BASIC PATHOPHYSIOLOGY

A conceptual approach

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SECOND EDITION

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Preface

The second edition of *Basic Pathophysiology* offers the reader the same conceptual approach, based on systems theory, as the first edition but with some important new additions. A new chapter on musculoskeletal pathophysiology is included, and the chapters on the endocrine and nervous systems have been completely rewritten. We have reviewed the current research findings in each of the conceptual areas presented in this book to make it as current as possible.

This textbook of basic pathophysiology has been written primarily for students in health-related fields. Students and practitioners of health care should find this approach to pathophysiology very meaningful. Concepts of pathophysiologic mechanisms have broad application to the areas of medicine, nursing, and allied health. All too often the student or practitioner has been faced with a need to understand disease mechanisms at a basic level in order to give intelligent and creative care. While many curricula offer courses in pathophysiology, a textbook that is both theoretic and conceptual has been lacking. The student in the past has been required to extensively review the physiologic, medical, pathologic, and nursing literature to gain information and ultimately to formulate concepts in pathophysiology. This textbook has organized the vast field of pathophysiologic knowledge, including the latest research results, into major *conceptual* areas. These concepts have been unified by the utilization of systems theory as it applies to living organisms. Disease as a loss of the steady state is continually emphasized. With this in mind therapeutic approaches are discussed as mechanisms that act to restore and maintain the steady state.

Each chapter in this book is preceded by a list of objectives. The student is encouraged to review these objectives carefully before beginning the study of the chapter. These objectives should later be used as an aid for the student in self-testing. Accomplishment of these objectives requires not only an increase in knowledge of specific disease states but also that the student form concepts and be able to use these concepts to solve problems. The suggested readings at the end of each chapter are provided for those students who wish to further increase their knowledge of pathophysiology. This textbook is not a dictionary of diseases but rather a conceptual approach to disease mechanisms. Students wishing to learn the signs and symptoms of unusual disease conditions are therefore referred to textbooks of internal or clinical medicine.

Although each chapter is complete in itself, it is generally expected that cohesiveness is achieved by study of the entire book. It is only after study of the many mechanisms of disease in the various organ systems that the student will begin to appreciate the tremendous interaction of the systems in response to disease.

This textbook should also serve as a valuable reference for students enrolled in all core-curriculum, science-based courses. Although many excellent textbooks are available to support the medical, nursing, and allied health content, few of them offer a conceptual, comprehensive, and scientific approach to disease in terms of pathophysiologic mechanisms. Thus, this textbook will be an adjunct to core textbooks and should prove very useful in both the study of theory and in practice. Furthermore, the use of systems theory throughout the book may serve to unify without squelching each individual's own style of health care delivery. Systems theory in general is broadly pertinent to health care and is often part of the conceptual framework of many nursing and other

health-related curricula. Students will appreciate its significance even more in the light of the content presentation of this textbook.

We would like to express our appreciation to colleagues who reviewed new sections of the second edition:

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We also wish to again express our gratitude to our children and husbands for their continuing support and sacrifice, which helped us in the completion of this second edition.

Maureen W. Groër
Maureen E. Shekleton

Contents

PART ONE

Health and disease: man as an open system

1

The steady state and pathophysiology: adaptive and compensatory mechanisms of health and disease

Health and disease are extremely complex concepts and are interpreted in many different ways. Health is not only a physiologic parameter but a psychologic and cultural one as well. Furthermore, the belief that the state of "wellness" is determined in large part by the individual complicates arriving at a precise definition of health and disease. Nevertheless, in terms of physiologic functioning it is possible to define normality and abnormality within certain limits and to measure certain phenomena that change with disease.

When the normal physiology of an organism is so disrupted that the function of the organism deteriorates and the organism becomes unstable and subject to further loss of regulation, pathophysiologic mechanisms are likely to arise, and disease results. There are, of course, many integrated defense mechanisms, compensations, coping devices, and adaptations that the organism organizes to protect itself from the effects of pathophysiology during a disease episode. For example, at a very basic level this response can be seen in the property of autoregulation in the vascular beds. When cells become hypoxic, various metabolites, such as carbon dioxide, hydrogen ions, lactic acid, and adenine, accumulate. These substances exert a vasodilatory effect on the arterioles and precapillary sphincters that supply the tissue beds, thus increasing the blood delivered to the hypoxic cells. This adaptation allows the cells to survive during any pathophysiologic process that produces hypoxia. Thus a characteristic of health is the ability, through complicated regulatory and compensatory mechanisms, to respond to threats against homeostasis or the *steady state;* disease can be thought of as a breakdown of these mechanisms and thus a loss of the steady state.

Pathophysiology is the study of mechanisms by which disease occurs in living organisms, the responses of the body to the disease process, and the effects of these pathophysiologic mechanisms on normal function. It is a science that seeks to coordinate the signs and symptoms of disease with an understanding of the biology of the disease process at all levels of organization: molecular, cellular, tissue, and so forth. Pathophysiology involves the coordination of laboratory research with the clinical signs and symptoms of the disease. The two are intimately entwined. While much basic research has led to broad clinical applications in the understanding, diagnosis, and treatment of disease, the converse process has also been extremely important. Much basic research has been the direct result of clinical observations of the characteristics of a disease state. The unraveling of the immune system resulted from astute observation of the relationship between increased plasma cells and immunoglobulin proliferation in patients with multiple myeloma. From this observation came the impetus to study the properties of plasma cells and immunoglobulins, which are now known to be a major foundation of immunity.

Since pathophysiology is such a complex science, involving not only the pathogenesis of disease and the response of the organism to the disease but also the effects of the disease process on normal physiology as a whole, one can say that pathophysiology is a relatively new science. The further development of this science requires both basic research into the biology of disease and continuing observations by trained and prepared minds. Those who care for the sick are in an excellent position to make major contributions to the knowledge of pathophysiology.

It is the purpose of this chapter to introduce the student to the concept that knowledge of diseases is more than memorization of signs and symptoms. When the mechanisms by which disease occurs are understood and the nature of the compensatory and adaptative response is clear, the signs and symptoms are predictable. It should be obvious that pathophysiology cannot be comprehended unless the student has an excellent knowledge of normal physiology. It is not the purpose of this book to present normal physiology except for an occasional review of pertinent material. It is, however, a fortunate circumstance that many times an in-depth understanding of pathophysiology will clarify the understanding of normal physiology. Several excellent textbooks on normal human physiology are listed at the end of this chapter for use as review material and in conjunction with this book.

This textbook is organized around the concept of the human organism as an open system, constantly seeking the steady state. Systems theory, which describes this approach, has many applications to physiology and pathophysiology. First used in engineering and computer science, it has since been applied to chemistry, biology, psychology, sociology, and other disciplines with great success. The elements of systems theory will be discussed and various disease states will be described in terms of systems theory. This chapter concludes with a detailed model of pathophysiology not only to illustrate the application of systems theory to pathophysiology but also to introduce the reader to the possibilities of interacting factors that may be involved in the pathogenesis and propagation of disease.

SYSTEMS THEORY AND THE HUMAN ORGANISM AS AN OPEN SYSTEM

General systems theory was first proposed in 1928 for living organisms by Ludwig von Bertalanffy. The theory deals with the peculiarities of living organisms that interact greatly with the environment and that at first glance then seem to be thermodynamically unique. Systems theory explains the nature of the incredible organization found in life with regard to thermodynamics and the dynamic equilibrium that is maintained in living things and that is required for the organism to remain whole, functional, and alive.

The second law of thermodynamics states that in a closed or isolated system the *entropy*, which is basically the randomness or disorder of a system, tends to reach a maximum. This is not difficult to understand if one imagines a chemical reaction such as the ionization of sodium chloride in water. A crystal of salt has more structure and therefore a higher degree of energy and lower level of entropy before it is placed in water, but after it dissolves in water the Na^+ and Cl^- ions disperse freely and evenly throughout the water, and the disorder of the sodium chloride is obviously much greater than before dissolution. It also takes much less energy to maintain the dissolved and dispersed state of the sodium chloride as compared to that required to maintain the organization of the sodium chloride crystal. It is a tendency then of this system, which consists of sodium chloride and water, to reach a level of maximum entropy according to the second law. According to systems theory, the entropic state is the most probable state as well. It is inconceivable that the Na^+ and Cl^- ions would randomly recombine to form the original salt crystal. The probability of this occurring is infinitesimal; therefore we define entropy as the most probable state.

The Na^+ and Cl^- system does not exchange freely with the environment and is isolated or *closed*. In contrast, living systems are *open* in the sense that a constant exchange with the environment is absolutely required in order for the living organism to maintain its special equilibrium. The open system does not tend toward the true equilibrium, which is highly entropic, of the closed system, but rather toward dynamic equilibrium, which we call the *steady state*. This does not imply, however, that the second law of thermodynamics is violated by living organisms; rather the living system is open to its environment and must be analyzed within that framework.

Since living organisms take up and release

matter and energy during metabolism, use of food molecules for energy requires that their molecular bonds be broken down. Metabolism produces energy for work, and also results in the formation of heat as a by-product. No biologic process is 100% efficient, and heat is always produced and returned to the environment. While the chemical bonds of the food molecule may have been broken down, the energy contained within these bonds has not been lost, but is transmuted into heat or work. The loss of order and organization, originally present in the molecular bonds and exemplified by the amount of heat released, is a measure of the entropy of the system. The use of the free energy as work by the system is a measure of the constancy of the steady state (Fig. 1-1).

Maintenance of the uniquely balanced steady state of the living open system requires constant input of energy from the environment. The natural tendency toward entropy is balanced by this input. If the open system is in the steady state, the entropy is controlled by dynamic interactions within the subsystems of the organism and with the environment. For example, the positive entropy that results from the irreversible catabolism of food molecules is equally balanced by many different physical and biologic phenomena usually acting together. The heat load produced through metabolism is removed through well-regulated thermoregulatory processes, and heat is dissipated into the environment through evaporation, radiation, convection, or conduction. If the human organism were a closed rather than open system, the entropy level would continually increase. Metabolic byproducts and heat would accumulate instead of being returned to the environment. Disruptions at every level of organization would ensue. The open system of the human is therefore characterized by a remarkable ability to balance energy and entropy inputs and outputs, so that entropy levels do not increase. However, in many disease states and as aging occurs the ability to maintain this balance is lost, and the ultimate result is an increase in the entropy of the system. In the open system of humans and their environment the entropy of the living organism may be low, while the overall entropy of the environment with which humans interact is universally increasing. In a sense humans deplete the environment of order and organization in order to maintain the steady state. However, all organisms die eventually, thus in a sense returning to the environment in highly entropic states.

Disease, when it interferes with the steady state of the open system, can be interpreted as increasing the entropy levels of the organism. Entropy and free energy are quantifiable terms, and a knowledge of the derivation of these terms is useful when discussing such diverse phenomena as biologic transport, osmotic work, action potentials, and pathophysiologic breakdowns of the steady state. A simple formula for calculating any change in free energy or entropy in a reaction is:

$$\Delta F = \Delta H - T\Delta S$$

where ΔF is change in free energy, ΔH is change in heat content or *enthalpy*, ΔS is change in entropy, and T is temperature.

Because the ΔH is always constant at a given temperature, the ΔF becomes more negative as entropy increases. It is also apparent in this formula that entropy is temperature dependent. A reaction that increases free energy requires the input of energy and is termed *endergonic*, whereas reactions that decrease free energy release energy (in forms such as heat) and are termed *exergonic*. Another formula that relates the ΔF to the equilibriim constant of a reaction is

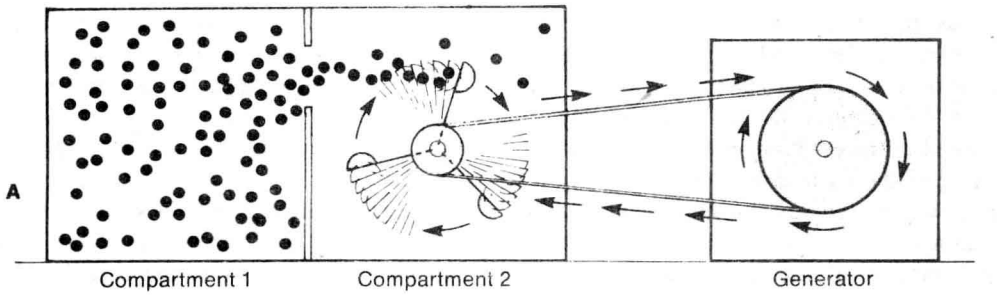
$$\Delta F = -RT \ln K$$

or

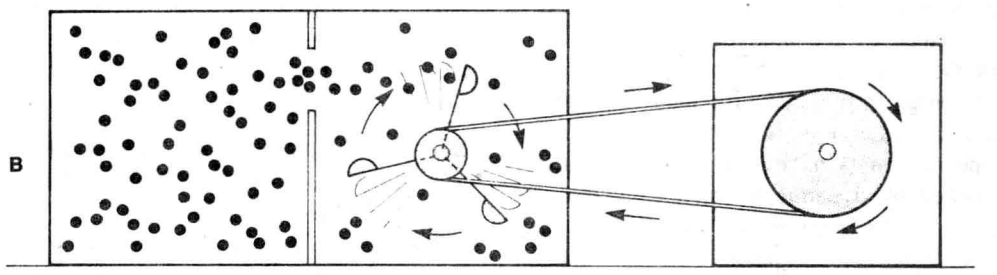
$$\Delta F = -2.303\, RT \log K$$

where R is gas constant, K is equilibrium constant, and T is temperature.

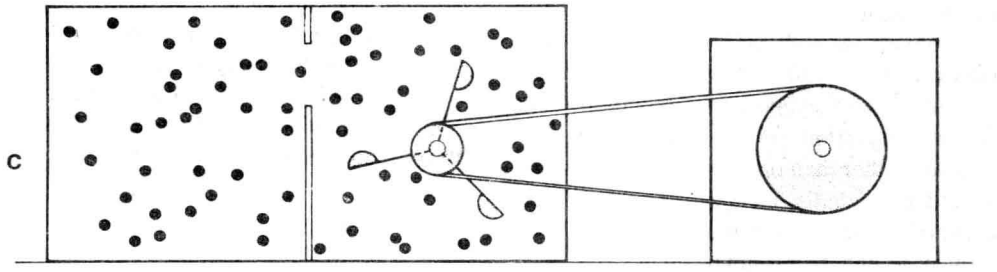
The relationship of these formulas to pathophysiology is quite simple. If disease is thought of as increasing the entropy of the organism, it can be seen that the change in free energy becomes more and more negative. To maintain a balance the organism must increase its free energy through



Molecules move in same general direction from compartment 1 to compartment 2, causing wheel to turn and run generator.



As distribution becomes more random, motion slows.



System becomes equalized and motion stops.

Fig. 1-1. Entropy and energy model. When there is order and organization in system, **A,** in which molecules are localized to compartment *1*, movement of molecules generates energy. As entropy of system increases, **B,** there is less and less energy generated. **C,** No energy is generated due to a totally random state of maximum entropy for this system. In living systems there is structure and tremendous organization, such that entropy is balanced by large inputs of free energy, and a steady state is maintained. As system ages or becomes diseased, the overall entropy tends to increase.

mechanisms that increase the order of the system. Compensatory mechanisms and adaptations do precisely this, but if they are inadequate in the face of progressive pathophysiology, the entropy levels will continue to increase, the order and organization of the organism will be progressively compromised, and death will eventually occur.

What has traditionally been known in physiology as homeostasis is in reality the steady state. Living organisms are made up of subsystems, which all act to maintain dynamic equilibrium. This steady state is governed by the tendency of the biologic system to maintain itself, to regulate processes that are constantly fluctuating, and to generally preserve the organism in the changing environment. An important characteristic of the steady state is the property of *equifinality*, which means that the end result of biologic processes can be reached through a variety of ways. Systems are able to adapt through various physiologic processes to alterations in the environment and thus maintain the steady state such that particular characteristics of the organism are always the same. For example, the blood glucose concentration must be maintained within certain limits, and there are several routes or mechanisms by which the body regulates this. It is only when disease is present that these regulatory processes may be greatly interfered with, and the blood glucose level may not be regulated carefully. A disease such as *diabetes mellitus* interferes with the steady state of the organism by disrupting blood glucose regulation; the ramifications of this disease process are manifold and could eventually result in death (maximal entropy) if treatment is not instituted.

CYBERNETIC REGULATION OF THE STEADY STATE

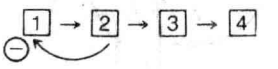
Organisms act to maintain the steady state by a variety of mechanisms, and terms have been borrowed from cybernetics to explain these various phenomena. Regulation of metabolic functions is an obvious requirement of the steady state if an open system requires a balance in the flow of energy and matter between the organism and the environment. Two types of *feedback loops*, positive and negative, operate in the regulation of metabolism. These feedback mechanisms allow metabolic reactions, hormonal action, and concentrations of critical substances to be controlled. Feedback loops may be open or closed; in biologic regulation most feedback loops are closed. These are illustrated in the box above. In the open loop the system operates in a one-way direction and thus acts quickly. The level of the last component is controlled only by the level of the first component in the chain. The closed loop offers the advantage of "fine tuning" of the concentrations of the various components in the chain. It is called a feedback system in that information is fed back to other components in the chain so that the system "knows" at what rate the reactions of which it consists must proceed.

Open loop feedback

[1] → [2] → [3] → [4]

In this model the concentration of [1] and the reaction rate of [1] → [2] will determine the concentration of [4].

Closed loop feedback



In this simple model the concentration of [2], [3], and [4] is determined by the concentration of [2], in that the production of [2] and the reaction of [1] → [2] is regulated. "Information" about the concentration of [2] is fed back to [1]. This is also an example of negative feedback, since the concentration of [2], when it reaches a certain level, will act to inhibit [1] → [2] as indicated by the ⊖.

The example of negative feedback that is often easiest to understand is that involving the production of an endocrine hormone by a trophic hormone. The blood levels of substance *X* (Fig. 1-2) must be carefully regulated to maintain the steady state. Therefore it is the blood level of *X* that controls the release of the trophic hormone. Without the stimulation of the trophic hormone, the hor-

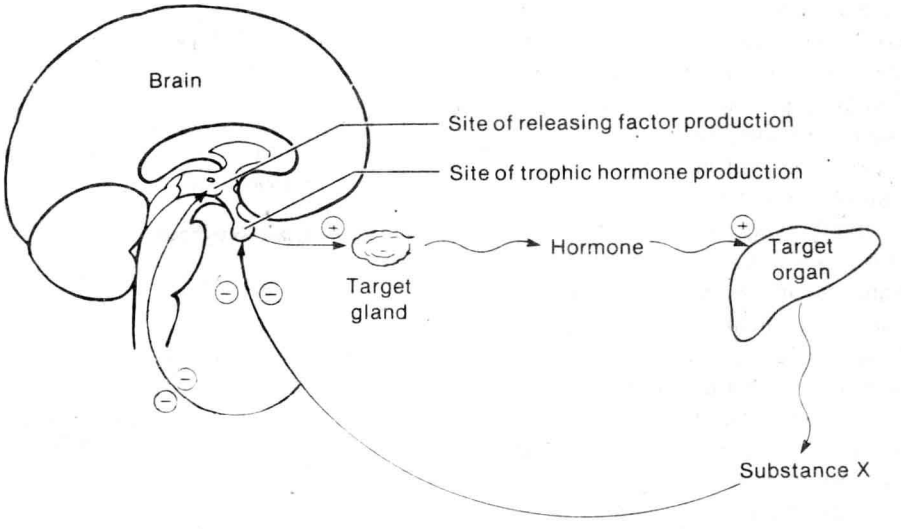
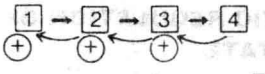


Fig. 1-2. Negative-feedback regulation. Negative-feedback regulation of substance *X*, product of target organ, is achieved by inhibitory effect of substance *X* (output of free target organ) on production and release of both releasing factor (which stimulates release of trophic hormone) and trophic hormone (which stimulates target gland to secrete its hormone); ⊖ indicates inhibition.

mone from its target gland cannot stimulate the production and release of substance *X* from the organ. The trophic hormone production is stimulated by a releasing factor from the brain. Imagine what would happen if disease prevented the negative feedback of substance *X* on both the glandular source of the trophic hormone and the releasing factor source. The system would continue to produce trophic hormone, which would act on the endocrine gland, which would continue to produce the hormone. The ultimate result would be higher and higher levels of *X*. This interruption would result in a tendency of this open system to increase its entropy and to disrupt the steady state. Thus the operation of negative feedback is essential to the maintenance of the steady state. Negative feedback loops have inherent in them some sort of set-point sensor, so that the system "recognizes" the optimal levels of the substances it is regulating. This kind of information is genetically determined, and the processes by which it is sensed by the system are not well understood at this time.

Positive feedback loops also occur in biologic organisms. They are reactions in which the later components in the chain (see box below) perpetuate the production of the first components. Such loops could occur in processes such as autocatalysis or in metabolic pathways that are used as energy sources such that catabolism exceeds anabolism. These loops would result in a temporary increase in entropy of the system. Positive feed-

Positive feedback



In this model the concentration of [4] is also regulated, not by inhibition of the various reactions in the sequences, but by stimulation. Thus, as [4] accumulates, it acts to stimulate [3] → [4], and so on, such that as [4] builds up, it continually acts to increase its own production on and on.

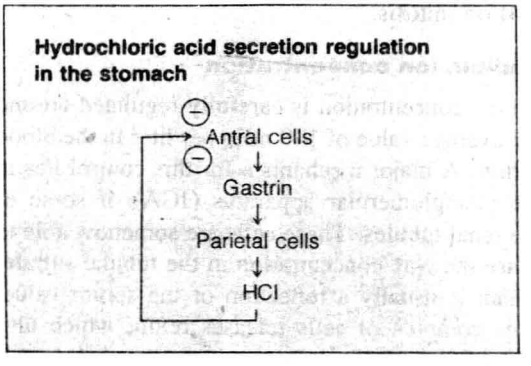
back loops are common in pathophysiologic perpetuation of disease. For example, atherosclerotic hypertension (discussed later in this chapter) results finally in positive feedback mechanisms that enhance and propagate the initial step in the chain of events, which is hypertension.

INTERRUPTIONS OF THE STEADY STATE

This textbook will examine pathophysiologic mechanisms as disorders of steady state regulation. Therefore it is important for the student to understand these mechanisms and to be able to relate them to disease. A number of common disease entities will be examined as disorders of normal regulation that result in disruption of the steady state. These are meant as illustrative models rather than as detailed discourses on pathogenesis and pathophysiology. The reader is referred to the appropriate chapters for further information.

Interruptions of mucosal integrity

The box below illustrates the normal negative feedback control on the secretion of hydrochloric acid by the parietal cells of the stomach lining. Hydrochloric acid is a highly ionized strong acid, and the lining of the stomach is protected from autodigestion through the secretion of an alkaline layer of mucus, through dilution of the acid by food and other secretions, and through regulation of hydrochloric acid production. Hydrochloric acid secretion is regulated through negative feedback



control of the antral cells, which release gastrin when food is present in the stomach. When the pH reaches a set point of 2.0 the antral cells become inhibited and no longer release gastrin. A decrease in gastrin leads to a decrease in parietal cell secretion, and thus the pH is regulated.

Further regulation of antral cells is through parasympathetic stimulation, and vagal activity is known to be increased in patients with peptic ulcer.

It is thought that ulceration of the stomach or duodenum can result either from hypersecretion of hydrochloric acid or from a breakdown in the normal protective barriers to autodigestion. The regulation of vagal parasympathetic outflow is at the level of the cerebral cortex and hypothalamus. Stress is thought to be associated with the development of peptic ulcer partly through increased vagal activity, although cortisone may also be pathogenic and is released by the adrenal cortex in stress situations. Distension of the stomach and certain food substances known as *secretagogues* also stimulate these antral cells to produce gastrin. A potent stimulant found in high concentration in the stomach lining is histamine, which is believed to act directly on the parietal cells to stimulate hydrochloric acid release. When the regulation of hydrochloric acid is disturbed, resulting in hypersecretion, ulceration in the stomach or more commonly in the duodenum may result. It has also been shown that ulcer patients have higher than normal nocturnal secretion of hydrochloric acid when the stomach is empty.

When ulceration of the stomach or duodenal mucosa does occur, there are a number of pathophysiologic consequences (Fig. 1-3). Edema and interstitial hemorrhage may result, leading possibly to histamine release as part of the overall inflammatory reaction that occurs as back diffusion of hydrochloric acid through the broken tissue barrier occurs. Plasma and blood proteins leak into the interstitium and may be lost into the gastric or duodenal lumen. Excavation of the normal tissue may be so severe that perforation of the stomach or dodenal wall, massive hemorrhage, and shock re-

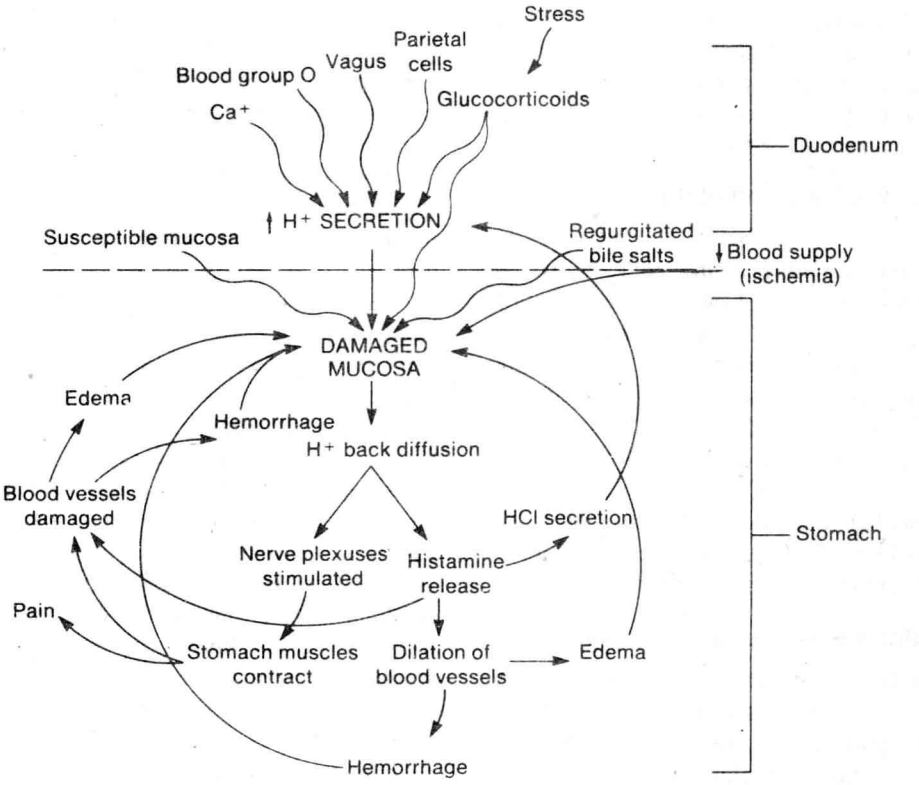


Fig. 1-3. Pathophysiology of peptic ulcer. Either an increase in H^+ secretion or a decrease in integrity of stomach mucosa can lead to ulcer formation. Once an actual ulcer forms, damaged mucosa is perpetuated by back diffusion of H^+, edema, and hemorrhage.

sults. It can be seen that the slightest breakdown in the wall of the stomach or duodenum may lead to further pathophysiologic phenomena, which aggravate the ulceration even further.

Interruption in mitotic division

A characteristic of malignant cancer cells appears to be the loss of regulation of cell division, which is normally regulated by both tissue and humoral factors such as *chalones, antichalones,* and a phenomenon known as *density-dependent inhibition*. Cell division within tissue appears to be controlled in part by the actual physical crowding of the tissue by the cells and ground substance that compose it. In cancer, both in vivo and in vitro, this regulation is lost, and cell division continues in an uncoordinated and uncontrolled manner. Cancer cell proliferation therefore is at least in part perpetuated by the lack of negative feedback (Fig. 1-4) on mitosis.

Sodium ion concentration

Na^+ concentration is carefully regulated around the average value of 140 mEq per liter in the blood serum. A major mechanism for this control lies in the juxtaglomerular apparatus (JGA) of some of the renal tubules. These cells are somehow able to sense the Na^+ concentration in the tubular filtrate, which is usually a reflection of the serum value. This complex of cells releases renin, which ultimately causes aldosterone to be released from certain cells of the adrenal cortex. Aldosterone then