative to the unfolded DNA molecule. The core of the nucleosome consists of eight **histone** molecules (called an **octamer**). Two loops of DNA (approximately 146 nucleotide pairs) are wrapped around the core **octamer**. The DNA extends between each particle as a 2-nm filament that joins adjacent nucleosomes. When chromatin is extracted from the nucleus, the nucleosomal substructure of chromatin is visible in transmission electron microscopy (TEM) and is often described as "beads on a string"
- In the next step, a long strand of nucleosomes is coiled to produce a 30-nm chromatin fibril. Six nucleosomes form one turn in the coil of the chromatin fibril, which is approximately 40-fold shorter than unfolded DNA. Long stretches of 30-nm chromatin fibrils are further organized into **loop domains** (containing 15,000 to 100,000 base pairs), which are anchored into a **chromosome scaffold** or nuclear matrix composed of nonhistone proteins. In heterochromatin, the chromatin fibers are **tightly packed** and **folded** on each other; in euchromatin, the chromatin fibrils are more **loosely arranged**.
- Chromosomes
- In dividing cells, chromatin is condensed and organized into discrete bodies called **chromosomes**.
- During mitotic division, chromatin fibers formed from chromatin loop domains attached to a flexible **protein scaffold** undergo condensation to form **chromosomes** [Gr., colored bodies]. Each chromosome is formed by two **chromatids** that are joined together at a point called the **centromere**. The double nature of the chromosome is produced in the preceding synthetic (S) phase of the **cell cycle**, during which DNA is replicated in anticipation of the next mitotic division.
- Telomere
- The area located at each end of the chromosome is called the **telomere**. Telomeres shorten with each cell division. Recent studies indicate that telomere length is an important indicator of the **lifespan of the cell.** To survive indefinitely (become “immortalized”), cells must activate a mechanism that maintains telomere length. For example, in cells that have been transformed into malignant cells, an enzyme called telomerase is present that adds repeated nucleotide sequences to the telomere ends.

- With the exception of the mature gametes, the egg and sperm, human cells contain 46 chromosomes organized as **23 homologous pairs** (each chromosome in the pair has the same shape and size). Twenty-two pairs have identical chromosomes (i.e., each chromosome of the pair contains the same portion of the genome) and are called **autosomes**. The 23rd pair of chromosomes are the **sex chromosomes**, designated **X** and **Y**. Females contain two **X** chromosomes; males contain one **X** and one **Y** chromosome. The chromosomal number, 46, is found in most of the somatic cells of the body and is called the **diploid (2n)** number. To simplify the description of chromosomal number and DNA changes during **mitosis** and **meiosis**, we use the lowercase letter **(n)** for chromosome number and lowercase letter **(d)** for DNA content. Diploid chromosomes have the **(2d)** amount of DNA immediately after cell division but have twice that amount—that is, the **(4d)** amount of DNA—after the S phase (next lecture)
- As a result of meiosis, eggs and sperm have only 23 chromosomes, the haploid (1 n) number, as well as the haploid (Id) amount of DNA. The somatic chromosome number (2 n) and the diploid (2d) amount of DNA are reestablished at fertilization by the fusion of the sperm nucleus with the egg nucleus.
- Nucleolus
- The nucleolus stains intensely with **hematoxylin** and basic dyes
- The nucleolus is the site of ribosomal RNA (rRNA) synthesis and initial ribosomal assembly. The nucleolus is a nonmembranous region of the nucleus that surrounds transcriptionally active rRNA genes. **It is the primary site of ribosomal production and assembly.** The nucleolus varies in size but is particularly well developed in cells active in protein synthesis. Some cells contain more than one nucleolus. The nucleolus has three morphologically distinct regions:

1. Fibrillar centers
2. Fibrillar material (pars fibrosa)
3. Granular material (pars granulosa)

- **Fibrillar centers** contain DNA loops of five different chromosomes (13, 14, 15, 21, and 22) that contain rRNA genes, RNA polymerase I, and transcription factors.
- **Fibrillar material** (pars fibrosa) contains ribosomal genes that are actively undergoing transcription and large amounts of rRNA.
- **Granular material** (pars granulosa) represents the site of initial ribosomal assembly and contains densely packed preribosomal particles.
- Nuclear Envelope

- **The nuclear envelope, formed by two membranes with a perinuclear cisternal space between them, separates the nucleoplasm from the cytoplasm.**
- The nuclear envelope provides a selectively permeable membranous barrier between the nuclear compartment and the cytoplasm, and it encloses the chromatin. The nuclear envelope is assembled from two (outer and inner) nuclear membranes with a **perinuclear cisternal space** between them. The perinuclear clear cisternal space is continuous with the cisternal space of the rER. The two membranes of the envelope are perforated at intervals by **nuclear pores** that mediate the active transport of proteins, ribonucleoproteins, and RNAs between the nucleus and cytoplasm. The membranes of the nuclear envelope differ in structure and functions:
- **The outer nuclear membrane**
- **The inner nuclear membrane**
- **The outer nuclear membrane** closely resembles the membrane of the endoplasmic reticulum and in fact is continuous with rER membrane. Polyribosomes are often attached to ribosomal docking proteins present on the cytoplasmic side of the outer nuclear membrane.
- **The inner nuclear membrane** is supported by a rigid network of intermediate protein filaments attached to its inner surface called the **nuclear (fibrous) lamina**. In addition, the inner nuclear membrane contains specific and several lamina-associated proteins that bind to chromosomes and secure the attachment of the nuclear lamina.
- Nuclear pores
- **The nuclear envelope has an array of openings called nuclear pores**.
- At numerous sites, the paired membranes of the nuclear envelope are punctuated by 70- to 80-nm “openings” through the envelope. These nuclear pores are formed from the merging of the inner and outer membranes of the nuclear envelope. With an ordinary TEM, a diaphragm-like structure appears to cross the pore opening. Often, a small dense body is observed in the center of the opening. Because such profiles are thought to represent either ribosomes or other protein complexes (transporters) captured during their passage through the pore at the time of fixation, the term central plug/transporter is commonly used to describe this feature.
- **During cell division, the nuclear envelope is disassembled to allow chromosome separation and is later reassembled as the daughter cells form**. In late prophase of cell division, enzymes (kinases) are activated that cause phosphorylation of the nuclear lamins and other lamina-associated proteins of the nuclear envelope.

- After phosphorylation, the proteins become soluble, and the nuclear envelope disassembles. The lipid component of the nuclear membranes then disassociates from the proteins and is retained in small cytoplasmic vesicles. The replicated chromosomes then attach to the microtubules of the mitotic spindle and undergo active movement. Reassembly of the nuclear envelope begins in late anaphase, when phosphatases are activated to remove the phosphate residues from the nuclear lamins. During telophase, the nuclear lamins begin to repolymerize and form the nuclear lamina material around each set of daughter chromosomes. At the same time, vesicles containing the lipid components of the nuclear membranes and structural membrane protein components fuse, and an envelope is formed on the surface of the already-reassembled nuclear lamina. By the end of telophase, formation of a nuclear envelope in each daughter cell is complete.
- Nucleoplasm
- **Nucleoplasm is the material enclosed by the nuclear envelope exclusive of the chromatin and the nucleolus.**
- Although crystalline, viral, and other inclusions are sometimes found in the nucleoplasm , until recently, morphologic techniques showed it to be amorphous. It must be assumed, however, that many proteins and other metabolites reside in or pass through the nucleus in relation to the synthetic and metabolic activity of the chromatin and nucleolus. New structures have recently been identified within the nucleoplasm, including intranuclear lamin-based arrays, the protein filaments emanating inward from the nuclear pore complexes, and the active gene-tethered RNA transcription and processing machinery itself.

5. Cell cycle. Mitosis. Meiosis

CELL RENEWAL

- **Somatic cells in the adult organism may be classified according to their mitotic activity.**
- **Static cell populations** consist of cells that no longer divide (postmitotic cells), such as cells of the central nervous system and skeletal or cardiac muscle cells. Under certain circumstances, some of these cells (i.e., cardiac myocytes) may enter mitotic division.
- **Stable cell populations** consist of cells that divide episodically and slowly to maintain normal tissue or organ structure. These cells may be stimulated by injury to become more mitotically active. Periosteal and perichondrial cells, smooth muscle cells, endothelial cells of blood vessels, and fibroblasts of the connective tissue may be included in this category.

- **Renewing cell populations** may be slowly or rapidly renewing but display regular mitotic activity. Division of such cells usually results in two daughter cells that differentiate both morphologically and functionally or two cells that remain as stem cells. Daughter cells may divide one or more times before their mature state is reached. The differentiated cell may ultimately be lost from the body.
- **Slowly renewing populations** include smooth muscle cells of most hollow organs, fibroblasts of the uterine wall, and epithelial cells of the lens of the eye. Slowly renewing populations may actually slowly increase in size during life, as do the smooth muscle cells of the gastrointestinal tract and the epithelial cells of the lens.
- **Rapidly renewing populations** include blood cells, epithelial cells and dermal fibroblasts of the skin, and the epithelial cells and subepithelial fibroblasts of the mucosal lining of the alimentary tract.
- **CELL CYCLE**
- **The cell cycle represents a self-regulated sequence of events that controls cell growth and cell division.**
- For renewing cell populations and growing cell populations, including embryonic cells, and cells in tissue culture, the goal of the cell cycle is to produce two daughter cells, each containing chromosomes identical to those of the parental cell. The cell cycle incorporates two principal phases: the **interphase**, representing continuous growth of the cell, and the **M-phase** (mitosis), characterized by the partition of the genome. Three other phases, G1 (gap1) phase, S (synthesis) phase, and G 2 (gap2) phase, further subdivide **interphase**. Rapidly renewing populations of human cells progress through the full cell cycle in about 24 hours. Throughout the cycle, several internal quality control mechanisms or **checkpoints** represented by biochemical pathways control transition between cell-cycle stages. The cell cycle stops at several checkpoints and can only proceed if certain conditions are met—for example, if the cell has reached a certain size. Checkpoints monitor and modulate the progression of cells through the cell cycle in response to intracellular or environmental signals.
- **G1 phase**
- **The G1 phase is usually the longest and the most variable phase of the cell cycle, and it begins at the end of M phase.**
- During the G1 phase, the cell gathers nutrients and **synthesizes RNA and proteins** necessary for DNA synthesis and chromosome replication. The cells progress through this phase is monitored by two checkpoints: (1) the **restriction checkpoint**, which is sensitive to the size of the cell, the state of the cell's physiologic processes, and its

interactions with extracellular matrix; and (2) the **G1 DNA-damage checkpoint**, which monitors the integrity of newly replicated DNA. For instance, if the DNA has irreparable damage, then the G1 DNA-damage checkpoint detects the high levels of **tumor-suppressing protein p53** and it does not allow the cell to enter the S phase. The cell will then most likely undergo **programmed cell death** (**apoptosis**).

- The **restriction checkpoint** (or "point of no return“) is the most important checkpoint in the cell cycle. At this checkpoint, the cell self-evaluates its own replicative potential before deciding to either enter the S phase and the next round of cell division or to retire and leave the cell cycle. A cell that leaves the cycle in the G1 phase usually begins terminal differentiation by entering the **Go phase** (“O” stands for “outside” the cycle). Thus, the G1 phase may last for only a few hours (average 9 to 12 hours) in a rapidly dividing cell, or it may last a lifetime in a nondividing cell. This checkpoint is mediated by interactions between the retinoblastoma susceptibility protein (pRb) and a family of **essential transcription factors** (E2F) with target promoters. In normal cells, proper interaction between pRb and E2F turns off many genes and blocks cell-cycle progression.
- S-Phase
- **In the S phase, DNA is replicated**. Initiation of DNA synthesis marks the beginning of the S phase, which is about 7.5 to 10 hours in duration. The DNA of the cell is **doubled** during the S phase, and new chromatids are formed that will become obvious at prophase or metaphase of the mitotic division. Chromosome replication is initiated at many different sites called **replicons** alongn the chromosomal DNA. Each replicón has a specifically assigned time frame for replication during S phase. Presence of the S DNA-damage checkpoint in this phase monitors quality of replicating DNA.
- G2-Phase
- **In the G 2 phase, the cell prepares for cell division.**
- During this phase, the cell examines its replicated DNA in preparation for cell division. This is a period of cell growth and reorganization of cytoplasmic organelles before entering the mitotic cycle. The G2 phase may be as short as 1 hour in rapidly dividing cells or of nearly indefinite duration in some polyploid cells and in cells such as the primary oocyte that are arrested in G2 for extended periods. Two checkpoints monitor DNA quality: the **G2 DNA-damage checkpoint** and the **unreplicated-DNA checkpoint**. The latter checkpoint prevents the progression of the cell into the M phase before DNA synthesis is complete.
- Regulation of the Cell Cycle

- Passage through the cell cycle is driven by proteins that are cyclically synthesized and degraded during each cycle.
- A number of cytoplasmic protein complexes regulate and control the cell cycle. Some of these proteins function as biochemical oscillators, whose synthesis and degradation are coordinated with specific phases of the cycle. Cellular and molecular events induced during the increase and decrease of different protein levels are the basis of the cell-cycle "engine."
- Other proteins actively monitor the quality of the molecular processes at the different checkpoints distributed throughout the cycle (described above). The protein complexes at the checkpoints may drive the cell into and out of the cell cycle, stimulating growth and division when conditions are favorable and, conversely, stopping or reducing the rate of cell division when conditions are not favorable.
- A two-protein complex consisting of **cyclin** and a **cyclin-dependent kinase (Cdk)** helps power the cells through the checkpoints of cell-cycle division.
- The reserve **stem cell population** may become activated and **reenter the cell cycle**. Cells identified as reserve stem cells may be thought of as Go cells that may be induced to reenter the cell cycle in response to injury of cells within the tissues of the body.
- Activation of these cells may occur in normal wound healing and in repopulation of the seminiferous epithelium after intense acute exposure of the testis to X-irradiation or during regeneration of an organ, such as the liver, after removal of a major portion. If damage is too severe, even the reserve stem cells die, and there is no potential for regeneration.
- **Mitosis**
- Mitosis occurs in the M phase.
- Mitosis nearly always includes both **karyokinesis** (division of the nucleus) and **cytokinesis** (division of the cell) and lasts about 1 hour. Mitosis takes place in several stages described in more detail below. Separation of two identical daughter cells concludes the M phase. The M phase possesses two checkpoints: the **spindle-assembly checkpoint**, which prevents premature entry into anaphase, and the **chromosome-segregation checkpoint**, which prevents the process of cytokinesis until all of the chromosomes have been correctly separated.
- **The mitotic catastrophe caused by malfunction of cell-cycle checkpoints may lead to cell death and tumor cell development.**
- Cell division is a crucial process that increases the number of cells, permits renewal of cell populations, and allows wound repair.

- Mitosis is a process of chromosome segregation and nuclear division followed by cell division that produces two daughter cells with the same chromosome number and DNA content as the parent cell. The term mitosis is used to describe the **equal partitioning of replicated chromosomes and their genes into two identical groups.**
- The process of cell division includes division of both the nucleus (karyokinesis) and the cytoplasm (cytokinesis).
- The process of cytokinesis results in distribution of nonnuclear organelles into two daughter cells. Before entering mitosis, cells duplicate their DNA. This phase of the cell cycle is called the S or synthesis phase. At the beginning of this phase, the chromosome number is (2n), and the DNA content is also (2 d); at the end, the chromosome number remains the same (2n), and the DNA content doubles to (4d).
- Mitosis follows the S phase of the cell cycle and is described in four phases.
    - **Prophase**
    - **Metaphase**
    - **Anaphase**
    - **Telophase**
- Prophase begins as the replicated chromosomes condense and become visible. As the chromosomes continue to condense, each of the four chromosomes derived from each homologous pair can be seen to consist of two **chromatids**. The sister chromatids are held together by the ring of proteins called **cohesins** and the **centromere**.
- In late prophase or **prometaphase** (sometimes identified as a separate phase of mitosis), the nuclear envelope begins to disintegrate into small transport vesicles and resembles the sER. The nucleolus, which may still be present in some cells, also completely disappears in prometaphase.
- In addition, a highly specialized protein complex called a **kinetochore** appears on each chromatid opposite to the centromere. The protein complexes that form kinetochores in the centromere region of chromatid are attached to specific repetitive DNA sequences known as **satellite DNA**, which are similar in each chromosome.
- Microtubules of the developing **mitotic spindle** attach to the kinetochores and thus to the chromosomes.
- Metaphase
- Metaphase begins as the mitotic spindle, consisting of three types of microtubules, becomes organized around the **microtubule-organizing centers** (**MTOCs**) located at opposite poles of the cell. The first type, the astral microtubules, is nucleated from the 7-tubulin rings in a star-like fashion around each MTOC. The second type, the polar

microtubules, also originates from the MTOC; however, these microtubules grow away from the MTOC. The third type, the **kinetochore microtubules**, emanates from the MTOC to probe the cytoplasm in search of kinetochores. When a kinetochore is finally captured by a kinetochore microtubule, it is pulled toward the MTOC, where additional microtubules will attach. The kinetochore is capable of binding between 30 and 40 microtubules to each chromatid. In some species, kinetochore microtubules are formed by MTOC-independent mechanisms that involve kinetochores. Kinetochore microtubules and their associated motor proteins direct the movement of the chromosomes to a plane in the middle of the cell, the equatorial or metaphase plate.

- Anaphase
- Anaphase begins at the initial separation of sister chromatids. This separation occurs when the **cohesins** that have been holding the chromatids together break down. The chromatids then begin to separate and are pulled to opposite poles of the cell by the molecular motors (**dyneins**) sliding along the kinetochore microtubules toward the MTOC.
- Telophase
- Telophase is marked by the reconstitution of a nuclear envelope around the chromosomes at each pole.
- The chromosomes uncoil and become indistinct except at regions that will remain condensed in the interphase nucleus. Hie nucleoli reappear, and the cytoplasm divides (cytokinesis) to form two daughter cells. Cytokinesis begins with the furrowing of the plasma membrane midway between the poles of the mitotic spindle. The separation at the cleavage furrow is achieved by a contractile ring consisting of a very thin array of actin filaments positioned around the perimeter of the cell. Within the ring, **myosin II molecules** are assembled into small filaments that interact with the **actin filaments**, causing the ring to contract. As the ring tightens, the cell is pinched into two daughter cells. Because the chromosomes in the daughter cells contain identical copies of the duplicated DNA, the daughter cells are genetically identical and contain the same kind and number of chromosomes. The daughter cells are (2d) in DNA content and (2n) in chromosome number.
- Meiosis
- Meiosis involves two sequential nuclear divisions followed by cell divisions that produce gametes containing half the number of chromosomes and half the DNA found in somatic cells.

- The zygote (the cell resulting from the fusion of an ovum and a sperm) and all the somatic cells derived from it are diploid (2 n) in chromosome number; thus, their cells have two copies of every chromosome and every gene encoded on this chromosome. These chromosomes are called homologous chromosomes because they are similar but not identical; one set of chromosomes is of maternal origin, the other is from the male parent. The gametes, having only one member of each chromosome pair, are described as haploid (1n). **During gametogenesis, reduction in chromosome number to the haploid state (23 chromosomes in humans) occurs through meiosis, a process that involves two successive divisions, the second of which is not preceded by an S phase**. This reduction is necessary to maintain a constant number of chromosomes in a given species. Reduction in chromosome number to (1 n) in the first meiotic division is followed by reduction in DNA content to the haploid (Id) amount in the second meiotic division.
- Phases in the process of meiosis are similar to the phases of mitosis.
- Prophase I
- The prophase of meiosis I is an extended phase in which pairing of homologous chromosomes, synapsis (close association of homologous chromosomes), and recombination of genetic material on homologous chromosomes is observed. Prophase I is subdivided into the following five stages:
- Leptotene
- Zygotene
- Pachytene
- Diplotene
- Diakinesis
- **Leptotene**. This stage is characterized by the condensation of chromatin and by the appearance of chromosomes. Sister chromatids also condense and become connected with each other by meiosis-specific cohesion complexes (Rec 8 p). At this phase, pairing of homologous chromosomes of maternal and paternal origin is initiated. Homologous pairing can be described as a process in which chromosomes actively search for each other. After finding their mates, they align themselves side by side with a slight space separating them.
- **Zygotene**. Synapsis, the close association of homologous chromosomes, begins at this stage and continues throughout pachytene. This process involves the formation of a synaptonemal complex, a tripartite structure that binds the chromosomes together. The synaptonemal complex is often compared to railroad tracks with an additional third rail positioned in the middle between two others. The cross ties in this track are represented

by the transverse filaments that bind the scaffold material of both homologous chromosomes together.

- **Pachytene**. At this stage, synapsis is complete. Crossing-over occurs early in this phase and involves transposition of DNA strands between two different chromosomes.
- **Diplotene**. Early in this stage, the synaptonemal complex dissolves, and the chromosomes condense further. Homologous chromosomes begin to separate from each other and appear to be connected by newly formed junctions between chromosomes called **chiasmata** (sing., chiasma). Sister chromatids still remain closely associated with each other. Chiasmata indicate that crossing-over may have occurred.
- **Diakinesis**. The homologous chromosomes condense and shorten to reach their maximum thickness, the nucleolus disappears, and the nuclear envelope disintegrates.
- **Metaphase I**
- Metaphase I is similar to the metaphase of mitosis except that the **paired chromosomes are aligned at the equatorial plate** with one member on either side. The homologous chromosomes are still held together by **chiasmata**. At late metaphase, chiasmata are cleaved and the chromosomes separate. Once the nuclear envelope has broken down, the spindle microtubules begin to interact with the chromosomes through the multilayered protein structure, the **kinetochore**, which is usually positioned near the centromere. The chromosomes undergo movement to ultimately align their centromeres along the equator of the spindle.
- Anaphase I and Telophase I
- Anaphase I and telophase I are similar to the same phases in mitosis except that the **centromeres do not split**. The sister chromatids, held together by **cohesin complexes** and by the centromere, remain together. A maternal or paternal member of each homologous pair, now containing exchanged segments, moves to each pole. Segregation or random assortment occurs because the maternal and paternal chromosomes of each pair are randomly aligned on one side or the other of the metaphase plate, thus contributing to genetic diversity. At the completion of meiosis I, the cytoplasm divides. Each resulting daughter cell (a secondary sperm atocyte or oocyte) is haploid in chromosome number (In) and contains one member of each homologous chromosome pair. The cell is still diploid in DNA content (2 d).
- Meiosis II

  After meiosis I, the cells quickly enter meiosis II without passing through an S phase. Meiosis II is an equatorial division and resembles mitosis. During this phase, the proteinase enzyme **separase** cleaves the cohesion complexes **between the sister**

chromatids. Cleavage of the cohesin complexes in the region of the centromere releases the bond between both centromeres. This cleavage allows the sister chromatids to separate at anaphase II and move to opposite poles of the cell. During meiosis II, the cells pass through prophase II, metaphase II, anaphase II, and telophase II. These stages are essentially the same as those in mitosis except that they involve a haploid set of chromosomes (In) and produce daughter cells that have only haploid DNA content (1 d). Unlike the cells produced by mitosis, which are genetically identical to the parent cell, the cells produced by meiosis are **genetically unique**.

6. Spermatogenesis and oogenesis

Mature germ cells are also termed gametes. There are **male gametes, the spermatozoa (sperm cells)**, and **female gametes, the oocytes (egg cells)**. Through the fusion of the gametes during the fertilization a zygote is created, the first cell of a new individual. In order for it to have the normal number of 46 chromosomes, each of the gametes has half, i.e., 23 chromosomes. The **reduction of the number of chromosomes and the recombination of the genetic material** are processes, both of which occur during meiosis. Meiosis is a special form of cell division that only takes place in **gametogenesis**.

Gametogenesis mainly describes how the oocytes in the ovary and the spermatozoa in the testicles are **generated during the period of human sexual maturity.**

The **male gametes** are produced in large numbers in the testicles from puberty onwards and for the rest of the man's life. Several million of them are present in a typical ejaculate.

The **female gametes** - oocytes - are already generated and stored during the embryonic and fetal periods and a certain number of them (1 - 2 million) are present in both **ovaries** when a baby girl is born. The number of the oocytes in the ovaries is thought to constantly diminish right up to menopause. During the fertile period in the life of a woman, from menarche until menopause, roughly **400 oocytes** (approximately 13 periods x 30 years) are ovulated. Hormonal regulation, operating in cycles, is responsible for the maturing and expulsion of the oocytes from the follicles.

Spermatogenesis

Spermatogenesis is initiated in the male testis with the beginning of puberty. This comprises the entire **development of the spermatogonia (former primordial germ cells) up to sperm cells**. The gonadal cords that are solid up till then in the juvenile testis develop a lumen with the start of puberty. They then gradually transform themselves into spermatic canals that eventually reach a length of roughly 50-60 cm. They are termed convoluted seminiferous tubules (**Tubuli**

seminiferi contorti) and are so numerous and thin that in an adult male testicle their collective length can be 300 to 350 meters. They are coated by a germinal epithelium that exhibits two differing cell populations: some are sustentacular cells (= **Sertoli's cells**) and the great majority are the **germ cells in various stages of division and differentiation**.

The development of the germ cells begins with the **spermatogonia** at the periphery of the seminal canal and advances towards the lumen over **spermatocytes I** (primary spermatocytes), **spermatocytes II** (secondary spermatocytes), **spermatids** and finally to **mature sperm cells**.

Developmental stages of spermatogenesis

In the course of spermatogenesis the **germ cells move** towards the lumen as they mature. The following developmental stages are thereby passed through:

A-spermatogonium

B-spermatogonium

Primary spermatocyte (= spermatocyte order I)

Secondary spermatocyte (= spermatocyte order II)

Spermatid

Sperm cell (= spermatozoon)

The approximate **64 day** cycle of the spermatogenesis can be subdivided into four phases that last differing lengths of time:

Among the **spermatogonia** (all in all, over 1 billion in both testicles) that form the basal layer of the germinal epithelium, several types can be distinguished: **certain type A** cells are seen as spermatogonia that divide mitotically and reproduce themselves (**homonymous division**), whereby the spermatogonia population is maintained.

The beginning of spermatogenesis is introduced through the so-called **heteronymous** division, in which the daughter cells (**second group of type A cells**) remain bound together by **thin bridges of cytoplasm**. Through the preservation of these cytoplasmic connections, spermatogonia are inducted into the spermatogenesis process.

After a further mitotic division **type B spermatogonia** are engendered that also divide themselves mitotically into primary spermatocytes (I).

The freshly created **primary spermatocytes (I)** now enter into the first meiosis. They then go immediately into the S phase (that is, into the **preleptotene** meiosis), double their internal DNA, leave the basal compartment and reach the special milieu of the luminal compartment. Following the S phase, these cells attain the complex stage of the **prophase of the meiosis** and become thereby **noticeably visible** with a **light microscope**.

This prophase, which lasts **24 days**, can be divided into five sections:

Leptotene

Zygotene

Pachytene

Diplotene

Diakinesis

In the prophase in every germ cell a new combination of maternal and paternal genetic material occurs. After the long prophase follow the metaphase, anaphase and telophase that take much less time. One primary spermatocyte yields two secondary spermatocytes.

The **secondary spermatocytes** go directly into the second meiosis, out of which the spermatids emerge. Since in the secondary spermatocytes neither DNA reduplication nor a recombination of the genetic material occurs, the second meiosis can take place quickly. It lasts only around five hours and for that reason secondary spermatocytes are rather seldom seen in a histological section. Through the division of the chromatids of a secondary spermatocyte, two haploid spermatids arise that contain only half the original DNA content.

Besides the sperm cells the **spermatids** are the smallest cells of the germinal epithelium. In a process lasting several weeks (so-called spermiogenesis or spermiohistogenesis) they are transformed into sperm cells with the active assistance of the Sertoli's cells.

Spermiogenesis (spermatohistogenesis)

The differentiation of the spermatids into sperm cells is called spermiogenesis. It corresponds to the final part of spermatogenesis and comprises the following individual processes that partially proceed at the same time:

Nuclear condensation: thickening and reduction of the nuclear size, condensation of the nuclear contents into the smallest space.

Acrosome formation: Forming a cap (acrosome) containing enzymes that play an important role in the penetration through the pellucid zone of the oocyte.

Flagellum formation: generation of the sperm cell tail.

Cytoplasma reduction: elimination of all unnecessary cytoplasm.

Nuclear condensation

The nucleus becomes smaller, denser and takes on a characteristic, flattened form. Seen from above, the nucleus is oval and, from the narrow side, is pear-shaped. The acrosome lies over the tip. Nucleus and acrosome form the sperm cell's head that is bound to the mid-piece by a short neck.

Acrosome formation

The Golgi complex engender the vesicles, which then merge into a larger formation that settles

close to the cell nucleus and finally inverts itself like a cap over the largest part of the nucleus. The acrosome corresponds functionally to a lysosome and thus contains lysosomal enzymes (hyaluronidase among others).

Development of the flagellum

The future axonemal structure grows out of one centriole (distal). This consists of a bundle of nine peripheral double microtubules and two single ones in the center. During its development, through the rotation of the nucleus and acrosomal vesicle, the flagellum primordium comes to lie on the opposite side of the acrosome.

Cytoplasmic reduction

The cytoplasm of the spermatids that is no longer needed is phagocytized by Sertoli's cells or is disposed of in the lumen of the tubules. A clump of cytoplasm, though, can remain hanging on the neck and mid piece of the sperm cell for a little while.

During sperm cell production considerable individual variations exist that are also partially influenced by psychological factors. Per day roughly 100 million sperm cells are produced. It is said that in each ejaculate an average number of 50-200 million sperm cells are present (WHO standard value: over 40 million).

In the **genital primordium** the following processes then take place:

A **wave of proliferation** begins that lasts from the 15th week to the 7th month: primary germ cells arise in the cortical zone via mitosis of **oogonia clones**, bound together in cellular bridges, that happens in rapid succession. The **cell bridges** are necessary for a synchronous onset of the subsequent meiosis.

With the onset of the meiosis (earliest onset in the prophase in the 12th week) the designation of the germ cells changes. They are now called **primary oocytes**.

The primary oocytes become arrested in the diplotene stage of prophase I (the prophase of the **first** meiotic division). Shortly before birth, all the fetal oocytes in the female ovary have attained this stage. The meiotic resting phase that then begins is called the **dictyotene** and it lasts till **puberty**, during which each month (and in each month thereafter until menopause) a pair of primary oocytes complete the first meiosis. Only a few oocytes (secondary oocytes plus one polar body), though, reach the second meiosis and the subsequent ovulation. The remaining oocytes that mature each month become atretic.

The primary oocytes that remain in the ovaries can stay in the dictyotene stage up to menopause, in the extreme case, without ever maturing during a menstrual cycle.

While the oogonia transform into primary oocytes, they become restructured so that at the end of prophase I (the time of the dictyotene) each one gets enveloped by a single layer

of **flat**, **follicular epithelial cells** (descendents of the coelomic epithelium). (oocyte + follicular epithelium = **primordial follicle**).

Oogenesis

Structure of the ovary

An ovary is subdivided into **cortical**(ovarian cortex) and **medullary compartments** (ovarian medulla).

Both blood and lymph vessels are found in the loose connective tissue of the ovarian medulla.

In the **cortical compartment** the oocytes are present within the **various follicle stages**.

The sex hormones influence the primordial follicles to grow and a restructuring to take place. From the primordial follicles the primary follicles, secondary follicles, and tertiary follicles develop in turn. Only a **small percentage** of the primordial follicles reach the tertiary follicle stage - the great majority meet their end beforehand in the various maturation stages. Large follicles leave scars behind in the cortical compartment and the small ones disappear without a trace.

The tertiary follicles get to be the largest and, shortly before ovulation, can attain a diameter up to 2.5 mm through a special spurt of growth. They are then termed graafian follicles.

The follicle stages from primordial follicle to tertiary follicle

Primordial follicle

At the time of **birth** all the surviving primary oocytes are surrounded by **thin, single layers** of so-called follicular epithelial cells. These are delimited from the rest of the ovarian stroma by a thin basal lamina. Follicular epithelial cells are former coelomic epithelial cells. The primordial follicles always form the **majority of the follicles in the ovary**.

Under the influence of the sex hormones **some of them** are able to **develop further** to one or more of the subsequent stages in the following 50 years. Although this further development can already take place sporadically in the time before birth and up to puberty, the main part occurs as soon as a regular hormonal cycle is established. Particularly the last phase of the maturation of a tertiary follicle to become a large follicle, ready to rupture, remains reserved for the time of regular cycles.

Primary follicle

In the transition of the primordial follicles into primary follicles the follicular epithelium that surrounds the oocyte becomes iso- to highly prismatic.

Secondary follicle

When primary follicles survive, secondary follicles with follicular epitheliums encompassing **multiple rows** are engendered. This is now called the **stratum granulosum**. In the secondary follicles a glycoprotein layer, the pellucid zone, between the oocyte and follicular

epithelium becomes visible. Cytoplasmic processes of the granulosa cells that lie upon it reach the oocyte through the **pellucid zone** and thereby assure their maintenance function. Outside the basal lamina the stroma ovarii organizes itself to become theca folliculi cells.

Tertiary follicle

If the secondary follicles survive, tertiary follicles are engendered. Their identifying characteristic is a fluid-filled cavity, the **antral follicle**. The oocyte lies at the edge in a mound made of granulosa epithelial cells, the **cumulus oophorus**. In the meantime it has grown so large that its cellular nucleus has attained the size of a whole primordial follicle. The connective tissue around the follicle has already clearly differentiated itself into a theca interna, well supplied with capillaries, out of large, lipid-rich cells (hormone production) and a theca externa, which forms a transition to the stroma ovarii and contains larger vessels.

1. Oocyte
2. Pellucid zone
3. Stratum granulosum
4. Theca interna
5. Theca externa
6. Antral follicle
7. Cumulus oophorus (Granulosa cells, together with the oocyte)
8. Basal lamina between theca and stratum granulosum

Decisive for a successful follicle growth is a well-developed net of capillaries in the theca interna. The precise steering mechanism that leads to the selection of a follicle and its subsequent maturation to become a graafian follicle is still unknown. Before ovulation a growth spurt of the tertiary follicles takes place.

Graafian follicle

This corresponds to an especially large tertiary follicle that can be expected to suffice for ovulation

The ovarian cycle

Of the roughly 500'000 follicles that are present in the two ovaries at the beginning of sexual maturity, only around 480 reach the graafian follicle stage and are thus able to release oocytes (ovulation). This number is simply derived by multiplying the number of cycles per year (12) and the number of years in which a woman is fertile (40).

The hormonal cycle:

Cyclic changes in the hormone household (hormonal cycle), governed by the hypothalamic-pituitary system, are responsible for the periodicity of the ovulation. In a woman, the **rhythmic hormonal influence** leads to the following cyclic events:

the **ovarian cycle (follicle maturation)** that peaks in the ovulation and the subsequent luteinization of the granulose cells

cyclic alterations of the **endometrium** that prepare the uterine mucosa so fertilized oocytes can "nest" there. In the absence of implantation, the mucosa will be eliminated (menstrual bleeding)

In the **center** of this hormonal control is the **hypothalamamics-hypophysial (pituitary gland) system** with the two hypophysial gonadotropins FSH and LH. The pulsating liberation of GnRH by the hypothalamus is the fundamental precondition for a normal control of the cyclic ovarian function. This cyclic activity releases FSH and LH, both of which stimulate the maturation of the follicles in the ovary and trigger **ovulation**. During the ovarian cycle, estrogen is produced by the theca interna and follicular cells (in the so-called follicle phase) and progesterone by the corpus luteum (so-called luteal phase).

The control circuit of the hormonal cycle has two essential control elements:The **pulsatile** liberation of GnRH, as well as FSH and LH

The **long-loop feedback-effect** of estrogen and progesterone on the hypothalamic-hypophysial-system (these two hormones are synthesized in the [ready to rupture] follicle and so originate in the ovary, thus the name "long loop").

As a rule, the **ovarian cycle lasts 28 days**. It is subdivided into two phases:

Follicle phase: **recruitment** of a so-called follicle cohort and, within this, the selection of the **mature follicle**. This phase ends with **ovulation**. **Estradiol** is the steering hormone. Normally, it lasts 14 days, but this can **vary considerably!**

Luteal phase: **progesteron production** by the "yellow body" (= corpus luteum) and lasts 14 days (relatively **constant**).

7. Fertilization

The female genital tract

The ovary and the dominant follicle

Roughly a week before the midpoint of the menstrual cycle the **dominant follicle** develops in one of the two ovaries. This grows faster than the other tertiary follicles and prepares itself for ovulation. It reaches a diameter of up to 25 mm and is also known then as the **graafian follicle**.

Ovulation

The oocyte in the cloud of cumulus cells following ovulation

In the fallopian tube, the secondary oocyte is surrounded by the corona radiata and scattered parts of cumulus cells (so-called cumulus cell cloud). The fluid that lies in between is sticky and stringy (effect of the hyaluronic acid) with a high concentration of progesterone (to attract the spermatozoa).

Spermatozoa maturation steps

Looking at a spermatozoon **one distinguishes**:

Head

Neck

Mid-piece

Principal piece

Endpiece

The head contains the condensed nucleus, which is covered on the top by an acrosome, a cap-like vesicle. Hydrolyzing enzymes that play an important role in the penetration of the protective coverings of the oocyte (corona radiata and pellucid zone) are stored in the vesicle.

The acrosome, in terms of volume, takes up around 40% of the head.

The cervical canal

After the ejaculation the sperm cells are cloaked by a slightly alkaline, buffering seminal plasma that protects them from the acidic vaginal milieu. Nevertheless a large portion of the sperm cells meets there their end. The survivors are attracted by the alkaline, sperm-friendly **milieu of the cervix**.

At the time of ovulation the properties of the cervix mucus changes from a "sperm-hostile "environment to a very "sperm-friendly" one.

Before the ovulation the cervical canal is **narrow** and the cervix mucus is **strongly meshed** (it forms the so-called **cervical barrier**) that hinders the passage of sperm cells.

At the **time of ovulation** the cervix wall becomes **looser** and the canal **wide**. The folds of the mucosa increase in number and let deeper and branched crypts come into being; there are then also **more cervix glands**.

Under the influence of the estradiol that increases shortly before ovulation the **cervix mucus is restructured** and the mucus barrier becomes passable **for sperm cells**.

With the restructuring of the cervical barrier the mucus becomes **thinner and more fluid**. Therein meandering passages coated with specific **chemotactic molecules** form that the sperm cells will prefer in order to pass through the cervix.

The passage through the cervical canal is an important step for the selection of the sperm cells. The cervical **mucus barrier functions as a filter** in which atypical sperm cells remain hanging. They are hindered in ascending by means of a hydrodynamic effect. Through this simple mechanism it is assured that only normally formed and highly mobile sperm cells are able to overcome the cervical mucus barrier.

Sperm cell capacitation

After the ejaculation the sperm cells go through several essential physiological changes during their time in the female genital tract before they, at the end, are able to penetrate the oocyte membrane.

The first change in this cascade is **capacitation**. The sperm cells accomplish this during the ascension through the female genital tract (in contact with its secretions). It has to do with a physiological maturation process of the sperm cell membranes, which is seen as the precondition for the next step to follow, namely the acrosome reaction.

Capacitation is a functional maturation of the spermatozoon. The changes take place via the sperm cell membrane in which it may be that receptors are made available through the removal of a glycoprotein layer. The area of the acrosomal cap is also so altered thereby that the acrosome reaction becomes possible.

Through the membrane alterations, the motile properties of the spermatozoon also change. **Discharging whipping movements of the tail** together with larger sideways **swinging movements of the head** take place. This type of motility is designated as hyperactivity. One can therefore say that the visible consequences of capacitation consist in hyperactivity of the spermatozoon.

Capacitation is what one calls the changes that lead to hyperactivity of the spermatozoon and which later allow the spermatozoon to go through the acrosome reaction.

Penetrating the cumulus cells

In vivo -the spermatozoa arrive in waves at the oocyte that is surrounded by cumulus cells. When fertilization is carried out in a test-tube, the amount of sperm cells introduced must be carefully observed because if there are too few, no fertilization occurs.

Enzymes are set free by the acrosome reaction; the hyaluronidase **dissolves the intercellular matrix** between the cumulus cells, other enzymes dissolve the pellucid zone that lies around the oocyte.

Normally, the acrosome reaction of the spermatozoa takes place first when they encounter the pellucid zone. In a small percentage of the sperm cells, though, the acrosome reaction occurs spontaneously, just as when a small percentage of the cells experience capacitation immediately following ejaculation. This circumstance assures that a small amount of **hyaluronidase** is present from the very beginning and, when the wave of sperm cells meets the oocyte, a few of them are thus assisted in making their way to the pellucid zone. Upon arriving at the pellucid zone, these sperm cells themselves undergo an acrosome reaction and a further amount of hyaluronidase and other enzymes are released. In this way, the throng of cumulus cells is further loosened up and more and more sperm cells obtain the possibility of undergoing the acrosome reaction themselves at the pellucid zone.

The **hyperactivity** of the spermatozoa caused by the capacitation is a decisive factor that contributes to the spermatozoa being able, with the whipping motions of their tails, to go through the mass of cumulus cells, in the beginning even without much assistance from the hyaluronidase. Summarizing, we have here to do with a directed "attack" of many sperm cells on the structures surrounding the oocyte, with the final goal of making it possible for **one single** spermatozoon to unite with the oocyte.

The contact with the pellucid zone

When the sperm cells encounter the pellucid zone they bind themselves there. Following the **binding of the sperm cells to the pellucid zone** the **acrosome reaction is then induced** through ZP3 (zona protein 3).

The changes that occur on the **cell membrane of the spermatozoon** while going through capacitation are also decisive for the success of the acrosome reaction. Both the binding to the pellucid zone as well as the subsequent acrosome reaction depend on the function of the cell membrane.

The acrosome reaction

During the acrosome reaction the contents of the acrosome are released outwardly. The cell membrane of the spermatozoon fuses with the outer membrane of the acrosome. The contents of the acrosome flow out through the resulting pores.

A prerequisite for the success of the acrosome reaction is the previous binding of the spermatozoon to the pellucid zone.

That the zona-binding represents a decisive step in the fertilization cascade can perhaps be seen in the fact that the **zona-binding is species specific**; the subsequent binding of the oocyte membrane onto the oolemma, on the other hand, is not.

When the acrosome reaction has been completed, the spermatozoon is now covered at its upper end only by the former inner membrane of the acrosome. For the further progress of the fertilization this is decisive because structures are thereby uncovered which are necessary for contact with the oocyte. One consequence of this is that changes appear, especially in the **post-acrosomal membrane area** of the spermatozoon.

The penetration of the pellucid zone

The enzymes that are released in the immediate vicinity of the pellucid zone by the acrosome reaction dissolve it locally and thus create a way through it for the sperm cells. A number of enzymes that have been released are involved. The best known are the already mentioned hyaluronidase and acrosin, whereby the acrosin makes it possible for the spermatozoa to get through the pellucid zone.

The docking mechanism of the spermatozoon onto the oocyte (the key-lock principle)

The final penetration of the spermatozoon into the oocyte can only take place after a complex sequence of processes have occurred for both the spermatozoon and the oocyte.
At the molecular level the recognition of the spermatozoon and its attachment to the oolemma, the oocyte membrane, functions via a key-lock principle.
Keys and locks are receptor proteins, inserted into the cell membranes of spermatozoon and oocyte and having great mutual affinity.
In order for the docking to be successful, the corresponding membrane location has to first be uncovered, which is achieved by means of the complete and error-free course of the acrosome reaction.
The course of the acrosome reaction is the precondition for the membrane coalescence between spermatozoon and oocyte.
The docking triggers a cascade of events with the following goals:
Polyspermy block: The penetration of further sperm cells should be hindered
Hardening of the pellucid zone as a mechanical protection of the embryo
Entry of the spermatozoon into the oocyte
Termination of the 2nd meiosis of the oocyte with expulsion of the 2nd polar body
Preparation at the molecular level of the oocyte for unpacking the paternal DNA
The polyspermy block
As soon as a spermatozoon has docked, further sperm cells must be hindered from also doing the same. In the **oolemma** as well as in the **pellucid zone** the appropriate changes occur.

The docking triggers a **rapid wave of depolarization** in the oolemma, leading to changes in the membrane surface.

The depolarization wave then also causes small cortical **vesicles**, found on the inside of the oolemma, to **empty out their contents into the perivitelline space**. The pellucid zone is "hardened" thereby. It no longer allows sperm cells to pass through unhindered. From this time on, and over the next few days, the pellucid zone provides excellent protection for the developing zygote.
The entry of the spermatozoon into the oocyte (impregnation)
After the spermatozoon has docked onto the oolemma, a coalescence of the two membranes takes place. This makes it possible for the structures lying inside the spermatozoon to enter the cytoplasma of the oocyte. One calls this process the **impregnation of the oocyte**. Among other things the **nucleus** with the highly concentrated DNA, the **centrosome** that lies across the

nucleus in the neck region and the mid piece with the mitochondria and the kinocilium (tail) are transferred.

The genetic material, lying in the nucleus and coming from the father, is unpacked and is used for building the paternal pronucleus. In what follows, the centrosome plays an important role in the convergence of the two pronuclei. Later - after the subsequent division - it will also be responsible for building the first division spindle of the new creature. All centrosomes in the bodily cells of a human originate from that of the father.

Other sperm components transferred to the oocyte cytoplasm, like the kinocilium, are dissolved. Effective processes also exist for eliminating sperm mitochondria from the cytoplasm of the oocyte.

Thus, all mitochondria in the bodily cells of an individual normally derive from the mother alone

1. Oolemma
2. Cell membrane of the spermatozoon
3. Kinocilium
4. Nucleus (compact) of the spermatozoon
5. Centrosome of the spermatozoon

The termination of the second meiosis of the oocyte

At the moment of impregnation one encounters the following condition in the secondary oocyte, which was created shortly before ovulation:

The **mitotic spindle**, arrested in the metaphase of the second meiosis, becomes **active** again due to the impregnation. From the docking and impregnating spermatozoon a **signal** for a resumption and termination of the second oocyte meiosis is triggered. One speaks now of an **impregnated oocyte**.

In the two hours following impregnation the mitotic spindle pulls the chromatids, situated around the equator, apart so that in the oocyte only 1n1C remains. A **new formation of the 2nd polar body** takes up the other 1n1C. The remaining first polar body bound by a thin cytoplasma bridge receives the same signal and also divides.

The **termination of the second meiosis** implies the division of the secondary oocyte (1n,2C) into a **mature oocyte** (1n,1C) by the expulsion of the **2nd polar body** (1n,1C) into the perivitelline space.

In what follows the structures of the mitotic spindle dissolve. Mitotic spindles formed in the future will be formed from the centrosome introduced by the father.

Introduction into the creation and development of the pronuclei

After the spermatozoon has impregnated the oocyte, i.e., has delivered the paternal portion of the genetic material, things are now set into motion within the oocyte so that the paternal as well as the maternal genetic information are put into a form that allows both to be brought together in a proper way. The unpacked DNA is enclosed in the slowly forming **paternal and maternal pronuclei**. During a synthesis phase the duplication of the DNA occurs in them.

After the synthesis phase, which takes almost a day, the DNA condenses into chromosomes. These promptly order themselves on the zygote's mitotic spindle so this can divide into the two-cell stage.

In the following, these processes are explained in greater detail.

The formation of the paternal pronucleus

Via the head of the spermatozoon an extremely thickly packed, haploid chromosome set (1n1C) has penetrated into the cytoplasma of the oocyte. This specially condensed DNA must be unpacked as a first step, i.e., decondensed. The protamines that are wrapped around the DNA strands are expanded and decomposed. With the help of enzymes and molecules from the cytoplasma the oocyte gradually expands the paternal pronucleus. A nucleic membrane encloses the decondensing DNA. The formation of a (pro)nucleus is necessary for the subsequent synthesis phase in which the DNA is duplicated.

The formation of the zygote

After the two pronuclei have come as close together as they can, **no merging of them takes place**, i.e., a fitting together of the chromosomes of the two pronuclei within a single nucleic membrane does not happen. It is much more accurate to say that the **nucleic membranes of both pronuclei dissolve**and the chromosomes of both align themselves on the spindle apparatus at the equator.

The zygote, the first cell of a new organism with an individual genome (2n4C) is created by the alignment of the maternal chromosomes together with the paternal ones on a common spindle apparatus.

The mitotic spindle divides the chromosomes that have just been brought together into the two first cells of the embryo. This proceeding towards the **two-cell stage** occurs **on average between 22 and 26 hours** after fertilization.

8. Early embryogenesis

- Following a successful fertilization the preimplantation period that lasts for around 6 days ensues.

- While the fertilized oocyte wanders from the ampulla through the fallopian tube into the uterine cavity, an implantation-ready blastocyst develops through cell divisions. At the end of the sixth day after fertilization the blastocyst embeds itself in the endometrium.
- **The cleavage divisions up to the morula stage**
- Approximately 24 hours after fertilization the impregnated oocyte begins with the first cleavage division.
- Morula
- The **morula**, a collection of around 30 cells (blastomere), is created at about 96 hours. Because these cells arise only through the cleavage of the zygote and all are found inside the pellucid zone, which cannot expand, no growth is seen. Every new cell is thus only half as large as the cell from which it derives. The name of this stage comes from its resemblance to a mulberry, since it really looks like **a collection of spherical cells**.
- **How a blastocyst is engendered**
- On the 4th day after insemination the outermost cells of the morula that are still enclosed within the pellucid zone begin to join up with each other (so-called compaction). An epithelial cellular layer forms, thicker towards the outside, and its cells flatten out and become smaller. The cells contact one another by means of tight junctions and gap junctions. A cavity forms in the interior of the blastocyst into which fluid flows (the so-called blastocyst cavity). The two to four innermost cells of the preceding morula develop into the so-called inner cell mass of the blastocyst. The actual embryo will develop solely from these cells (embryoblast). These cells are concentrated at one pole, the embryonic pole of the blastocyst. What has thus been formed is an outer cell mass (the trophoblast), consisting of many flat cells, and the embryoblast, formed from just a few rounded cells. The ratio between the number of embryoblast cells to those making up the trophoblast amounts to roughly 1:10. From the trophoblast the infantile part of the placenta and the fetal membranes will arise.
- **The emergence of the blastocyst (hatching)**
- Around the end of the fifth day the embryo frees itself from the enveloping pellucid zone. Through a series of expansion-contraction cycles the embryo bursts the covering. This is supported by enzymes that dissolve the pellucid zone at the abembryonic pole. The rhythmic expansions and contractions result in the embryo bulging out of and emerging from the rigid envelope. This "first birth" is called hatching.
- **The polarity of the embryo**
- The polarity of the embryo is seen in the forming of **embryonic** and **abembryonalic** poles. This is obvious when observing a blastocyst where an inner cell mass

(**ICM**) has formed. This is **concentrated at one pole** in the interior of the hollow sphere and is made from blastomeres.

- **The migration of the embryo through the fallopian tube**
- Implantation
- The implantation (nidation) of the blastocyst in the uterine endometrium, **begins** between the **6th and 7th day** following the fertilization and ends around the 12th day with the formation of the primitive utero-placental circulation. A basic developmental stage is involved here that is absolutely necessary for the survival of the nutrient-poor blastocyst (the oocyte has no yolk). The implantation of the human embryo is **interstitial**, whereby the blastocyst is taken up in the endometrium and completely embedded there. This extremely important stage not only allows separation of the embryo from the outer world, it also makes an intimate contact with the maternal organism possible, guaranteeing the delivery of nutrients that are indispensable for further development.
- Site of implantation
- The main functions of the uterus are **receiving the embryo**, sheltering the **fetus** during pregnancy and delivering the newborn at term. The uterus is a pear-shaped, muscular, hollow organ with a triple-layered wall: an outer tunica serosa, the **perimetrium**, a thick tunica muscularis, the **myometrium**, and an inner tunica mucosa, the **endometrium**. The endometrium is the layer in which the implantation takes place. This layer experiences morphologic and functional changes that are closely associated with the cyclic release of **sexual hormones**. In absence of periodic hormonal influence, i.e., before puberty or following menopause, this tissue has a **constant morphology and thickness**. Following the menarche the uterus prepares itself in each menstrual cycle for receiving a fertilized oocyte. This takes place via the proliferation and differentiation of the endometrium. If the implantation does not occur, the functional (outermost) layer of the endometrium is shed and expulsed, leading to menstruation.
- The endometrium consists of a single-layered prismatic epithelium with or without cilia (depending on how far along the menstruation cycle is) and its basal lamina, uterine glands, and a specialized, cell-rich connective tissue (stroma) containing a rich supply of blood vessels. One recognizes the spiral arteries (end branches of the uterine arteries as well as a venous outflow system.
- **Endometrial functions**
- Cyclic alterations of the uterine glands and blood vessels during the course of the menstruation, as preparation for the implantation
- Location where the blastocyst is normally implanted

- Location where the placenta develops
- **Normal implantation zone**
- In order that implantation can take its normal course, the **blastocysts** and the **uterine mucosa must be able to interact**. These two, independent structures must, therefore, undergo **synchronous** changes. The implantation normally takes place in the **superior and posterior walls of the uterine body** (corpus uteri) in the functional layer of the endometrium during the secretory phase of the cycle.
- **Stages**
- Adplantation of the blastocyst on the endometrium
- Adhesion of the blastocyst to the endometrium
- Invasion of the trophoblast and embedding
- **Invasion of the trophoblast and embedding**
- The trophoblast differentiates into **two different cell masses**, shortly before it comes into contact with the endometrium:
- the outer syncytiotrophoblast (ST)
- the inner cytotrophoblast (CT)
- The **cytotrophoblast**, deep inside, consists in an inner irregular layer of ovoid, single-nucleus cells. This is also where **intensive mitotic activity** takes place.In the periphery the **syncytiotrophoblast** forms a **syncytium**, i.e., a multi-nucleic layer without cell boundaries that arises from the fusion of cytotrophoblast cells. The syncytiotrophoblast produces **lytic enzymes** and secretes factors that cause apoptosis of the endometrial epithelial cells. The syncytiotrophoblast also crosses the basal lamina and penetrates into the stroma that lies below, eroding the wall of capillaries. With the implantation of the blastocyst in the endometrium the syncytiotrophoblast develops quickly and will entirely surround the embryo as soon as it has completely embedded itself in the endometrium.
- The uterine mucosa reacts to the implantation by the **decidual reaction**. The syncytiotrophoblast cells phagocytize the apoptotic decidual cells of the endometrium and resorb the proteins, sugars and lipids that have been formed there. They also erode the canals of the endometrial glands and the capillaries of the stroma.
- **In the middle of the 2nd week** extracellular vacuoles appear in the ST. They join together forming **lacunae**. Initially these lacunae are filled with tissue fluids and uterine secretions. Following the erosion of the maternal capillaries, their blood fills the lacunae that later develop further into intervillous spaces. The **invasive growth of the ST** ceases in the **zona compacta** of the endometrium. At around the 13th day the **primitive utero-placental circulatory system** arises.

- At the end of the 2nd week, when implantation has ended, the embryonic bud consists schematically of two hemispheric cavities that lie on one another: the **amniotic cavity** (dorsal) and the **umbilical vesicle (primory yolk sac)** (ventral).

  The floor of the amniotic cavity is formed by the **epiblast**, and the roof of the umbilical vesicle by the **hypoblast**. These two layers, which lie on one another, form the embryo or the double-layered embryonic disc.

2 семестр

1. **Introduction**

At the light microscope level, the **cells** and **extracellular components** of the various organs of the body exhibit a recognizable and often distinctive pattern of organization. This organized arrangement reflects the cooperative effort of cells performing a particular function. Therefore, an organized aggregation of cells that function in a collective manner is called a **tissue.**

Despite their disparate structure and physiologic properties, all organs are made up of only four basic tissue types.

Introduction

Epithelium (epithelial tissue) covers body surfaces, lines body cavities, and forms glands.

Connective tissue underlies or supports the other three basic tissues, both structurally and functionally.

Muscle tissue is made up of contractile cells and is responsible for movement.

Nerve tissue receives, transmits, and integrates information from outside and inside the body to control the activities of the body.

Epithelial tissue

Epithelial tissue

Epithelium is characterized by close cell apposition and presence at a free surface.

Epithelial cells, whether arranged in a single layer or in multiple layers, are always contiguous with one another. In addition, they are usually joined by specialized cell-to-cell junctions that create a barrier between the free surface and the adjacent connective tissue. The **intercellular space** between epithelial cells is minimal and devoid of any structure except where junctional attachments are present.

Classifications of epithelium are usually based on the shape of the cells and the number of cell layers rather than on function.

Muscle tissue

Muscle tissue

Muscle tissue is categorized on the basis of a functional property, the ability of its cells to contract.

Muscle cells are characterized by large amounts of the contractile proteins actin and myosin in their cytoplasm and by their particular cellular arrangement in the tissue. To function efficiently to effect movement, most muscle cells are aggregated into distinct bundles that are easily distinguished from the surrounding tissue.

Muscle cells are typically elongated and oriented with their long axes in the same direction. The arrangement of nuclei is also consistent with the parallel orientation of muscle cells.

Muscle tissue

The bulk of the cytoplasm consists of the contractile proteins actin and myosin, which form thin and thick myofilaments, respectively. **Skeletal muscle** and **cardiac muscle** cells exhibit cross-striations that are produced largely by the specific arrangement of myofilaments. **Smooth muscle** cells do not exhibit cross-striations because the myofilaments do not achieve the same degree of order in their arrangement.

Nervous tissue

Nervous tissue

Nerve tissue consists of nerve cells (neurons) and associated supporting cells of several types. Although all cells exhibit electrical properties, nerve cells or **neurons** are highly specialized to transmit electrical impulses from one site in the body to another; they are also specialized to integrate those impulses. Nerve cells receive and process information from the external and internal environment and may have specific sensory receptors and sensory organs to accomplish this function. Neurons are characterized by two different types of processes through which they interact with other nerve cells and with cells of epithelia and muscle. A single, long **axon** (sometimes longer than a meter) carries impulses away from the **cell body**, which contains the neuron's nucleus. Multiple **dendrites** receive impulses and carry them toward the cell body. (In histologic sections, it is usually impossible to differentiate axons and dendrites because they have the same structural appearance.) The axon terminates at a neuronal junction called a **synapse** at which electrical impulses are transferred from one cell to the next by secretion of **neuromediators**.

Connective tissue

Connective tissue

Connective tissue is characterized on the basis of its extracellular matrix.

Unlike epithelial cells, connective tissue cells are conspicuously separated from one another. The intervening spaces are occupied by material produced by the cells. This extracellular material is called the **extracellular matrix**. The nature of the cells and matrix varies according to the

function of the tissue. Thus, classification of connective tissue takes into account not only the cells but also the composition and organization of the extracellular matrix.

2. Epithelial tissue

Introduction

Epithelium is an avascular tissue composed of cells that cover the **exterior body surfaces** and line **internal closed cavities** (including the vascular system) and **body tubes** that communicate with the exterior (the alimentary, respiratory, and genitourinary tracts). Epithelium also forms the **secretory portion (parenchyma) of glands** and their ducts. In addition, specialized epithelial cells function as **receptors for the special senses** (smell, taste, hearing, and vision).

Functions

Protection

Absorption

Secretion

Exchange

Characteristic features of epithelial tissue

Very cellular with little intercellular space (20 nm)

Usually avascular

Cells rest on a basement membrane

Cells show polarity

Cells may display surface modifications

Cell polarity

Epithelial cells exhibit distinct **polarity**. They have an **apical domain**, a **lateral domain**, and a **basal domain**.

Specializations of the Basal Surface (Basal Domain)

Epithelial cells rest on a **basement membrane**, consisting of a **basal lamina** and a **reticular lamina**, which provide an underlying foundation for the cells. The term “basement membrane” is used in light microscopy observation, although the basement membrane is often difficult to visualize with the light microscope. The terms “basal lamina” and “reticular lamina” are ultrastructural terms and refer to features that require electron microscopy to be seen. Epithelial cells produce their own basement membrane. Cells are anchored to the basement membrane by **hemidesmosomes**, junctions that connect the cells to the underlying basement membrane. **Basal plasma membrane enfolding** may also be present in some

epithelial cells (e.g., salivary gland excretory duct epithelium). This is a corrugation of the cell membrane in the basal (and sometimes lateral) regions of the cell, which increases cell surface area and is involved in ion and fluid transport. There are many **mitochondria** in the vicinity of the plasma membrane enfolding. These produce adenosine triphosphate (ATP) for active transport. The combination of the plasma membrane enfolding and the concentration of mitochondria result in a striated appearance in some of the epithelial cells.

THE LATERAL DOMAIN AND ITS SPECIALIZATIONS IN CELL-TO-CELL ADHESION

The **lateral surface** of epithelial cells contains cell junctions and cell adhesion molecules that are responsible for the cohesive nature of epithelial tissue. Intercellular connections of the epithelial cells include **tight junctions (zonula occludens)**, that completely surround the apical cell borders to seal the underlying intercellular clefts from the outside environment; **adhering junctions (zonula adherens)**, found just beneath the tight junction, also forming a band-like junction surrounding the entire cell and serving to attach adjacent cells; **desmosomes (macula adherens)**, located beneath the adhering junctions, also assist in cell to cell attachment (the **junctional complex** is composed of tight junction, adhering junction, and desmosome); and **gap junctions**, which are **communicating junctions**, provide a low-resistance channel to permit passage of ions and small molecules between adjacent cells. Gap junctions are present not only in epithelial tissues, but they can also be found in many other tissues (smooth muscle, cardiac muscle, and nerve tissues) in the body. However, gap junctions are not present in skeletal muscle, blood cells, and spermatozoa.

Classification of Epithelia

By number of layers:

1) Unilayered, or simple

2) Multilayered, or stratified

By shape of the cells:

1) squamous

2) Cuboidal

3) Columnar

4) Pseudostratified

5) Transitional

Classification of Epithelial Tissues

Epithelium can be classified as **simple** or **stratified** based on the number of layers of cells. If there is a single layer of cells, it is referred to as *simple* epithelium. If there are two or more layers of cells, it is considered to be *stratified* epithelium. Epithelium is also classified

according to the shape of the cells in the most superficial layer. If the surface cells are flattened in shape, it is called **squamous epithelium**. If surface cells are cuboidal in shape, it is called **cuboidal epithelium**. If the surface cells are tall, with their height much greater than their width, it is called **columnar epithelium**. If the surface cells change shape in response to stretching and relaxing, it is called **transitional epithelium** (**urothelium**). As described below, these terms may be variously combined to designate layers of cells and shapes forming the superficial layer of the epithelium. In some cases, the height of an epithelial cell represents the level of metabolic activity. For example, epithelial cells lining the thyroid follicle usually exhibit as simple cuboidal epithelium. However, when the follicle cells are in a high metabolic state, they form a simple columnar epithelium. By contrast, when the follicle cells are in a low metabolic state, they form a simple squamous epithelium.

SIMPLE SQUAMOUS EPITHELIUM

SIMPLE CUBOIDAL EPITHELIUM

SIMPLE COLUMNAR EPITHELIUM

PSEUDOSTRATIFIED COLUMNAR EPITHELIUM

STRATIFIED SQUAMOUS EPITHELIUM

STRATIFIED CUBOIDAL EPITHELIUM

STRATIFIED COLUMNAR EPITHELIUM

TRANSITIONAL EPITHELIUM

3. GLANDS

Introduction

Typically, glands are classified into two major groups according to how their products are released

Exocrine glands secrete their products onto a surface directly or through epithelial ducts or tubes that are connected to a surface. Ducts may convey the secreted material in an unaltered form or may modify the secretion by concentrating it or adding or reabsorbing constituent substances.

Endocrine glands lack a duct system. They secrete their products into the connective tissue, from which they enter the bloodstream to reach their target cells. The products of endocrine glands are called **hormones**.

In some epithelia, individual cells secrete substances that do not reach the bloodstream but rather affect other nearby cells. Such secretory activity is referred to as **paracrine signaling**. Cells that produce paracrine substances (paracrines) release them into the subjacent extracellular matrix. The paracrine secretion has very limited signaling range; it reaches the

target cells by diffusion. For example, the endothelial cells of the blood vessels impact the vascular smooth muscle cells by releasing multiple factors that cause either contraction or relaxation of the vascular wall.

Exocrine glands are classified as either unicellular or multicellular.

Unicellular glands are the simplest in structure. In unicellular exocrine glands, the secretory component consists of single cells distributed among other nonsecretory cells. A typical example is the **goblet cell**, a mucus-secreting cell positioned among other columnar cells. Goblet cells are located in the surface lining and glands of the intestines and in certain passages of the respiratory tract.

Multicellular glands are composed of more than one cell. They exhibit varying degrees of complexity. Their structural organization allows subclassification according to the arrangement of the secretory cells (parenchyma) and the presence or absence of branching of the duct elements. The simplest arrangement of a multicellular gland is a cellular sheet in which each surface cell is a secretory cell. For example, the lining of the stomach and its gastric pits is a sheet of mucus-secreting cells

Other multicellular glands typically form tubular invaginations from the surface. The end pieces of the gland contain the secretory cells; the portion of the gland connecting the secretory cells to the surface serves as a duct. If the duct is unbranched, the gland is called **simple**; if the duct is branched, it is called **compound**. If the secretory portion is shaped like a tube, the gland is **tubular**; if it is shaped like a flask or grape, the gland is **alveolar** or **acinar**; if the tube ends in a sac-like dilation, the gland is **tubuloalveolar**. Tubular secretory portions may be straight, branched, or coiled; alveolar portions may be single or branched. Various combinations of duct and secretory portion shapes are found in the body. Classification and description of exocrine glands may be found in the next slide.

Cells of exocrine glands exhibit different mechanisms of secretion.

The cells of exocrine glands have three basic release mechanisms for secretory products

Merocrine secretion. This secretory product is delivered in **membrane-bounded vesicles** to the apical surface of the cell. Here vesicles fuse with the plasma membrane and extrude their contents by exocytosis. This is the most common mechanism of secretion and is found, for example, in pancreatic acinar cells.

Apocrine secretion. The secretory product is released in the apical portion of the cell, surrounded by a thin layer of cytoplasm within an envelope of plasma membrane. This mechanism of secretion is found in the **lactating mammary gland**, where it is responsible for releasing large lipid droplets into the milk.

Holocrine secretion. The secretory product accumulates within the maturing cell, which simultaneously undergoes destruction orchestrated by **programmed cell death** pathways. Both secretory products and cell debris are discharged into the lumen of the gland. This mechanism is found in **sebaceous glands of skin** and the **tarsal (Meibomian) glands of the eyelid**.

4. BLOOD

Functions

Blood's many functions include:

delivery of nutrients and oxygen directly or indirectly to cells,

transport of wastes and carbon dioxide away from cells,

delivery of hormones and other regulatory substances to and from cells and tissues,

maintenance of homeostasis by acting as a buffer and participating in coagulation and thermoregulation, and

transport of humoral agents and cells of the immune system that protect the body from pathogenic agents, foreign proteins, and transformed cells (i.e., cancer cells).

Consistence

Blood consists of cells and their derivatives and a protein-rich fluid called plasma.

Blood cells and their derivatives include:

erythrocytes, also called **red blood cells (RBCs)**;

leukocytes, also known as **white blood cells (WBCs)**; and

thrombocytes, also termed **platelets**.

Plasma is the liquid extracellular material that imparts fluid properties to blood. The relative volume of cells and plasma in whole blood is approximately 45% and 55%, respectively. The volume of packed erythrocytes in a sample of blood is called the **hematocrit (HCT)** or **packed cell volume (PCV)**. The hematocrit is measured by centrifuging a blood sample to which anticoagulants have been added, and then calculating the percentage of the centrifuge tube volume occupied by the erythrocytes compared with that of the whole blood

Plasma proteins consist primarily of albumin, globulins, and fibrinogen.

Albumin is the main protein constituent of the plasma, accounting for approximately half of the total plasma proteins. It is the smallest plasma protein (about 70 kDa) and is made in the liver. Albumin is responsible for exerting the concentration gradient between blood and extracellular tissue fluid. This major osmotic pressure on the blood vessel wall, called the **colloid osmotic pressure**, maintains the correct proportion of blood to tissue fluid volume. If a significant amount of albumin leaks out of the blood vessels into the loose connective

tissue or is lost from the blood to urine in the kidneys, then the colloid osmotic pressure of the blood decreases, and fluid accumulates in the tissues. (This increase in tissue fluid is most readily noted by swelling of the ankles at the end of a day.) Albumin also acts as a carrier protein; it binds and transports hormones (thyroxine), metabolites (bilirubin), and drugs (barbiturates).

Globulins include the **immunoglobulins** (**- globulins**), the largest component of the globulin fraction, and **non-immune globulins** (**-globulin** and **-globulin**). The immunoglobulins are antibodies, a class of functional immune system molecules secreted by plasma cells. **Non-immune globulins** are secreted by the liver. They help maintain the osmotic pressure within the vascular system and also serve as carrier proteins for various substances such as copper (by ceruloplasmin), iron (by transferrin), and the protein **hemoglobin** (by haptoglobin). Non-immune globulins also include fibronectin, lipoproteins, coagulation factors, and other molecules that may exchange between the blood and the extravascular connective tissue.

Fibrinogen, the largest plasma protein (340 kDa), is made in the liver. In a series of cascade reactions with other coagulation factors, soluble fibrinogen is transformed into the insoluble protein **fibrin** (323 kDa). During conversion of fibrinogen to fibrin, fibrinogen chains are broken to produce fibrin monomers that rapidly polymerize to form long fibers. These fibers become cross-linked to form an impermeable net at the site of damaged blood vessels, thereby preventing further blood loss. With the exception of these large plasma proteins and regulatory substances, which are small proteins or polypeptides, most plasma constituents are small enough to pass through the blood vessel wall into the extracellular spaces of the adjacent connective tissue.

Plasma facts

Serum is the same as blood plasma except that clotting factors have been removed.

The interstitial fluid of connective tissues is derived from blood plasma.

Erythrocytes are anucleate, biconcave discs.

Erythrocytes or **red blood cells (RBCs)** are anucleate cells devoid of typical organelles. They function only within the bloodstream to bind oxygen for delivery to the tissues and, in exchange, bind carbon dioxide for removal from the tissues. Their shape is that of a biconcave disc with a **diameter of 7.8 m**, an edge thickness of 2.6 m, and a central thickness of 0.8 m. This shape maximizes the cell's surface area (140 m2), an important attribute in gas exchange. The life span of erythrocytes is approximately **120 days**. In a healthy individual, approximately 1% of erythrocytes are removed from circulation each day due to senescence (aging); however, bone marrow continuously produces new erythrocytes to replace those lost.

The majority of aged erythrocytes (90%) are phagocytosed by macrophages in the spleen, bone marrow, and liver.

The shape of the erythrocyte is maintained by a specialized cytoskeleton that provides the mechanical stability and flexibility necessary to withstand forces experienced during circulation.

Erythrocytes contain hemoglobin, a protein specialized for the transport of oxygen and carbon dioxide. Erythrocytes transport oxygen and carbon dioxide bound to the protein **hemoglobin** (68 kDa). The function of hemoglobin is to bind oxygen molecules in the lung (requiring high oxygen affinity) and then, after transporting it through the circulatory system, to unload oxygen in the tissues (requiring low oxygen affinity). A monomer of hemoglobin is similar in composition and structure to myoglobin, the oxygen-binding protein found in striated muscle. The disc shape of the erythrocyte facilitates gas exchange because more hemoglobin molecules are closer to the plasma membrane than they would be in a spherical cell. Thus, gases have less distance to diffuse within the cell to reach a binding site on the hemoglobin.

LEUKOCYTES

Leukocytes are subclassified into two general groups. The basis for this division is the presence or absence of prominent **specific granules** in the cytoplasm. As previously noted, cells containing specific granules are classified as **granulocytes** (neutrophils, eosinophils, and basophils), and cells that lack specific granules are classified as **agranulocytes** (lymphocytes and monocytes). However, both agranulocytes and granulocytes possess a small number of nonspecific **azurophilic granules**, which are lysosomes.

Neutrophils

Neutrophils are the most numerous WBCs as well as the most common granulocytes.

Neutrophils measure 10 to 12 m in diameter in blood smears and are obviously larger than erythrocytes. Although named for their lack of characteristic cytoplasmic staining, they are also readily identified by their multilobal nucleus; thus, they are also called **polymorphonuclear neutrophils** or *polymorphs*. Mature neutrophils possess two to four lobes of nuclear material joined by thinner nuclear strands. The arrangement is not static; rather, in living neutrophils, the lobes and connecting strands change their shape, position, and even number. The chromatin of the neutrophil has a characteristic arrangement. Wide regions of heterochromatin are located. chiefl y at the periphery of the nucleus in contact with the nuclear envelope. Regions of euchromatin are located primarily at the center of the nucleus with relatively smaller regions contacting the nuclear envelope. In women, the **Barr**

body (the condensed, single, inactive X chromosome) forms a drumstick-shaped appendage on one of the nuclear lobes.

Neutrophils are motile cells; they leave the circulation and migrate to their site of action in the connective tissue.

An important property of **neutrophils** and other leukocytes is their motility. Neutrophils are the most numerous of the first wave of cells to enter an area of tissue damage. Their migration is controlled by the expression of **adhesion molecules** on the neutrophil surface that interact with corresponding ligands on endothelial cells and are often involved in cell binding.

Phagocytosed bacteria are killed within phagolysosomes by the toxic reactive oxygen intermediates produced during respiratory burst.

Phagocytosed bacteria can also be killed by a diverse arsenal of oxygen-independent killing mechanisms utilizing bacteriolytic enzymes and antimicrobial peptides.

Inflammation and wound healing also involve monocytes, lymphocytes, eosinophils, basophils, and fibroblasts.

Eosinophils

Eosinophils are about the same size as neutrophils, and their nuclei are typically bilobed. As in neutrophils, the compact heterochromatin of eosinophils is chiefly adjacent to the nuclear envelope, whereas the euchromatin is located in the center of the nucleus.

Eosinophils are named for the large, eosinophilic, refractile granules in their cytoplasm.

The cytoplasm of eosinophils contains two types of granules: numerous, large, elongated specific granules and azurophilic granules (otherwise, the eosinophil contains only a sparse representation of membranous organelles).

Azurophilic granules (primary granules) are lysosomes. They contain a variety of the usual **lysosomal acid hydrolases** and other hydrolytic enzymes that function in the destruction of parasites and hydrolysis of antigen–antibody complexes internalized by the eosinophil.

Specific granules (secondary granules) of eosinophils contain a **crystalloid body** that is readily seen with the TEM, surrounded by a less electron-dense matrix. These crystalloid bodies are responsible for the refractivity of the granules in the light microscope. They contain four major proteins: an arginine-rich protein called **major basic protein (MBP)**, which accounts for the intense acidophilia of the granule; **eosinophil cationic protein (ECP)**; **eosinophil peroxidase (EPO)**; and **eosinophil-derived neurotoxin (EDN)**.

Eosinophils are associated with allergic reactions, parasitic infections, and chronic inflammation.

Eosinophils develop and mature in the bone marrow. Once released from the bone marrow, they circulate in peripheral blood and then migrate to the connective tissue. Eosinophils are activated by interactions with IgG, IgA, or secretory IgA antibodies.

Basophils

Basophils are about the same size as neutrophils and are so named because the numerous large granules in their cytoplasm stain with basic dyes.

Basophils are the least numerous of the WBCs, accounting for less than 0.5% of total leukocytes.

Often, several hundred WBCs must be examined in a blood smear before one **basophil** is found.

The basophil cytoplasm contains two types of granules: specific granules, which are larger than the specific granules of the neutrophil, and nonspecific azurophilic granules.

Azurophilic granules (primary granules) are the lysosomes of basophils and contain a variety of lysosomal acid hydrolases that are similar to those in other leukocytes.

specific granules (secondary granules) exhibit a grainy texture and myelin figures when viewed with the TEM. These granules contain a variety of substances, namely, heparin, histamine, heparan sulfate, leukotrienes, IL-4, and IL-13. **Heparin**, a sulfated glycosaminoglycan, is an anticoagulant. **Histamine** and **heparan sulfate** are vasoactive agents that among other actions cause dilation of small blood vessels. **Leukotrienes** are modified lipids that trigger prolonged constriction of smooth muscles in the pulmonary airways. **Interleukin-4 (IL-4)** and **interleukin-13 (IL-13)** promote synthesis of IgE antibodies.

Basophils are functionally related to, but not identical with, mast cells of the connective tissue.

Both mast cells and basophils bind an antibody secreted by plasma cells, **IgE**, through high-affinity Fc receptors expressed on their cell surface. The subsequent exposure to, and reaction with, the antigen (allergen) specific for IgE triggers the activation of basophils and mast cells and the release of vasoactive agents from cell granules. These substances are responsible for the severe vascular disturbances associated with **hypersensitivity reactions** and **anaphylaxis**.

Lymphocytes

Lymphocytes are the main functional cells of the lymphatic or immune system.

Lymphocytes are the most common agranulocytes and account for about 30% of the total blood leukocytes. In understanding the function of the lymphocytes, one must realize that most lymphocytes found in blood or lymph represent recirculating **immunocompetent cells**

(i.e., cells that have developed the capacity to recognize and respond to antigens and are in transit from one lymphatic tissue to another). Therefore, lymphocytes are different in several aspects from other leukocytes:

Lymphocytes are not terminally differentiated cells. When stimulated, lymphocytes are capable of undergoing divisions and differentiations into other types of effector cells.

Lymphocytes can exit from the lumen of blood vessels into tissues and subsequently can recirculate back into blood vessels.

Despite the fact that common lymphoid progenitor cells originate in the bone marrow, lymphocytes are capable of developing outside the bone marrow in tissues associated with the immune system

Three functionally distinct types of lymphocytes are present in the body: T lymphocytes, B lymphocytes, and NK cells.

The characterization of lymphocyte types is based on their function, not on their size or morphology.

T lymphocytes (T cells) are so named because they undergo differentiation in the thymus.

B lymphocytes (B cells) are so named because they were first recognized as a separate population in the bursa of Fabricius in birds or bursa-equivalent organs (e.g., bone marrow) in mammals.

Natural killer (NK) cells develop from the same precursor cell as B and T cells and are so named because they are programmed to kill certain types of transformed cells.

Monocytes

Monocytes are the precursors of the cells of the mononuclear phagocytotic system.

Monocytes are the largest of the WBCs in a blood smear (average diameter, 18 m). They travel from the bone marrow to the body tissues, where they differentiate into the various phagocytes of the mononuclear phagocytotic system—that is, connective tissue macrophages, osteoclasts, alveolar macrophages, perisinusoidal macrophages in the liver (Kupffer cells), and macrophages of lymph nodes, spleen, and bone marrow among others. Monocytes remain in the blood for only about 3 days.

Monocytes transform into macrophages, which function as antigen-presenting cells in the immune system.

During inflammation, the monocyte leaves the blood vessel at the site of inflammation, transforms into a tissue macrophage, and phagocytoses bacteria, other cells, and tissue debris. The monocyte–macrophage is an **antigen- presenting cell** and plays an important role in immune responses.

THROMBOCYTES

Thrombocytes are small, membrane-bounded, anucleate cytoplasmic fragments derived from megakaryocytes.

Thrombocytes (platelets) are derived from large polyploidy cells (cells whose nuclei contain multiple sets of chromosomes) in the bone marrow called **megakaryocytes**. In platelet formation, small bits of cytoplasm are separated from the peripheral regions of the megakaryocyte by extensive **platelet demarcation channels**.

The membrane that lines these channels arises by invagination of the plasma membrane; therefore, the channels are in continuity with the extracellular space. The continued development and fusion of the platelet demarcation membranes result in the complete partitioning of cytoplasmic fragments to form individual platelets. After entry into the vascular system from the bone marrow, the platelets circulate as discoid structures about 2 to 3 m in diameter. Their life span is about 10 days.

5. Blood formation (4 h)

Hemopoiesis (hematopoiesis) includes bothe**rythropoiesis** and **leukopoiesis** (development of red and white blood cells, respectively), as well as **thrombopoiesis** (development of platelets). Blood cells have a limited life span; they are continuously produced and destroyed. the ultimate objective of hemopoiesis is to maintain a constant level of the different cell types found in the peripheral blood. Both the human erythrocyte (life span of 120 days) and the platelet (life span of 10 days) spend their entire life in the circulating blood. Leukocytes, however, migrate out of the circulation shortly after entering it from the bone marrow and spend most of their variable life spans (and perform all of their functions) in the tissues.

In the adult, erythrocytes, granulocytes, monocytes, and platelets are formed in the **red bone marrow**; lymphocytes are also formed in the red bone marrow and in the lymphatic tissues.

Hemopoiesis is initiated in early embryonic development.

During fetal life, botherythrocytes and leukocytes are formed in several organs before the differentiation of the bone marrow. the first or **yolk-sac phase** of hemopoiesis begins in the third week of gestation and is characterized by the formation of “blood islands” in the wall of the yolk sac of the embryo. In the second, or **hepatic phase**, early in fetal development, hemopoietic centers appear in the liver. Blood cell formation in these sites is largely limited to erythroid cells, although some leukopoiesis occurs in the liver. the liver is the major blood-forming organ in the fetus during the second trimester. the third or **bone marrow phase** of fetal hemopoiesis and leukopoiesis involves the bone marrow (and other lymphatic tissues)

and begins during the second trimester of pregnancy. After birth, hemopoiesis takes place only in the red bone marrow and some lymphatic tissues, as in the adult. The precursors of both the blood cells and germ cells arise in the yolk sac.

Monophyletic Theory of Hemopoiesis

According to the monophyletic theory of hemopoiesis, blood cells are derived from a common hemopoietic stem cell.

Considerable circumstantial evidence has for many years supported the **monophyletic theory** of hemopoiesis in which all blood cells arise from a common stem cell. Decisive evidence for the validity of the monophyletic theory has come with the isolation and demonstration of the **hemopoietic stem cell (HSC)**. the hemopoietic stem cell, also known as *pluripotential stem cell* (PPSC), is capable not only of differentiating into all the blood cell lineages but also of self-renewal (i.e., the pool of stem cells is self-sustaining). Recent studies indicate that HSCs also have the potential to differentiate into multiple non–blood cell lineages and contribute to the cellular regeneration of various tissues and multiple organs. During embryonic development, HSCs are present in the circulation and undergo tissue-specific differentiation in different organs. Human HSCs have been isolated from umbilical cord blood, fetal liver, and fetal and adult bone marrow. In the adult, HSCs have the potential to repair tissues under pathologic conditions (e.g., ischemic injury, organ failure).

A hemopoietic stem cell (HSC) in the bone marrow gives rise to multiple colonies of progenitor stem cells.

In the bone marrow, descendants of the HSC differentiate into two major colonies of multipotential progenitor cells: the common myeloid progenitor (CMP) cells and the common lymphoid progenitor (CLP) cells. Ultimately, **common myeloid progenitor (CMP) cells**, which were previously called *colony-forming units– granulocyte, erythrocyte, monocyte, megakaryocyte* (CFU-GEMM), differentiate into specific **lineage-restricted progenitors.** These include the following:

Megakaryocyte/erythrocyte progenitor (MEP) cells

Granulocyte/monocyte progenitor (GMP *or* CFUGM) cells

Common lymphoid progenitor (CLP) cells

The **common lymphoid progenitor (CLP) cells** are capable of differentiating into T cells, B cells, and natural killer (NK) cells. these multipotential CLP cells previously have been called *colony-forming units–lymphoid* (CFU-L). The NK cells are thought to be the prototype of T cells; they both possess similar capability to destroy other cells.

Development of Erythrocytes (Erythropoiesis)

The first microscopically recognizable precursor cell in erythropoiesis is called the *proerythroblast.* the **proerythroblast** is a relatively large cell measuring 12 to 20 m in diameter. It contains a large spherical nucleus with one or two visible nucleoli. the cytoplasm shows mild basophilia because of the presence of free ribosomes. Although recognizable, the proerythroblast is not easily identified in routine bone marrow smears.

The basophilic erythroblast is smaller than the proerythroblast, from which it arises by mitotic division. the nucleus of the **basophilic erythroblast** is smaller (10 to 16 m in diameter) and progressively more heterochromatic with repeated mitoses. the cytoplasm shows strong basophilia because of the large number of free ribosomes (polyribosomes) that synthesize hemoglobin. the accumulation of hemoglobin in the cell gradually changes the staining reaction of the cytoplasm so that it begins to stain witheosin. At the stage when the cytoplasm displays both acidophilia, because of the staining of hemoglobin, and basophilia, because of the staining of the ribosomes, the cell is called a **polychromatophilic erythroblast**.

Development of Erythrocytes (Erythropoiesis)

the staining reactions of the **polychromatophilic erythroblast** may blend to give an overall gray or lilac color to the cytoplasm, or distinct pink (acidophilic) and purple (basophilic) regions may be resolved in the cytoplasm. the nucleus of the cell is smaller than that of the basophilic erythroblast, and coarse heterochromatin granules form a checkerboard pattern that helps identify this cell type.

The orthochromatophilic erythroblast is recognized by its increased acidophilic cytoplasm and dense nucleus.

At this stage, the orthochromatophilic erythroblast is no longer capable of division.

Development of Erythrocytes (Erythropoiesis)

The polychromatophilic erythrocyte has extruded its nucleus.

Polychromatophilic erythrocytes are also (and more commonly) called **reticulocytes**. In normal blood, reticulocytes constitute about 1% to 2% of the total erythrocyte count. However, if increased numbers of erythrocytes enter the bloodstream (as during increased erythropoiesis to compensate for blood loss), the number of reticulocytes increases.

Mitoses occur in proerythroblasts, basophilic erythroblasts, and polychromatophilic erythroblasts.

At each of these stages of development, the erythroblast divides several times. It takes about a week for the progeny of a newly formed basophilic erythroblast to reach the circulation. Nearly all erythrocytes are released into the circulation as soon as they are formed; bone marrow is not a storage site for erythrocytes. Erythrocyte formation and release are regulated

by **erythropoietin**, a 34 kDa glycoprotein hormone synthesized and secreted by the kidney in response to decreased blood oxygen concentration.

Hemoglobin recycling

Erythrocytes have a life span of about 120 days in humans. When erythrocytes are about **4 months (120 days) old**, they become senescent. the macrophage system of the spleen, bone marrow, and liver phagocytoses and degrades the senescent erythrocytes. the **heme** and **globin** dissociate, and the globin is hydrolyzed to amino acids, which enter the metabolic pool for reuse. the iron on the heme is released, enters the iron-storage pool in the spleen in the form of **hemosiderin** or **ferritin**, and is stored for reuse in hemoglobin synthesis. the rest of the heme moiety of the hemoglobin molecule is partially degraded to **bilirubin**, bound to albumin, released into the bloodstream, and transported to the liver, where it is conjugated and excreted via the gallbladder as the **bilirubin glucuronide** of bile.

Development of Thrombocytes (Thrombopoiesis)

Each day, bone marrow of a healthy adult produces about $1x10^{11}$ platelets, a number that can increase 10-fold in time of increased demand. The thrombocytopoiesis from the bone marrow progenitors is a complex process of cell divisions and differentiation that requires the support of interleukins, colony-stimulating factors, and hormones.

Thrombocytes (platelets) develop from a bipotent megakaryocyte/ erythrocyte progenitor (MEP) cell that differentiates into a megakaryocyte-committed progenitor (MKP) cell and finally into a megakaryocyte.

Development of Thrombocytes (Thrombopoiesis)

Further development proceeds toward a unipotent **megakaryocyte-committed progenitor (MKP) cell** (or CFU-Meg), which further develops into the **megakaryoblast**. the megakaryoblast that develops from this MKP is a large cell (about 30 m in diameter) with a nonlobed nucleus. No evidence of platelet formation is seen at this stage. Successive **endomitoses** occur in the megakaryoblast (i.e., chromosomes replicate), but neither karyokinesis nor cytokinesis occurs. Under stimulation by **thrombopoietin**, a 30 kDa glycoprotein hormone produced by liver and kidney, ploidy increases from 8*n* to 64*n* before chromosomal replication ceases. the cell then becomes a platelet-producing megakaryocyte, a cell measuring 50 to 70 m in diameter with a complex multilobed nucleus and scattered azurophilic granules. Both the nucleus and the cell increase in size in proportion to the ploidy of the cell. With the TEM, multiple centrioles and multiple Golgi apparatuses are also seen in these cells.

Development of Granulocytes (Granulopoiesis)

Granulocytes originate from the multipotential **common myeloid progenitor (CMP)** stem cell, which differentiates into **granulocyte/monocyte progenitors (GMPs)** under the influence of cytokines such as GM-CSF, granulocyte colony stimulating factor (G-CSF), and IL-3. GM-CSF is a cytokine secreted by endothelial cells, T cells, macrophages, mast cells, and fi broblasts. It stimulates GMP cells to produce granulocytes (neutrophils, eosinophils, and basophils) and monocytes. the **neutrophil progenitor (NoP)** undergoes six morphologically identifi able stages in the process of maturation: myeloblast, promyelocyte, myelocyte, metamyelocyte, band (immature) cell, and mature neutrophil. Eosinophils and basophils undergo a morphologic maturation similar to that of neutrophils. GMP cells, when induced by GM-CSF, IL-3, and IL-5, differentiate to **eosinophil progenitors (EoPs)** and eventually mature to eosinophils. Lack of IL-5 causes the GMP cells to differentiate into **basophil progenitors (BaPs)**, which produce basophils. One cannot differentiate eosinophilic or basophilic precursors from neutrophilic precursors morphologically in the light microscope until the cells reach the myelocytic stage when the specific granules appear.

Development of Granulocytes (Granulopoiesis)

Myeloblasts are the first recognizable cells that begin the process of granulopoiesis.

The myeloblast matures into a promyelocyte.

Promyelocytes are the only cells to produce azurophilic granules.

Recognition of the neutrophil, eosinophil, and basophil lines is possible only in the next stage—the myelocyte—when specific (secondary) and tertiary granules begin to form.

Myelocytes first exhibit specific granules.

Myelocytes continue to divide and give rise to metamyelocytes.

The metamyelocyte is the stage at which neutrophil, eosinophil, and basophil lines can be clearly identified by the presence of numerous specific granules.

Development of Granulocytes (Granulopoiesis)

In the neutrophil line, the band (stab) cell precedes development of the first distinct nuclear lobes.

the nucleus of the **band (stab) cell** is elongated and of nearly uniform width, giving it a horseshoe-like appearance. Nuclear constrictions then develop in the band neutrophil and become more prominent until two to four nuclear lobes are recognized; the cell is then considered a **mature neutrophil**, also called a **polymorphonuclear neutrophil** or **segmented neutrophil**. Although the percentage of band cells in the circulation is almost always low (0% to 3%), it may increase in acute or chronic inflammation and infection.

Development of Monocytes

The multipotential CMP stem cell also gives rise to the cells that develop along the monocyte–macrophage pathway.

Monocytes are produced in the bone marrow from a GMP stem cell that can mature into a monocyte or another of the three granulocytic cell lines. In addition, GMP gives rise to dendritic cells. the transformation of MoPs to monocytes takes about 55 hours, and the monocytes remain in the circulation for only about 16 hours before emigrating to the tissues where they differentiate under influence of both GM-CSF and M-CSF into tissue macrophages. their subsequent life span is not yet fully understood.

Development of Lymphocytes (Lymphopoiesis)

Development and lineage commitment of CLP cells depend on the expression of a variety of transcription factors.

Although lymphocytes continuously proliferate in the peripheral lymphatic organs, the bone marrow remains the primary site of lymphopoiesis in humans. Progeny of the **common lymphoid progenitor (CLP)** cells that express **GATA-3 transcription factor** are destined to become **T lymphocytes**. these cells that express GATA-3 leave the bone marrow as pre–T lymphocytes and travel to the thymus, where they complete their differentiation and thymic cell education. they then enter the circulation as long-lived, small T lymphocytes. Another transcription factor, **Pax5**, activates B-cell–specific genes in CLP cells destined to become **B lymphocytes**. In mammals, these cells originate in **bursa-equivalent organs** such as the bone marrow, gut-associated lymphatic tissue, and spleen. Although a number of transcription factors have been identified in the development of lymphoid cell lineages, little is known about factors that may influence development and lineage commitment of NK cells.

6. Connective Tissues (4 h)

Connective tissue is a type of tissue in which cells usually occupy less space than the extracellular material, and which serves in most cases to bind organs to each other (for example, the way a tendon connects muscle to bone) or to support and protect organs. Most cells of a connective tissue are not in direct contact with each other, but are well separated by extracellular material. Connective tissue is the most abundant, widely distributed, and histologically variable of the primary tissues. Mature connective tissues fall into three broad categories: *fibrous connective tissue, supportive connective tissue* (cartilage and bone), and *fluid connective tissue* (blood).

Functions

Binding of organs. Tendons bind muscle to bone, ligaments bind one bone to another, fat holds the kidneys and eyes in place, and fibrous tissue binds the skin to underlying muscle.

Support. Bones support the body and cartilage supports the ears, nose, trachea, and bronchi.

Physical protection. The cranium, ribs, and sternum protect delicate organs such as the brain, lungs, and heart; fatty cushions around the kidneys and eyes protect these organs.

Immune protection. Connective tissue cells attack foreign invaders, and connective tissue fiber forms a "battlefield" under the skin and mucous membranes where immune cells can be quickly mobilized against disease agents.

Movement. Bones provide the lever system for body movement, cartilages are involved in movement of the vocal cords, and cartilages on bone surfaces ease joint movements.

Storage. Fat is the body's major energy reserve; bone is a reservoir of calcium and phosphorus that can be drawn upon when needed.

Heat production. Metabolism of brown fat generates heat in infants and children.

Transport. Blood transports gases, nutrients, wastes, hormones, and blood cells.

EMBRYONIC CONNECTIVE TISSUE

Embryonic mesenchyme gives rise to the various connective tissues of the body.

Mesoderm, the middle embryonic germ layer, gives rise to almost all of the connective tissues of the body. An exception is the head region, where specific progenitor cells are derived from ectoderm by way of the neural crest cells. Through proliferation and migration of the mesodermal and specific neural crest cells, a **primitive connective tissue** referred to as **mesenchyme** (in the head region, it is sometimes called **ectomesenchyme**) is established in the early embryo. Maturation and proliferation of the mesenchyme give rise not only to the various connective tissues of the adult but also to muscle, the vascular and urogenital systems, and the serous membranes of the body cavities. The manner in which the mesenchymal cells proliferate and organize sets the stage for the kind of mature connective tissue that will form at any specific site.

Embryonic connective tissue is present in the embryo and within the umbilical cord.

Embryonic connective tissue is classified into two subtypes:

• **Mesenchyme** is primarily found in the embryo. It contains small, spindle-shaped cells of relatively uniform appearance. Processes extend from these cells and contact similar processes of neighboring cells, forming a three-dimensional cellular network. Gap junctions are present where the processes make contact. The extracellular space is occupied by a viscous ground substance. Collagen and reticular fibers are present; they are very fi ne and relatively sparse. The paucity of collagen fibers is consistent with the limited physical stress on the growing fetus.

• **Mucous connective tissue** is present in the umbilical cord. It consists of a specialized, almost gelatin-like ECM composed mainly of hyaluronan; its ground substance is frequently referred to as **Wharton's jelly**. The spindle-shaped cells are widely separated and appear much like fibroblasts in the near-term umbilical cord (e.g., the cytoplasmic processes are thin and difficult to visualize in routine hematoxylin and eosin [H&E] preparation). Wharton's jelly occupies large intercellular spaces located between thin, wispy collagen fibers. Some of the cells isolated from Wharton's jelly express significant amounts of mesenchymal stem cell markers and have the ability to differentiate under adequate condition into

7. **Fibrous Connective Tissue (Connective Tissue proper)**

Connective tissue proper comprises a very diverse group of tissues, both functionally and structurally.

Structural functions of connective tissue proper:

Forms a portion of the wall of hollow organs and vessels and the stroma of solid organs

Forms the stroma of organs and subdivides organs into functional compartments

Provides padding between and around organs and other tissues

Provides anchorage and attachment (e.g., muscle insertions)

Provides a medium for nutrient and waste exchange

Lipid storage in adipocytes

Defense and immune surveillance function via lymphoid and phagocytic cells

All connective tissues are composed of two basic components, which vary widely among different types of connective tissue. The components of connective tissues are:

Cells (e.g., fibroblasts and macrophages)

Extracellular matrix

Fibers (e.g., collagen and elastic fibers)

Ground substance

Cells of Connective Tissue

Connective tissue cells can be subdivided into two major groups:

Resident cells are derived from mesenchyme and are continuously present in the tissue (e.g., fibroblasts and adipocytes).

Migratory cells enter and leave the blood stream to migrate through and function in connective tissues (e.g., neutrophils and macrophages [monocytes]).

Fibroblasts

Synthesize and maintain fibers and ground substance

Major resident cell in connective tissue proper

Active and inactive fibroblasts

Active fibroblast

Large, euchromatic, oval nucleus

Cytoplasm not usually visible but contains abundant rough endoplasmic reticulum and Golgi

Elongated, spindle-shaped cells

High synthetic activity

Inactive fibroblast

Small, heterochromatic, flattened nucleus

Reduced cytoplasm and organelles

Low synthetic activity

Macrophages

Derived from blood monocytes; monocytes enter connective tissue from the bloodstream and rapidly transform into macrophages that function in phagocytosis, antigen processing, and cytokine secretion.

Comprise the mononuclear phagocyte system of the body; include Kupffer cells in the liver, alveolar macrophages in the lung, microglia the central nervous system, Langerhan's cells in the skin, and osteoclasts in bone marrow

Macrophages

Structure

Heterochromatic, oval nucleus with an indentation in the nuclear envelope and marginated chromatin

Cytoplasm usually not visible unless it contains phagocytosed material

Mast cells

Mediate immediate hypersensitivity reaction and anaphylaxis by releasing immune modulators from cytoplasmic granules, in response to antigen binding with cell surface antibodies

Mast cells

Structure

Round to oval-shaped cells

Round, usually centrally located nucleus

Well-defined cytoplasm filled with secretory granules containing immune-modulatory compounds (e.g., histamine and heparin)

Plasma cells

Secrete antibodies to provide humoral immunity

Derived from B-lymphocytes

Structure

Oval-shaped cells

Round, eccentrically located nucleus with heterochromatin clumps frequently arranged like the numerals on a clock-face

Basophilic cytoplasm due to large amounts of rough endoplasmic reticulum

Well-developed Golgi complex appears as a distinct, unstained region in the cytoplasm near the nucleus and, for that reason, is often referred to as a "negative Golgi."

Adipose cells (adipocytes, fat cells)

Store lipids

Types

Yellow fat (unilocular)

Brown fat (multilocular)

Yellow fat (unilocular)

Each cell contains a single droplet of neutral fat (triglycerides) for energy storage and insulation.

Minimal cytoplasm, present as a rim around the lipid droplet

Flattened, heterochromatic, crescent-shaped nucleus that conforms to the contour of the lipid droplet

Can occur singly, in small clusters or forming a large mass, which is then referred to as adipose connective tissue

Brown fat (multilocular)

Cells contain numerous, small lipid droplets.

Large numbers of mitochondria

Present mostly during early postnatal life in humans, abundant in hibernating animals for heat production

White blood cells (WBCs, leukocytes)

These cells enter and leave the blood stream to migrate through, and function in, connective tissues. The most common WBCs encountered in connective tissue proper are lymphocytes, neutrophils, and eosinophils.

Lymphocytes (T and B lymphocytes)

Small spherical cells with sparse cytoplasm and a round heterochromatic nucleus, often with a small indentation B cells enter connective tissue where they transform into plasma cells and secrete antibodies. T cells are primarily located in lymphatic tissues and organs; however,

T cells can be present in connective tissue proper under certain circumstances (e.g., organ transplantation).

Neutrophils (polymorphonuclear leukocytes, PMNs)

Spherical cells with a heterochromatic nucleus with three to five lobes

Pale-staining cytoplasmic granules

Highly phagocytic cells that are attracted to sites of infection

Eosinophils

Spherical cells with a bilobed nucleus

Cytoplasmic granules stain intensely with eosin.

Modulate the inflammatory process

Extracellular Matrix. *Fibers*

Collagen fibers

Tropocollagen

Basic collagen molecule consisting of three alpha subunits intertwined in a triple helix; collagen types are distinguished by their subunit composition.

Produced by fibroblasts and other matrix-forming cells

Secreted into the matrix, where they spontaneously orient themselves into fibrils with a 64-nm repeating banding pattern

Major collagen types

Type I. Fibrils aggregate into fibers and fiber bundles; most widespread distribution; "interstitial collagen."

Type II. Fibrils do not form fibers; present in hyaline and elastic cartilages

Type III. Fibrils aggregate into fibers; present surrounding smooth muscle cells and nerve fibers; forms the stroma of lymphatic tissues and organs

Type IV. Chemically unique form of collagen that does not form fibrils; major component of the basal lamina

Elastic fibers

Composed primarily of elastin; produced by fibroblasts

Elastin forms the central amorphous core of the fiber, which is surrounded by microfibrils.

Unique chemical properties of elastin provide for elasticity.

Elastic fibers occur in nearly all connective tissues in varying amounts and are intermixed with collagen fibers. When present exclusively, they constitute elastic connective tissue.

Frequently difficult to differentiate from collagen with conventional stains

Reticular fibers

Collagen type III fibers

Highly glycosylated and stain with silver (argyrophilic)

When they are the major fiber fiber type (e.g., in the stroma of lymphoid organs), they constitute reticular connective tissue.

Ground substance

Functions

Forms a gel-like matrix of variable consistency in which cells and fibers are embedded

Provides a medium for passage of molecules and cells migrating through the tissue

Contains adhesive proteins that regulate cell movements

Components of ground substance

Tissue fluid. Contains salts, ions and soluble protein

Glycosaminoglycans (GAGs)

Long, unbranched polysaccharides composed of repeating disaccharide units, which are usually sulfated

Large negative charge of the sugars attracts cations, resulting in a high degree of hydration. The matrix formed ranges from a liquid passageway to a viscous shock absorber.

GAGs are generally attached to proteins to form *proteoglycans*.

Proteoglycan aggregate. Many proteoglycans are attached to hyaluronic acid, which is itself a glycosaminoglycan.

Adhesive glycoproteins. For example, fibronectin and laminin.

Classification of Connective Tissue

Connective Tissue Proper

Loose (areolar)

Dense

Loose (areolar) connective tissues

Highly cellular, numerous cell types present

Fewer and smaller caliber collagen fibers compared with dense

Abundant ground substance, allows for diffusion of nutrients and wastes

Highly vascularized

Provides padding between and around organs and tissues

Dense connective tissue

Fewer cells, mostly fibroblasts

Highly fibrous with larger caliber collagen fibers, provides strength

Minimal ground substance

Poorly vascularized

Types

Dense, irregular connective tissue. Fiber bundles arranged in an interlacing pattern; forms the capsule of organs and the dermis of the skin

Dense regular connective tissue. Parallel arrangement of fiber bundles; restricted to tendons and ligaments

Connective Tissues with Special Properties

Adipose connective tissue. Consists of accumulations of adipocytes that are partitioned into lobules by septa of connective tissue proper. Provides energy storage and insulation

Blood and hematopoietic (blood-forming) tissues

Elastic connective tissue. Regularly arranged elastic fibers or sheets (e.g., the vocal ligament)

Reticular connective tissue. A loosely arranged connective tissue whose fibers are reticular fibers. Forms the stroma of hematopoietic tissue (e.g., bone marrow) and lymphoid organs (e.g., lymph node and spleen).

Mucoid connective tissue. Embryonic connective tissue with abundant ground substance and delicate collagen fibers; present in the umbilical cord

Supportive Connective Tissues

Cartilage

Bone

8. Cartilage. Chondrogenesis

Composition is similar to that of all connective tissues:

Cells

Extracellular matrix consisting of fibers, ground substance, and tissue fluid

Cartilage is avascular and possesses no lymph vessels or nerves.

Types of cartilage

A. Hyaline. Provides nonrigid support

B. Elastic. Provides support with large amount of flexibility

C. Fibrocartilage. Provides strength under stress

Components of Cartilage

Perichondrium. Connective tissue surrounding cartilage tissue. Layers include:

Fibrous layer. Outer portion, composed of dense connective tissue, serves as a source of reserve cells for the chondrogenic layer.

Chondrogenic layer. Inner, more cellular portion contains chondroblasts and blends imperceptibly into cartilage tissue proper.

Cells

Chondroblasts

Lie on the surface of cartilage in the chondrogenic layer of perichondrium

Secrete extracellular matrix around themselves, thus becoming chondrocytes

Chondrocytes

Are chondroblasts that have surrounded themselves with matrix

Lie within cartilage in potential spaces called **lacunae**

Secrete and maintain extracellular matrix

Are frequently located in *isogenous groups*, a cluster of chondrocytes, resulting from the proliferation of a single chondrocyte

Extracellular matrix. Both flexible and noncompressible

Composition

Fibers. Collagen fibrils and fibers predominate in hyaline cartilage and fibrocartilage, respectively; elastic fibers predominate in elastic cartilage.

Ground substance. Tissue fluid surrounds proteoglycan aggregates bound to collagen fibers. Collectively, these form a firm gel, which resists compressive forces.

Subdivisions

Territorial matrix immediately surrounds chondrocytes. This matrix stains more intensely with hematoxylin due to the high concentration of proteoglycans.

Interterritorial matrix is the lighter-staining matrix outside the territorial matrix and between isogenous groups.

Growth of Cartilage

Cartilage is capable of two kinds of growth, appositional and interstitial.

With the onset of matrix secretion, cartilage growth continues via a combination of two processes:

appositional growth, the process that forms new cartilage at the surface of an existing cartilage; and

interstitial growth, the process that forms new cartilage within an existing cartilage mass.

Types of Cartilage: *Hyaline cartilage*

Is the most common cartilage type and is hyaline (glassy) in appearance

Contains collagen type II fibers that have the same refractive index as ground substance and, therefore, are not visible with the light microscope by conventional staining methods

Stains blue with conventional dyes, due to the relative abundance of its ground substance matrix

Possesses numerous isogenous groups

Types of Cartilage: *Hyaline cartilage*

Function and distribution. Forms most of the cartilages of the body, comprises the fetal skeleton, attaches ribs to the sternum, forms epiphyseal plates, and lines articular surfaces. (The lack of a perichondrium on the articular cartilages provides a smooth, glassy articular surface.)

Clinical Correlation: Osteoarthritis

Osteoarthritis, a degenerative joint disease, is one of the most common types of joint diseases. The pathogenesis of osteoarthritis is unknown, but it is related to aging and injury of articular cartilage. Most individuals show some evidence of this disease by age 65. The disease is characterized by chronic joint pain with various degrees of joint deformity and destruction of the articular cartilage. Osteoarthritis commonly affects weight-bearing joints: hips, knees, lower lumbar vertebra, and joints of the hand and foot. There is a decrease in proteoglycan content, which results in reduction in intercellular water content in the cartilage matrix. Chondrocytes also play an important role in the pathogenesis of osteoarthritis. By producing interleukin-1(IL -1) and tumor necrosis factor (TNF -), the production of metalloproteinases is stimulated, whereas synthesis of type II collagen and proteoglycans by the chondrocyte is inhibited. In the early stages of the disease, the superficial layer of the articular cartilage is disrupted. Eventually, destruction of the cartilage extends to the bone, where the exposed subchondral bone becomes a new articular surface. These changes result in progressive reduction of mobility and increased pain with joint movement. Osteoarthritis has no cure, and treatment focuses on relieving pain and stiffness to allow a greater range of joint movement. Osteoarthritis may stabilize with age, but more often, it slowly progresses with eventual long-term disability.

Elastic cartilage

Has a visible network of interlacing elastic fibers in addition to collagen type II fibers

Possesses fewer isogenous groups than does hyaline cartilage.

Elastic cartilage is found in the external ear, the walls of the external acoustic meatus, the auditory (Eustachian) tube, and the epiglottis of the larynx. The cartilage in all of these locations is surrounded by a perichondrium similar to that found around most hyaline cartilage. Unlike hyaline cartilage, which calcifies with aging, the matrix of elastic cartilage does not calcify during the aging process.

Fibrocartilage

Is a functional and structural intermediate between hyaline cartilage and the dense connective tissues

Possesses abundant collagen type I fibers, arranged in either a regular or irregular configuration. These collagen fibers cause this cartilage to stain pink with eosin.

Has minimal ground substance. The ground substance that is present is usually located immediately around the chondrocytes.

Possesses few isogenous groups

Fibrocartilage

Combines great tensile strength with flexibility

Frequently found where a tendon or a ligament attaches to a bone (regular arrangement of fibers)

Located in the pubic symphysis and knee cartilages (irregular fiber arrangement)

Regressive Changes in Cartilage

Occur in cartilage more frequently than in many other tissues

Regressive changes also occur in the hyaline cartilage of the epiphyseal plate and represent critical steps in endochondral bone formation.

Stages of regression

Chondrocytes hypertrophy and secrete alkaline phosphatase that provides a calcifiable matrix.

Calcium phosphate is deposited in the matrix, prohibiting diffusion of nutrients to the chondrocytes.

Chondrocytes die, leaving behind empty lacunae and the calcified matrix.

Chondrogenesis. Appositional growth

New cartilage cells produced during appositional growth are derived from the inner portion of the surrounding perichondrium. The cells resemble fibroblasts in form and function, producing the collagen component of the perichondrium (type I collagen). When cartilage growth is initiated, however, the cells undergo a differentiation process guided by an expression of the transcription factor SOX-9. The cytoplasmic processes disappear, the nucleus becomes rounded, and the cytoplasm increases in amount and prominence. These changes result in the cell becoming a chondroblast. Chondroblasts function in cartilage matrix production, including secretion of type II collagen. The new matrix increases the cartilage mass, while new fibroblasts are produced simultaneously to maintain the cell population of the perichondrium.

Chondrogenesis. Interstitial growth

New cartilage cells produced during interstitial growth arise from the division of chondrocytes within their lacunae. This is possible only because the chondrocytes retain the ability to divide and the surrounding matrix is distensible, thus permitting further secretory

activity. Initially, the daughter cells of the dividing chondrocytes occupy the same lacuna. As new matrix is secreted, a partition is formed between the daughter cells; at this point, each cell occupies its own lacuna. With continued secretion of matrix, the cells move even farther apart from each other. The overall growth of cartilage thus results from the interstitial secretion of new matrix material by chondrocytes and by the appositional secretion of matrix material by newly differentiated chondroblasts

9. Bones. Osteogenesis

Provides structural support, giving shape and form to the body

Provides movement through the insertion of muscles

Serves as a stored source for calcium and phosphate

Contains bone marrow (myeloid tissue)

Histological preparation of bone

Ground bone preparation. Unpreserved bone is ground to a thinness where light can be transmitted through it. Because no preservation has occurred, neither cells nor organic matrix survive. Lamellae, lacunae, canaliculi, and general architecture of inorganic matrix are well displayed.

Decalcified bone. Cells are fixed (preserved) and inorganic matrix removed by decalcification. Good detail of organic matrix (cells, periosteum, etc.) is maintained, but lamellae and inorganic matrix are difficult to distinguish.

Gross Appearance of Bone, Macroscopic Structure

Compact bone. Appears as a solid mass to the naked eye, covering the exterior of bones and forming the shaft of long bones.

Spongy or *cancellous bone*. Gross appearance is like a sponge, with a labyrinth of bony spicules and intervening spaces that are filled with loose connective tissue or red marrow and at least one blood vessel. Spongy bone is located in the interior of bones.

Architecture of a Long Bone

The ***diaphysis*** (shaft), composed of compact bone, is hollow and is usually lined by a thin band of spongy bone.

An ***epiphysis***, the knob at either end of the diaphysis, is composed of a thin rim of compact bone. The spongy bone in its interior houses red marrow.

Metaphysis. Flared region between diaphysis and epiphysis.

Epiphyseal plate. Hyaline cartilage separating epiphysis and metaphysis in growing bones. Growth in bone length occurs as hyaline cartilage in the epiphyseal plate goes through various stages of regression, providing a framework on which bone is deposited.

When the hyaline cartilage in the epiphyseal plate is exhausted, growth stops. The epiphysis and metaphysis fuse in the adult, leaving an epiphyseal line as a remnant of the epiphyseal plate.

Marrow

Red marrow, found in all bones of the fetus, is restricted to spongy bone areas of selected bones in the adult and contains hematopoietic tissue that forms blood cells.

Yellow marrow, found in the shafts of long bones in the adult, consists mainly of adipose connective tissue that retains the potential to become red marrow under hemorrhagic stress.

Articular cartilage is composed of hyaline cartilage and covers articular surfaces of bone. This cartilage does not possess a perichondrium; the glassy, smooth cartilage provides a good articulating surface.

Components of Bone. *Extracellular matrix*

Organic portion, osteoid. Secreted by osteoblasts

Collagen type I *fibers* comprise the majority of the organic matrix. Their predominance causes bone to stain pink with eosin.

Ground substance is minimal, composed of glycosaminoglycans such as chondroitin sulfate, keratan sulfate, and some glycoproteins that avidly bind calcium.

Inorganic portion. Calcium and phosphate, in the form of hydroxyapatite crystals, are deposited along the collagen fibrils and form 50% of the dry weight of bone. This ossified matrix renders bone impermeable to diffusion of nutrients and requires that bone be well vascularized.

Components of Bone. Cells. *Osteoblasts*

Located on all exterior surfaces of bone as the innermost portion of the periosteum or in the endosteum lining all interior bony surfaces

Inactive osteoblasts are flattened cells with heterochromatic nuclei.

Active osteoblasts are stellate and contain organelles necessary for protein, primarily collagen, production. These cells synthesize high levels of alkaline phosphatase.

Function to synthesize bone

Secrete osteoid first

In the presence of alkaline phosphatase, osteoblasts facilitate the deposition of calcium phosphate, thus mineralizing the osteoid.

Components of Bone. Cells. *Osteocytes*

Are osteoblasts that have completely surrounded themselves by bony matrix and, therefore, must lie within, rather than on, bone tissue. These flattened, inactive cells lie in *lacunae* (spaces) in the bone and extend long processes from the cell body. These processes lie in narrow tunnels called *canaliculi* and connect, via gap junctions, with adjacent osteocytes and/or osteoblasts at the bone surface.

Function to transport materials between blood and bone and to maintain surrounding matrix; they do not divide or secrete matrix.

Osteoclasts

Are large cells with 15–20 or more nuclei and vacuolated, frothy cytoplasm. A ruffled border, the highly enfolded cell membrane facing the bone, is the site of bone resorption.

Are located on internal surfaces as part of the endosteum or on external surfaces as part of the osteogenic layer of the periosteum.

Osteoclasts lie in depressions in the bone, *Howship's lacunae*, which form as osteoclasts resorb bone.

Resorb bone via the acid phosphatase and proteolytic enzymes they secrete

Surface coverings

Periosteum. Double layer of connective tissue surrounding the outer surface of bones, except for articular surfaces

Layers

Fibrous layer. Outer layer of dense connective tissue that serves as a reserve-cell source for the osteogenic layer

Osteogenic layer. Inner, more cellular layer, contains osteoblasts and osteoclasts. Site of bone deposition and resorption, respectively.

Well vascularized and richly innervated

Endosteum

Is composed of a single row of osteoblasts, osteoclasts, and/or osteo-progenitor cells that lines all interior surfaces of bone except for lacunae and canaliculi

Serves as a means of bone growth and/or resorption

Microscopic Appearance of Bone (Related to the Age of a Bone)

Woven or *immature bone* is the first bone deposited.

May be either spongy or compact

Referred to as woven bone because fibers are deposited in a random array

Contains osteocytes that are more numerous and spherical than those of lamellar bone. These osteocytes are not in any orderly arrangement.

Is less well mineralized than lamellar bone and, therefore, appears bluer than lamellar bone with hematoxylin and eosin stains

Is usually resorbed and replaced by lamellar bone

Lamellar or *mature bone*

Replaces most woven bone or may be deposited *de novo*

May be either spongy or compact

Is referred to as lamellar bone because the matrix is deposited in layers or lamellae

Fibers are deposited in parallel array within a lamella.

Osteocytes are fewer and flatter than those in woven bone and are organized in rows between the lamellae.

Better mineralized than woven bone

Bone is not a static structure and is constantly being resorbed and reconstructed. Therefore, lamellar bone is also resorbed and reconstructed throughout life.

Architecture of Adult, Compact Lamellar Bone

Outer circumferential lamellae. Stacks of lamellae extend at least partially around the outer circumference of a long bone. Deposition of these lamellae by the periosteum results in increased thickness in the wall of the diaphysis.

Inner circumferential lamellae. Stacks of lamellae extend at least partially around the inner circumference of a long bone facing the marrow cavity. Deposition of these lamellae by the endosteum results in increased thickness of the wall of the diaphysis.

Architecture of Adult, Compact Lamellar Bone

Haversian systems, *osteons*

Primary structures of compact lamellar bone

Cylinders of concentric lamellae, deposited by endosteum, that run parallel to the long axis of a bone

Composition

Central *Haversian canal*

Appears round in cross-section with a smooth periphery

Contains a blood vessel(s) and loose connective tissue

Is lined with an endosteum

Concentric lamellae (4–20) surround the Haversian canal.

Collagen fibers are in parallel alignment within a single lamella, wrapping helically around the Haversian canal.

Pitch of the helix varies with each lamella in the osteon.

Provides great strength to a long bone

An osteon is formed by the centripetal deposition of the concentric lamella (i.e., outer lamella is the oldest).

Additional lamellae/structures associated with adult, compact lamellar bone

Interstitial lamellae. Portions of Haversian systems that remain after resorption of the rest of the osteon. These lamellae are interposed between other, complete Haversian systems.

Volkmann's canals. Channels oriented perpendicularly between adjacent Haversian canals, interconnecting these canals with each other and with the surfaces of bone. Volkmann's canals contain blood vessels that transport blood from the surface of bone to blood vessels within Haversian canals.

Cement lines. Thin, refractive lines that are collagen poor and stain, therefore, with hematoxylin. Cement lines are located:

- Around Haversian systems, demarcating where resorption stopped and the formation of a new osteon began
- Beneath and between circumferential lamellae, denoting where deposition of lamellae halted for a period of time and then began again

Bone Growth, Deposition, and Resorption

Bone Growth

- New, adult bone is always laid down on preexisting bone or cartilage.
- Bone growth is always appositional, with either endosteum or periosteum laying down lamellae of bone. Interstitial growth is impossible in bone because its rigid, ossified matrix does not allow osteocytes to secrete additional matrix or to divide.

Bone Growth, Deposition, and Resorption

Bone Deposition

- Newly deposited bone assumes the shape of the bone or cartilage on which it is deposited
- In spongy, lamellar bone, new lamellae are laid down by osteoblasts in the endosteum located at the periphery of each trabecula, thus increasing its thickness.
- In compact lamellar bone, new lamellae are laid down either as outer circumferential lamellae by osteoblasts in the periosteum or as inner circumferential lamellae and Haversian systems (osteons) by the endosteum.

Bone Resorption

Bone Resorption

- Removal of bone by osteoclasts for remodeling during growth and/or to mobilize calcium throughout life
- Resorption process
  - Osteoclasts on the periosteal and endosteal surfaces resorb bone from bone surfaces.
  - *Resorption canal*
    - Is a cylindrical, longitudinal tunnel formed as compact bone on the interior of bone is resorbed

Bone Resorption

Appears in cross-section as an irregularly shaped, bony surface lined with an endosteum containing osteoclasts

Usually extends past cement lines, eroding through portions of several osteons. Therefore, remnants of resorbed osteons may surround the resorption canal.

Is not lined by concentric lamellae as are osteons

When resorption stops, osteoblasts begin filling in a resorption canal by centripetal (from outside to inside) deposition of new lamellae, forming a new osteon. The newest lamella of this secondary osteon is the one adjacent to the Haversian canal.

Remains of partially resorbed Haversian systems around this secondary osteon are called interstitial lamellae.

Bone Development

Bone development can be classified as **intramembranous ossification** and **endochondral ossification**, according to the mechanism of its initial formation.

(1) *Intramembranous ossification* is the process by which a condensed mesenchyme tissue is transformed into bone. A cartilage precursor is not involved; instead, mesenchymal cells serve as **osteoprogenitor cells**, which then differentiate into **osteoblasts**. Osteoblasts begin to deposit the bone matrix.

Bone Development

(2) *Endochondral ossification* is the process by which **hyaline cartilage** serves as a **cartilage model** precursor. This hyaline cartilage proliferates, calcifies, and is gradually replaced by bone. Osteoprogenitor cells migrate along with blood vessels into the region of the calcified cartilage. These cells become osteoblasts, which then begin to deposit the bone matrix on the surface of the calcified cartilage matrix plate. Endochondral ossification involves several events. The development of long bone is a good example of endochondral formation. In this particular case, the hyaline cartilage undergoes proliferation and calcification in the **epiphyseal plates**. This epiphyseal cartilage can be divided into five recognizable zones: **reserve zone**, **proliferation zone**, **hypertrophy zone**, **calcification zone**, and **ossification zone**

Overview

Bone is a specialized type of connective tissue characterized by a **mineralized extracellular matrix** that stores calcium and phosphate. Bone contributes to the skeleton, which supports the body, protects vital structures, provides mechanical bases for body movement, and harbors bone marrow.

GENERAL STRUCTURE OF BONES

Bones are classified according to shape. **Long bones** are tubular in shape and consist of two ends (**proximal** and **distal epiphyses**) and a long shaft (**diaphysis**). **Metaphysis** is the junction between the diaphysis and the epiphysis. Bone is covered by **periosteum**, a connective tissue membrane that attaches to the outer surface by **Sharpey's fibers**. Periosteum contains a layer of osteoprogenitor (periosteal) cells that can differentiate into osteoblasts.

Bone cavities are lined by **endosteum**, a single layer of cells that contains osteoprogenitor (endosteal) cells, osteoblasts, and osteoclasts.

Bones articulate with neighboring bones by **synovial joints**, a movable connection.

The articular surfaces that form contact areas between two bones are covered by hyaline (articular) cartilage.

CELLS AND EXTRACELLULAR MATRIX

Osteoblasts differentiate from osteoprogenitor cells and secrete **osteoid**, an unmineralized bone matrix that undergoes mineralization triggered by matrix vesicles.

Osteocytes are mature bone cells enclosed within **lacunae** of bone matrix. They communicate with other osteocytes by a network of long cell processes occupying **canaliculi**, and they respond to mechanical forces applied to the bone.

Osteoclasts differentiate from hemopoietic progenitor cells; they resorb bone matrix during bone formation and remodeling. They differentiate and mature under the control of the **RANK–RANKL signaling mechanism**.

Bone matrix contains mainly type I collagen along with other noncollagenous proteins and regulatory proteins.

GENERAL STRUCTURE OF BONE TISSUE

Bone tissue formed during development is called **immature (woven) bone**. It differs from **mature (lamellar) bone** in its collagen fiber arrangement.

Bone tissue is classified as either **compact** (dense) or **spongy** (cancellous). Compact bone lies outside and beneath the periosteum, whereas an internal, sponge-like meshwork of trabeculae forms spongy bone.

Mature (lamellar) bone is mostly composed of **osteons (Haversian systems**). These concentric lamellar structures are organized around an **osteonal (Haversian) canal** that contains the vascular and nerve supply of the osteon. **Perforating (Volkmann's) canals** are perpendicularly arranged and connect osteonal canals to one another.

The **lacunae** between concentric lamellae contain **osteocytes** that are interconnected with other osteocytes and the osteonal canal via **canaliculi**.

BONE FORMATION

The development of bone is classified as **endochondral** (a cartilage model serves as the precursor of the bone) or **intramembranous ossification** (without involvement of a cartilage precursor).

Flat bones of the skull, mandible, and clavicle develop by intramembranous ossification; all other bones develop by endochondral ossification.

In **endochondral ossification**, the **hyaline cartilage model** is formed. Next, osteoprogenitor cells surrounding this model differentiate into bone-forming cells that initially deposit bone on the cartilage surface (periosteal **bony collar**) and later penetrate the diaphysis to form the **primary ossification center**.

Secondary ossification centers develop later within the epiphyses.

Primary and secondary ossification centers are separated by the **epiphyseal growth plate**, providing a source for new cartilage involved in bone growth seen in children and adolescents.

Epiphyseal growth plate has several zones (reserve cartilage, proliferation, hypertrophy, calcifi ed cartilage, and resorption). Resorbed calcified cartilage is replaced by bone.

BONE GROWTH, REMODELING, AND REPAIR

Elongation of endochondral bone depends on the **interstitial growth of cartilage** on the epiphyseal growth plate.

Bone increases in width (diameter) by **appositional growth** of new bone that occurs between the compact bone and the periosteum.

Bone is constantly being remodeled throughout life by **bone-remodeling units** composed of osteoclasts and osteoblasts. This process allows bone to change shape in response to mechanical load.

Bone can repair itself after injury either by a **direct (primary)** or **indirect (secondary)** bone healing process.

After injury, periosteal cells become activated to produce **soft (fibrocartilage) callus**, which is subsequently replaced by **hard (bony) callus**.

PHYSIOLOGIC ASPECTS OF BONE

Bone serves as a **reservoir for Ca^{2+}** in the body. **Ca^{2+}** may be removed from bone if the circulating level of Ca2 in the blood falls below the critical value. Likewise, excess Ca2 may be removed from the blood and stored in bone.

Maintenance of blood **Ca^{2+}** levels is regulated by the **parathyroid hormone (PTH)**, secreted by the parathyroid glands, and **calcitonin**, secreted by the thyroid gland.

PTH stimulates both osteocytes and osteoclasts (indirectly via RANK–RANKL signaling pathways because osteoclasts do not have PTH receptors) to resorb bone, thereby increasing $\mathbf{Ca^{2+}}$ levels in the blood.

Calcitonin inhibits bone resorption by inhibiting the effects of PTH on osteoclasts, thereby lowering blood $\mathbf{Ca^{2+}}$ levels.

10. Muscles. Skeletal, smooth, cardiac

Muscle tissue is specialized for the ability to shorten or contract. While all cells possess the cellular machinery necessary for shape change and contraction, these structures are significantly more prominent in muscle cells. For some muscle types, the cells are nonproliferative due to this high degree of specialization and differentiation.

Muscle contraction is accomplished by the reciprocating sliding of intracellular filaments composed of actin and myosin.

Muscle tissue comprises the "flesh" of the body and much of the walls of hollow organs. Due to its high degree of specialization, unique terms are used for certain structures in muscle cells:

Individual muscle cells are called ***muscle fibers.***

The cytoplasm of muscle fibers is called ***sarcoplasm***.

The muscle fiber plasma membrane is called the ***sarcolemma***.

The smooth endoplasmic reticulum is called the ***sarcoplasmic reticulum***.

Classification of Muscle

Functional classification is based on the type of neural control.

Voluntary

Involuntary

Structural classification is based on the presence or absence of crossstriations.

Striated

Nonstriated (smooth)

Combined functional and structural classification

Skeletal muscle

Striated and *voluntary*

Found mostly attached to the skeleton

Cardiac muscle

Striated and *involuntary*

Composes the majority of the heart wall (myocardium)

Smooth (visceral) muscle

Nonstriated and *involuntary*

Found mostly in the walls of hollow organs and vessels

Skeletal Muscle

Connective tissue investments of a skeletal muscle

Function

Separate muscle into compartments

Transmit the force of contraction to insertion points

Components

Endomysium. Reticular fibers surrounding each muscle fiber plus the external (basal) lamina produced by the muscle fiber

Perimysium. Dense connective tissue surrounding groups of fibers and dividing the muscle into fascicles

Epimysium. Dense connective tissue surrounding the entire muscle, blends with the deep fascia and tendons

Hierarchy of skeletal muscle organization

Myofilaments. Visible only with the electron microscope; composed primarily of *actin*, which forms 5-nm wide *thin filaments*, and *myosin*, which forms 15-nm wide *thick filaments*

Myofibrils. Visible with the light microscope, 1–2 microns wide, oriented parallel to the long axis of the cell; composed of bundles of overlapping myofilaments that are arranged in register, producing an alternating light-dark, striated banding pattern

Muscle fiber. Specialized term for a muscle cell, 10–100 microns wide; sarcoplasm is filled with hundreds of myofibrils, which are oriented parallel to each other and to the long axis of the muscle fiber.

Muscle fascicle. Collection of muscle fibers surrounded by perimysium; collections of muscle fascicles are surrounded by the epimysium and form a muscle.

Structure of skeletal muscle fibers

Largest fiber type, fibers can be 1–30mm in length and 10–100 microns in diameter.

Each muscle fiber is cylindrical, unbranched, and multinucleated.

The multiple nuclei are located at the periphery of the muscle fiber immediately beneath the *sarcolemma*.

Extensive smooth endoplasmic reticulum is called the *sarcoplasmic reticulum*.

Each fiber is surrounded by an external lamina (basal lamina), which contributes to the endomysium of the muscle fiber.

Fibers can increase in size (hypertrophy) but not in number (hyperplasia).

Structure of skeletal muscle fibers

Fibers show prominent, alternating light and dark bands (cross-striations) due to the alignment and overlap of the myofilaments within myofibrils. Myofilaments within a myofibril are arranged in register and adjacent myofibrils are similarly aligned, causing the banding pattern seen at both the light and electron microscopic levels.

Structure of skeletal muscle fibers

A band appears dark and contains actin and myosin.

I band appears light and contains actin only.

Z disc (or Z line), composed of alpha-actinin, is located in the center of the I band.

H zone is located in the center of the A band and represents the area where actin is not present.

M line is located in the center of the H band and represents areas of cross-connections between myosin filaments.

Structure of skeletal muscle fibers

Sarcomere

Contractile unit of striated muscle fibers, seen in both skeletal and cardiac muscle fibers

Extends from Z-line to Z-line

Sarcomeres are repeated in series along the length of each myofibril. Adjacent myofibrils maintain the alignment of sarcomeres.

Alterations in sarcomeres during contraction

Sarcomeres shorten.

Z-line interval narrows.

Width of H and I bands decrease as actin is pulled past the myosin.

A band width remains unchanged.

Coordination of skeletal muscle fiber contraction

A complex system of intracellular, membranous structures called the triad insures coordinated contraction throughout the muscle fiber by (1) allowing the nervous impulse to penetrate and simultaneously reach all parts of the muscle fiber; and (2) releasing calcium in response to the nervous impulse. These functions are accomplished by the “triad.”

Triads. Composed of one *T-tubule* plus two adjacent *terminal cisterns* of the sarcoplasmic reticulum

T-tubules are invaginations of the sarcolemma that occur at the junction between A and I bands of the myofibrils.

Terminal cisterns are expanded portions of the sarcoplasmic reticulum that lie adjacent to the T tubule and release calcium to initiate contraction.

Role of triad in muscle contraction

A nerve impulse arriving at the muscle fiber depolarizes the sarcolemma at the neuromuscular junction.

The membrane depolarization propagates along the sarcolemma and extends down the T-tubules.

T-tubule depolarization is transmitted to the terminal cisterns and the remainder of the sarcoplasmic reticulum, causing release of stored calcium.

Calcium initiates the interaction between actin and myosin myofilaments, leading to muscle contraction.

Calcium is recaptured by sarcoplasmic reticulum during relaxation.

Mechanism of contraction, sliding filament model

At regions where actin and myosin myofilaments overlap, release of calcium causes the head groups of myosin to contact the actin filament.

Hydrolysis of ATP causes a change in the configuration of the myosin head group, resulting in a sliding of the actin myofilament past the myosin by the ratcheting action of the myosin head groups. Since the actin filaments are anchored at the Z-line, the result of the sliding is shortening of the sarcomere.

Associated structures

Neuromuscular junction (motor end plate)

Specialized "synapse" between the terminals of a motor axon and the sarcolemma of a muscle fiber

Motor unit. Consists of the motor neuron, its axon, and all the muscle fibers it innervates

Proprioceptors

Sensory receptors, encapsulated by connective tissue, serve to regulate muscle tension and tone.

Types

Muscle spindle. Highly modified skeletal muscle fibers, intrafusal fibers, are aligned with and surrounded by normal skeletal muscle fibers.

Golgi tendon organs. Located within tendons

Embryonic Development of the Skeletal Muscle

During the course of embryonic development, mesenchymal progenitor cells originating from the somites, undergo a multistep differentiation process to form muscle fibers and muscle mass. Each somitic area (occipital, cervical, thoracic, lumbar and sacral) contributes to the formation of muscles. Muscle satellite cells are formed during embryonic development

as well, and persist in a quiescent state in the adult muscles, ensuring restoration of muscle cells following any type of muscle injury.

Cardiac Muscle

Cardiac muscle occurs only in the myocardium of the heart and, to a variable extent, in the roots of large vessels where they join the heart.

Structure of cardiac muscle fibers

Intermediate in size between skeletal and smooth muscle

Fibers are cylindrical, branch, and form interwoven bundles.

Usually one nucleus per fiber located in the center

Organelles are clustered at the poles of the nucleus.

Myofilament organization into myofibrils is identical to skeletal muscle. Cross-striations and bands identical to skeletal muscle are present, but not as prominent.

Intercalated discs

Junctional complexes that are unique to cardiac muscle fibers

Consist of specialized cell junctions and interdigitations of the sarcolemma at the ends of the fibers

Contain three types of junctions

Fascia adherens. Similar to zonula adherens of epithelia; serve to attach cardiac muscle fibers and anchor actin filaments of the terminal sarcomeres at the ends of the cell. Acts as a hemi-Z-line.

Desmosomes. Bind ends of fibers together

Gap junctions. Provide ionic coupling between fibers

Coordination of cardiac muscle contraction

Sarcomeres, myofibrils, and myofilaments are the same as skeletal muscle fibers.

T-tubules are located at the level of the Z-lines, rather than at junction of A and I bands as in skeletal muscle.

No triads. Sarcoplasmic reticulum is not as well developed as in skeletal muscle fibers and does not form terminal cisterns. Contraction is initiated by intracellular calcium release.

Contraction can spread through the myocardium due to the presence of gap junctions that allow calcium to flow from one fiber into another.

Embryonic Development of the Heart:

The cardiovascular system is the first system to form and function in an embryo, and the heart is the first functional organ. In the mouse embryo, 50 founder cells make up the earliest heart precursor cells and are detectable as early as E6.5, on either side of the midline in the epiblast of early gastrula stage embryos. The human heart develops on day 18 or 19

following fertilization. In response to induction signals from the underlying endoderm, the mesoderm in the cardiogenic area forms the cardiogenic cords. A hollow center forms within the cords, giving rise to the endocardial tubes. With lateral folding of the embryo, the paired endocardial tubes approach each other and fuse into a single tube called the primitive heart tube (human: day 21 following fertilization; mouse: E8.0). On the day 22, the primitive heart tube develops into five distinct unpaired regions and begins to pump blood. Between days 23 and 28 (mouse E8.5-10.0), the primitive heart tube elongates unevenly, twisting and folding to form a U-shape and then an S-shape. As a result, the atria and ventricles of the future heart assume their final adult positions. Further heart development involves remodeling of the chambers and the formation of septa and valves to form a four-chambered heart.

Smooth Muscle

Smooth muscle occurs mostly as sheets, which form the walls of most hollow organs with the exception of the heart. Smooth muscle is also prominent in the walls of blood vessels, many respiratory passageways, and some genital ducts.

Structure of smooth muscle fibers

Smallest fiber type, length varies from 20 microns in blood vessels to 500 microns in the uterus

Unbranched spindle-shaped fibers are elongated with tapering ends and unbranched.

Possess a single, centrally placed, oval nucleus, which can appear spiraled or “inch-worm”–shaped when the fiber is contracted.

Organelles are clustered at the poles of the nucleus.

Nonstriated; no myofibrils are present.

External (basal) lamina is present along with reticular fibers.

Abundant gap junctions

Capable of both hypertrophy and hyperplasia

Organization of the contractile proteins

Actin and myosin myofilaments are present, but they are not organized into myofibrils.

Myofilaments overlap as in striated muscle and crisscross throughout the sarcoplasm, forming a reticulum.

Dense bodies

Serve as insertion points for myofilaments to transmit the force of filament sliding

Contain alpha-actinin and, thus, resemble Z-lines of striated muscle

Present in the cytoplasm and associated with the sarcolemma

Coordination of smooth muscle contraction

No T-tubules are present; however, fibers do have a rudimentary sarcoplasmic reticulum.

Sliding filament mechanism. Regulated by intracellular release of calcium but with some differences from striated muscle fibers

Types of smooth muscle

Visceral smooth muscle

Occurs in sheets in the wall of hollow organs (e.g., digestive tract)

Minimally innervated; contraction spreads in peristaltic waves facilitated by large numbers of gap junctions.

Specialized for slow, prolonged contraction

Multiunit smooth muscle

Richly innervated

Specialized for precise, graded contraction (e.g., iris of the eye)

11. Nervous tissue

Nervous tissue is highly specialized to employ modifications in membrane electrical potentials to relay signals throughout the body.

Neurons form intricate circuits that (1) relay sensory information from the internal and external environments; (2) integrate information among millions of neurons; and (3) transmit effector signals to muscles and glands.

Anatomical subdivisions of nervous tissue

Central nervous system (CNS)

Brain

Spinal cord

Peripheral nervous system (PNS)

Nerves

Ganglia (singular, ganglion)

Cells of Nervous Tissue.

Neurons

Functional units of the nervous system; receive, process, store, and transmit information to and from other neurons, muscle cells, or glands

Composed of a cell body, dendrites, axon and its terminal arborization, and synapses

Form complex and highly integrated circuits

Supportive cells

Outnumber neurons 10 : 1

Provide metabolic and structural support for neurons, insulation (myelin sheath), homeostasis, and phagocytic functions

Comprised of astrocytes, oligodendrocytes, microglia, and ependymal cells in the CNS; comprised of Schwann cells in the PNS

Structure of a “Typical” Neuron

Cell body (soma, perikaryon)

Nucleus

Large, spherical, usually centrally located in the soma

Highly euchromatic with a large, prominent nucleolus

Cytoplasm

Well-developed cytoskeleton

Intermediate filaments (*neurofilaments*). 8–10 nm in diameter

Microtubules. 18–20 nm in diameter

Abundant rough endoplasmic reticulum and polysomes (*Nissl substance*)

Well-developed Golgi apparatus

Numerous mitochondria

Dendrite(s)

Usually multiple and highly branched at acute angles

May possess *spines* to increase surface area for synaptic contact

Collectively, form the majority of the receptive field of a neuron; conduct impulses toward the cell body

Organelles

Microtubules and neurofilaments

Rough endoplasmic reticulum and polysomes

Smooth endoplasmic reticulum

Mitochondria

Axon

Usually only one per ne

Generally of smaller caliber and longer than dendrites

Branches at right angles, fewer branches than dendrites

Organelles

Microtubules and neurofilaments

Lacks rough endoplasmic reticulum and polysomes

Smooth endoplasmic reticulum

Mitochondriauron

Axon

Axon hillock. Region of the cell body where axon originates

Devoid of rough endoplasmic reticulum

Continuous with *initial segment* of the axon that is a highly electrically excitable zone for initiation of nervous impulse

Usually ensheathed by supporting cells

Transmits impulses away from the cell body to

Neurons

Effector structures. Muscle and glands

Terminates in a swelling, the terminal bouton, which is the presynaptic element of a synapse

Multipolar neuron.

Most numerous and structurally diverse type

Efferent. Motor or integrative function

Found throughout the CNS and in autonomic ganglia in the PNS

Pseudounipolar neuron

Afferent. Sensory function

Found in selected areas of the CNS and in sensory ganglia of cranial nerves and spinal nerves (dorsal root ganglia)

Bipolar neuron

Afferent. Sensory function

Found associated with organs of special sense (retina of the eye, olfactory epithelium, vestibular and cochlear ganglia of the inner ear)

Developmental stage for all neurons

Arrangement of Neuronal Cell Bodies and their Processes

In both CNS and PNS, cell bodies are found in clusters or layers and axons travel in bundles. These groupings are based on common functions and/or common connections.

Synapse

The function of the synapse is to alter the membrane potential of the postsynaptic target cell to either facilitate or inhibit the likelihood of the stimulus to be propagated by the postsynaptic cell. Most neurons receive thousands of synaptic contacts, both stimulatory and inhibitory, and the algebraic sum of these inputs determines whether the postsynaptic cell will depolarize.

Synapse

Classified according to postsynaptic target

Axodendritic. Most common

Axosomatic

Axoaxonic. Mostly occur at presynaptic terminals

Neuromuscular junction

Structure of the synapse

Presynaptic component

Distal end of the axon branches, each branch terminating in a swelling or button called the *terminal bouton.*

Bouton contains *synaptic vesicles/granules*, which contain neurotransmitters and numerous mitochondria.

Synaptic gap/cleft. Separation (20–30nm) between pre- and postsynaptic cells.

Postsynaptic component

Formed by the membrane of the postsynaptic neuron or muscle cell and contains receptors for neurotransmitters

Membrane shows a *postsynaptic density* or thickening on its cytoplasmic side.

Bouton en passant. "Bouton-like" swellings along the length of an axon, allows a single axon to contact many distant cells. Common in smooth muscle innervation.

The Reflex Arc

The reflex arc is the simplest neuronal circuit and includes each of the elements discussed above. These circuits provide rapid, stereotyped reactions to help maintain homeostasis. To begin the reflex, a pseudounipolar, sensory neuron is activated by a receptor. The axon carries an afferent signal from the skin into the spinal cord where it synapses on a multipolar association neuron or interneuron. The interneuron signals a multipolar, motor neuron whose axon then carries an efferent signal to skeletal muscle to initiate contraction.

Supportive Cells

Supporting cells of the CNS (neuroglial cells); outnumber neurons 10:1

Astrocytes

Stellate morphology

Types

Fibrous astrocytes in white matter

Protoplasmic astrocytes in gray matter

Functions

Physical support

Transport nutrients

Maintain ionic homeostasis

Take up neurotransmitters

Form glial scars (gliosis)

Supportive Cells

Oligodendrocytes

Present in white and gray matter

Interfascicular oligodendrocytes are located in the white matter of the CNS, where they produce the myelin sheath.

Ependymal cells. Line ventricles

Microglia

Not a true neuroglial cell; derived from mesoderm whereas neuroglial cells, as well as neurons, are derived from ectoderm

Highly phagocytic cells

Supporting cells of the PNS. *Schwann cells*

Satellite Schwann cells surround cell bodies in ganglia

Ensheathing Schwann cells

Surround unmyelinated axons. Numerous axons indent the Schwann cell cytoplasm and are ensheathed only by a single wrapping of plasma membrane.

Produce the myelin sheath around axons

Myelin Sheath

The *myelin sheath* is formed by the plasma membrane of supporting cells wrapping around the axon. The sheath consists of multilamellar, lipid-rich segments produced by Schwann cells in the PNS and oligodendrocytes in the CNS.

Functions

Increases speed of conduction (*saltatory conduction*)

Insulates the axon

Similar structure in CNS and PNS with some differences in protein composition

Myelin Sheath

Organization

Internode. Single myelin segment

Paranode. Ends of each internode where they attach to the axon

Node of Ranvier. Specialized region of the axon between myelin internodes where depolarization occurs.

In the PNS, each Schwann cell associates with only one axon and forms a single internode of myelin.

In the CNS, each oligodendrocyte associates with many (40–50) axons (i.e. each oligodendrocyte forms multiple internodes on different axons).

Connective Tissue Investments of Nervous Tissue

Peripheral nervous system

Endoneurium. Delicate connective tissue surrounding Schwann cells; includes the basal lamina secreted by Schwann cells as well as reticular fibers

Perineurium. Dense tissue surrounding groups of axons and their surrounding Schwann cells, forming fascicles; forms the bloodnerve barrier

Epineurium. Dense connective tissue surrounding fascicles and the entire nerve

Central nervous system *Meninges*

Pia mater

Thin membrane lying directly on the surface of the brain and spinal cord

Accompanies larger blood vessels into the brain and spinal cord

Arachnoid membrane

Separated from pia mater by connective tissue trabeculae

Encloses the *subarachnoid space*, which contains blood vessels and the *cerebrospinal fluid (CSF)* produced by the cells of the choroid plexus

Together with pia mater, constitute the *leptomeninges*; inflammation of these membranes produces meningitis

Dura mater

Outermost of the meninges

Dense connective tissue that includes the periosteum of the skull

11. ГЛОССАРИЙ

General Terms The following general terms are commonly used in histology.

afferent - conveying toward an organ, as an afferent lymphatic vessel, or afferent nerve; efferent -conveying away from an organ, as efferent lymphatic vessel or efferent nerve. These terms are used with reference to an understood organ.

capsule - a structure enclosing an organ, usually composed of dense connective tissue.

cortex - the outer portion of an organ, distinguished from its inner, medullary portion.

hilus or hilum - a depression or pit at that part of an organ where the vessels and nerves enter.

lumen - the cavity or channel within a tube or hollow organ. (Abluminal=on the side away from the lumen; as "the basal lamina is on the abluminal side of the endothelium". adluminal- toward the lumen; as "the microvilli are on the adluminal side of the gut absorptive epithelium.")

medulla - the inner portion of an organ, usually in the center.

mucosa - a mucous membrane, comprised of several layers (an epithelium, lamina propria, and often a muscularis mucosae).
parenchyma - the essential elements of an organ; a general term used to designate the functional elements of an organ as distinguished from its framework, or stroma.
stroma - the supporting tissue or scaffolding of an organ, as distinguished from its functional element, or parenchyma.
septum, pl. septa -the dividing wall or partition usually between lobes of an organ.
serosa - a serous membrane, comprised of a mesothelium and underlying connective tissue, lining the serous cavities of the body.
trabecula, pl. trabeculae - a supporting or anchoring strand of connective tissue, usually extending from a capsule into the substance of the enclosed organ.

Etymology
Although it is no longer true that the study of Latin, and to a lesser extent Greek, is prerequisite for the study of medicine, the composition of today's medical vocabulary makes it evident why study of these languages was once considered necessary. No less than 75% of the vocabulary of anatomy is derived from Greek and Latin words. Thus, some familiarity with these two languages will simplify the task of learning a basic vocabulary and of comprehending new words as they are encountered.

Many of the terms that we use as part of the regular vocabulary retain the original Latin words like "tunica" (=a covering or coat), "vas" (=a vessel), and "stratum" (=a layer) and they are not defined here. This Appendix is prepared principally to explain the meaning of the most commonly encountered Latin and Greek combining forms of words that have undergone some change in the transfer to English.

Many histological terms are composed of a combination of two or more word elements with an '"o" or "i" usually inserted between the two roots to facilitate pronunciation. Thus the word "osteocyte" is derived from the nouns "oste-" (bone) and "-cyte" (cell). By knowing the meanings of the roots used in the prefix, root and suffix of the terms you encounter, you can understand and remember many of the words you will learn as part of your medical career.
Prefixes (pre=in front of, before, + fix=to fasten) Many compound terms consist of a root word preceded by a prefix, commonly a preposition, adverb, or adjective.
a- (=no) agranulocyte
auto- (=self) autosome, autocrine

bi- (=two, twice) binucleate, binocular

circum- (=around) circumferential lamellae, circumvallate

con- (=with, together) concentric, condensing

demi- (=half) demilune

dis- (=apart, away from) discontinuous

ect- (=outside) ectoderm, ectopic

end- (=inside) endocardium, endoderm

epi- (=upon, after) epiphysis, epimysium

erythr- (=red) erythrocyte, erythropoiesis

eu- (=good, normal) euchromatin, eukaryote

exo- (=outside) exocrine, exocytosis

extra- (=outside of, beyond) extrapulmonary, extracellular

heter- (=other) heterochromatin, heterolysosome

hyper- (=above, beyond, extreme) hypertrophy, hyperplasia

hypo- (=under, below) hypodermis, hypothalamus

inter- (=among, between) interlobar, intercalated

intra- (=inside, within) intralobular, intracellular

juxta- (=near to) juxtaglomerular cell

leuko- (=white) leukocyte

macro- (=long, large) macrophage, macroscopic

mega- (=great, large) megakaryocyte

mes- (=middle) mesenchyme, mesangial

meta- (=after, beyond) metaphysis, metarteriole

micro- (=small) microscope, microtubule

mono- (=only, sole) monocyte, mononuclear

multi- (=many, much) multivesicular, multinucleate

neo- (=new, young) neocortex, neonatal

neutro- (=neither) neutrophil

non- (=not) nonkeratinized, nonciliated

para- (=beside, beyond) paracrine, paracortex

peri- (=around) perikaryon, periosteum

poly- (=much, many) polyploid, polyribosomes

post- (=after, behind in time or place) postsynaptic, postmitotic

pre- (=before in time or place) precapillary, preadipocyte

pseudo- (=false) pseudostratified

pro- (=before in time or place) proerythrocyte, procollagen

stereo- (=solid, having three dimensions) stereocilia

sub- (=under, below) subcutaneous, submucosa

supra- (=above, beyond) suprarenal, supravital

syn-, sym- (=with, together) syncytium, symphysis

trans- (=through, across, beyond) transendothelial, transcytosis

Roots Latin or Greek roots commonly found in combined words.

aden- (=gland) adenohypophysis

adip- (=fat) adipocyte

bronchi- (=windpipe) bronchiole

cardi- (=heart) myocardium

chondr- (=cartilage) chondrocyte

cyt- (=cell) cytoplasm

dendr- (=tree) dendrite, dendritic cell

derm- (=skin) epidermis

desm- (=band, ligament) desmosome

fibr- (=fiber) fibroblast

fili- (=thread) filiform

gastr- (=stomach) gastrointestinal

hem-, hemat- (=blood) hemoglobin

hepat- (=liver) hepatocyte

kary- (=nut, nucleus) megakaryocyte, perikaryon

kerat-(=horn) keratinocyte

lact- (=milk) lactiferous duct

lip- (=fat) lipofuscin

lys- (=loose, dissolve) lysosome

my- (=muscle) myofibril

nephr- (=kidney) nephron

neur-(=nerve) neurofilament

nucle- (=kernal) nucleoplasm

odont- (=tooth) odontoblast

ost(e)- (=bone) osteocyte

ov-, oo- (=egg) oviduct, oocyte

pod- (=foot) podocyte

sarco- (=flesh) sarcoplasm

theca- (=case, box) theca folliculi

Suffixes (sub=under + fix=to fasten). Latin or Greek derivations that are added to other roots to form nouns or adjectives.

-blast (=bud, a growing thing in its early stages) osteoblast, fibroblast

-clast (=break) osteoclast

-crine (=separate off) endocrine, merocrine

-cyte (=cell) osteocyte, monocyte

-elle, -cle, -ole, -ule (=a diminutive) lobule, spicule, canaliculus, caveolae, corpuscle

-form (=shape) filiform, fusiform

-oid (=form) sinusoid, nucleoid

-phage, phago- (=eat) macrophage, phagocyte

-phil, -philia (=like, have affinity for) acidophilic, hydrophilic

-phobe, -phobic (=fear, dread) chromophobe, hydrophobic

-some (=body) lysosome, chromosome

12. ПРИЛОЖЕНИЯ