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УТВЕРЖДАЮ

Директор Высшей школы управления здоровьем, клинической психологии и сестринского образования
_____ О.Ю. Алешкина
«26» 04 2024 г

ФОНД ОЦЕНОЧНЫХ СРЕДСТВ
ДЛЯ ПРОВЕДЕНИЯ ПРОМЕЖУТОЧНОЙ АТТЕСТАЦИИ

Дисциплина: Английский язык для специальных целей

Направление подготовки: 32.04.01 Общественное здравоохранение

Квалификация: Магистр

ДОКУМЕНТ ПОДПИСАН
ЭЛЕКТРОННОЙ ПОДПИСЬЮ

Сертификат: 48517EBE13A5C41892B0D7D68542308B
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Действителен: с 22.04.2024 до 16.07.2025

1. КАРТА КОМПЕТЕНЦИЙ

Контролируемые компетенции	Планируемые результаты обучения
УК-4 Способен применять современные коммуникативные технологии, в том числе на иностранном(ых) языке(ах), для академического и профессионального взаимодействия	**ИД 4.1** Знает основы выстраивания эффективной коммуникации с партнерами в процессе профессионального взаимодействия на государственном и иностранных языках; основы теории коммуникации; основные правила письменной и устной коммуникации на иностранном языке; принципы успешной коммуникации; виды и способы коммуникации, обеспечивающие эффективное академическое взаимодействие; **ИД 4.2** Умеет применять базовые коммуникативные навыки в академических и профессиональных целях; уметь выстраивать эффективную коммуникацию на иностранном языке; вести деловую переписку, учитывая особенности стилистики официальных и неофициальных писем, социокультурные различия в формате корреспонденции на государственном и иностранном (-ых) языках; **ИД 4.3** Владеет умением выполнять перевод академических и профессиональных текстов с иностранного (-ых) на государственный язык; различными коммуникативными навыками, применимыми в академическом и профессиональном общении медицинских работников.

2. ПОКАЗАТЕЛИ ОЦЕНИВАНИЯ ПЛАНИРУЕМЫХ РЕЗУЛЬТАТОВ ОБУЧЕНИЯ

Семестр	Шкала оценивания	
	«не зачтено»	**«зачтено»**
знать		
2	Студент не способен самостоятельно выделять главные положения в изученном материале дисциплины. Не знает основных правил произношения, словообразования и словоупотребления; базового фонда общеупотребительной и терминологической лексики; основ чтения, перевода и реферирования специального медицинского текста; грамматического и стилистического оформления устного высказывания.	Студент самостоятельно выделяет главные положения в изученном материале и способен дать краткую характеристику основным идеям проработанного материала дисциплины. Знает основные правила произношения, словообразования и словоупотребления; базовый фонд общеупотребительной и терминологической лексики; основы чтения, перевода и реферирования специального медицинского текста; грамматического и стилистического оформления устного высказывания. Показывает глубокое понимание лексико-грамматической, структурной и логической организации специального медицинского текста; основных положений текста и смысла всего текста в целом; причинно-следственных, логических и системообразующих связей в структуре текста.
уметь		
2	Студент не умеет правильно произносить, интонировать и анализировать изученную лексику; использовать изученный лексико-грамматический материал при работе со специальным медицинским текстом; выполнять перевод и реферирование текста; строить устное высказывание, отвечать на вопросы экзаменатора.	Студент умеет правильно произносить, интонировать и анализировать изученную лексику; использовать изученный лексико-грамматический материал при работе со специальным медицинским текстом; выполнять вполне грамотный перевод и реферирование текста; строить устное высказывание, отвечать на вопросы экзаменатора.
владеть		
2	Студент не владеет основными правилами произношения, словообразования и словоупотребления; базовым фондом общеупотребительной и терминологической лексики; основами чтения, перевода и реферирования специального медицинского текста; грамматического и стилистического оформления устного высказывания, ответа на вопрос экзаменатора.	Студент показывает глубокое и полное владение всем объемом изучаемой дисциплины, владеет основными правилами произношения, словообразования и словоупотребления; базовым фондом общеупотребительной и терминологической лексики; основами чтения, перевода и реферирования специального медицинского текста; грамматического и стилистического оформления устного высказывания, ответа на вопрос экзаменатора.

3. ОЦЕНОЧНЫЕ МАТЕРИАЛЫ ДЛЯ ПРОВЕДЕНИЯ ПРОМЕЖУТОЧНОЙ АТТЕСТАЦИИ

КОМПЛЕКТ

Вопросов (закрытого типа)

1. Выберите правильный вариант ответа:
The man was operated on ... appendicitis.
a) against
b) –
c) from
d) for

2. Выберите правильный вариант ответа:
Look ... her skin. It has got a yellowish colour.
a) for
b) to
c) on
d) at

3. Выберите правильный вариант ответа:
Pancreas is a long thin gland lying ... the stomach.
a) below
b) above
c) after
d) on

4. Выберите правильный вариант ответа:
Respiratory diseases are associated … many complications.
a) of
b) with
c) for
d) –

5. Выберите правильный вариант ответа:
Never show that you are afraid ... injections.
a) –
b) of
c) for
d) from

6. Выберите правильный вариант ответа:
I hope that ... my mother ... my father will help me.
a) either...or
b) not so...as
c) as...as
d) neither...or

7. Выберите правильный вариант ответа:
.... therapeutic ... surgical treatment was effective and the patient's condition became worse.

a) Either...or
b) Both...and
c) Neither...nor
d) Not so...a

8. Выберите правильный вариант ответа:
His temperature is not so ... as it was before the injection.
a) higher
b) high
c) the highest
d) more higher

9. Выберите правильный вариант ответа:
... came to visit me when I was ill.
a) Anything
b) Anybody
c) Nobody
d) Anyone

10. Выберите правильный вариант ответа:
She always tried to do it …
a) herself
b) oneself
c) oneselves
d) ourselves

11. Выберите правильный вариант ответа:
Obstetrics ... very interesting to study.
a) is
b) are
c) were
d) been

22. Выберите правильный вариант ответа:
The initial diagnosis made by the doctor appeared to be correct. ... confirmed by X-ray examination.
a) It was
b) They were
c) It is
d) They are

13. Выберите правильный вариант ответа:
Some students ... part in our experiment because they were interested in Biology.
a) take
b) taking
c) took
d) taken

14. Выберите правильный вариант
If you come at 5 o'clock we ... . Come at 6, please.
a) work
b) shall be working

c) be working
d) are working

15. Выберите правильный вариант
I can’t make the diagnosis. I ... anything like this.
a) has seen
b) seen
c) haven't seen
d) was seen

16. Выберите правильный вариант
I ... got any good ideas about it.
a) am not
b) haven't
c) have
d) was not

17. Выберите правильный вариант
It is known that in this case physiotherapy ... improve the patient's condition.
a) don't
b) doesn't
c) not
d) is not

18. Выберите правильный вариант
The boy with pneumonia ... the necessary treatment.
a) is giving
b) were given
c) gave
d) was given

19. Выберите правильный вариант
X-ray examination ... in 2 hours.
a) will do
b) is doing
c) will be done
d) have done

20. Выберите правильный вариант
If you want to be healthy you ... pay attention to your meals.
a) can
b) should
c) may
d) need

21. Выберите правильный вариант
… the injection of penicillin the nurse left the ward.
a) Giving
b) Having given
c) Given
d) Was given

22.Выберите правильный вариант перевода:
Instruments to be used should be sterilized.
a)Инструменты должны быть использованы для стерилизации.
b)Инструменты необходимо использовать при стерилизации.
c)Инструменты для стерилизации должны быть использованы.
d)Инструменты, которые будут использоваться, следует стерилизовать.

23. Выберите правильный вариант перевода:
To prevent the recurrence of the disease he was administered antibiotics.
a)После предотвращения рецидива болезни ему назначили антибиотики.
b)Для предотвращения рецидива болезни ему назначили антибиотики.
c)Ему назначили антибиотики после рецидива болезни.
d) Из-за рецидива болезни ему назначили антибиотики.

24. Выберите правильный вариант перевода:
It is too late to perform an operation.
a) Это очень поздно делать операцию.
b) Это слишком поздно оперировать.
c) Поздно делать операцию тоже.
d) Делать операцию слишком поздно.

25. Выберите правильный вариант перевода:
One knows that not all types of antibiotics are effective.
a) Кто-то знает, что не все типы антибиотиков эффективны.
b) Не все типы антибиотиков, известные нам, эффективны.
c) Известно, что не все типы антибиотиков эффективны.
d) Он знает, что не все типы антибиотиков эффективны.

ЭТАЛОН ОТВЕТОВ

1 b	11 a	21 b
2 d	12 a	22 d
3 a	13 c	23 b
4 b	14 b	24 d
5 b	15 c	25 c
6 a	16 b	
7 c	17 b	
8 b	18 d	
9 c	19 c	
10 a	20 b	

Результаты апробации и стандартизации:
«отлично» 25-23 правильных ответов;
«хорошо» 16-22 правильных ответов;
«удовлетворительно» 10-15 правильных ответов;
«неудовлетворительно» 9 и меньше правильных ответов.

Вопросы для зачета (открытого типа)

I. Medical education

1. Where can a person get higher medical education in Russia (in Great Britain, in the USA)?
2. How can a person enter a higher medical school?
3. How long does the medical education last in Russia (in Great Britain, in the USA)?
4. What periods is the course of studies in Russia (in Great Britain, in the USA) divided into?
5. What subjects do the students study?

II. Saratov State Medical University (SSMU)

1. When was SSMU founded?
2. Who was the founder and the first rector of the University?
3. When did the medical faculty of the University become an independent medical Institute?
4. What faculties were opened at Saratov Medical Institute in 1930?
5. What faculties are there at SSMU now?

III. Matter

1. What is matter?
2. What are the states of matter?
3. What do physics and chemistry study?
4. What are physical and chemical properties of matter?
5. What are analysis and synthesis?

IV. Cytology

1. What is cytology?
2. What is a cell?
3. What are the main organelles of the cell?
4. What is phagocytosis?
5. What if pinocytosis?

V. Genetics

1. What is genetics?
2. What is the basic unit of heredity?
3. What controls hereditary traits?
4. What is mitosis?
5. What is meiosis?

VI. Chemistry

1. What does chemistry study?
2. What are the main types of substances?
3. What properties do substances have?
4. What are physical properties of substances?
5. What are chemical properties of substances?

VII. Microbiology

1. What is microbiology?
2. What are the most common microorganisms?
3. What are the portals of entry of infection?
4. What is bacteraemia?
5. What is viraemia?

VIII. Human body

1. What is a human organism?
2. What are the main parts of the human body?
3. What are the systems of the body?
4. What cavities are there in the human body?

5. What paired organs are there in the human body?

IX. Musculo-skeletal system

1. What is the skeleton? What is the skeleton composed of?
2. How many bones are there in the skeleton of the adult?
3. What are the bones of the trunk?
4. What does the upper (lower) extremity consist of?
5. What are the functions of the musculo-skeletal system?

X. Respiratory system

1. What organs is the respiratory system composed of?
2. Where are the respiratory organs located?
3. What is the structure of the lungs?
4. How is the process of respiration carried out?
5. What are the functions of the respiratory system?

XI. Cardio-vascular system

1. What is the cardio-vascular system composed of?
2. What are the main branches of the circulatory system?
3. Where is the heart located?
4. What does the heart consist of?
5. What are the main functions of the cardio-vascular system?

XII. Digestive system

1. What organs is the gastro-intestinal tract formed by?
2. Where is the stomach located?
3. What parts is the intestine divided into?
4. What are the subdivisions of the small (large) intestine?
5. What are the main functions of the digestive system?

Вопросы для зачета (открытого типа)

I. History of medicine

1. What are the three main stages in the history of medicine?
2. What are the main achievements in ancient medicine?
3. What are the main achievements in medicine of Middle Ages?
4. What are the main achievements in modern medicine?
5. What are the names of the most famous scientists in the history of medicine?

II. N.I. Pirogov

1. When was N.I. Pirogov born?
2. Where and how did he study?
3. At what age did N.I. Pirogov begin to work as a professor of surgery?
4. What is N.I. Pirogov famous for?
5. When did he die?

III. World Health Organization (WHO)

1. When was WHO founded?
2. How many member states are there in WHO?
3. What are the main goals of WHO?
4. What are the forms of activities of WHO?
5. Where are the headquarters of WHO stationed?

IV. Cooperation in medicine

1. What are the three types of international cooperation in medicine?
2. What is multilateral cooperation? What are its main forms?
3. What is bilateral cooperation? Give examples.

4. What are the forms of Russian-British and Russian-American cooperation?
5. What is unilateral cooperation? How is it rendered?

V. Respiratory diseases

1. What are the most common respiratory diseases?
2. What are the main etiological and risk factors of respiratory diseases?
3. What are the most typical signs and symptoms of respiratory diseases?
4. What methods of examination are used in diagnosing respiratory diseases?
5. What are the main principles of treatment of patients with respiratory diseases?

VI. Cardio-vascular diseases

1. What are the most common cardio-vascular diseases?
2. What are the main etiological and risk factors of cardio-vascular diseases?
3. What are the most typical signs and symptoms of cardio-vascular diseases?
4. What methods of examination are used in diagnosing cardio-vascular diseases?
5. What are the main principles of treatment of patients with cardio-vascular diseases?

VII. Gastro-intestinal diseases

1. What are the most common gastro-intestinal diseases?
2. What are the main etiological and risk factors of gastro-intestinal diseases?
3. What are the most typical signs and symptoms of gastro-intestinal diseases?
4. What methods of examination are used in diagnosing gastro-intestinal diseases?
5. What are the main principles of treatment of patients with gastro-intestinal diseases?

VIII. Diseases of the liver and bile ducts (hepato-biliary diseases)

1. What are the most common hepato-biliary diseases?
2. What are the main etiological and risk factors of hepato-biliary diseases?
3. What are the most typical signs and symptoms of hepato-biliary diseases?
4. What methods of examination are used in diagnosing hepato-biliary diseases?
5. What are the main principles of treatment of patients with hepato-biliary diseases?

IX. Infectious diseases

1. What are the most common infectious diseases?
2. What are the main etiological and risk factors of infectious diseases?
3. What are the most typical signs and symptoms of infectious diseases?
4. What are the main principles of treatment of patients with infectious diseases?
5. What are the most common methods to prevent infectious diseases?

КОМПЛЕКТ

ОРИГИНАЛЬНЫХ ТЕКСТОВ ДЛЯ РЕФЕРИРОВАНИЯ И ПЕРЕВОДА на зачете

MULTIFACTORIAL INHERITANCE

The term multifactorial inheritance refers to the process in which a disease or abnormality- is the result of the additive effect of one or more abnormal genes and environmental factors. The disorders attributed to this process include some of the most common malformations as well as medical conditions like allergic disorders, schizophrenia, and some types of hyperlipidemia. The number of genes involved is not known. Some investigators have postulated that the genes involved are "minor genes," which individually are not harmful but have a cumulative effect that is harmful; others postulate that genes that exert a major effect are also involved. Few of the environmental factors have been identified in humans; studies of conditions caused by multifactorial inheritance in animals emphasize their relevance. Some of

the nongenetic features identified in humans include seasonal variation in the occurrence of the disorder, increased frequency in families living in poor socioeconomic conditions, and uterine factors. A considerable amount of data must be available on many effected persons and their families before the disease or malformation is attributed to multifactorial inheritance. This term should not be used whenever the cause of familial occurrence is poorly understood.

Some of the features of multifactorial inheritance are similar to mendelian inheritance of single mutant genes, e.g., the incidence of specific conditions varies according to racial background; this racial predisposition persists after migration to other countries.

Most of the, features of multifactorial inheritance, however, are quite different from those observed in mendelian inheritance of a single mutant gene: (1) There is a similar rate of recurrence (usually 2-10%;) among all first-degree relatives (parents, siblings, and offspring of the affected infant). For example, if a couple has had 1 child with deft lip and palate, the risk that the next will be affected is about 4%; if 1 parent has cleft-lip and palate, the chance that the 1st child will have the same malformation is also about 4%. (2) Some disorders have a sex predilection. For example, pyloric stenosis' is much more common in males, whereas congenital dislocation of hips is much more common in females. (3) If there is an altered sex ratio, the affected person of the sex less likely to be affected is much more apt to have affected children. For example, a woman who had pyloric stenosis as an infant has a 25% chance of having a child similarly affected; the risk for the children of the father who had pyloric stenosis is only 4%. (4) The likelihood that both of identical twins will be affected with the same malformation is less than 100% but much greater than the chance that both nonidentical twins will be affected. This distribution contrasts with that of mendelian inheritance, in which identical twins always share a disorder due to a single mutant gene. (5) The risk of recurrence in subsequent pregnancies depends on the outcome in previous pregnancies. For example, the risk of recurrence for deft lip and palate is 4% for a couple with 1 affected child, but 9% after they have had 2 affected children. (6) The risk of abnormality in offspring is directly related to the severity of the malformation. For example, the infant who has congenital intestinal aganglionosis of a long segment of bowel has a greater chance of having an affected sibling than the infant who has aganglionosis of only a small segment.

GENERAL CLINICAL PRINCIPLES IN GENETIC DISORDERS

The Negative Family History A child with a genetic disease or malformation is usually the only known affected member of his or her family. This reflects the fact that the rates of recurrence are very low for common abnormalities of the chromosomes and for conditions attributed to multifactorial inheritance. For example, the recurrence risk for Down syndrome associated with trisomy-21 is 1%; for conditions attributed to multifactorial inheritance it varies from 2-10%. The recurrence risk for disorders with a mendelian pattern of inheritance is much higher (e.g., 25% for autosomal recessive disorders), but in small families it is more likely that autosomal recessive disorder will affect only l of 3 or,4 children rather than 2. In the case of autosomal dominant disorders, the child may be affected by a spontaneous genetic mutation rather than by inheriting the mutant gene from an affected parent. Generally speaking, a negative family history may be misleading.

Environmental Factors Since the family history is usually negative for the disorder under consideration, the parents often blame themselves and look for environmental factors which might have been the cause. The physician should anticipate their feelings of guilt and carefully discuss the events, including medications taken, to which congenital disorders may be attributed inappropriately parents.

Genetic Heterogeneity A single clinical manifestation may have more than 1 cause. An elevation in serum phenylalanine may be associated with classic phenylketonuria (either absence or deficiency of phenylalanine hydropxylase); absence or deficiency of the enzyme pteridin reductase; or deficient biopterin synthesis. Arachnodactyly may be an isolated characteristic of a

tall, thin person, or it may be a feature of a number of genetic disorders, including Marfan syndrome and contractural arachnodactyly.

ALTERATIONS IN BODI TEMPERATURE

DISTURBANCES OF HEAT REGULATION

CONTROL OF BODY TEMPERATURE In health, the body temperature of human beings is maintained within a narrow range despite extremes in environmental conditions and physical activity. This is also true for most birds and mammals, and such animals are termed *homeothermic,* or warm-blooded. An almost invariable accompaniment of systemic illness is a disturbance in temperature regulation, usually an abnormal elevation, or *fever.* In fact, fever is such a sensitive and reliable indicator of the presence of disease that thermometry is probably the commonest clinical procedure in use. Even in the absence of a frank febrile response, interference with heat regulation by disease is evident. This may take the form of flushing, pallor, sweating, shivering, and abnormal sensations of cold or warmth, or it may consist of erratic fluctuations of body temperature within normal limits when a patient is at bed rest.

Heat production The major source of basal heat production is through thyroid thermogenesis and the action of adenosine triphosphatase (ATPase) on the sodium pump of all membranes. The muscles are most important in promoting increased heat production through increased shivering. Heat production by muscle is of particular importance because the quantity can be varied according to the need. In most circumstances this variation consists of small increases and decreases in the number of nerve impulses to the muscles, causing inapparent tensing or relaxing. When, however, there is a strong stimulus for heat production, muscle activity may increase to the point of shivering, or even to a generalized rigor.

Heat loss Heat is lost from the body in several ways. Small amounts are used in warming food or drink and in the evaporation of moisture from the respiratory tract. Most heat is lost from the surface of the body, by *convection,* i.e., the transfer of heat to a fluid medium. Heat loss by convection depends on the existence of a temperature gradient between the body surface and the ambient air. A second mechanism for heat loss is *radiation,* which may be defined as an exchange of electromagnetic energy between (he body and the radiant environment. *Evaporation* is the third major mechanism for dissipating heat and is particularly important when the ambient temperature exceeds that of the body.

The principal method of regulating heat loss is by varying the volume of blood flowing to the surface of the body. A rich circulation in the skin and subcutaneous tissues carries heat to the surface, where it can escape. In addition, sweating increases heat loss by providing water to be vaporized. The sweat, or eccrine, glands are under the control of the sympathetic nerves which, in this instance, mediate cholinergic stimuli. Heat loss by sweating may be tremendous, and as much as 1 liter per hour of sweat may be evaporated. The amount of heat loss through sweating is also dependent upon the humidity in the air. The greater the humidity, the less the ability to lose heat through sweat.

When there is need for conservation of heat, adrenergic autonomic stimuli cause a sharp reduction in the blood flow to the surface. This causes vasocontriction and transforms the skin and subcutaneous tissue into layers of insulation.

Heat transfer within the body. This depends upon *conduction* i. e., the transfer of heat between adjacent organs, and upon *circulatory convection,* which is governed by bulk movement of body fluids and which is responsible for the transfer of heat between the cells and the bloodstream. It is useful, although oversimplified, to visualize the body as a central core at uniform temperatures surrounded by an insulating shell. The role of the shell as a mediator for heat conservation and heat loss is determined in part by its blood supply and by vasoconstriction or vasodilatation. Although insulation is relatively uniform throughout the body, some parts, such as the digits, are particularly susceptible to cold because of the increased surface-to-volume ratio. Moreover, blood that reaches the digits has already been cooled on the way. Insulation may be enhanced by the addition of clothing.

Neural control of temperature The control of body temperature, integrating the various physical and chemical processes for heat production or heat loss, is a function of cerebral centers located in the hypothalamus. A high-decerebrate animal has a normal temperature if the hypothalamus is left intact. On the other hand, an animal whose brainstem has been sectioned loses ability to control body temperature, which consequently tends to vary with the environment, a condition referred to as *poikilothermia.* Animal experiments suggest that the preoptic anterior hypothalamus and some centers in the spinal cord have neurons which respond directly to local temperature and act as a sensor for internal temperature. This function is distinct from the integrative function which responds to temperature-sensitive structures all over the body.

FACTORS AFFECTING NEURAL CONTROL OF TEMPERATURE The temperature-regulating system is a negative feedback control system, and possesses three elements essential to such a system: (1) receptors which sense the existing central temperatures; (2) effector mechanisms, consisting of the vasomotor, sudomotor, and metabolic effectors, and (3) integrative structures which determine whether the existing temperature is too high or too low and which activate the appropriate motor response. It is a negative feedback system because a rise in central temperature initiates mechanisms for losing heat while a fall in central temperature activates mechanisms for heat production and heat conservation. The activation of these effector responses is governed by a central integrative mechanism which may be compared with a thermostat and which responds to a variety of stimuli, such as the sensory impulses engendered in flushing or sweating, behavioral impulses, exercise, endocrine influences, and probably the temperature of the blood circulating through the hypothalamic centers. In a sense all these stimuli reset the thermostat.

A classic example of the endocrine influence on temperature is the effect of menstruation. The mean body temperature of women is higher during the second half of the menstrual cycle than it is between the onset of menstruation and the time of ovulation. The sensations of intense heat followed by diaphoresis that characterize the vasomotor instability experienced by some women at the menopause are undoubtedly the result of endocrine imbalance. The activation of the adrenal medulla in response to cold is another example of the relationship between the endocrine system and the thermoregulatory apparatus.

DISORDERS ASSOCIATED WITH HIGH TEMPERATURES Heat syndromes Four clinical syndromes are associated with high environmental temperature: *heat cramps, heat exhaustion, exertional heat injury,* and *heat stroke.* Although each of these entities may be separated from the other on clinical grounds, there is considerable overlap between them, and they may be considered as a series of syndromes along a single spectrum. The incidence of heat syndromes is unknown, but during an ordinary summer about 200 cases of heat stroke are reported. During the heat wave of July 1980, 1265 deaths from heat stroke were reported—784 from Kansas City and St. Louis alone. Heat syndromes occur primarily at elevated temperatures (>90°F) and at high humidities (>60%); and elderly individuals, those with mental illness or alcoholism or who receive antipsychotic drugs, diuretics, and anticholinergics, or those who reside in poorly ventilated places without air conditioning are most susceptible. Heat syndromes are especially prevalent during the first days of a heat wave before effective acclimatization can occur.

COUGH AND HEMOPTYSIS

COUGH Cough, one of the most frequent cardio respiratory symptoms, is an explosive expiration which provides a means of clearing the tracheo bronchial tree of secretions and foreign bodies.

MECHANISM Coughing may be initiated either voluntarily or reflex. As a defensive reflex it has both afferent and efferent pathways. The *afferent limb* includes cough receptors

within the sensory distribution of the trigeminal, glossopharyngeal, superior laryngeal, and vagus nerves. The *efferent limb* includes the recurrent laryngeal nerve (which causes glottic closure) and the spinal nerves (which cause contraction of the thoracic and abdominal musculature). The *sequence of a cough* includes an appropriate stimulus, which initiates a deep inspiration. This is followed by glottic closure, relaxation of the diaphragm, and muscle contraction against a closed glottis so as to produce maximally positive intrathoracic and intraairway pressures. These positive intrathoracic pressures result in a narrowing of the trachea, produced by an infolding of its more compliant posterior membrane. Once the glottis opens, the combination of a large pressure differential between the airways and the atmosphere coupled with this tracheal narrowing produces flow rates through the trachea close to the speed of sound. The shearing forces, which are developed aid in the elimination of mucus and foreign materials. A tracheostomy short-circuits glottic closure and therefore decreases the effectiveness of the cough mechanism.

ETIOLOGY Cough is produced by inflammatory, mechanical, chemical, and thermal stimulation of the cough receptors. *Inflammatory* stimuli are initiated by edema and hyperemia of the respiratory mucous membranes, and by irritation from exudative processes. Such stimuli may arise either in the airways (as in laryngitis, tracheitis, bronchitis, and bronchiolitis) or in the alveoli (as in pneumonitis and lung abscess). *Mechanical* stimuli are produced by inhalation of particulate matter, such as dust particles, and by compression of the air passages and pressure or tension upon these structures. Lesions associated with airway compression may be either extramural or intramural in type. The former include aortic aneurysms, granulomas. Pulmonary neoplasms, and mediastinal tumors: intramural lesions include bronchogenic carcinoma, bronchial adenoma, foreign bodies, granulomatous endobronchial involvement, and contraction of airway smooth muscle (bronchial asthma). Pressure or tension upon the air passages is usually produced by lesions associated with a decrease in pulmonary compliance. Examples of specific causes include acute and chronic interstitial fibrosis pulmonary edema, and atelectasis. *Chemical* stimuli may result from inhalation of irritant gases, including cigarette smoke and chemical fumes. Finally, *thermal* stimuli may be produced by inhalation of either very hot or cold air.

Cough is commonly associated with episodic wheezing secondary to bronchoconstriction in symptomatic patients with bronchial asthma. Recent reports have drawn attention to patients with chronic, persistent cough as the *sole* presenting manifestation of bronchial asthma. Such patients are characterized by (1) absence of a history of episodic wheezing and (2) no evidence of expiratory airflow obstruction by spirometry, but (3) hyperreactive airways (characteristic of asthma) when challenged with a cholinergic agent, methacholine.

DIAGNOSTIC EVALUATION When one is considering the above list of causes, чanswers to the following general questions will significantly narrow the diagnostic possibilities: Is the cough acute or chronic? Is it productive of sputum or nonproductive? A chronic productive cough may be caused by diseases such as chronic bronchitis, pulmonary tuberculosis, and pulmonary neoplasms. Are the findings on physical examination of the chest normal or abnormal? Is the chest roentgenogram normal or abnormal?

Features of the history, physical examination, chest roentgenogram, screening pulmonary function studies (static lung volumes and dynamic flow rates), and sputum examination may indicate a specific cause. The *history* may indicate specific diagnoses. Acute episodes of cough may be associated with such viral infections as acute tracheobronchitis or pneumonitis or with bacterial bronchopneumonia. Cough associated with an acute febrile episode and associated with hoarseness is usually produced by viral laryngotracheobronchitis. The character of the cough may suggest the anatomic site of involvement: the patient with a "barking" type of cough may have epiglottal involvement, while the cough associated with tracheal or major airway involvement is often loud and "brassy." Cough associated with generalized wheezing may be produced by acute bronchospasm. The time of occurrence of a cough may indicate a specific cause: a cough which occurs selectively at night suggests congestive heart failure; one related to meals suggests a tracheoesophageal fistula, a hiatal hernia, or an esophageal diverticulum; a

cough precipitated by a change in position suggests a lung abscess or a localized area of bronchiectasis. The description of sputum or secretions produced in conjunction with the cough may also be helpful: putrid sputum suggests a lung abscess; bloody sputum, bleeding (see "Hemoptysis." be- low), frothy and pink-tinged sputum, pulmonary edema; mucoid and massive sputum, alveolar cell carcinoma; purulent and/or large amounts of sputum, lung abscess and bronchiectasis.

On *physical examination* the character of the auscultatory findings may suggest the site of disease: inspiratory stridor and wheezing» may be present in laryngeal disease, inspiratory and expiratory bronchi favor tracheal and major airway involvement, coarse subcrepitant inspiratory rales may indicate interstitial fibrosis and/or edema, fine crepitant rales may indicate a process such as pneumonitis or pulmonary edema, which fills the alveoli with fluid. The *chest roentgenogram* may reveal the cause of the cough; it may show an intrapulmonary mass lesion, which may be either central or peripheral (Chap. 284) an alveolar filling process which may be pneumonic or nonpneumonic an area of honeycombing and cyst formation which may indicate an area of localized bronchiectasis, or bilateral hilar adenopathy which may indicate sarcoidosis or a lymphoma.

Screening pulmonary function studies may also indicate specific diagnoses. Significant expiratory obstruction to airflow (as determined from a forced expiratory flow maneuver), coupled with a history of cough and significant sputum production, suggests that irrespective of other lesions the patient has significant bronchitis. Decreased lung volume (as determined from the static lung volumes) indicates that a restrictive type of lung disease is presentreduction of lung volumes produced by thoracic, pleural, alveolar, or interstitial disease. Finally, a careful *sputum examination* may be more enlightening than a patient's description of the character of the sputum. Examination shows whether the sputum is thin or viscid, purulent or not, foul-smelling or not, blood-tinged or not, scant or copious. Gram stain and culture of the deep-cough specimen may reveal a specific bacterial, fungal, or mycoplasmal causation, while sputum cytology may result in a positive diagnosis of a pulmonary neoplasm.

Two features of cough should be highlighted: (1) A Cough is often so common in the cigarette smoker as to be ignored or minimized. *Any change in the nature or character of a chronic cigarette cough should initiate immediate diagnostic evaluation, with particular attention directed to detection of bronchogenic carcinoma.* (2) Female patients are inclined to swallow sputum and not to expectorate as male patients do. This tendency may lead to the incorrect conclusion that a cough in a female patient is irritative and nonproductive.

CHRONIC HYPOTENSION

Although many patients have been treated for chronic "low blood pressure," most of them, with systolic pressures in the range of 90 to 110 mmHg, are normal and may actually have a greater life expectancy than those with "normal" pressures. Patients with true chronic hypotension may complain of lethargy, weakness, easy fatigability, and dizziness or faintness, especially if arterial pressure is lowered further when the erect position is assumed. These symptoms are presumably due to a decrease in perfusion of the brain, heart, skeletal muscle, and other organs.

Chronic hypotension occasionally results from severe reductions of the cardiac output. The major endocrine causes of chronic hypotension are associated with deficient gluco- and mineralocorticoid secretion and resultant reductions of the in-travascular and interstitial fluid volume. Hypotension is usually more pronounced in patients with primary adrenocortical insufficiency than in those with hypopituitarism because secretion of the sail-retaining adrenocortical hormone, aldosterone, is partially preserved in pituitary insufficiency.

Malnutrition, cachexia, chronic bed rest, and a variety of neurologic disorders may result in chronic hypotension, especially in the standing position. Interference with the neural pathways anywhere between the vasomoior center and the efferent sympathetic nerve endings on the blood vessels or heart may prevent the vasoconstriction and increase in cardiac output which occur as a

normal response to a reduction in arterial pressure. Multiple sclerosis, amyotrophic lateral sclerosis, sy-ringomyelia, syphilitic or diabetic tabes dorsalis, peripheral neuropathies, spinal cord section, diabetic neuropathy, extensive lumbodorsal sympathuctomy, and the administration of drugs interfering with nerve transmission in the sympathetic nervous system are all associated with orthostatic hypotension.

HYPERTENSION

DIAGNOSIS Patients with elevations of arterial pressure are usually asymptomatic, and the blood pressure abnormality often arouses attention only incidentally during military, life insurance, or other periodic physical examinations.

ETIOLOGY A specific cause for the elevated arterial pressure cannot be defined for most patients with hypertension. The percentage of patients with so-called idiopathic, essential, or primary hypertension is high, varying from 80 to 95 percent depending on both the patient population and how extensive the "routine" evaluation is. More specific etiologic relationships have been established for a smaller group of patients with systemic hypertension. Primary renal diseases associated with the development of serious hypertension (as distinguished from renal damage secondary to hypertension) have been recognized for years, although in many cases the exact mechanism of blood pressure elevation is unknown. In some instances it is due to activation of the renin-angiotensin-aldosterone axis; in others, perhaps it is related to a reduced ability to excrete sodium and the sequence already described.

The most clearly defined etiologic relationships in the development of hypertension are found among the endocrine disorders. Adrenocortical hormones have also been implicated in the hypertensive syndromes associated with tumors or hyperplasia of the anterior pituitary (Cushing's syndrome, primary hyperaldosteronism. As well as with various congenital or hereditary enzyme defects (hypertensive adrenogenital syndromes). Secretion of excessive quantities of the pressor catecholamines, norepinephrine and epinephrine, associated with pheochromocytomas, i.e., chromaffin cell tumors arising from the adrenal medulla or sympathetic ganglia, is also commonly associated with hypertension. Up to 50 percent of patients with acromegaly may have hypertension, but the mechanism of their blood pressure elevation is less clear.

EFFECTS OF HYPERTENSION Patients with untreated hypertension die prematurely, most commonly due to heart disease, with strokes and renal failure also frequently occurring.

APPROACH TO THE PATIENT WITH HYPERTENSION The physician's first task is to determine whether or not a patient with a given level of arterial pressure has hypertension. Then, determinations of the extent of pretreatment evaluation, whether or not to treat, how to treat, and how frequently to reevaluate are necessary. In general, it is preferable to measure arterial pressure on several occasions prior to starting therapy using a mercury sphygmomanometer with the patient seated. Initial history, physical examination, and laboratory evaluation should be directed at uncovering correctable secondary forms of hypertension.

An assessment of the following areas in the medical history 'is particularly important: family or personal history of hypertension; drugs or dietary factors which may aggravate the hypertension, e.g., high salt intake, oral contraceptives, and hormones; cardiovascular risk factors including diabetes mellitus, smoking, lipid abnormalities, or strokes; cardiac or renal disease; and symptoms suggestive of secondary forms of hypertension, e.g., muscle cramps and weakness associated with primary aldosteronism or episodic headaches, palpitations, and sweating associated with pheochromocytoma.

The *physical examination* should include a standing blood pressure, height, weight, funduscopic examination, assessment of thyroid size, bruits in neck or abdomen, peripheral pulses including determination of synchrony between upper and lower extremities, examination of the heart for size, rate, murmurs, gallops, auscultation of the lungs, examination of the

abdomen for masses, and particularly kidney size, and a neurologic examination to assess the presence of deficits associated with a stroke.

The basic *laboratory evaluation* should consist of hematocrit, urinalysis, blood urea nitrogen or creatinine, serum potassium, ECG, and chest x-ray. Often blood glucose, uric acid, and cholesterol determinations and a blood count are also useful, particularly since they may be part of a battery of automated blood tests that as a group are about the same price as the individual tests listed above. Other studies to identify secondary forms of hypertension may be indicated on the basis of the initial therapy or physical examination.

If the diastolic pressure is consistently higher than 90 mm Ug, therapy is almost always indicated unless contraindications exist.

Therapy should be directed at reducing the arterial pressure to or near normal levels, since studies have documented the morbidity and mortality are reduced. In order to minimize drug side effects in achieving this goal, a "step-care approach' has been advocated. The principle involves initiating therapy with a small dose of a single drug, usually a thiazide diuretic increasing the dose of that drug, and then adding a beta-adrenergic blocker and. if necessary, other drugs one at a time. The therapeutic regimen should be revised as dictated by the arterial pressure measured at periodic intervals. The frequency of reevaluation should be as often as weekly while blood pressure is being lowered in patients with initial diastolic pressures greater than 115 mmHg, and approximately every 4 months in symptom-free patients on stable treatment programs.

The specific drugs are discussed elsewhere. However, it is important to emphasize here that control of arterial pressure is a lifelong endeavor the success of which is often dependent on the physician's ability to motivate the patient to adhere to the therapeutic program and to recognize the pharmacologic interactions and adverse reactions of antihypertensive agents.

ANOREXIA, NAUSEA, AND VOMITING

Anorexia, or loss of the desire to eat, is a prominent symptom in a wide variety of intestinal and extraintestina1 disorders. It must be clearly differentiated from satiety and from specific food intolerance. Anorexia occurs in many disorders and as a result *by itself is of little if specific diagnostic value.* The mechanisms whereby hunger and appetite are modified in various disease states are poorly understood. Normally food intake is regulated by two hypothalamic centers - a lateral "feeding center" and a ventromedial "satiety center." The latter inhibits the feeding center following a meal, leading to the sensation of satiety. There is increasing evidence to suggest that the brain-gut peptide cholecystokinin (CCK) has a satiety effect and is involved in the regulation of feeding behavior. Anorexia is commonly seen in diseases of the gastrointestinal tract and liver. For example, it may precede the appearance of jaundice in hepatitis, or it may be a prominent symptom in gastric carcinoma. In the setting of intestinal disease, anorexia should be clearly differentiated from *sitophobia,* or fear of eating because of subsequent or associated discomfort. In such S. circumstances, appetite may persist, but the ingestion of food is curtailed nonetheless. Sitophobia may be seen, for example, in regional enteritis (especially with partial obstruction) or in patients with gastric ulcer following partial or total gastrectomy. Anorexia may also be a prominent feature of severe extraintestinal diseases. For example, anorexia may be profound in severe congestive heart failure and is often associated with cardiac glycoside intoxication. It may be a major symptom in patients with uremia, pulmonary failure, and various endocrinopathies (e.g., hyperparathyroidism, Addison's disease, and panhypopituitarism). Anorexia also often accompanies psychogenic disturbances, such as anxiety or depression.

NAUSEA AND VOMITING Nausea and vomiting may occur independently of each other, but generally they are so closely allied that they may conveniently be considered together *Nausea* denotes the feeling of the imminent desire to vomit, usually referred to the throat or epigastrium. *Vomiting* refers to the forceful oral expulsion of gastric contents; *retching* denotes the labored rhythmic respiratory activity that frequently precedes emesis. Extremely forceful

projectile vomiting is a special form of vomiting which has significance because it connotes the presence of increased intracranial pressure.

Nausea often precedes or accompanies vomiting. It is usually associated with diminished functional activity of the stomach and alterations of the motility of the duodenum and small intestine. Accompanying severe nausea there is often evidence of altered autonomic (especially parasympathetic) activity: pallor of the skin, increased perspiration, salivation, and the occasional association of hypotension and bradycardia (vaso-vagal syndrome). Anorexia is also often present.

Following a period of nausea and a brief interval of retching, a sequence of involuntary visceral and somatic motor events occurs, resulting in emesis. The stomach plays a relatively passive role in the vomiting process, the major ejection force being provided by the abdominal musculature. With relaxation of the gastric fundus and gastroesophageal sphincter a sharp increase in intraabdominal pressure is brought about *by* forceful contraction of the diaphragm and abdominal wall. This together with concomitant annular contraction of the gastric pylorus, results in the expulsion of gastric contents into the esophagus. Increased intrathoracic pressure results in the further movement of esophageal contents into the mouth. Reversal of the normal direction of esophageal peristalsis may play a role in this process. Reflex elevation of the soft palate during the vomiting act prevents the entry of the material into the nasopharynx, whereas reflex closure of the glottis and inhibition of respiration help to prevent pulmonary aspiration.

Repeated emesis may have deleterious effects in a number of different ways. The process of vomiting itself may lead to traumatic rupture or tearing in the region of the cardioesophageal junction, resulting in massive hematemesis, the Mallory-Weiss syndrome. Prolonged vomiting may lead to dehydration and the loss of gastric secretions (especially hydrochloric acid), resulting in metabolic alkalosis with hypokalemia. Finally, in states of central nervous system depression (coma, etc.), gastric contents may be aspirated into the lungs, with a resulting aspiration pneumonitis.

Clinical classification Nausea and vomiting are common manifestations of organic and functional disorders. The precise mechanisms triggering vomiting in the various clinical states are poorly understood, making classification of mechanisms difficult. The categories mentioned below serve to illustrate some of the many disorders which may be accompanied by nausea and vomiting.

Many *acute abdominal emergencies* which lead to the "surgical abdomen" are associated with nausea and vomiting. Notably, vomiting may be seen with inflammation of a viscus as in acute appendicitis or acute cholecystitis, obstruction of the intestine, or acute peritonitis.

In many of the disorders involving *chronic indigestion* nausea and vomiting may be prominent. Emesis may *be either* spontaneous or self-induced and may lead to relief of symptoms, as for example, in uncomplicated peptic ulcer. Nausea and vomiting may accompany the distention and pain seen in the aerophagic syndromes. Often in patients with chronic indigestion, nausea and vomiting may be provoked by specific foods *(e.g.,* fatty foods), for reasons that are poorly understood.

Acute systemic infections with fever, especially in young children, are frequently accompanied by vomiting and often by severe diarrhea. The mechanism whereby infections remote from the gastrointestinal tract produce these manifestations is unclear. Viral, bacterial, and parasitic infections of the intestinal tract may be associated with severe nausea and vomiting, often with diarrhea. Severe nausea and vomiting may be prominent in viral hepatitis, even before the appearance of jaundice.

Central nervous system disorders which lead to increased intracranial pressure may be accompanied by vomiting, often projectile. Brain swelling due to inflammation, anoxemia, acute hydrocephalus, neoplasms, etc., may thus be complicated by vomiting. Disorders of the labyrinthine apparatus and its central connections which underlie vertigo may be accompanied by vomiting with nausea and retching. Acute labyrinthitis and Meniere's disease are examples of such disturbances. Migraine headaches, tabetic crises, and acute meningitis are additional

examples of disorders of the nervous system which may lead to vomiting. In the reactive phase of hypotension with syncope, there may also be nausea and vomiting.

Severe nausea and vomiting may be present in *acute myocardial infarction,* especially of the posterior wall of the heart. Nausea and vomiting may also be seen in *congestive heart failure*, perhaps in relation to congestion of the liver. The possibility that these symptoms may be due to drugs (e.g., opiates or digitalis) should always be borne in mind in patients with cardiac disease.

Nausea and vomiting commonly accompany several *endocrinologic disorders,* including diabetic acidosis and adrenal insufficiency, especially adrenal crises. The morning sickness of early pregnancy is another instance of nausea and vomiting possibly related to hormonal changes.

The *side effects of many drugs and chemicals* include nausea and vomiting. In some instances this is because of gastric irritation which stimulates the medullary vomiting center.

Psychogenic vomiting means vomiting which may occur as part of any emotional upset on a transitory basis or more persistently as part of a psychic disturbance. Close observation will usually disclose the condition to be one of regurgitation rather than of vomiting, and weight loss may not correspond at all to the patient's description of the frequency and severity of vomiting. Anorexia nervosa is an emotional disturbance which may be associated not only with anorexia but also with vomiting. Often patients with emotional disorders and vomiting maintain a relatively normal state of nutrition because a relatively small amount of the ingested food is vomited.

CHEMICAL INTERVENTION

The chemical substances administered for medical purposes include not only drugs but also vaccines, hormones, anesthetics and even foods. All such measures lend themselves to use, abuse and misuse

A medical student asks: "Why is it that most of the drugs we prescribe are destroyed in the liver? How could nature have designed the liver to destroy drugs manufactured by man millions of years later?" The answer lies in the still dimly perceived universe of chemical reactions embodied in all living organisms. In those organisms that eat, food must be turned into the chemicals of life. The liver plays a key role in this extraordinary performance. Most of the blood that leaves the stomach and the intestines must pass through the liver before reaching the rest of the body. The liver is thus strategically placed to process nutrients and to detoxify poisons that might be ingested with the food.

It is therefore not surprising that when a chemist manufactures a drug, which somehow must alter the chemistry of the patient, the general structure of the new chemical has already been anticipated by the liver. The chemical structure of a refined drug is often similar to a naturally occurring substance. For example, alkaloids such as opium, from which heroin is derived, flourished in poppy plants that preceded man on the earth. Detoxification of such chemicals in the liver can be regarded as one of the developments that enabled the species to survive". In the Garden of Eden the liver must have protected Adam from alkaloids, if not from the apple.

This relation between drugs and the liver illustrates two general aspects of man's chemical intervention in his own physiology. The first aspect is that life itself is an awe-inspiring multitude of natural chemical reactions. Sir Macfarlane Burnet put it succinctly: "It is very humbling to realize that there is more information packed into the head of one spermatozoon than there is in all the volumes of the *Journal of Biochemistry."* The second aspect is that when man deliberately alters these reactions, whether through chemicals derived from nature or through those manufactured by man in imitation of nature, there is a simultaneous potential for healing and for injury, sometimes for life or for death.

It is small wonder, then, that in man's ancient and even recent efforts at chemical intervention the health benefits have been far outweighed by chemical mayhem. In past centuries harmful agents were often prescribed by physicians (a little arsenic as a tonic) or imbibed

unwittingly (lead in the wine goblets and cooking utensils of ancient Rome). Destruction has been and still is sought out recklessly by some in opium or heroin addiction. Oliver Wendell Holmes was largely correct when he observed that "if all the drugs in the pharmacopoeia save three were dumped into the ocean, it would be so much the better for our patients and so much the worse for the fish." At the beginning of the 20th century there were only about six reliable and effective pharmaceutical preparations, namely digitalis (still helpful in many kinds of heart disease), morphine, quinine (for malaria), diphtheria antitoxin, aspirin and ether. Two other successful means of chemical intervention were also available: immunization against smallpox and rabies. This pharmacopoeia remained basically unchanged until about die time of World War II. Since then drugs and other substances that can, if employed wisely, usefully affect the chemistry of life have been produced in startling numbers.

The food we eat provides the chemicals the body needs to continue functioning. Much remains to be learned about what constitutes an optimal diet. Except where food intake is affected by peculiar food customs, by poverty, by social upheavals such as war, by drug addiction, by alcoholism or by some other illness, the nutrition of man today is generally much better than it was at any time in the past. It is difficult otherwise to explain the increased stature of people of many nations.

This is not to say that we now have the best diet possible. Most of us in the U.S. and in many other countries eat too much. The. ideal amounts of animal fats, vegetable fats, proteins, carbohydrates, roughage, vitamins and minerals in the diet are still matters for investigation and debate. Even with our limited knowledge, however, physicians are able to prescribe special diets that are clearly beneficial for people with certain inborn errors of metabolism. For example, sprue is an illness that often causes diarrhea and malnutrition because of poor absorption of food in the small intestine. The inborn error in sprue has not yet been discovered, but it is known that patients with sprue are intolerant of gluten, a sticky protein found in wheat and some other foods. As long as gluten is consumed, patients subject to sprue suffer from the symptoms of the disease. The delicately fringed microscopic lining of the small intestine becomes peculiarly blunted and inefficient. Good health can almost always be restored simply by omitting gluten from the diet.

Lactose, the sugar found in milk, is not itself absorbed in the bloodstream. Its molecule is first cleaved in the small intestine into the smaller molecules of glucose and galactose, two sugars that can be readily absorbed. The cleavage of lactose into glucose and galactose is accomplished by an enzyme called lactase. After infancy some people develop a deficiency of lactase. When a person with a lactase deficiency drinks a large amount of milk, diarrhea and various kinds of abdominal discomfort often ensue. The remedy is a diet that does not contain lactose. Intolerance for lactose is an inherited metabolic trait.

Sprue and lactase deficiency illustrate a small number of conditions in which a specific diet constitutes effective chemical intervention. In some other illnesses, probably also of genetic origin, certain diets can provide partial or occasional relief. For example, there is one kind of diabetes (characterized by the excretion of glucose into the urine) that appears in people who are too fat. This diabetes is greatly ameliorated by a diet low enough in calories to ensure an optimal weight.

A number of diets that are of no proved value at all are widely publicized and sold. For example, some diets are said to be therapeutic for various mental illnesses, but there is no proof that this is so. Others are based, mistakenly but profitably, on the notion that low blood sugar (hypoglycemia) 'is a very common ailment and aim to correct it even when it is not present. There are individuals who do show various types of periodic lowering of the blood-sugar concentration, but these illnesses are not common and should be diagnosed and treated only by a physician. In fact, if any unusual diet is embarked on, it should only be on a physician's advice.

The ready availability of pure vitamins has made it possible to halt many diseases that are caused by the absence of certain vitamins in the diet or by the inability to absorb them. Pernicious anemia, which was once invariably fatal, can now be managed with infrequent and inexpensive injections of vitamin B-12. Vitamins are often taken unnecessarily. Vitamin C

prevents or cures scurvy, once a lethal disease of sailors and others long-removed from fresh fruits and vegetables, but there is no convincing evidence that it cures or prevents colds. Fortunately it is harmless, even in large doses, as are the B vitamins. Vitamins A and D, on the other hand, are poisonous in very large doses.

With some exceptions, tampering with ordinary nutritional habits is not beneficial. Nearly everyone with an adequate diet thrives, in spite of wide variations in what normal people eat. This is in striking contrast to the difficulties that may be encountered when, because of illness or accident or surgery, a patient cannot eat and must be nourished intravenously. Depending on the conditions, the problem may be relatively simple. For example, a patient who is otherwise well nourished and healthy but who cannot eat for a few days after surgery may require only appropriately sterile and optimal concentrations of glucose and salt.

The situation is quite different when the patient has extensive bowel disease and must be nourished intravenously for two months. A host of problems, some of them well understood and others poorly, confront the physician. He must worry about the concentration of such elements as sodium, potassium, calcium, magnesium and phosphorus. He must devise ways of infusing adequate amounts of protein or of amino acids, the molecules of which protein is made. Intravenous protein is expensive and carries with it some risks. Constant infusions require exceedingly careful techniques to avoid inflammation of the veins and serious infections. In spite of such difficulties chemical intervention to provide complete nutrition by intravenous feeding has been accomplished and is a monumental achievement.

GENETIC ASPECTS 0F DISEASE

GENETIC PRINCIPLES More than one-fifth of the proteins (and hence genes) in each human being exist in a form that differs from the one present the majority of the population. This remarkable genetic variability, or polymorphism, among "normal" people accounts for much of the naturally occurring variation in body traits such as height, intelligence, and blood pressure. Moreover, these genetic differences cause variability in the ability of individuals to handle every environmental challenge, including those that produce disease. Thus, human disease can be conlered to occur as a result of an interaction between an individual's genetic makeup and the environment. In certain diseases, however, the genetic component is so overwhelming that expresses itself in a predictable manner without a requirement for extraordinary environmental challenges. Such diseases are termed *genetic disorders.*

MOLECULAR BASIS OF GENE EXPRESSION All hereditary information is transmitted from parent to offspring through the inheritance of specific molecules of deoxyribonucleic acid DNA). DNA is a linear polymer composed of pyrine and py-ridine bases whose sequence ultimately determines the sequence of amino acids in every protein molecule made by the body. The four types of bases in DNA are arranged in groups three, each group forming a code word, or codon, that signifies a particular amino acid. A *gene* represents the total sequence of bases in DNA that specifies the amino acid sequence with a single polypeptide chain of a protein molecule. Genetic information encoded in the DNA of the chromosomes is first transcribed into a *ribonucleic acid* (RNA) copy. During transcription the ribose nucleotides align themselves ng the DNA according to base-pairing rules. Thus, adenine DNA pairs with uridine of RNA, cytosine pairs with gua, thyrnine pairs with adenine, and guanine pairs with cytose. The ribose bases are joined together by RNA polymerase. The resulting *RNA transcript* forms the template for transla into the amino acid sequence of a protein. The DNA of many genes is fragmented into discrete coding regions (exons) separated by noncoding regions (introns or intervening sequences). The *coding regions* contain the information specifying the sequence of amino acids in the polypeptide chain. The *intervening sequences* are composed of sequences of bases that act as spacers between the coding regions; they are not translated into protein. The transcription of DNA produces a faithful copy of the entire gene sequence; thus, the RNA transcript contains a mosaic of coding and intervening sequences. The RNA transcript is edited

in the nucleus before it passes into the cytoplasm. In the editing process, the intervening sequences are excised and the coding regions are spliced together to form One continuous gene.

After processing, the edited RNA, which is called *messenger RNA* (mRNA) leaves the nucleus and enters the cytoplasm where it becomes associated with *ribosomes* and thereby serves as a template for the ribosomal synthesis of proteins. Each of the 20 precursor amino acids for protein synthesis is attached in the cell cytoplasm to specify molecules called *transfer RNA* (tRNA). Each tRNA contains a sequence of purine and pyrimidine bases that is "complementary" to a specify codon in the mRNA. These tRNA molecules with their attached amino acids line up along the mRNA molecule in the precise order dictated by the mRNA code. Under the action of a variety of cytoplasmic enzymes (initiation factors, elongation factors, and termination factors), peptide bonds are formed between the various amino acids, and the completed protein is released from the ribosome.

MAINTENANCE OF GENETIC DIVERSITY THROUGH TRANSMISSION AND SEGREGATION OF GENES It is estimated that the amount of DNA in the nucleus of each human cell is sufficient to code for more than 100,000 genes and hence to specify more than 100,000 polypeptide chains. The genes are arranged in a linear sequence of DNA that together with certain histone proteins form rod-shaped bodies called *chromosomes.* Each somatic cell contains 46 chromosomes, arranged in 23 pairs, one of each pair derived from each of the individual's parents. Thus, each individual inherits two copies of each chromosome and hence two copies of each gene. The chromosomal location of the two copies of each gene is termed the *genetic locus.* When a gene occupying a genetic locus exists in two or more diffйrent forms, these alternate forms of the gene are referred to as *alleles.*

In humans, a given gene always rйsides at a specified genetic locus on one particular chromosome. For example, the genetic locus for the Rh blood group is on the short arm of chromosome 1; at this chromosomal site there are two Rh genes, one on chromosome I derived from the mother and the other on chromosome 1 derived from the father. When two genes at the same genetic locus are identical, the individual is a homozygote. When the two genes differ (i.e., two alleles are present at the locus), the individual is a heterozygote. Each normal human is heterozygous at approximately 20 percent of genetic loci and homozygous at 80 percent.

The genetic information carried on chromosomes is transmitted to daughter cells under two diffйrent sets of circum-stances. One of these occurs whenever a somatic cell (i.e., a nongerm cell) divides. This process called mitosis, functions to transmit identical copies of each gene to each daughter cell, thus maintaining a uniform genetic makeup in ail cells of a single individual. The other set of circumstances prevails when genetic information is to be transmitted from one individual to an offspring. This process, called meiosis, functions to produce germ cells (i.e., ova or spermatozoa) that possess only one copy of each parental chromosome, thus allowing for new combinations of chromosomes to occur when ovum and sperm cell fuse during fertilization.

During the process of meiosis, the 46 chromosomes of an immature germ cell arrange themselves in 23 pairs at the center of the nucleus, each pair being composed of one chromosome derived from the mother and its homologous chromosome derived from the father. At a specified point in the meiotic process, the two partner chromosomes separate, only one of each pair going into each daughter cell, or gamete. Thus, meiosis produces gametes with a reduction in the number of chromosomes from 46 to 23, each game having received one chromosome from each of the 23 pairs. The assortment of Chromosomes within each pair is random so that each cell receives a different combination of maternal and paternal chromosomes. During the process of fertilization, the fusion of ovum and sperm cell, each of which has 23 chromosomes, results ultimately in an individual with 46 chromosomes.

The independent assortment of chromosomes into gametes during meiosis produces an enormous diversity among the possible genotypes of the progeny. For each 23 pairs of chromosomes, there are 2^{23} different combinations of chromosomes that could occur in a gamete,

and the likelihood that one set of parents will produce two offspring with the identical complement of chromosomes is one in 2^{23}or one in 8,4 million (assuming no monozygotic or identical twins).

RECOMBINATION Adding to the genetic diversity in humans is the phenomenon of *genetic recombination.* During meiosis, when homologous chromosomes are paired, bridges frequently from between corresponding regions of the chromosome pair. These bridges, or *chiasmata* are regions in which the two chromosomes break at identical points along their length and subsequently rejoin, the distal segments having been switched from one homologous chromosome to another. This process is designated *crossing over.* Although no net change in the amount of genetic material occurs during crossing over, a recombination of genes does occur. For example, consider a chromosome with two loci A and B, located at opposite ends of the same chromosome.

CELLS AND AGING

Frederic Verzar, the Swiss dean of gerontologists, once said: "Old age is not an illness; it is a continuation of life with decreasing capacities for adaptation." Only recently has his view of aging as a progressive failure of the body's homeoslatic adaptive responses gained wide acceptance. There has been a strong tendency to confuse aging with many diseases frequently associated with it especially cancer and atherosclerosis. Each, in fact, probably accelerates the other.

The obvious characteristics of aging arc well known: graying and loss of hair, loss of teeth, wrinkling of skin, decreased muscle mass, and increased fat deposits. The physiological signs of aging are gradual deterioration in function and capacity to respond to environmental stress. Thus, basic kidney and digestive metabolic rates decrease, as does the ability to maintain a constant internal environment despite changes in temperature, diet, and oxygen supply. These manifestations of aging are related to a decrease in the actual number of cells in the body (100,000 brain cells are lost each day) and to the disordered functioning of the cells that remain.

The extracellular components of tissues also change with age. *Collagen* fibers, responsible for the strength of tendons, increase in number and change in quality with aging. These changes in arterial walls are as much responsible for the loss of elasticity as those in arteriosclerosis. *Elastin,* another constituent of the intercellular matrix, is responsible for the elasticity of blood vessels and skin. It thickens, fragments, and acquires a greater affinity for calcium with age changes that may be associated with the development of arteriosclerosis.

Several kinds of cells in the body heart cells, skeletal muscle cells, neurons are incapable of replication. Experiments have proved that many other cell types are limited when it comes to cell divisions. Embryonic fibro-blast cells grown outside the body divided only 50 times and then stopped. Other experiments showed that the number of divisions correlated with the donor's age. The finite lifetime of cultured human cells has been observed in many other normal cell types including skin, brain, liver, and smooth muscle. No exception has been found to the general rule that normal cells possess a finite capacity to divide. The number of divisions also correlated with the normal life span to the different species from which the cells were obtained strong evidence for the hypothesis that cessation of mitosis is a normal, genetically programmed event.

Just as the factors that limit the life of an individual cell are unknown, so are those that restrict the growth or life of a tissue or organ. At menopause the ovary ceases to function. Certain ovarian cells die long before the rest of the female body. Perhaps similar mechanisms determine longevity.

Some investigators have studied aging from the standpoint of immunology. The ability to develop antibodies is said to diminish with age. Senescence, according to researchers, results in the older person's immunological system having a "shotgun," rather than a specific, response to foreign protein. This shotgun response may include an autoimmune reaction that attacks and gradually destroys the individual's own normal tissue and organs.

AGING HYPOTHESES

Most gerontologists believe that aging is a manifestation of the genetic coding within the cells of an organism. A logical extension of the concept of development that begins from the moment of conception, aging must be part of the ongoing genetic expression of events that guides us through embryological and fetal development, through childhood changes, adolescence, and maturity. Three general hypotheses are used as a basis for additional research.

The first hypothesis proposes that, as time passes, the information-processing apparatus of cells begins to make more and more errors. As a result, faulty enzymes would lead to a decline in the functional capability of the cells. Experiments designed to study protein synthesis in aging cells have not produced evidence that supports this hypothesis.

The second hypothesis proposes that many of the genes along the DNA molecule are repeated in identical sequences, making the genetic message very redundant. When an active gene is damaged, it is replaced by another of the copies. Thus, as a person lives, the copies are gradually used up, errors accumulate, and functional losses result. Therefore, the greater the redundancy, the greater the life span.

The third hypothesis proposes that aging is a continuation of a normal sequence of genetic signals that regulate development. This hypothesis suggests that "aging genes" are activated in the proper sequence, which causes a slowing down of biochemical pathways that are expressed in the recognizable changes of aging.

Two cell lines are known to escape from the inevitability of aging or death. These are germ cells and cancer cells. Perhaps these cell lines share a common genetic mechanism that makes them immortal. Fertilization is a process that resets or reprograms a cell's clock by re-shuffling genetic information. Viruses can invade a cell's DNA and reshuffle the DNA to reset the clock within the cell. These mechanisms make it certain that each member of a species is programmed to die but they ensure that the species will survive.

CANCER

Any cell capable of mitotic division can undergo neoplastic transformation. Thus, cancers can only arise from those tissues that have active stem cells or cells that can revert to an active mitotic stale, such as liver hepatocytes or the small lymphocytes. Cancers cannot arise from irreversible postmitotic cells of cardiac or skeletal muscle or neuronal tissue.

Cancer invariably starts with a single cell that undergoes a transformation and then produces a clonal expansion forming a tumor mass. Since all the cells are clones of the original transformed cells, these cells also are clonogenic and they can also divide indefinitely. Thus, a neoplastic clone becomes immortal.

The molecular mechanisms that can trigger the change in the initial cell are very diverse. Several pathways that could produce the neoplastic transformation have been described. Some of these produce genetic alterations within the cell. Others seem to reactivate silenced genes that were important during earlier development. Somatic mutations alter the genome by giving rise to deletions or rearrangements of the nuclear DNA. Some viruses induce tumors when they insert themselves into the cellular DNA and thus introduce new additional "genetic" information that leads to the altered behavior.

When normal cells change into neoplastic cells, they develop a very "antisocial" behavior toward the normal cells. Malignant cells characteristically invade adjoining tissues and grow into otherwise inappropriate locations. They grow rapidly and in irregular patterns. The most devastating feature of their behavior is their ability to disassociate themselves from the proliferating mass and enter the lymphatic or blood systems. When such cancer cells find an appropriate location, they invade the new territory and form a secondary site of tumor growth.

CONSEQUENCES OF NEOPLASMS

Neoplasms can affect the host in many ways. Benign growths do not invade the surrounding tissue nor do they metastasize and so their effects are restricted m their site of origin. They can elicit very dangerous responses, or their effects can be trivial. For example, a small strictly benign tumor in the subcutaneous tissue of the arm in could pose a cosmetic problem but probably very little else. On the other hand, a perfectly benign tumor can actually kill the host if it grows in a vital region such as the brain. There, a benign tumor could, by virtue of its increasing size, exert pressure and crush some vital center. Therefore, while the word benign may imply a kind or generous attitude, benign tumors should be carefully examined; they are not inconsequential. Benign tumors of endocrine glands can result in uncontrollably high levels of the circulating hormone with disastrous effects. Benign tumors can be surgically removed, thus eliminating any disease.

Malignant neoplasms (cancers) can not also duplicate the effects of benign tumors but they act more aggressively and cause more destruction because they grow at a much faster rate. Their effects are widespread because of their metastatic activity. The rapidly growing cells compete nutritionally with the normal cells. Thus, frequently, patients with advanced cancer appear malnourished. The advanced cancer patient dies from an episode of pneumonia or systemic sepsis.

Malignant tumors are treated in a variety of ways and often in a combination of ways. Curative therapy involves surgery to remove the neoplasm, irradiation, and chemotherapy. In some research hospitals immunotherapy employing monoclonal antibodies is being studied.

AN APPROACH TO INFECTIOUS DISEASES

THE SCOPE OF INFECTIOUS DISEASES The vast majority of human and animal diseases of known etiology are produced by biologic agents: viruses, rickettsias, bacteria, mycoplasma, Chlamydia, fungi, protozoa, or nematodes. No small part of the past and present importance of infectious diseases in medical practice is attributable to their enormous frequency and the public health implications of their contagiousness. However, developments in sanitary engineering, vector control, immunization, and specific chemotherapy have modified the situation favorably. Although important exceptions remain infectious diseases as a class are more easily prevented and more easily cured than any other major group of disorders. Despite the elimination of some infectious diseases such as smallpox and the profound reduction in the morbidity and mortality rates of many, humans are by no means free of infection. In fact, the total human load of disease produced by microbial parasites has decreased only modestly, primarily through smallpox and malaria control and better health care in developing countries. As certain specific microbial infections have been controlled, others have emerged as troublesome therapeutic and epidemiologic problems. With the introduction of cytotoxic drugs, massive irradiation in the treatment of malignant diseases, and immunosuppressive agents to control the rejection of transplanted organs, the insertion of prosthetic devices into the bloodstream, and the progressive longevity of people with chronic degenerative diseases, infections due to organisms previously considered saprophytic or commensal have increased. These infections have also been termed opportunistic. As Dubos has pointed out, microbial infections appear to form an inherent part of human life.

Because of better environmental sanitation and other measures that now prevent contact with many microbial agents, and the development of acquired immunity early in childhood, certain infections have been seen more frequently in adults. For example, as contact with poliomyelitis virus in childhood declined in many countries, paralytic poliomyelitis became more common in young adults. Hemophilus influenzae meningitis and pneumonia is being reported more frequently in adults than heretofore, and decreasing infection with the tubercle bacillus raises questions about the status of antituberculous immunity in adults. For reasons that are not clear, hepatitis A is predominantly a disease of young adults, while non - A, non-B hepatitis tends to occur in individuals over 35 years of age. As antimicrobial agents reduce the mortality associated with certain common infections, other microbes emerge as important causes

of human disease. If an infection occurs during or immediately following a course of chemotherapy, it is often caused by a microorganism that is resistant to the drug that was given; such an infection is termed a superinfection. While it is relatively unusual nowadays for patients to die of uncomplicated pneumococcal pneumonia, a disease readily handled with available antimicrobials, it is common to see serious disease produced by microorganisms which are much more resistant even though they are often part of the normal microbial flora in humans. These include staphylococci, gram-negative enteric bacilli, and a variety of anaerobes and fungi. One important mechanism by which resistance is conferred on gram-negative enteric bacteria is the action of R factors.

THE PARASITE AND THE HOST. The interaction between microorganism and humans that results in infection and disease is complex. Much has been learned about the way in which microbes enter the body, the ways in which they produce tissue injury, the influence of specific immunity and "nonspecific" resistance of the host, and the mechanisms of recovery. It is not yet possible to transfer in any specific way much of the information that has been acquired to the individual patient with an infection. However, considerable progress is being made. Examples are the sexual transmission of hepatitis A virus; the major role that Chlamydia are found to play in the causation of pelvic inflammatory disease; the role of Norwalk and rotaviruses in infectious diarrheas; and advances in antimicrobial therapy in containing heretofore difficult-to-treat bacteria .

INFECTION AND CLINICAL DISEASE. It is well known that microorganisms of different species or different strains of the same species vary widely in their capacity to produce disease and that human beings are not equally susceptible to the disease caused by a given bacterium or virus. Furthermore, while a specific infectious disease will not occur in the absence of the causative organism, the mere presence of the organism in the body does not lead invariably to clinical illness. Indeed, the production of symptoms in humans by many parasites is the exception rather than the rule, and the *subclinical infection* or the "carrier» state" is the usual host-parasite relationship. *Disease* in a clinical sense is not synonymous with the presence of the organism or injection in a microbiological sense. In fact, for most organisms the number of subclinical infections far exceeds that of clinical disease.

MECHANISMS OF INJURY. It is customary to refer to bacteria or other microorganisms that are capable of producing disease as *pathogenic*. *Virulence*, the degree of pathogenicity, should be distinguished from invasiveness, the ability to spread and disseminate in the body. For example, *Clostridium tetani* is pathogenic and, by virtue of its exotoxin, highly virulent, but it is almost completely lacking in invasiveness. Moreover, in certain circumstances and in certain anatomic locations, mildly "pathogenic" organisms can produce fatal disease, or highly "pathogenic" species can multiply without producing any harmful effect.

A few microorganisms produce toxins that account for the tissue damage and physiological alterations of infection. *Hypersensitivity* to components of the organism is demonstrable in several infections to account for the manifestations of disease. For many pathogenic agents, an explanation of their damaging effects upon the host is incomplete or wholly lacking. Generally, therefore, the aim of therapy is to stop multiplication or to kill the microorganisms with appropriate drugs: in diseases caused by toxin-producing organisms, the use of antitoxin (as in tetanus or diphtheria) is the definitive procedure, and chemotherapy is of secondary importance. A relatively new example of a toxin-mediated infection is the toxic shock syndrome, in which the toxin is elaborated by S.aureus. In this situation, this ordinarily invasive organism does not usually invade local tissues.

The tendency of certain pathogenic organisms *to localize in certain cells or organs* and to produce disease in a specific anatomic site or evoke a combination of symptoms referable to certain organs often suggests the identity of the causative organism. For example, the pneumococcus usually causes infection in the lung, but almost never in the kidney, and *H.influenzae* infections are confined almost solely to the respiratory tract and meninges.

Similarly, in the presence of disease known to be caused by a given agent, involvement of other tissues can be anticipated or predicted. Examples include the multiple lung abscesses which are so characteristic of hematogenously disseminated staphylococcal disease and the metastatic skin lesions which complicate Pseudomonas bacteremia.

RESISTANCE AND SUSCEPTIBILITY. Many so-called host factors are known to influence the likelihood that disease will occur if organisms enter the tissues, or to play a determining role in the outcome once the infection has become established. These include natural or acquired antibodies, interferon, properdin, phagocytic activity, and the level of the inflammatory response, which is generally manifested by cellular activity such as chemotaxis, phagocytosis, and release of lysozomal enzymes.

In experimental animals, sex, microbial strain, age, route of infection, the presence of specific antibody, associated diseases, nutritional state, and the use of such procedures as exposure to ionizing radiation or high environmental temperature or administration of mucin, antimetabolites, adrenal steroids, epinephrine, and metabolic analogues can be shown to exert a profound effect on infection by bacteria, viruses, fungi, and other agents.

In humans, these factors are no less important, although controlled studies are lacking for many. Alcoholism; diabetes; deficiency or absence of immunoglobulins; defects in cellular immunity; malnutrition; chronic administration of steroid hormones, chronic lymphedema; ischemia; the presence of foreign bodies such as bullets, calculi, or bone fragments; obstruction of a bronchus, the urethra, or any hollow tube; agranulocytosis or congenital defects in bactericidal or virucidal activity; various blood dyscrasias, and many other circumstances influence susceptibility to systemic or local infection. Furthermore, in those instances where the extenuating condition is remediable, the probability of recovery is enhanced.

PRINCIPLES OF NEOPLASIA: APPROACH TO DIAGNOSIS AND MANAGEMENT

Physicians practicing internal medicine should be familiar with the various implications of the diagnosis of cancer in their patients. Cancer is not one disease. There are more than 100 clinically distinct forms of cancer, with differing biological behavior and clinical manifestations. The internist should be especially familiar with the natural history and treatment of common forms of malignancy, such as those of the breast, lung, and gastrointestinal tract. These epithelial cancers comprise over 50 percent of the cancers usually encountered. The magnitude of the cancer problem may be appreciated by a few statistics: one of four Americans will develop cancer during his or her lifetime, and over 420,000 Americans will die of cancer in 1983. Not only is cancer a major health problem, but the management and care of cancer patients is often complex.

With the development of medical oncology as a subspecialty of internal medicine, the internist is playing an ever-increasing role in the care of the cancer patient.

The diagnosis and management of cancer require knowledge of general internal medicine and an understanding of the characteristics of the growth and spread of malignant neoplasms. For example, a nodular lesion in the lung must be evaluated for the possibility of neoplastic as well as granulomatous disease. Intermittent rectal bleeding must be appraised for benign or malignant neoplasms as well as for inflammatory bowel disease. Cushing's syndrome requires evaluation for bilateral adrenal hyperplasia as well as for an oat-cell carcinoma of the lung capable of producing adrenocorticotropic hormone (ACTH).

This chapter presents an overview of the biology and etiology of neoplasia and summarizes an approach to the diagnosis, staging, and treatment of cancer. The pathophysiologic changes occurring as a consequence of the tumor as a local mass, as a result of metastases, or from the elaboration of various substances by tumor are discussed.

BIOLOGY OF NEOPLASIA

Cancer is a term used to characterize abnormal growth of cells which may result in the invasion of normal tissues or the spread to distant organs, termed *metastasis.* The degree of malignancy of a cancer is based upon the propensity of these cells for invasion and distant spread. A metastasis is a neoplastic lesion arising from another cancer, with which it is no longer in contiguity. Regardless of mechanism, separation of malignant cells from the primary cancer is an essential part of the neoplaslic process. The basic concept that metastases arise directly from the constituent cells of primary cancer originates from observations of histologic similarities between the two. The mode of transport of cells from the primary to the presumptive secondary lesions is inferred from the many observations of cancer cells infiltrating tissues and invading blood vessels and lymphatic channels, and the recognition of circulating cancer cells in the blood of patients with cancer. However, many of the presumed circulating cancer cells have been determined to be megakaryocytes. In addition, the possibility that "metastases" could arise from the release of oncogenic viruses from the primary lesion requires further evaluation.

CYTOGENETICS

The characteristics of a particular tumor cell are, in general, permanent and stable and are inherited by descendants of that tumor cell. These characteristics may be explained best by structural alterations of the DNA in genes or chromosomes. These genetic structural changes may range from single gene mutations to gross chromosomal changes. These chromosomal changes may involve loss or gain of chromosomes, translocation of chromosomes, and changes in ploidy. Although the DNA and chromosomes of tumor cells may be clearly different from those of normal cells, the changes are not uniform from tumor to tumor, and no abnormality in the genetic material may be detectable in a substantial number of human tumors. Various techniques are available to analyze the DNA of normal and tumor cells, including the methods of nucleic acid hybridization. This technique allows comparison of analogous nucleotide chains from different cells by analyzing the product of each chain when allowed to interact. With use of radioactive RNA or DNA, comparable sequences of nucleotide chains from different cells can be quantified. Reverse transcriptase (RNA-directed DNA polymerase) has been used to synthesize isotope-labeled DNAs. These DNA templates have been used to show homologies, between murine leukemia virus and human leukemias and sarcomas, supporting the hypothesis of a viral etiology of human leukemia.

The most widely used technique for gross examination of genetic material is the examination of metaphase chromosomes. A tumor may be characterized by its "modal" karyotype, i.e. the number of chromosomes and the morphologic pattern of the largest percentage of cells. Major advances in cytogenetics have resulted from development of techniques to demonstrate chromosome banding, utilizing fluorescent acridine dyes, or by treatment of chromosomes by heat, alkali, or enzymes prior to staining. This permits accurate identification of individual chromosomes and regions within the chromosome, increasing the sensitivity of chromosome examination.

Only a few neoplastic diseases in humans are associated with a specific and characteristic chromosome abnormality; these include chronic myelogenous leukemia (CML), acute promyelocytic leukemia (APL), some lymphoproliferative disorders, and meningioma. In about 85 percent of the patients with CML, the material comprising approximately half of the long arm of a G22 chromosome is translocated to the end of a C9 chromosome. This abnormality (Philadelphia chromosome, Ph^1) involves all three hematopoietic cell lines, and has been interpreted as an acquired somatic cell mutation in the bone marrow, with preferential survival and proliferation of this clone. In APL, the material from the distal part of the long arm of an E17 chromosome is translocated to the end of a DI5 chromosome. This abnormality is present in approximately two-thirds of the patients with APL. In the lymphoproliferative disorders, an 8/14 translocation has been associated with most Burkitt's lymphomas and a marker I4q + has been found in the tumors of many patients with multiple myeloma, Hodgkin's disease, and non-Hodgkin's lymphomas. The chromosome abnormality associated with meningioma is

hypodiploid in contrast to the examples cited above, and frequently involves the deletion of chromosome G22.

Approximately 50 percent of patients with acute leukemia have detectable cytogenetic abnormalities. Although the abnormalities are not necessarily uniform, they are probably nonrandom. For any given patient they tend to remain characteristic and recur during a clinical relapse. Leukemias induced by radiation, drugs, *or* both such as occur in some patients with treated Hodgkin's disease, have a much higher percentage of chromosomal abnormalities. The use of chromosome-banding techniques may result in grouping of patients with common etiologies or prognoses. Cytogenetic studies also may occasionally be useful in the diagnosis of "preleukemia" when abnormal karyotypes are present.

For technical reasons, only a limited number of chromosome studies have been performed in solid tumors. Cytogenetic abnormalities are frequent and major in solid tumors such as melanoma, lung cancer, and colon cancer. Significant aneu-ploidy is present in almost all tumors. In melanoma the variation from cell to cell is substantial and has been interpreted as evidence for multiple cell lines, cytogenetic instability, and rapid clonal evolution toward more malignant behavior.

ETIOLOGY

Although the etiology of cancer, in humans cannot yet be explained at the molecular level, it is clear that genetic composition of the host is important in cancer induction. Related immunologic factors may predispose the host to a putative carcinogen. There is some evidence that viruses may play a role in the neoplastic process. In addition, both environmental and therapeutic agents have been identified as carcinogens.

INFLUENZA

Influenza is an acute respiratory infection of specific viral etiology characterized by sudden onset of headache, myalgia, fever, and prostration. The terms *influenza* and "flu" should be restricted to those cases with clear-cut epidemiologic or laboratory evidence of infection with influenza viruses.

HISTORY

According to the best available records, influenza was uncommon in Europe during the nineteenth century until the pandemic of 1889. Subsequently, the frequency and severity of epidemics increased, culminating in the disastrous pandemic of 1918, which caused an estimated 20 to 40 million deaths. The mortality rate from the disease has decreased progressively since 1918 owing in part to the introduction of antibiotics and also to such factors as possible change in virulence of the virus and improved living standards.

ETIOLOGY

There are three distinct antigenic types of influenza virus, designated A, B, and C. Infection with one type confers no immunity to the other two. On the basis of intrinsic properties, the three types are grouped in a virus family named Orthomyxoviridae. The influenza viruses contain a single, segmented, negative-strand RNA genome. They are spherical or filamentous enveloped particles, 80 to 120 nm in diameter, with glycoprotein structures termed *hemagglutinin (H)* and *neuraminidase (N),* which protrude from the envelope. The former are responsible for attachment of virus to cell receptors; the latter enzymatically degrades the active receptor substance, frees virus from attachment sites if cell penetration is unsuccessful, and functions in the release of infectious virus from cells during the replication cycle. The H and N are antigenic and elicit antibodies which correlate with the prevention of infection and disease. Antihemagglutinin antibodies are more potent than those elicited by the N antigen.

The three types of influenza viruses are biologically related by their infectivity for chick embryos, capacity to agglutinate erythrocytes in vitro, and affinity for respiratory epithelium of various mammals.

EPIDEMIOLOGY

Influenza A. Influenza A viruses are the cause of outbreaks of disease almost annually and reach epidemic proportions every 2 or 3 years. Pandemics occur every decade or so.

Influenza, especially type and infection, is a recurring disease, because the virus undergoes continuous antigenic variation with time, involving the surface antigens H and N. This progressive, but not necessarily regular, change produces viruses to which segments of the population become susceptible in numbers somewhat in proportion to the extent of antigenic variation. Thus the annual interepidemic outbreaks are not as severe nor as extensive as the less frequent epidemics. The origin of pandemic viruses is unknown, but they appear to arise by a different mechanism. The segmented genome of type A influenza virus exhibits a high recombination frequency. Consequently, a recombinational event between human and non-human type A influenza viruses, or between two human type A viruses in the same host, could possibly give rise to antigenically different subtypes.

It was also noted that many older people did not become ill during the 1968 epidemic, and it was found that many of them possessed antibody to this subtype that was probably acquired in the period 1889 to 1890, when the subtype then prevalent shared antigenic properties with the 1968 subtype. There is also evidence that the 1957 virus shared antigens with the subtype that was prevalent before 1890, although owing to the time lapse there were too few older people with antibody to have a measurable effect on the pandemic.

Variants within subtypes are identified by the site of first isolation of the new strain and the year of its isolation. Differentiation among variants is important because vaccines to one variant show a progressive loss of protective effect against later emerging variants, so that after about 3 years the vaccine will have little effect.

Influenza A viruses infect pigs, horses, and fowl especially ducks and turkeys. H and N antigens of some of these viruses are related to H and N antigens of human influenza A viruses. The internal matrix protein of the virus is an antigen common to all influenza A viruses. The name *swine influenza* was given to the agent that caused the 1918 pandemic because an epidemic of influenza that occurred among swine at that time was thought possibly to have spread to swine from infected people. The swine agent has continued to infect swine populations since that time. The pandemic A (H3N2) strain of 1968 shared antigens with an agent isolated from horses in 1963. Despite these findings and considerable experimentation with induction of infection across species lines, there is no solid evidence that lower animals are involved in the natural history of human influenza.

Influenza A epidemics start abruptly, reach a peak in 2 to 3 months, and subside almost as rapidly. The attack rate is variable but was noted in 1957 to exceed 50 percent in urban populations. An additional 25 percent of individuals may show serologic evidence of infection without clinical manifestations. Experiences in 1957 proved conclusively that crowding, even in summer months or in tropical countries, is a major factor predisposing to epidemics. Schoolchildren, in particular, appear to be the primary focus and disseminators of infection in the United States. If the general immunity of a population is at low levels, community-wide epidemics may occur within a short period after the introduction of new strains of virus. If, however, immune individuals predominate, the case rate will rise slowly and may not reach epidemic proportions.

The mortality rate from all causes always increases markedly during epidemics of influenza. In the fall and winter of 1957 to 1958 it was estimated that 40 million persons in the United States became ill with influenza, and the total number of influenza-associated deaths was reported to be in excess of 8000. In addition, approximately 60,000 more deaths from various causes occurred during this period than would be expected under normal conditions. The greatest incidence of excessive mortality occurred among infants under 1 year of age and adults over 60 years of age. Data from a small series of cases clearly indicate that influenza is frequently fatal in individuals with preexisting pulmonary or cardiac disease, regardless of age. Chronic rheumatic heart disease with mitral stenosis, in particular, appears to predispose to fatal influenza pneumonia.

Influenza B and C

Influenza B virus infection occurs sporadically or in localized outbreaks, particularly in schools and military camps and every 4 to 6 years causes more discrete epidemics than influenza A. Although influenza B virus possesses H and N coal proteins, it undergoes less variation than influenza A viruses, and it is not now the practice to designate the virus by these antigens. Illness with influenza B infection is less serious than that caused by influenza A viruses. The most serious problem with influenza B infections is a complication. Reye's syndrome, characterized by encephalopathy and fatty changes in the liver and other organs. Illness with influenza C is rarely detected, although antibody surveys indicate a wide prevalence of the infection.

PATHOGENESIS

Influenza is primarily an infection of the respiratory epithelium that is produced by inoculation with virus from respiratory secretions of infected persons. Experimental studies show that a small number of virus particles inhaled in a small-particle aerosol or severalfold larger doses in liquid suspension dropped in the nose will produce the disease. Infection thus could result from transfer of infected secretions by personal contact or fomites or, probably much more frequently, by inhalation of aerosols generated by sneezes, coughs, and other expiratory discharges of infected individuals.

After inoculation, the virus multiplies to maximum titers in a few days. Cells lining the respiratory tract, including ciliated epithelium, alveolar cells, mucous gland cells, and macrophages may become infected. Neutrophil leukocytes and endothelial cells do not appear to become infected. Evidence of virus infection by specific immunofluorescence is most conspicuous in cells that show fewest morphologic changes. Infected ciliated cells undergo degeneration after a day or so and are characterized by swelling of nuclei with shift from a longitudinal to a transverse position in the cell. Cytoplasmic changes are granulation, vacuolation, and swelling. Ultimately cells become necrotic and slough, in some areas to be replaced by flattened and metaplastic epithelial regrowth.

THE HISTORY OF GENETICS

What is Genetics? Genetics is usually defined as the transmission of traits from one generation to the next. Although correct in its meaning, the definition is rather vague. Genetics not only involves the transmission of traits from generation to generation, but it also involves every biological occurrence in an organism. The history of genetics beginning with the ideas of Aristotle up till the re-discovery of Mendel's work has undergone many changes both in theory and discovery.

The history of Genetics most often begins with the ideas of Aristotle and Hippocrates. Their basic belief on Genetics included the determination of sex and inheritance of disease based upon the idea of Spontaneous Generation. They believed that sex of the offspring depended upon which testes produced the semen that fertilized the egg. Through this, Darwin later labeled the theory Pangenesis. Darwin believed that gremmules were manufactured by every part of our body, which then collected in the semen producing the basis of heredity. This theory was Darwin's defense for the theory of Acquired Characteristics. Although Pangenesis was believed by most people, Aristotle came to the conclusion that characteristics weren't inherited, but the ability of producing these characteristics were.

Another theory that was proposed during this time was Preformation. Preformation stated that entire miniature individuals lived in the germ cells and matured in the womb of the female. It was unknown during this time how traits were passed on so scientist concluded that somehow aspects of the parents' bodies were transferred in miniature individuals known as homunculus. As we entered the 18^{th} and 19^{th} century the improvement of the microscope helped disprove the Theories of Spontaneous Generation and Preformation. With this, the question of how traits were inherited was still unknown.

Gregor Mendel, better known as the Father of Genetics, was the first scientist to show traits had a predictable pattern. He had succeeded were many others failed by luckily choosing

simple and unchanging traits. The seven traits Mendel chose were 1. Difference in form of the ripe seed 2, Difference in color of seed endosperm 3, Difference in color of seed coat 4, Difference if form of ripe pods 5, Difference in colors of unripe pods 6, Difference in position of the flowers and 7, Difference in length of stem. With these different characteristics Mendel made thousands of different crosses in the garden pea, and established that indeed there was a pattern of transmission of traits. Resulting from his studies was the Law of Segregation and the Law of Independent Assortment. After completion of his eight years of investigation, Mendel presented his work before the Science Research Society. The significance of his work wasn't realized until 1900 when his work was re-discovered.

Three years after Mendel had completed his work; a German scientist by the name of Friedrich Miescher discovered nuclein. Miescher believed that this substance was storage for phosphorus rather than genetic material. During this time it was believed that protein was the basis of heredity because it was so complex. They didn't believe DNA wasn't the hereditary factor because it was so simple and easily understood. Miescher's discovery wasn't realized as an importance until 889 with the development of August Weismans Germ Plasm Theory. The Germ Plasm Theory suggested that each chromosome remained in tact from generation to generation and it was passed on by the germ cell. He also concluded that each chromosome contains all hereditary elements to produce an individual. In other words the chromosomes were responsible for the transportation of hereditary material. The Germ Plasm Theory gave rise to the Chromosome Theory of E.B. Wilson. Wilson's chromosome Theory stated that chromatin is very similar to nuclein and that inheritance might be effected by the transmission of chemical compounds from parent to offspring. Without realizing it Wilson was talking of genes. Both the Germ Plasm Theory and Chromosome Theory explained nuclein as DNA and DNA as genes by which transmit heredity.

Walter S. Sutton developed his own theory and it suggested that chromosomal pairs were equally important as the segregating pair of gene alleles. Correns and Hugo De Vries assisted Sutton's Chromosome Theory. Correns assumed there were different orders of alleles that allowed for recombination. Sutton then ran into a problem with his theory when he noticed there weren't enough chromosomes to identify each gene in a whole chromosome. Hugo de Vries proposed that sometimes those genes were possibly exchanged freely during meiosis. With this developed the Theory of Crossing Over.

The phenomenon of crossing over is the exchange of genetic material between two or four chromatids of a tetrad during synapsis. These chromatids join at a point called the chiasmata, and it is there were segments of chromatids are exchanged. It is important to know that crossing over can occur a multiple number of times per tetrad. Crossing over plays a major role in the reassortment of alleles into different recombinations, which leads to genetic diversity. If it weren't for crossing over all chromosomes would remain the same except for and occasional mutation. After the crossing over process one can no longer distinguish between maternal and paternal chromosomes since the DNA is now combined. This solution showed that Independent Assortment wasn't as regular as a flip of a coin. The discovery of linkage eventually resolved this difficulty.

Correns first reported linkage. He crossed strains of stocks in which one had anthocyanin in the petals and seeds and had hoary leaves and stems; while the other had white flowers and seeds, and smooth leaves and stems. After the cross, Correns failed to recover any recombinations and believed only in complete linkage. Bateson on the other hand was the first to report incomplete linkage. He crossed two gene pairs involved in distinguishing purple flowers from red ones and long pollen grains from small ones. The two situations that arose were 1. Two dominates were contributed by the same parent and 2. One dominant and one recessive gene came from each parent. The result of this made the estimation of the recombination of genes very difficult and imperfect. With the discovery of linkage, de Vries Theory of Crossing Over was proven to be correct.

The first suggestion of a particular characteristic to a particular chromosome was made in 1901. C.E. McClung believed the *X* chromosome was the male determining factor. He came to this conclusion by counting 22 *X* chromosomes in the female and 23 X chromosomes in the male. Since the male retained one more X chromosome than the female, he believed it to be the main factor in the determination of sex. McClung's assumption turned out to be incorrect. In 1905 N.M. Stevens showed the correct relationship to be as followed. The presence of *XX* chromosomes showed clearly to be a female and the combination of the XY chromosomes resulted in a male. (Sturtevant 41) Through further studies, the most important element was shown to be that *Y* bearing sperm produced male offspring and X bearing sperm produced female offspring. In 1922, through the work of *Drosophilia melanogaster*, Bridges discovered many different sexes. He uncovered the supermale, superfemale and the intersex. In the example below, it is important to know the X autosome is female determinant and *the A* autosome is male determinant. The supermale is produced by the fusion of an *X+A+A* egg with a sperm not carrying an X autosome forming an *X, 3A* zygote. A problem discovered in the supermale was that it was sterile. An X+X+A egg fertilized with a X+A sperm forms the superfemales. This *3X, 2A* zygote than runs into problems. They are delayed in their development and rarely able to survive. In the intersex form, the individual is neither male nor female, but a mixture of both. The formation consists of an *X+A+A* egg with normal *X+A* sperm to form a *2X, 3A* zygote. Through studies on the intersex form it was decided each character of an individual is effected by an unknown number of genes which change development from one direction to the opposite.

Another important factor in the study of genetics is continuous variation. Galton discussed this in his Law of Ancestral Inheritance. It correlated the resemblance between parent and offspring. As discussed in H.J. Muller's Variation Due to Change in Individual Gene, there were thousands of genes that played an important role in determining cell substance and cell structure. Galton's Law of Inheritance is an alternate interpretation due to Mendel's principle of random breeding. Galton also discussed the idea of "Nature vs. Nurture," but a scientist by the name of W. Johannsen applied the meaning behind the idea. Through his work Johannsen, was able to distinguish between inherited and environmentally produced traits. He came to the conclusion that inherited variation were minute in their appearance while environmentally produced variations were large. The introduction of environmentally produced variation developed another method of studying the inheritance of characteristics by selection. Most of the effects of selection are due to the sorting out and build up of modifying genes. These genes then produced characteristics of an organism to help them become more adapted. This adaptation implies the expressed variation due to changes in individual genes or better known as mutation. By this, it was determined that selection works on genes already present in the organism. The understanding of how selection operates has become very important in applying genetics to the problems of evolution. Thus evolution isn't caused by inheritance and variation, but by the inheritance of variation. Muller introduced another method by which he believed genes affected characteristics. It suggested there was some connection between chromosome behavior and gene structure, but he insured us that it was only a possibility.

MICROBIOLOGY AND MEDICINE

Applications of microbiology have given medicine its greatest successes in the diagnosis, prevention and cure of disease. The conquest of epidemic and fatal infections has seemed to be so conclusive that the main challenge in medicine is now often seen to lie in other fields, such as those of the mental illnesses and degenerative diseases, but a major shift of attention away from the problems of infection could be dangerous. The relative freedom of society from fatal infections depends on the continued, informed deployment of complex counter- measures: on correct diagnosis and treatment of infections, full implementation of immunization programmes, alert epidemiological surveillance and rigorous environmental sanitation.

Moreover, on a global scale, infection is far from defeated. In the developing nations of the world, an estimated 10 million people (predominantly young children) die each year from the

effects of infectious diarrhoeas, measles, malaria, tetanus, diphtheria and whooping cough alone. The tragedy is that we have the means to hand to prevent nearly all these deaths.

Even in the developed world infective illnesses are still extremely common and make up much of the work of family and hospital doctors. At least quarters of all illness for which patients consult their doctors are infective, and a substantial proportion of patients acquire infection while in hospital. Intensive farming methods and a shift in eating habits to pre-prepared 'fast foods' have led to a sharp increase in food-related infection. In hospitals, new approaches to therapy that deplete the competence of the patient's immune system to cope with infection, as well as the increasing use of shunts, intravenous cannulae and prosthetic devices, all provide the ever-resourceful microbes with new opportunities .to invade the host. Surprisingly, 'new' agents of infectious disease continue to be recognized. The most notorious of these is undoubtedly the human immunodeficiency virus (HIV), the causative agent of acquired immune deficiency syndrome (AIDS). The rise and spread of this condition provides a sobering reminder of the potential impact of microbial disease. It is as essential now as it ever was that medical personnel should be well trained in matters relating to infection.

Microbiology is the study of living organisms of microscopic size. The term was introduced by the French chemist Louis Pasteur, whose demonstration that fermentation was caused by the growth of bacteria and yeasts (1857-60) provided a main impetus for the development of the science. The term *microbe* was first used by Sedillot in 1878, but is now commonly replaced by that of *micro-organism.* The microbes of medical interest include *protozoa,* the smallest animals, *fungi,* including moulds and yeasts, *bacteria,* which have much smaller, simpler cells, and *viruses,* the smallest and simplest of all. Most viruses are less than 0.2 micrometres (μm) in diameter and so are not resolvable with the light microscope. Because they lack a cellular structure and can replicate only within a living host cell, viruses are sometimes regarded as components of their host rather than as micro-organisms, but since they are organized bodies, capable of reproducing themselves in different hosts, and of surviving outside their hosts, it is justifiable as well as convenient to classify them as micro-organisms. Although *helminths* (parasitic worms) are macroscopic, they cause infection and their study falls within the province of microbiologists. Students should, therefore, be familiar with their properties.

DEVELOPMENT OF MICROBIOLOGY

Micro-organisms were first seen about 1675 by the Dutchman Antony van Leeuwenhoek. His microscopes consisted of a single biconvex lens that magnified about x 200 and resolved bodies with diameters down to about 1 μm. He found many micro-organisms in materials such as water, mud, saliva and the intestinal contents of healthy subjects, and he recognized them as living creatures ('animalcules') because they swam about actively. That he saw bacteria as well as the larger microbes is known from his measurements of their size ('one-sixth the diameter of a red blood corpuscle') and his drawings of the forms we now recognize as cocci (spheres), bacilli (rods) and spirochaetes (spiral filaments).

Leeuwenhoek observed that very large numbers of bacteria appeared in watery infusions of animal or vegetable matter which were left to stand for a week or two at room temperature. He believed that these huge populations were the progeny of a few parental organisms, or seeds that were originally present in the materials of the infusion or had entered it from the air. Other scientists suggested that the organisms arose by *spontaneous generation,* i.e. by the spontaneous conversion of dead organic matter into living microbes, and this suggestion began a controversy that lasted for 200 years. The necessary techniques were perfected only after much further work, particularly that by Lazzaro Spallanzani (1765, 1776) and Louis Pasteur (1860-64). Pasteur's flasks of infusions, sterilized by autoclaving at 115-120°C, always remained sterile despite the entry of unheated air through a dust-stopping 'swan neck' or cotton-wool stopper, and so finally proved the absence of spontaneous generation.

Although this conclusion was long delayed, the work on spontaneous generation had the valuable outcome of establishing many of the basic techniques of bacteriology. Convenient

nutrient media for preparing growths, or *cultures,* of bacteria in the laboratory were derived from Leeuwenhoek's meat and vegetable infusions, and reliable methods were developed for the sterilization and maintenance of sterility of culture media and equipment. The mechanism of bacterial reproduction by asexual fission was discovered by De Saussure (1760) and the need for high temperatures for sterilization was explained by Ferdinand Cohn's (1876) discovery that certain bacteria form heat-resistant spores. Other techniques essential for the rapid progress of bacteriology were developed by the German bacteriologist Robert Koch, who in 1877 described methods for the easy microscopic examination of bacteria in dried, fixed films stained with aniline dyes, and in 1881 devised the simple method for isolating pure *cultures* of bacteria by plating out mixed material on a solid culture medium on which the progeny of single bacteria grow in separate colonies.

MICRO-ORGANISMS AND DISEASE

Only a small proportion of the micro-organisms that abound in nature are disease-producing, or *pathogenic,* for man. Most are *free-living* in soil, water and similar habitats, and are unable to invade the living body. Some free-living microorganisms obtain their energy from daylight or by the oxidation of inorganic matter, but the majority feed on dead organic matter and is termed *saprophytes.* In contrast, a *parasite* lives in or on, and obtains its nourishment from, a living host. In medical usage, the term 'parasite' is nowadays usually reserved for parasitic protozoa, helminths and arthropods. The last usually affect the outside of the body and are termed *ectoparasites. Commensal* micro-organisms constitute the normal flora of the healthy body. They live on the skin and on the mucous membranes of the upper respiratory tract, intestines and vagina, and obtain nourishment from the secretions and food residues. Since normally they do not invade the blood or tissues, they are generally harmless, but under certain circumstances, as when the' body's defences are impaired, they may invade the tissues and cause disease, thus acting as *opportunistic pathogens.* True pathogens are the micro-organisms that are adapted to overcoming the normal defences of the body and invading the tissues; their growth in the tissues, *or* their production of poisonous substances *(toxins),* damages the tissues and causes the manifestations of disease. The process of microbial invasion of the body is called *infection,* and a microbial disease is often called an *infective disease.* Those infective diseases that are readily communicable from person to person are called *infectious* or *contagious.*

IMMUNITY AND IMMUNIZATION

It was an ancient observation, reported for instance by Fracastoro, that persons who had suffered from a distinctive disease, such as smallpox or measles, resisted it on subsequent exposures and rarely contracted it a second time. Such an acquired immunity is *specific,* i.e. effective only against the same type of infection as that previously suffered (or, exceptionally, a closely related one, as when cowpox immunizes against smallpox).

LABORATORY DIAGNOSIS OF INFECTIONS

The signs and symptoms of some infective diseases may be specific for a particular micro-organism, e.g. the circumscribed boil of the staphylococcus and the characteristic rash of chickenpox, but those of many infections are unspecific, and any of several different pathogenic organisms may be the cause of an illness such as sore throat, bronchitis, pneumonia, meningitis, diarrhoea, wound sepsis and fever. In these cases, laboratory help is required to elucidate the cause. The reliability of that help depends on the correct techniques being used in collecting the appropriate specimens from the patient, and doctors must be properly instructed in these procedures. The precise identification of the patient's pathogenic organisms is generally necessary for the effective use of a selective chemotherapeutic drug. In other words, the doctor has to identify and treat specific infections rather than clinical syndromes. Since, moreover, different strains of many bacterial species differ in their susceptibility to particular drugs, it is usually desirable for the bacterium isolated from the patient to be tested for its drug sensitivity in the laboratory.

EPIDEMIOLOGY AND THE PREVENTION OF INFECTION

A knowledge of the sources, mechanisms of transmission and predisposing conditions of an infection makes it possible to devise preventive measures such as neutralization of the sources, interference with the mechanisms of transmission and removal of the predisposing conditions. Microbiology is thus closely concerned with *epidemiology,* which is the study of the factors that influence the prevalence and distribution of diseases in the community. The reporting of laboratory diagnoses of specific communicable infections to the health officer concerned with preventive measures plays an important part in guiding his day-to-day activities, and the collection of records of laboratory findings helps to guide national policies for immunization and environmental hygiene.

Sources of infection are the habitats in which the pathogenic microbes ordinarily grow and from which they are disseminated to susceptible hosts. Inanimate objects which carry the pathogens through the environment in a surviving, but non-growing, condition are known as *vehicles* of infection. Many species of pathogens are derived exclusively or mainly from *ill patients* as their source, but many others grow in, and are disseminated from, healthy persons, known as *carriers,* in whom they cause only a limited, subclinical infection. The existence of carriers was first demonstrated about 1900 in studies of typhoid fever initiated by Koch, and their importance as sources of infection is due to their mobility and lack of recognition in the community. Some infections, called *zoonoses,* have their sources in animals, which are the natural hosts of the pathogen, e.g. rabies, bubonic plague, brucellosis and leptospirosis. They are transmissible from animal to man, but not ordinarily from man to man, so that prevention depends on the control of human contact with the infected animals. As well as these kinds of *exogenous* infections from external sources, there are also many infections, termed *endogenous,* which are due to the opportunistic invasion of tissues by a commensal, or 'carried', organism that hitherto grew harmlessly elsewhere in the body, e.g. infections of the lung with pneumococci previously resident in the throat. The prevention of endogenous infections depends on the avoidance of predisposing conditions that impair the tissue defences.

Epidemiological observations may suggest by what mechanisms an infection is transmitted and so lead to the formulation of preventive measures even when the causal micro-organism is still unknown. In 1846, for instance, in a maternity clinic in Vienna, Ignaz Semmelweis deduced that puerperal fever was caused by a putrefactive agent which doctors picked up on their hands when attending patients or performing necropsies and then transferred into the birth canal when assisting women at childbirth. He reduced the number of deaths from 8.3 to 2.3% of mothers by requiring staff regularly to wash their hands in hypochlorite solution until they were free from the smell of putrefaction.

In comparable work, the anaesthetist John Snow (1849, 1854) showed that the geographical distribution of cholera in London was related to the sources of the supplies of drinking water, and concluded that the 'peculiar poison of the disease' was spread in patients' faeces, which contaminated water later drunk by other persons (faecal-oral transmission). Measures subsequently taken to ensure the purity of drinking water by protection, filtration and chlorination have led to the decline of cholera, typhoid fever and other water-borne infections.

The development of the techniques of antiseptic and aseptic surgery for the prevention of wound sepsis had its origin in the conception by Joseph Lister (1867) that if, as shown by Pasteur, bacteria were the cause of the fermentation and putrefaction of dead organic matter, they might well also be the cause of suppuration in living tissues. By covering operation wounds with dressings soaked in carbolic acid to kill any bacteria present in them and to exclude others from entry, and by disinfecting his hands and instruments, he greatly reduced the incidence of sepsis in his patients.

The discovery that blood-sucking arthropods spread certain diseases led to prevention by measures for the control of these vectors. In 1893 Theobald Smith and F. L. Kilborne first showed that Texas fever of cattle was spread by ticks that bite an infected cow and transmit its blood to another animal. Subsequently, it was shown that malaria was transmitted by anopheles

mosquitoes (Ronald Ross, 1898), yellow fever by aedes mosquitoes (Reed and co-workers, 1900). bubonic plague by the rat flea (Liston and co-workers, 1905) and typhus fever by lice (Charles Nicolle, 1909). Campaigns of vector control by the use of insecticides and other means have since been conducted for the prevention of these diseases.

Although infective illness has remained common during the last 100 years, developed countries have seen a phenomenal decrease in the death rate from infections. In Scotland, deaths from the principal infectious diseases contributed, at a rate of 1167 per 100 000 of the population per annum, more than a half of all deaths, in the quinquennium 1861-65, whereas in 1961-65 they were reduced to the rate of 111 per 100 000 and contributed only one-tenth of all deaths (see Fig. 1.1). A similar decline in deaths from infectious disease occurred in England and Wales and predated the availability of effective chemotherapy. Since the steep decline in deaths began more than a century before preventive and curative medicine became significantly effective, the earlier reduction in deaths must have been due to improvements in nutrition and living conditions which increased the resistance of individuals to the point that they generally recovered from their many infections. Subsequently, and particularly with the introduction of immunization programmes and antimicrobial therapy in the last 50 years, medicine has made a more substantial contribution to the saving of life.

HEADACHE

The term *headache* should encompass all aches and pains located in the head, but in common language its application is restricted to unpleasant sensations in the region of the cranial vault.

Headache, along with fatigue, hunger, and thirst, represents the most frequent human discomforts. Medically speaking, its significance is often abstruse, for it may stand as a symptomatic expression of disease or of some minor tension or fatigue, incident to the affairs of the day. Fortunately, in most instances it reflects the latter, and only exceptionally does it warn of serious disease seated in intracranial structures. But it is this dual significance, the benign and the potentially malignant, that keeps the physician on the alert. Systematic approach to the headache problem necessitates a broad knowledge of the medical and" surgical diseases of which it is a symptom and a clinical methodology which leaves none of the common and treatable causes unexplored.

GENERAL CONSIDERATIONS

In the introductory chapter on pain, reference was made to the necessity, when dealing with any painful state, of determining its quality, location, duration, and time course, and conditions, which produce, exacerbate, or relieve it. When headache is considered in these terms, a certain amount of useful information is obtained by careful history, but perhaps less than one might expect. Unfortunately, physical examination of the head itself is seldom useful.

As to quality of cephalic pain, the patient is rarely helpful in describing it. In fact persistent questioning on that point occasions surprise, for the patient usually assumes that the word *headache* should have conveyed enough information to the examiner about the nature of the discomfort. Most headaches are dull, deeply located, and of aching character, a pain recognizable as of the type that usually arises from structures deep to the skin. Seldom is there reported the superficial burning, smarting, or stinging type of pain localized to the skin. When asked to analogize the sensation to another sensory experience, the patient may make some allusion to tightness, pressure, or bursting feeling, terms which then give clue to a muscular tension or a psychologic state.

Queries about the intensity of the pain are seldom of much value since they reflect more the patient's attitude toward the condition and a customary way of reporting things that happen than the true severity. As usual the bluff, hearty person tends to minimize discomfort, whereas the neurotic dramatizes it. Degree of incapacity is a better index. A severe migraine attack seldom allows performance of the day's work. The pain, which awakens the patient from sleep at night, or prevents sleep, is also more likely to have a demonstrable organic basis. As a rule, the

most intense cranial pains are those that accompany subarachnoid hemorrhage and meningitis, which have grave implications, or migraine and paroxysmal nocturnal orbitotemporal (cluster) headaches, which are benign.

Data regarding *location* of the headache are apt to be more informative. If the source is in deep structures (extracranial, i.e., subdermal, or muscular), as is usually the case, the correspondence with the site of the pain is fairly precise. Inflammation of an extracranial artery causes pain well localized to the site of the vessel. Lesions of paranasal sinuses, teeth, eyes, and upper cervical vertebrae induce less sharply localized pain but one that is still referred in a regional distribution that is fairly constant. Intracranial lesions in the posterior fossa cause pain in the occipital-nuchal region, homolateral if the lesion is one - sided. Supratentorial lesions induce frontotemporal pains, again homolateral to the lesion if it is on one side. But localization can also be very uninformative or misleading. Ear pain, for example, although it may mean disease in the ear, more often is referred from other regions, and eye pain may be referred from parts as remote as the occiput or cervical spine.

Duration and *time-intensity* curve of headaches in both the attack itself and their life profile are most useful. Of course the headache of bacterial meningitis or subarachnoid hemorrhage occurs usually in single attacks over a period of days. Single, brief, momentary (1 to 2 s) pains in the cranium are presently uninterpretable and are significant only because they indicate no serious underlying disease. Migraine of the classic type has its onset in the early morning hours or daytime, reaches its peak of severity in a half hour or so, lasts, unless treated, for several hours up to 1 to 2 days, and is often terminated by sleep. In the life history a frequency of more than a single attack every few weeks is exceptional. A migraine patient having several attacks per week usually proves to have a combination of migraine and tension headaches. In contrast to this is the nightly occurrence (2 to 3 h after onset of sleep) over a period of several weeks to months of the rapidly peaking, nonthrobbing orbital or supraorbital pain of cluster headache, which tends to dissipate within an hour. The headache of intracranial tumor characteristically can occur at any time of day or night, can interrupt sleep, varies in intensity, and lasts a few minutes to hours. The life profile is one of increasing frequency and intensity over a period of months. Tension headache, once commenced, may persist continuously for weeks or months, though waxing and waning from hour to hour. Headache that bears a more or less constant relationship to certain biologic events and also to physical environmental changes may prove to be informative. Premenstrual headaches most typically relate to premenstrual tension during the period of oliguria and edema formation; they usually vanish after the first day of vaginal bleeding. The headaches of cervical arthritis are most typically intense after a period of inactivity, and the first movements in the morning are both difficult and painful. Hypertensive headaches, like those of cerebral tumor, tend to occur on waking in the morning, but, as with all vascular head aches, excitement and tension may provoke them. Headache from infection of nasal sinuses may appear, with clocklike regularity, upon awakening and in midmorning, and is characteristically worsened by stooping and jarring of the head. Eyestrain headaches naturally follow prolonged use of the eyes, as in reading, peering for a long time against glaring headlights in traffic, or watching the cinema. Atmospheric cold may evoke pain in the so-called fibrositic or nodular headache or when the underlying condition is arthritic or neuralgic. Anger, excitement, or irritation may initiate common migraine in certain disposed persons; this is more typical of common migraine than of the classic type. Change of position, stooping, straining, cough, and sexual intercourse are each known to produce a special type of headache, to be described further on. Exertional headaches, another well - known type, are usually benign (only 1 in 10 will have an intracranial lesion) and disappear within weeks to months.

PAIN - SENSITIVE STRUCTURES AND MECHANISMS OF HEADACHE

Understanding of headache has been greatly augmented by the observations of surgeons during operations. They inform us that the following cranial structures are sensitive to mechanical stimulation: (1) skin, subcutaneous tissue, muscles, arteries, and periosteum of skull; (2) delicate structures of eye, ear, and nasal cavity; (3) intracranial venous sinuses and their tributary veins; (4) parts of the dura at the base of the brain and the arteries within the dura mater and piaarachnoid; and (5) the trigeminal, glossopharyngeal, vagus, and first three cervical nerves. The bony skull much of the piaarachnoid and dura and the parenchyma of the brain lack sensitivity. Interestingly, pain is practically the only sensation produced by stimulation of the listed structures.

The pathways whereby sensory stimuli, whatever their source, are conveyed to the central nervous system are the trigeminal nerves for structures above the tentorium in the anterior and middle fossae of the skull, and the first three cervical nerves for those in the posterior fossa and infradural structures. The ninth and tenth cranial nerves supply part of the posterior fossa and refer the pain to the ear and throat. The tentorium is the border zone between the trigeminal and cervical innervation.

The pain of intracranial disease is referred, by a mechanism already discussed, to some part of the cranium lying within the areas supplied by the aforementioned nerves (the fifth, ninth, and tenth cranial nerves and the first three cervicals). There may be an associated local tenderness of the scalp at the site of reference. Dental or jaw pain may also have cranial reference. The pain of disease in other parts of the body is not referred to the head, although it may initiate headache by other means.

ABDOMEN

Abdomen is the lower part of the trunk. Above, and separated from it by the diaphragm or midriff, lies the thorax or chest, and below lies the pelvis, or basin, generally described as a separate cavity though directly continuous with that of the abdomen. Behind lie the spinal column and lower ribs which come within a few inches of the iliac or haunch bones; at the sides the protection afforded to the contained organs by the iliac bones and downsloping ribs is still more effective; but in front the whole extent is protected only by soft tissues. The latter consist of the skin, a varying amount of fat, three layers of broad, flat muscle, another layer of fat, and finally the smooth thin peritoneum which lines the whole cavity. The absence of rigidity allows of the necessary distension when food is taken into the stomach, and of the various important movements of the organs associated with digestion.

The principal contents of the abdominal cavity are digestive organs, i. e., stomach, intestines, and the associated glands, the liver and pancreas. The position of the stomach is above and to the left, of the liver above and to the right, both lying to a large extent under cover of the ribs, and occupying the hollow of the diaphragm, by which alone they are separated from the lungs and heart.

Against the back wall on either side lie the kidneys, protected also to a great extent by the last two ribs; and from the kidneys run the ureters or urinary ducts down along the back wall to the bladder in the pelvis. The pancreas lies across the spine in front of the kidneys, and upon the upper end of each kidney lies a suprarenal body. High up to the left and partly behind the stomach lies the spleen.

The great blood-vessels and nerves, the absorbent vessels and the glands connected with them, lie on the back wall, and the remainder of the space is taken up by the intestines or bowels, the large intestine lying in the flanks on either side in front of the kidneys and crossing below the stomach from right to left, while the small intestine hangs from the back wall in coils which fill up all spaces between the other organs. Hanging down from the stomach in front of the bowels is the omentum, or apron, containing a considerable amount of fat, and helping to protect the bowels from cold and injury.

BLOOD CELLS

The blood cells include red corpuscles (erythrocytes) and white corpuscles (leucocytes).

There are approximately five million red blood corpuscles per cubic millimeter of blood in healthy adult males and four and one-half million in females. The cells are small, pale-red, biconcave discs about 0.007—0.008 of a millimeter in diameter. They are not nucleated but are composed of a stroma which has the same composition as living protoplasm. The meshwork of the stroma of the red cell holds hemoglobin, a complex protein containing iron.

Red blood cells originate in the marrow of the long bones. About one billion red cells per minute are given off into the blood stream to balance the cells which are constantly disintegrating. The liver and the spleen both aid in this disintegration and in the conversion of the red cells constituents into substances that can be used again in the body.

Hemoglobin has the property of combining with oxygen to form oxyhemoglobin. The action is reversible. Thus the cells can carry oxygen from the alveoli of the lungs to the various tissues of the body where it is required in metabolic processes. They also pick up part of the carbon dioxide which enters the capillaries in the body tissues and carry it in combination with the reduced hemoglobin to the alveoli of the lungs. The remainder of the carbon dioxide produced by metabolism is carried in solution in the blood plasma, partly as sodium bicarbonate and partly as carbonic acid.

White blood corpuscles are living cells, averaging only about 5 to 7 thousand per cubic millimeter of blood. An increase in number is termed "leucocytosis" and a decrease, "leucopenia". Changes in the number of white cells accompany certain diseases, hence the blood examination is important in their diagnosis.

Some white corpuscles are manufactured in the blood-forming cells of the marrow bones, while other types are produced in the lymphoid tissue of lymph nodes. A constant supply is given off to the blood in order to maintain the proper number, but reserves are always ready for discharge in case of emergency so that the number can be greatly increased in a short time.

Without going into a detailed study of the various types of white cells, it is sufficient to state that from 60 to 75 per cent of them, commonly termed "leucocytes", are capable of ingesting and destroying bacteria (phagocytosis). An invasion of bacteria into the body immediately attracts a swarm of these cells to the site of the infection. The leucocytes pass out of the blood stream between the endothelial cells of the capillary walls. The pus which forms consists of white corpuscles, bacteria, and an exudate from the blood or from injured body cells. It is an indication of the defensive procedures going on and is usually accompanied by the signs of inflammation — swelling, heat, redness, and pain in the tissues.

BLOOD VESSELS

The tubes leading from the heart are arteries. Those have rather thick elastic walls made up of layers of smooth muscle and of connective tissue. They branch into smaller arteries or arterioles, which have much thinner walls. The inner coat of all blood vessels is a smooth layer, called the endothelium. It is continuous with the endocardium of the heart and is the only layer of cells on the walls of the capillaries.

When the wave of blood forced out of the heart by the contraction of the ventricle passes through the artery, it produces a distinct beat called the pulse, due to the impact of the blood against the elastic walls of the artery.

The pressure exerted by the blood on the walls of the arteries is termed blood pressure. It depends not only upon the force of the heartbeat but also upon the elasticity of the walls of the arteries, and the resistance offered by capillaries to the escape of blood into the veins. Blood pressure is measured in millimeters of mercury. It varies with age. From 100 to 130 millimeters is considered normal in the young adult. Physical exertion and emotional stress increase blood pressure while inactivity, fatigue, and undernutrition tend to lower it. Persistently high or low

pressure may be abnormal; hence blood pressure is usually taken during the physical examination.

The thin endothelial walls of the capillary network permit a constant interchange of materials. The cells of the tissues are thus bathed constantly by an intercellular fluid, called "tissue fluid", which is supplied with materials from the blood stream. Waste from the cells passes into this fluid and part of it enters the blood stream through the capillary walls.

The rate of flow of the blood in the capillary network is very slow. Each capillary is approximately 0.75 of a millimeter long, but it requires almost two seconds for the blood to pass through. The complete circuit of the blood through both pulmonary and systemic circulation requires approximately thirty seconds. The retardation of blood in the capillaries facilitates the interchange of materials.

Capillary tubes open and close in response to nerve stimulation and to chemical substances brought to them through the blood. Not all of them are open simultaneously. It has been estimated that more than half of the blood of the body would be contained in the capillaries if they were all open at once. This is in fact what occurs during traumatic shock. The amount of blood emptying into the heart in this case may be so reduced as to cause the failure of circulation.

As the blood passes on from the capillaries, it enters the small veins. These also have the power of contracting and relaxing but their walls are impermeable, due to an added layer of connective tissue. The prompt return of the blood is important because the proper filling of the heart with blood is an important factor in determining the force of its beat.

There are several factors that aid in returning the blood to the heart. The pressure due to the oncoming stream from arteries and capillaries serves to push it forward. Valves which open toward the heart are located along the veins with the exception of the large veins of the trunk. Bodily movements produce pressure upon the soft tubes of the veins and this forces the blood onward because the action of the valves permits escape only in the direction of the heart.

The chest, in breathing, acts as a bellows which constantly changes the pressure in the thoracic cavity. A decrease in pressure allows the blood from the veins of the body to flow into the large trunk veins. With each inspiration the pressure is increased and the blood is forced toward the heart. Deep breathing thus serves to stimulate the flow of venous blood back to the heart.

The tissue fluid does not return directly into the blood stream but passes into a closed system of tubes known as the lymphatics. The fluid which enters the lymphatics is termed "lymph". After it is collected from various parts of the body it is poured into the venous blood stream through two large ducts at points near the heart. Movement of lymph through the lymphatics is similar to the flow of venous blood toward the heart, being influenced by the action of valves, the pressure of bodily movements, and changes in thoracic pressure. The swelling that occurs in connection with sprains or bruises is due to the accumulation of more liquid in intercellular spaces than can be drained off readily by the lymphatics.

Along the course of lymphatic ducts are masses of lymphatic tissue known as lymph nodes. The enlargement of lymph nodes near the site of an infection suggests that bacteria or other harmful substances are caught in these and may be destroyed there.

BONE

Bone forms the greater portion of the mammalian skeleton and serves as a store for calcium salts.

Macroscopically, mammalian bone has either a spongy or compact structure. The first of these consists of a framework of intercrossing and connecting osseous bars of varying thicknesses and shapes. These branch, unite with one another, and partially surround intercommunicating spaces filled with bone marrow. The direction and the points of contact of these crossbars are so arranged as to give each part of the skeleton a maximum rigidity and

resistance to changes in shape. Compact bone appears as a continuous hard white mass in which spaces can be distinguished only with the microscope. A sharp boundary cannot be drawn between the two types of bone tissue for they are merely different arrangements of the same histologic elements: moreover, both compact and spongy osseous tissue are present in practically every bone.

In typical long bones (femur and humerus) the diaphysis (or shaft) consists of compact bone and contains in it voluminous, cylindrical, bone marrow cavity. The epiphysis (the bone at the end of the shaft) consists of spongy bone with a thin, peripheral cortex of compact bone. The cavities of this spongy bone are direct continuations of the bone marrow cavity of the diaphysis. In the flat bones of the skull, the compact substance forms a relatively thick layer on both surfaces between which there is a layer of spongy bone of varying thickness (diploe). The short and irregular bones usually consist of spongy substance covered by a layer of compact bone.

The modified connective tissue covering of a bone is called periosteum, while that lining the large cavities of bones is called endosteum.

Bone develops through a relatively simple transformation of connective tissue (intramembranous ossification) or by a complete replacement of cartilage (intracartilaginous or endochondral ossification) or, as is frequently the case, through a combination of both of these processes. With the further growth of a bone it undergoes a marked internal reconstruction. As a result of these changes the mature bone acquires a very complex structure.

Spongy bone. The spongy substance is simpler and less regular than the compact substance. In its embryonic development bone is always first laid down in the spongy form.

Spongy bone varies in its appearance in different parts of the skeleton. It may consist of: 1) tubes with a compact or perforated wall, 2) hollow globes, 3) narrow or wide plates or 4) massive irregularly cylindrical bars. All of these types of spongy bone substances are fitted for definite mechanical functions in individual bones, and their parts are usually arranged in those directions which correspond with the lines of the maximum of pressure or tension acting upon the particular part of the skeleton. The irregular trabeculae of the spongy substance consist of a varying number of closely adjoining bone plates or bone lamellae and incompletely subdivide the bone marrow cavity.

Compact bone. The regular arrangement of the lamellae in the compact substance is closely connected with the distribution of the blood vessels which nourish the bone. When studied under the microscope, the compact substance of the diaphysis of any long bone is seen to be penetrated by a number of cylindrical, branching and anastomosing canals 22 to 110 p wide. These are directed mainly along the length of the bone so that in cross section they appear as round openings and in longitudinal sections as long slits. These are the Haversian canals; in a living bone they contain blood vessels with a small amount of accompanying connective tissue. They communicate by the canals of Volkmann with the external surface of and with the bone marrow cavity. At the junction of the compact and the spongy bone, the Haversian canals of the former expand and pass directly over into the marrow spaces of the latter.

CIRCULATION

The importance of the blood and lymph in the transportation of material within the body is very great. Structurally the circulatory system consists of a medium, the blood, a muscular organ, the heart, which serves as a force pump, and a closed system of branching tubes, through which blood circulates.

Blood

The blood with its various constituents makes up approximately 7 per cent of the weight of the body. Its volume in the adult usually varies from four to five quarts. Blood carries two groups of constituents: a) substances which are specific parts of the blood, and b) nutrients and

waste materials in transit. The specific blood constituents include inorganic salts, plasma protein, immunizing agents, blood cells, antibodies and blood platelets.

Inorganic salts function in determining the osmotic pressure of the blood which must be kept in equilibrium with that of the body cells and the red blood cells. Calcium is essential in producing the chemical changes necessary in the coagulation of blood. It also influences the rate of the heartbeat. Phosphorus helps to maintain the neutral state of the blood. Iron is the essential constituent of the oxygen-carrying compound in red corpuscles.

Plasma protein makes up from 7 to *8* per cent of the weight of the plasma or liquid portion of the blood. One of the plasma proteins of particular interest is fibrinogen, which is essential in the clotting of the blood. A number of chemical changes are involved in the formation of a dot, but essentially it is brought about by the precipitation of fibrinogen in a fine network of fibrin needles whenever blood passes outside a blood vessel and comes in contact with other surfaces. The accumulation of red corpuscles in this mesh produces the clot.

The formation of a clot in the blood stream (thrombus) is as serious as would be the failure of blood to clot on exposure. If a thrombus lodges in a small artery it may block the circulation to some vital organ, either partially or completely.

The immunizing agents present in the blood consist of 1) foreign, water-soluble proteins which act as antigens and 2) colloidal substances of unknown chemical nature, or antibodies. The latter are produced by the body cells under the stimulation of antigens and give partial or complete immunity to the disease.

DIGESTIVE SYSTEM

The digestive system consists of the alimentary canal and related or accessory organs.

The alimentary canal is formed by the mouth, pharynx, esophagus, stomach, small intestine, large intestine and rectum.

The accessory structures are the teeth, tongue, salivary glands, hard and soft palates, liver, gallbladder and pancreas.

The alimentary tract from esophagus to rectum conforms to a definite structural plan. The layers from within outward are mucous, submucous, muscular and serous. In the esophagus the serous layer is lacking and the outer coat is fibrous in nature.

The organs of the digestive system contained in the abdomen are covered with the serous coat — the peritoneum. The peritoneum has two layers, the visceral and parietal.

The mouth is the first division of the alimentary tract. Important structures of the mouth are the tongue, which contains the end organ for taste, and the teeth which divide and mix the food. There are two sets of teeth, first the deciduous or milk teeth and later the permanent teeth.

The palatine tonsils are on the lateral walls of the oral pharynx between the palatine arches.

The oral and laryngeal portions of the pharynx serve as a channel for the passage of both food and air; food is conducted through it from the mouth to the esophagus and air from the nasal pharynx to the larynx.

The esophagus conveys food from the pharynx to the stomach.

The stomach is a dilated portion of the alimentary canal lying in the upper abdomen just under the diaphragm. It is a retaining and mixing reservoir in which the process of digestion begins.

The circular muscle layer is thickened at the pyloric and cardiac orifices to form sphincters. The glands of the fundus and body are most important in the secretion of gastric juice. They are formed mainly of chief and parietal cells.

The small intestine is a thin-walled muscular tube about 7 meters long. Its three portions are: duodenum, jejunum and ileum.

The bile and pancreatic ducts empty into the duodenum.

Special structural features of the small intestine are the villi and the circular folds. The intestinal glands or crypts of Lieberkiihn secrete the intestinal juice containing the digestive enzymes.

The large intestine is about 1.5 meters long and is divided into caecum, colon and rectum.

The large salivary glands consist of the parotid, the submaxillary and the sublingual. Ducts from the three pairs of glands open into the mouth.

The liver is the largest gland in the body. It is directly beneath the diaphragm on the right side of the abdomen. The liver cells are arranged in architectural units, called lobules.

The bile capillaries and sinusoids lie between chains of liver cells in the lobule. Branches of the portal vein, bile duct and hepatic arteries encircle the periphery of the lobule.

The liver secretes bile and has many other important functions such as stimulation of red bone marrow, production of fibrinogen, glycogemetic function and urea synthesis.

The gallbladder is a pear-shaped hollow sac attached to the under surface of the liver. It concentrates the bile.

The pancreas is a long slender organ with its head to the right in the loop of the duodenum, its body posterior to the stomach and its tail touching- the spleen on the left.

The pancreas forms an external secretion important in digestion and an internal secretion, insulin, concerned with carbohydrate metabolism.

HEART

Heart is a hollow muscular organ with four cavities, each provided at its outlet with a valve, whose function is to maintain the circulation of the blood. The two upper cavities are known as atria or auricles, the two lower ones as ventricles.

The heart lies in the chest between the two lungs, but projecting more to the left side than to the right. On the left side its apex reaches out almost to the nipple, and lies beneath the fifth rib, while its right border extends only a short distance, at most an inch, beyond the margin of the breastbone. Its lower border rests upon the diaphragm by which it is separated from the liver and stomach. Above, the heart extends to the level of the second rib, where the great vessels, the aorta on the right side and the pulmonary artery on the left, lie behind the breastbone.

The heart of an individual was described as, roughly, of the size and shape of the clenched fist. One end of the heart is pointed (apex), the other is broad (base).

Structure. The heart lies within a strong fibrous bag, known as the pericardium, and since the inner surface of this bag and the outer surface of the heart are both covered with a smooth, glistening membrane faced with flat cells and lubricated by a little serous fluid, the movements of the heart are accomplished almost without friction. The main thickness of the heart wall consists of bundles of muscle fibers.

Within all the cavities is a smooth lining membrane continuous with that lining the vessels which open into the heart. The investing smooth membrane is known as epicardium, the muscular substance as myocardium, and the smooth lining membrane as endocardium.

For the regulation of the heart's action there are important nervous connections, especially with the vagus and with the sympathetic nerves.

There is no direct communication between the cavities on the right side and those on the left; but the right auricle opens into the right ventricle by a large circular opening, and similarly the left auricle into the left ventricle. Into the right auricle open two large veins, the superior and inferior venae cavae, with some smaller veins from the wall of the heart itself, and into the left auricle open two pulmonary veins from each lung. One opening leads out of each ventricle, to the aorta in the case of the left ventricle, to the pulmonary artery from the right. As stated above there are four valves. Two of these are placed at the openings leading from auricle into ventricle, the "tricuspid valve" on the right side, the "mitral valve" on the left, so as completely to prevent blood from running back into the auricle when the ventricle contracts. Two more, the "pulmonary valve" and the "aortic valve, are placed at the entrance to these arteries, and prevent

regurgitation into the ventricles of blood which has been driven from them into the arteries. The noises made by these valves in closing are known as the heart sounds, and can be heard by anyone who applies his ear to the front of a person's chest.

Matter

Matter is a poorly defined term in science. The term has often been used in reference to a substance (often a particle) that has rest mass. Matter is also used loosely as a general term for the substance that makes up all observable physical objects.

All objects we see with the naked eye are composed of atoms. This atomic matter is in turn made up of interacting subatomic particles—usually a nucleus of protons and neutrons, and a cloud of orbiting electrons. Typically, science considers these composite particles matter because they have both rest mass and volume. By contrast, massless particles, such as photons, are not considered matter, because they have neither rest mass nor volume. However, not all particles with rest mass have a classical volume, since fundamental particles such as quarks and leptons (sometimes equated with matter) are considered "point particles" with no effective size or volume. Nevertheless, quarks and leptons together make up "ordinary matter," and their interactions contribute to the effective volume of the composite particles that make up ordinary matter.

Matter commonly exists in four states (or phases): solid, liquid and gas, and plasma. However, advances in experimental techniques have revealed other previously theoretical phases, such as Bose–Einstein condensates and fermionic condensates. A focus on an elementary-particle view of matter also leads to new phases of matter, such as the quark–gluon plasma. For much of the history of the natural sciences people have contemplated the exact nature of matter. The idea that matter was built of discrete building blocks, the so-called particulate theory of matter, was first put forward by the Greek philosophers Leucippus (~490 BC) and Democritus (~470–380 BC).

Albert Einstein showed that ultimately all matter is capable of being converted to energy (known as mass-energy equivalence) by the famous formula $E = mc^2$, where E is the energy of a piece of matter of mass m, times c^2 the speed of light squared. As the speed of light is 299,792,458 metres per second (186,282 mi/s), a relatively small amount of matter may be converted to a large amount of energy. An example is that positronsand electrons (matter) may transform into photons (non-matter). However, although matter may be created or destroyed in such processes, neither the quantity of mass or energy change during the process.

Matter should not be confused with mass, as the two are not quite the same in modern physics. For example, mass is a conserved quantity, which means that its value is unchanging through time, within closed systems. However, matter is not conserved in such systems, although this is not obvious in ordinary conditions on Earth, where matter is approximately conserved. Still, special relativity shows that matter may disappear by conversion into energy, even inside closed systems, and it can also be created from energy, within such systems. However, because mass (like energy) can neither be created nor destroyed, the quantity of mass and the quantity of energy remain the same during a transformation of matter (which represents a certain amount of energy) into non-material (i.e., non-matter) energy. This is also true in the reverse transformation of energy into matter.

Different fields of science use the term matter in different, and sometimes incompatible, ways. Some of these ways are based on loose historical meanings, from a time when there was no reason to distinguish mass and matter. As such, there is no single universally-agreed scientific meaning of the word "matter." Scientifically, the term "mass" is well-defined, but "matter" is not. Sometimes in the field of physics "matter" is simply equated with particles that exhibit rest mass (i.e., that cannot travel at the speed of light), such as quarks and leptons. However, in both physics and chemistry, matter exhibits both wave-like and particle-like properties, the so-called wave–particle duality.

Matter. Common definition

The DNA molecule is an example of matter under the "atoms and molecules" definition.

The common definition of matter is anything that has both mass and volume (occupies space). For example, a car would be said to be made of matter, as it occupies space, and has mass.

The observation that matter occupies space goes back to antiquity. However, an explanation for why matter occupies space is recent, and is argued to be a result of the Pauli exclusion principle. Two particular examples where the exclusion principle clearly relates matter to the occupation of space are white dwarf stars and neutron stars, discussed further below.

Relativity

In the context of relativity, mass is not an additive quantity, in the sense that one can add the rest masses of particles in a system to get the total rest mass of the system. Thus, in relativity usually a more general view is that it is not the sum of rest masses, but the energy–momentum tensor that quantifies the amount of matter. This tensor gives the rest mass for the entire system. "Matter" therefore is sometimes considered as anything that contributes to the energy–momentum of a system, that is, anything that is not purely gravity. This view is commonly held in fields that deal with general relativity such as cosmology. But in this view, light and other types of insubstantial energy may be part of matter.

The reason for this is that in this definition, electromagnetic radiation (such as light) as well as the energy of electromagnetic fields contributes to the mass of systems, and therefore appears to add matter to them. For example, light radiation (or thermal radiation) trapped inside a box would contribute to the mass of the box, as would any kind of energy inside the box, including the kinetic energy of particles held by the box. Nevertheless, isolated individual particles of light (photons) and the isolated kinetic energy of massive particles, are normally not considered to be matter.

A difference between matter and mass therefore may seem to arise when single particles are examined. In such cases, the mass of single photons is zero. For particles with rest mass, such as leptons and quarks, isolation of the particle in a frame where it is not moving, removes its kinetic energy.

A source of definition difficulty in relativity arises from two definitions of mass in common use, one of which is formally equivalent to total energy (and is thus observer-dependent), and the other of which is referred to as rest mass or invariant mass and is independent of the observer. Only the latter type of mass is loosely equated with matter (since it can be weighed). However, energies which contribute to the first type of mass may be weighed also in special circumstances, such as when trapped in a system with no net momentum (as in the box example above). Thus, a photon with no mass may add mass to a system in which it is trapped. Since such mass is measured as part of ordinary matter in complex systems, the "matter" status of "massless particles" becomes unclear in such systems. These problems contribute to the lack of a rigorous definition of matter in science, although mass is easier to define as the total stress-energy above (this is also what is weighed on a scale, and what is the source of gravity).

Cell

The **cell** is the basic structural, functional and biological unit of all known living organisms. Cells are the smallest unit of life that can replicate independently, and are often called the "building blocks of life".

Cells consist of a protoplasm enclosed within a membrane, which contains many biomolecules such as proteins and nucleic acids. Organisms can be classified as unicellular (consisting of a single cell; including most bacteria) or multicellular (including plants and animals). While the number of cells in plants and animals varies from species to species, humans contain about 100 trillion (10^{14}) cells. Most plant and animal cells are visible only under the microscope, with dimensions between 1 and 100 micrometres.

The cell was discovered by Robert Hooke in 1665. The cell theory, first developed in 1839 by Matthias Jakob Schleiden and Theodor Schwann, states that all organisms are composed of one or more cells, that all cells come from preexisting cells, that vital functions of an organism occur within cells, and that all cells contain the hereditary information necessary for regulating cell functions and for transmitting information to the next generation of cells. Cells emerged on Earth at least 3.5 billion years ago.

The word cell comes from the Latin cella, meaning "small room". It was coined by Robert Hooke in his book Micrographia (1665), in which he compared the cork cells he saw through his microscope to the small rooms monks lived in.

All cells, whether prokaryotic or eukaryotic, have a membrane that envelops the cell, separates its interior from its environment, regulates what moves in and out (selectively permeable), and maintains the electric potential of the cell. Inside the membrane, a salty cytoplasm takes up most of the cell volume. All cells (except red blood cells which lack a cell nucleus and most organelles to accommodate maximum space for hemoglobin) possess DNA, the hereditary material of genes, and RNA, containing the information necessary to build various proteins such as enzymes, the cell's primary machinery. There are also other kinds of biomolecules in cells. This article lists these primary components of the cell, then briefly describes their function.

Membrane

The cell membrane, or plasma membrane, surrounds the cytoplasm of a cell. In animals, the plasma membrane is the outer boundary of the cell, while in plants and prokaryotes it is usually covered by a cell wall. This membrane serves to separate and protect a cell from its surrounding environment and is made mostly from a double layer of phospholipids, which are amphiphilic (partly hydrophobic and partly hydrophilic). Hence, the layer is called a phospholipid bilayer, or sometimes a fluid mosaic membrane. Embedded within this membrane is a variety of protein molecules that act as channels and pumps that move different molecules into and out of the cell. The membrane is said to be 'semi-permeable', in that it can either let a substance (molecule or ion) pass through freely, pass through to a limited extent or not pass through at all. Cell surface membranes also contain receptor proteins that allow cells to detect external signaling molecules such as hormones.

Genetic material

Two different kinds of genetic material exist: deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Most cells use DNA for their long-term information storage. The biological information contained in an organism is encoded in its DNA sequence. RNA is used for information transport (e.g., mRNA) and enzymatic functions (e.g., ribosomal RNA). Transfer RNA (tRNA) molecules are used to add amino acids during protein translation.

Prokaryotic genetic material is organized in a simple circular DNA molecule (the bacterial chromosome) in the nucleoid region of the cytoplasm. Eukaryotic genetic material is divided into different, linear molecules called chromosomes inside a discrete nucleus, usually with additional genetic material in some organelles like mitochondria and chloroplasts (see endosymbiotic theory).

A human cell has genetic material contained in the cell nucleus (the nuclear genome) and in the mitochondria (the mitochondrial genome). In humans the nuclear genome is divided into 46 linear DNA molecules called chromosomes, including 22 homologous chromosome pairs and a pair of sex chromosomes. The mitochondrial genome is a circular DNA molecule distinct from the nuclear DNA. Although the mitochondrial DNA is very small compared to nuclear chromosomes, it codes for 13 proteins involved in mitochondrial energy production and specific tRNAs.

Foreign genetic material (most commonly DNA) can also be artificially introduced into the cell by a process called transfection. This can be transient, if the DNA is not inserted into the cell's genome, or stable, if it is. Certain viruses also insert their genetic material into the genome.

Cell

- **Cell nucleus**: A cell's information center, the cell nucleus is the most conspicuous organelle found in aeukaryotic cell. It houses the cell's chromosomes, and is the place where almost all DNA replication and RNA synthesis (transcription) occur. The nucleus is spherical and separated from the cytoplasm by a double membrane called the nuclear envelope. The nuclear envelope isolates and protects a cell's DNA from various molecules that could accidentally damage its structure or interfere with its processing. During processing, DNA is transcribed, or copied into a special RNA, called messenger RNA (mRNA). This mRNA is then transported out of the nucleus, where it is translated into a specific protein molecule. The nucleolus is a specialized region within the nucleus where ribosome subunits are assembled. In prokaryotes, DNA processing takes place in the cytoplasm.
- **Mitochondria and Chloroplasts**: the power generators: Mitochondria are self-replicating organelles that occur in various numbers, shapes, and sizes in the cytoplasm of all eukaryotic cells. Mitochondria play a critical role in generating energy in the eukaryotic cell. Respiration occurs in the cell mitochondria, which generate the cell's energy by oxidative phosphorylation, using oxygen to release energy stored in cellular nutrients (typically pertaining to glucose) to generate ATP. Mitochondria multiply by binary fission, like prokaryotes. Chloroplasts can only be found in plants and algae, and they capture the sun's energy to make ATP.
- **Endoplasmic reticulum**: The endoplasmic reticulum (ER) is a transport network for molecules targeted for certain modifications and specific destinations, as compared to molecules that float freely in the cytoplasm. The ER has two forms: the rough ER, which has ribosomes on its surface that secrete proteins into the ER, and the smooth ER, which lacks ribosomes. The smooth ER plays a role in calcium sequestration and release.
- **Golgi apparatus**: The primary function of the Golgi apparatus is to process and package the macromolecules such as proteins and lipids that are synthesized by the cell.
- **Lysosomes and Peroxisomes**: Lysosomes contain digestive enzymes (acid hydrolases). They digest excess or worn-out organelles, food particles, and engulfed viruses or bacteria. Peroxisomes have enzymes that rid the cell of toxic peroxides. The cell could not house these destructive enzymes if they were not contained in a membrane-bound system.
- **Centrosome** – the cytoskeleton organiser: The centrosome produces the microtubules of a cell – a key component of the cytoskeleton. It directs the transport through the ER and the Golgi apparatus. Centrosomes are composed of two centrioles, which separate during cell division and help in the formation of the mitotic spindle. A single centrosome is present in the animal cells. They are also found in some fungi and algae cells.
- **Vacuoles**: Vacuoles store food and waste. Some vacuoles store extra water. They are often described as liquid filled space and are surrounded by a membrane. Some cells, most notably Amoeba, have contractile vacuoles, which can pump water out of the cell if there is too much water. The vacuoles of eukaryotic cells are usually larger in those of plants than animals.

Origin of the first cell

Stromatolites are left behind bycyanobacteria, also called blue-green algae. They are the oldest known fossils of life on Earth. This one-billion-year-old fossil is from Glacier National Park in the United States.

There are several theories about the origin of small molecules that led to life on the early Earth. They may have been carried to Earth on meteorites (see Murchison meteorite), created at deep-sea vents, or synthesized by lightning in a reducing atmosphere (see Miller–Urey experiment). There is little experimental data defining what the first self-replicating forms were. RNA is thought to be the earliest self-replicating molecule, as it is capable of both storing genetic information and catalyzing chemical reactions (see RNA world hypothesis), but some

other entity with the potential to self-replicate could have preceded RNA, such as clay or peptide nucleic acid.

Cells emerged at least 3.5 billion years ago. The current belief is that these cells were heterotrophs. The early cell membranes were probably more simple and permeable than modern ones, with only a single fatty acid chain per lipid. Lipids are known to spontaneously form bilayered vesicles in water, and could have preceded RNA, but the first cell membranes could also have been produced by catalytic RNA, or even have required structural proteins before they could form.

Origin of eukaryotic cells

The eukaryotic cell seems to have evolved from a symbiotic community of prokaryotic cells. DNA-bearing organelles like the mitochondria and the chloroplasts are descended from ancient symbiotic oxygen-breathing proteobacteria and cyanobacteria, respectively, which were endosymbiosed by an ancestral archaean prokaryote.

There is still considerable debate about whether organelles like the hydrogenosome predated the origin of mitochondria, or vice versa: see the hydrogen hypothesis for the origin of eukaryotic cells.

Sex, as the stereotyped choreography of meiosis and syngamy that persists in nearly all extant eukaryotes, may have played a role in the transition from prokaryotes to eukaryotes. One view, on the origin of sex in eukaryotic cells, is that eukaryotic sex evolved from a prokaryotic sexual process termed transformation. According to this view, bacterial transformation is an adaptation for repairing DNA damages that arise during stressful conditions, and this role has been maintained in meiosis, where recombinational DNA repair is promoted. Thus the adaptive benefit of prokaryotic sex, recombinational repair, was maintained through the evolutionary transition from prokaryotes to single-celled eukaryotes.

In another view, an 'origin of sex as vaccination' theory suggests that the eukaryote genome accreted from prokaryan parasite genomes in numerous rounds of lateral gene transfer. Sex-as-syngamy (fusion sex) arose when infected hosts began swapping nuclearized genomes containing co-evolved, vertically transmitted symbionts that conveyed protection against horizontal infection by more virulent symbionts.

Gene

A **gene** is the molecular unit of heredity of a living organism. It is widely accepted by the scientific community as a name given to some stretches of deoxyribonucleic acids (DNA) and ribonucleic acids(RNA) that code for a polypeptide or for an RNA chain that has a function in the organism, though there still are controversies about what plays the role of the genetic material.[1] Living beings depend on genes, as they specify all proteins and functional RNA chains. Genes hold the information to build and maintain an organism's cells and pass genetic traits to offspring. All organisms have many genes corresponding to various biological traits, some of which are immediately visible, such as eye color or number of limbs, and some of which are not, such as blood type, increased risk for specific diseases, or the thousands of basic biochemical processes that comprise life. The word gene is derived from the Greek word genesis meaning "birth", or genos meaning "origin".

A modern working definition of a gene is "a locatable region of genomic sequence, corresponding to a unit of inheritance, which is associated with regulatory regions, transcribed regions, and or other functional sequence regions ". Colloquial usage of the term gene (e.g. "good genes", "hair color gene") may actually refer to an allele: a gene is the basic instruction—a sequence of nucleic acids (DNA or, in the case of certain viruses RNA), while an allele is one variant of that gene. Thus, when the mainstream press refers to "having" a "gene" for a specific trait, this is generally inaccurate. In most cases, all people would have a gene for the trait in question, but certain people will have a specific allele of that gene, which results in the trait variant. Further, genes code for proteins, which might result in identifiable traits, but it is the gene, not the trait, which is inherited.

Molecular inheritance

The duplication and transmission of genetic material from one generation of cells to the next is the basis for molecular inheritance, and the link between the classical and molecular pictures of genes. Organisms inherit the characteristics of their parents because the cells of the offspring contain copies of the genes in their parents' cells. In asexually reproducing organisms, the offspring will be a genetic copy or clone of the parent organism. In sexually reproducing organisms, a specialized form of cell division called meiosis produces cells called gametes or germ cells that are haploid, or contain only one copy of each gene. The gametes produced by females are called eggs or ova, and those produced by males are called sperm. Two gametes fuse to form a fertilized egg, a single cell that once again has a diploid number of genes—each with one copy from the mother and one copy from the father.

During the process of meiotic cell division, an event called genetic recombination or crossing-over can sometimes occur, in which a length of DNA on one chromatid is swapped with a length of DNA on the corresponding sister chromatid. This has no effect if the alleles on the chromatids are the same, but results in reassortment of otherwise linked alleles if they are different. The Mendelian principle of independent assortment asserts that each of a parent's two genes for each trait will sort independently into gametes; which allele an organism inherits for one trait is unrelated to which allele it inherits for another trait. This is in fact only true for genes that do not reside on the same chromosome, or are located very far from one another on the same chromosome. The closer two genes lie on the same chromosome, the more closely they will be associated in gametes and the more often they will appear together; genes that are very close are essentially never separated because it is extremely unlikely that a crossover point will occur between them. This is known as genetic linkage.

DNA replication and inheritance

The growth, development, and reproduction of organisms relies on cell division, or the process by which a single cell divides into two usually identical daughter cells. This requires first making a duplicate copy of every gene in the genome in a process called DNA replication. The copies are made by specialized enzymes known as DNA polymerases, which "read" one strand of the double-helical DNA, known as the template strand, and synthesize a new complementary strand. Because the DNA double helix is held together by base pairing, the sequence of one strand completely specifies the sequence of its complement; hence only one strand needs to be read by the enzyme to produce a faithful copy. The process of DNA replication is semiconservative; that is, the copy of the genome inherited by each daughter cell contains one original and one newly synthesized strand of DNA.

After DNA replication is complete, the cell must physically separate the two copies of the genome and divide into two distinct membrane-bound cells. In prokaryotes - bacteria and archaea - this usually occurs via a relatively simple process called binary fission, in which each circular genome attaches to the cell membrane and is separated into the daughter cells as the membrane invaginates to split the cytoplasm into two membrane-bound portions. Binary fission is extremely fast compared to the rates of cell division in eukaryotes. Eukaryotic cell division is a more complex process known as the cell cycle; DNA replication occurs during a phase of this cycle known as S phase, whereas the process of segregating chromosomes and splitting the cytoplasm occurs during M phase. In many single-celled eukaryotes such as yeast, reproduction by budding is common, which results in asymmetrical portions of cytoplasm in the two daughter cells.

Chromosomes

The total complement of genes in an organism or cell is known as its genome, which may be stored on one or more chromosomes; the region of the chromosome at which a particular gene is located is called its locus. A chromosome consists of a single, very long DNA helix on which

thousands of genes are encoded. Prokaryotes—bacteria and archaea—typically store their genomes on a single large, circular chromosome, sometimes supplemented by additional small circles of DNA called plasmids, which usually encode only a few genes and are easily transferable between individuals. For example, the genes for antibiotic resistance are usually encoded on bacterial plasmids and can be passed between individual cells, even those of different species, via horizontal gene transfer. Although some simple eukaryotes also possess plasmids with small numbers of genes, the majority of eukaryotic genes are stored on multiple linear chromosomes, which are packed within the nucleus in complex with storage proteins called histones. The manner in which DNA is stored on the histone, as well as chemical modifications of the histone itself, are regulatory mechanisms governing whether a particular region of DNA is accessible for gene expression. The ends of eukaryotic chromosomes are capped by long stretches of repetitive sequences called telomeres, which do not code for any gene product but are present to prevent degradation of coding and regulatory regions during DNA replication. The length of the telomeres tends to decrease each time the genome is replicated in preparation for cell division; the loss of telomeres has been proposed as an explanation for cellular senescence, or the loss of the ability to divide, and by extension for the aging process in organisms.

Whereas the chromosomes of prokaryotes are relatively gene-dense, those of eukaryotes often contain so-called "junk DNA", or regions of DNA that serve no obvious function. Simple single-celled eukaryotes have relatively small amounts of such DNA, whereas the genomes of complex multicellular organisms, including humans, contain an absolute majority of DNA without an identified function. However it now appears that, although protein-coding DNA makes up barely 2% of the human genome, about 80% of the bases in the genome may be expressed, so the term "junk DNA" may be a misnomer.

RESPIRATION

Respiration is the process in which air passes into and out of the lung with the object of allowing the blood to absorb oxygen and to give off carbon dioxide and water.

Mechanism of respiration. The air passes rhythmically into and out of the air passages, and mixes with the air already in the lungs, these two movements being known as inspiration and expiration.

Inspiration is due to a muscular effort which enlarges the chest in all three dimensions, so that the lungs have to expand in order to fill up the vacuum that would otherwise be left, and the air accordingly enters these organs by the air passages. It must be understood that there is no direct pull upon the lungs, each of which is simply suspended within the corresponding pleural cavity by its root, and made to fill this cavity in all conditions of the chest by the pressure of the outer air exerted through the nose, mouth, and air passages.

The increase of the chest in size from above downwards is mainly due to the diaphragm, whose muscular fibres by their contraction reduce its domed shape and cause it to descend, pushing down the abdominal organs beneath it. The increase from before back is mainly due to a tilting forwards of the lower end of the breastbone, and of the lower rib cartilages. The increase from side to side can best be understood by examining a skeleton, noting the very oblique position of the lower ribs, and observing how greatly the capacity of the chest is increased when each is raised taking its fixed points at the spine and breastbone.

The muscles which chiefly bring about these changes in ordinary, quiet inspiration are the diaphragm, intercostal muscles and levators of the ribs, while in forced or extraordinary inspiration, when a specially deep breath is taken, the sternomastoid, serratus magnus, trapezius, and pectoral muscles are also brought powerfully into play. One must note that many other muscles take part to a slight extent, steadying the spine and the upper and lower ribs, while even the muscles of the face and of the larynx are thrown rhythmically into activity, dilating the nostrils and the entrance to the larynx at each breath.

Expiration is in ordinary circumstances simply an elastic recoil, the diaphragm rising and the ribs sinking into the position that they naturally occupy, when muscular contraction is finished. Expiration occupies a slightly longer period than inspiration. In forced expiration many powerful muscles of the abdomen and thorax are brought into play, and the act may be made a very forcible one, as, for example, in coughing.

Nervous control. Respiration is usually either an automatic or a reflex act, each expiration sending up afferent, sensory impulses to the central nervous system, from which efferent impulses are sent down various other nerves to the muscles that produce inspiration.

From the recent researches it appears that there are several centres which govern the rate, force, etc., of the breathing, though all are presided over by a chief respiratory centre in the medulla oblongata, which is sometimes spoken of as the vital knot. Though this centre appears to be absolutely essential to life, it in turn is under the control of the higher centres in the cerebral hemispheres, through which the will acts, so that breathing can be voluntarily stopped, quickened, or otherwise changed at will.

It would be impossible, however, to cause death voluntarily holding the breath, because, as the blood becomes more venous, the vital centre in the medulla again assumes control and breathing recommences. Apart from changes due to willpower, the respirations follow one another rhythmically at the rate of about 18 per minute, being in general one for every four heartbeats.

Quantity of air. The lungs do not by any means completely empty themselves at each expiration and refill at each inspiration. An amount equivalent, in quiet respiration, to less than one-tenth of the total air in the lungs passes out and is replaced by the same quantity of fresh air, which mixes with the stale air in the lungs. This renewal, which in quiet breathing amounts to about 30 cubic inches or I pint of air or about 500 cc is known as the tidal air.

By a special inspiratory effort, one can, however, draw in about 180 cubic inches, i. e., over 6 pints of air or 3000 cc, this amount being known as complemental air. By a special expiratory effort too, after an ordinary breath one can expel much more than the tidal air from the lungs, this extra amount being known as the supplemental or reserve air, and amounting also to about 60 cubic inches or 1000 cc.

If one takes as deep an inspiration as possible and then makes a forced expiration, one breathes out the sum of these three, which is known as the vital capacity, and amounts to about 4000 cc in a healthy adult male of average size.

Over and above the vital capacity, the lungs contain air which cannot be emptied by the strongest possible expiration, and this residual air, which remains in the lungs even after death, amounts to at least another 1000—1500 cc.

SKELETAL MUSCLES

Skeletal Muscles as Organs of the Muscular System. The skeletal muscles are the organs of the muscular system. They number over 400 in the human body. Each has an arterial, venous, lymphatic and nervous supply as well as a connective tissue framework, the whole constituting an independent unit. However, muscles never act singly but in groups. We seldom contract an individual muscle; we execute a movement and in the performance of that movement whole groups of muscles are involved. Skeletal muscles, then, are grouped into a system which exhibits correlation and cooperation of its parts.

Attachments of Muscles. Each striated muscle consists of a body and two attachments. The body contains the muscular tissue, the attachments are composed of white fibrous tissue. The attachment of muscle to bone may be one of three types: direct to the periosteum, by means of a tendon, or by means of an aponeurosis. In a direct attachment the white fibers of the connective tissue framework of the muscle fuse with the fibrous layers of the periosteum of the bone. A tendon is a band or cord of white fibrous tissue serving to connect a muscle to a bone. The sarcolemma and the connective tissue surrounding the muscle bundles fuse with the collagenous fibers of the tendon. An aponeurosis is a heavy sheet of white fibrous tissue serving

to connect a muscle to a bone or in some instances to connect muscles. *Origin and insertion.* The more fixed attachment of a muscle which serves as a basis of action is called the origin. The movable attachment where the effects of movement are produced is the insertion. Generally the origin is near the spinal axis of the body while the insertion is peripheral.

Muscle action. If the attachments of a muscle are known, its action may be determined by recalling that the insertion moves toward the origin when the muscle contracts. Muscles are arranged in opposing or antagonistic groups: flexors and extensors, adductors and abductors, internal rotators and external rotators.

STOMACH

The stomach is a dilated portion of the alimentary canal, which in man has a shape somewhat resembling that of a pear. The larger end, known as the "fundus", lies in the hollow of the left side of the diaphragm. The upper part of the stomach, into which the gullet opens, is known as the cardiac part, while the lower and narrower portion is known as the pyloric part. The two openings into and out of the stomach are known as the cardia and the pylorus.

The stomach is slightly flattened from before backwards, and the two edges are known as the lesser curvature, which runs from one opening to the other direct, and the greater curvature, which sweeps round the fundus from the cardia to the pylorus.

The stomach hangs very freely suspended in the upper and left part of the abdomen, so that changes in its position and shape take place readily according to the amount of food it contains.

The stomach possesses four coats similar to those of the intestine, which are, from within outwards, a mucous membrane, submucous layer, muscular coat, and peritoneal coat. Mucous membrane lines the interior of the stomach and is of smooth, soft texture, though raised up into ridges when the stomach is empty. The surface can be seen with the naked eye to be thickly covered by minute pits into each of which several tube-shaped glands are found, on microscopic section, to open.

The surface of the mucous membrane is composed of a single layer of columnar cells, and these also line the pits referred to above. Each gland is composed of large cubical cells so arranged as ta form a tube, open at the upper end where it meets the pit, and closed beneath. These cells secrete the gastric juice which exudes from all the minute tubes as digestion is proceeding. Between the tubular glands lies some supporting connective tissue in which run numerous blood capillaries and lymph vessels.

STOMACH COATS

Submucous coat is a loose connective tissue layer which joins the mucous coat to the muscular coat, and in which the large blood vessels of the stomach run. The loose arrangement of its fibres allows the mucous membrane to glide freely over the muscular coat in the movements and variations in size of the stomach.

Muscular coat is of considerable thickness in the stomach, and is of great importance in varying the size of the organ according to the amount of food it contains, in making the peristaltic movements which mix the food with the digestive juice, and finally in expelling the softened food from the stomach into the small intestine. This coat consists of three layers, an outer one in which the fibres run lengthwise, a middle one where they are circular, and an inner layer in which they run obliquely across the stomach.

Peritoneal coat is similar to the peritoneum covering the other organs of the abdomen.

The stomach is abundantly supplied with blood from the coeliac axis, a short, wide artery which comes directly from the aorta and likewise gives branches to the liver, pancreas and spleen. There is a large arterial arch round either curvature, and from these two arches smaller branches run into the wall of the stomach and reach the submucous coat, from which minute branches are distributed to the other coats. The blood is collected by veins which ultimately return it to the portal vein.

The stomach is very richly supplied with nerves both from the nerve vagus and from the nerve sympathicus. The tenth cranial nerve (vagus) of each side has a long course down the side of the gullet, and after giving branches to the larynx, heart, lungs, and other .organs, terminates in the stomach. Other branches come from the solar plexus of the nerve sympathicus. These nerves form a plexus in the submucous coat and another in the muscular coat, which undoubtedly exert an influence over the secretions and movements of the organ.

THE GALL BLADDER

Gallstones (cholelithiasis)

Aetiology

Gallstones are found in 20% of the population in old age. Women account for 80% of patients. The exact cause of gallstones is unknown, but it is likely that three factors are important- metabolic, stasis and infection.

Metabolic

Bile is composed largely of water containing small amounts of bile salts, pigments, fatty acids and cholesterol. The gall bladder concentrates the bile up to tenfold and the poorly soluble fats are kept in solution by the detergent action of the bile salts. This balance will be upset if the concentration of solutes increases, or conversely if the concentration of bile salts diminishes. Thus bile pigment stones are commonly found in the presence of haemolytic anaemias or diseases which result in excessive haemolysis, e.g. malaria. The concentration of bile salts is reduced in liver disease, in the presence of infection, vitamin A deficiency and disease or excision of the terminal ileum which is the site of bile salt resorption from the gut. It is far from clear whether a high dietary cholesterol intake predisposes to gallstone formation, particularly since bile salts are themselves formed from cholesterol in the liver.

It is known, however, that a high fibre diet lowers the cholesterol concentration in the bile and conversely a high intake of refined sugar predisposes to stone formation. Moderate alcohol intake decreases the saturation of bile and, therefore, probably protects against stones.

Stasis

Minor congenital anatomic anomalies of the gall bladder or bile ducts are very common (up to 10%) and predispose to bile stasis and stone formation. The very presence of stones in any case means that stasis must be present since otherwise they would pass into the gut while still in small particle form. Progesterone relaxes smooth muscle and no doubt contributes to stasis and stone formation in multiparous women.

MICROBIOLOGY AND MEDICINE

Applications of microbiology have given medicine its greatest successes in the diagnosis, prevention and cure of disease. The conquest of epidemic and fatal infections has seemed to be so conclusive that the main challenge in medicine is now often seen to lie in other fields, such as those of the mental illnesses and degenerative diseases, but a major shift of attention away from the problems of infection could be dangerous. The relative freedom of society from fatal infections depends on the continued, informed deployment of complex counter- measures: on correct diagnosis and treatment of infections, full implementation of immunization programmes, alert epidemiological surveillance and rigorous environmental sanitation.

Moreover, on a global scale, infection is far from defeated. In the developing nations of the world, an estimated 10 million people (predominantly young children) die each year from the effects of infectious diarrhoeas, measles, malaria, tetanus, diphtheria and whooping cough alone. The tragedy is that we have the means to hand to prevent nearly all these deaths.

Even in the developed world infective illnesses are still extremely common and make up much of the work of family and hospital doctors. At least quarters of all illness for which patients consult their doctors are infective, and a substantial proportion of patients acquire infection while in hospital. Intensive farming methods and a shift in eating habits to pre-prepared 'fast foods' have led to a sharp increase in food-related infection. In hospitals, new approaches to

therapy that deplete the competence of the patient's immune system to cope with infection, as well as the increasing use of shunts, intravenous cannulae and prosthetic devices, all provide the ever-resourceful microbes with new opportunities .to invade the host. Surprisingly, 'new' agents of infectious disease continue to be recognized. The most notorious of these is undoubtedly the human immunodeficiency virus (HIV), the causative agent of acquired immune deficiency syndrome (AIDS). The rise and spread of this condition provides a sobering reminder of the potential impact of microbial disease. It is as essential now as it ever was that medical personnel should be well trained in matters relating to infection.

GALLBLADDER ANATOMY

The gallbladder is a pear-shaped organ that lies in the fossa on the underside of the liver, and is capable of holding 50 ml of bile. Attached to the large organ above by connective tissue, the peritoneum, and blood vessels, the gallbladder is divided into four parts: the fundus, or broad inferior end; the body, which is funnel-shaped and bound to the duodenum; the neck, which empties into the cystic duct; and the infundibulum, which lies between the body and the neck, and sags to form Hartmann’s pouch. The hepatic artery supplies both the cystic and hepatic ducts with blood, which drains out of the gallbladder through the cystic vein. Rich lymph vessels in the submucosal layer also drain the gallbladder, as well as the head of the pancreas.

The biliary duct system provides a passage for bile from the liver to the intestine and regulates bile flow. The gallbladder itself collects, concentrates, and stores bile. The normally functioning gallbladder also removes water and electrolytes from hepatic bile, increases the concentration of the larger solutes, and lowers its pH below 7. In gallbladder disease, bile becomes more alkaline, altering bile salts and cholesterol, and predisposing the organ to stone formation.

MECHANISMS OF CONTRACTION

The gallbladder responds to both sympathetic and parasympathetic innervation. Sympathetic stimulation inhibits muscle contraction; mild vagal stimulation causes the gallbladder to contract and the sphincter of Oddi to relax; stronger stimulation causes the sphincter to contract. The gallbladder also responds to substances released by the intestine. For instance, after chyme (semiliquid, partially digested food) enters the duodenum from the stomach, the duodenum releases cholecystokinin (CCK) and pancreozymin (PCZ) into the bloodstream, and stimulates the gallbladder to contract. The gallbladder also produces secretin, which stimulates the liver to secrete bile and CCK-PCZ. The gallbladder may also respond to some type of hormonal control, a theory based in part on the fact that the gallbladder empties more slowly during pregnancy.

THE HISTORY OF GENETICS

What is Genetics? Genetics is usually defined as the transmission of traits from one generation to the next. Although correct in its meaning, the definition is rather vague. Genetics not only involves the transmission of traits from generation to generation, but it also involves every biological occurrence in an organism. The history of genetics beginning with the ideas of Aristotle up till the re-discovery of Mendel's work has undergone many changes both in theory and discovery.

The history of Genetics most often begins with the ideas of Aristotle and Hippocrates. Their basic belief on Genetics included the determination of sex and inheritance of disease based upon the idea of Spontaneous Generation. They believed that sex of the offspring depended upon which testes produced the semen that fertilized the egg. Through this, Darwin later labeled the theory Pangenesis. Darwin believed that gremmules were manufactured by every part of our body, which then collected in the semen producing the basis of heredity. This theory was Darwin's defense for the theory of Acquired Characteristics. Although Pangenesis was believed by most people, Aristotle came to the conclusion that characteristics weren't inherited, but the ability of producing these characteristics were.

Another theory that was proposed during this time was Preformation. Preformation stated that entire miniature individuals lived in the germ cells and matured in the womb of the female. It was unknown during this time how traits were passed on so scientist concluded that somehow aspects of the parents' bodies were transferred in miniature individuals known as homunculus. As we entered the 18th and 19th century the improvement of the microscope helped disprove the Theories of Spontaneous Generation and Preformation. With this, the question of how traits were inherited was still unknown.

Gregor Mendel, better known as the Father of Genetics, was the first scientist to show traits had a predictable pattern. He had succeeded were many others failed by luckily choosing simple and unchanging traits. The seven traits Mendel chose were 1. Difference in form of the ripe seed 2, Difference in color of seed endosperm 3, Difference in color of seed coat 4, Difference if form of ripe pods 5, Difference in colors of unripe pods 6, Difference in position of the flowers and 7, Difference in length of stem. With these different characteristics Mendel made thousands of different crosses in the garden pea, and established that indeed there was a pattern of transmission of traits. Resulting from his studies was the Law of Segregation and the Law of Independent Assortment. After completion of his eight years of investigation, Mendel presented his work before the Science Research Society. The significance of his work wasn't realized until 1900 when his work was re-discovered.

CELLS AND AGING

Frederic Verzar, the Swiss dean of gerontologists, once said: "Old age is not an illness; it is a continuation of life with decreasing capacities for adaptation." Only recently has his view of aging as a progressive failure of the body's homeoslatic adaptive responses gained wide acceptance. There has been a strong tendency to confuse aging with many diseases frequently associated with it especially cancer and atherosclerosis. Each, in fact, probably accelerates the other.

The obvious characteristics of aging arc well known: graying and loss of hair, loss of teeth, wrinkling of skin, decreased muscle mass, and increased fat deposits. The physiological signs of aging are gradual deterioration in function and capacity to respond to environmental stress. Thus, basic kidney and digestive metabolic rates decrease, as does the ability to maintain a constant internal environment despite changes in temperature, diet, and oxygen supply. These manifestations of aging are related to a decrease in the actual number of cells in the body (100,000 brain cells are lost each day) and to the disordered functioning of the cells that remain.

The extracellular components of tissues also change with age. *Collagen* fibers, responsible for the strength of tendons, increase in number and change in quality with aging. These changes in arterial walls are as much responsible for the loss of elasticity as those in arteriosclerosis. *Elastin,* another constituent of the intercellular matrix, is responsible for the elasticity of blood vessels and skin. It thickens, fragments, and acquires a greater affinity for calcium with age changes that may be associated with the development of arteriosclerosis.