THE INTERPLAY OF NOXIOUS AGENTS, STRESS, AND DEPRIVATION IN THE ENGENDERMENT OF DISEASE[1]

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BEFORE focusing on the interrelationship of noxious agents, stress, and deprivation in the production of disease, it is interesting to note that concepts depicting each of them as an independent and sufficient cause of disease appeared at about the same time, the latter half of the nineteenth century. To be sure, noxious agents in the form of toxic substances, poisons, and vapors had been held to be responsible for disease long before this period, indeed back to antiquity. But recognition of bacteria in the origin of disease and what was to be their overshadowing and dominant position among the noxious agents, did not occur until the later era.

Despite their concurrent appearance, the concepts of noxious agents, stress, and deprivation in the etiology of disease emerge separately and unrelatedly. For one thing, noxious agents, especially infectious forms, and deprivation lead to different types of disease. Then too, each of the three pathogenic types was conceived to be sufficient as a sole cause. For example, Bacillus anthracis seemed adequate to produce anthrax; hence, there was no need to search for additional factors. Also, the very design of experimental studies on disease including application of newly developed technical methods tended to narrow the views on causation of a disease and to preclude a less simple concept that embraced multiple parts and their relationship. Finally, infection and deprivation, as producers of disease did not "catch on" and gain followers with equal attraction. The great epidemics, plagues, and pestilences rushing rapidly to a fatal termination were such dreadful menaces

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and scourges with a titanic toll of lives that they transcended all others as the most pressing problem of disease. Coupled with this fearful state of affairs were the rapid developments in bacteriology with microorganisms being isolated in pure cultures and fulfilling Koch's postulates as causes of these infectious diseases. These circumstances imparted to the germ theory not only independence and sufficiency but also dominance. As for stress, it was considered less for the diseases and injuries that it might produce than for the remarkable defense against it with which the body was provided. So in the views on the genesis of disease, noxious agents, stress, and deprivation appeared separately and with little or no connection between them. That was the main current of thought; today it is still the most prevalent. But there have been and are some students who believe that the formulation is not that simple.

To pick up the trail of this point of view, I shall delve into the archives of the remote as well as immediate past in quest of any pronouncement or indication of an appreciation of linkage between noxious agents, stress, and deprivation in the development of disease. Not a few minds have touched upon one or another member of the triad. But I shall restrict my consideration to the more or less full-blown concepts. Because each of them was built primarily around or emphasized one of the etiological principles, it is necessary to examine them in sufficient detail to determine whether other members of the triad have been associated with them. In this search for cognizance of relationships, I have only the written record to guide me in my interpretation. Viewed from the vantage of the present with its presumably more advanced state of knowledge, it is tempting to read into them a recognition of relationships which appear to be implicit though never openly expressed; or to seize upon and magnify a point which the author summarily dismissed with only a passing reference. Inadvertently the legal principle of *nunc pro tunc* tends to creep in to impart a meaning that may never have been intended. In construing

any writings, so much depends upon the bent of the interpreter.

Interestingly enough, it matters not whether we start with noxious agents, stress, or deprivation in their association in etiology, the others are ultimately met. But historically, noxious agents as sources of disease have a claim on priority. By noxious agents are meant agents or forces that are harmful, poisonous, deleterious or inimical to health, and are productive of disease and injury. Included among them in antiquity were toxic substances, poisons, morbific exhalations, and vapors. Likewise, the belief that something more entered into the pathogenesis of disease had equally early beginnings. In Hippocrates' writings on epidemic diseases (1) may be found a keen understanding of man's relationship to his universe; and the effect of environmental influences upon his health and his susceptibility to disease. In the opinion of this profound thinker, epidemic diseases were the product of inimical forces arising out of an imbalance in man's environment. His usage of the term *katastasis,* usually translated as constitution, connoted environmental factors of a meteorological nature contributing to the production of epidemic diseases.

Some 500 years later Galen (2, 3) brought forth a broad yet more particularized formulation which visualized epidemic pathogenesis as a threefold action: atmospheric katastasis, an internal factor, and a predisposing element. With one modification this view has a modern ring. Only the first item, atmospheric katastasis, connoting the miasmal doctrine of epidemic disease is obsolete; at the time of its writing, pathogenic microorganisms were yet to be recognized. Today, it would be called the specific component. Similarly in current concept and language, the internal factor would be the natural susceptibility of the group. And the predisposing element would include the category of environmental conditions enmeshed with the *modus vivendi.* After a long period of neglect this conception reappeared and in its modern version may be recognized in current thought.

During the seventeenth century a non-partisan to the

Galenical doctrine, Thomas Sydenham, who is so well remembered for directing thought to the natural history of disease, revived and added to the Hippocratic tradition. In essence Sydenham magnified katastasis and ascribed to it a significance beyond its originally imputed meteorological influence (3). The term epidemic constitution is of his coinage. But his views on epidemics are expressed with a certain abstruseness which is augmented linguistically by their rendition in Latin; hence, there is difference of opinion over what some of his statements mean. From these ambiguous and obscure writings Major Greenwood (4) has given his modernized interpretation of Sydenham's thesis: "The complete morbid process of an epidemic disease is made up of two parts; the first is specific. . . . The second part is generic, common to all species of epidemic diseases and a function of some terrestrial conditions included under the term 'epidemic constitution.'" Sydenham believed that these mysterious conditions brought about an occult alteration of the atmosphere. The epidemic constitution was regarded to be an essential, but not the sole factor in the pathogenic process.

Two centuries later came the germ theory of disease. Although its advent was foreshadowed (5, 6), its demonstration and establishment may be placed in the time of Pasteur and Koch. With its newly developed technic for studying disease, bacteriology not only attained the status of a separate science but also dominated the theory and practice of epidemiology. Epidemics were conceived solely in terms of causal organisms. The prevailing view became, as Major Greenwood (3) in a rather acid and ironic context puts it: ". . . when the means of infection and the vehicles of infection have been identified, the problem of an outbreak of herd sickness is solved." That principle was for most the final and complete word.

But for some epidemiologists of this century this doctrine had not settled all the problems. Indeed, the influenza pandemic of 1918 aroused one of the skeptics (7) to assert that despite the bacteriological triumphs and reign, two age-old

questions remained unanswered: the periodic recurrence of a disease in epidemic form and the relation between these recurrences and "what used to be called telluric and cosmic influences." Consideration of these topics necessarily led to reflection on the epidemic constitution. The British school of epidemiologists who thought in this vein appreciated the significance of the epidemic constitution while groping for enlightenment on its precise nature. Some identified it as telluric and cosmic influences which to them meant in more concrete terms, climatological and terrestrial factors. But they sensed that these were only a part, that something unknown to them remained.

In writing in 1919 Goodall (8) well characterizes the position when he asks: "How far have we advanced in our conceptions of the causation of epidemics since Sydenham's day? Not very far, I fear, as regards what he calls the epidemic constitution. I am of the opinion that we must still admit that there is a very important factor, or there are very important factors, still unknown, in the causation of epidemics. My conception of the causation of epidemics is that there are several causes at work, varying in number and importance for different epidemics and at different times; that an epidemic is the sum of several factors. Of recent years factors unknown to Sydenham have been brought to light. We know more about the influence of the ages of the persons exposed to attack, of their surroundings, of the seasons, of the part played by insects and animals, and so forth. We also have added to our stock of knowledge the whole of the bacteriological evidence. . . . Admitting a microorganism as a factor, and a very important factor, in the causation of disease, we still are driven in most instances to explaining the causation of the epidemicity of the microorganism; and in most instances, if not in all, we are very far from having attained that object. Sydenham recognized a few obvious causes of epidemics and epidemic diseases, more especially of the latter. But he was also well aware that other causes, which he believed to be the most important,

were still unknown to him, and especially those connected with the more important epidemics. To speak more correctly, all we have done has been to reduce the amount of the contents of this large magazine of unknown factors by withdrawing from it certain factors which we have been able to name, and transferring them to the store of known factors."

On a more optimistic note, Major Greenwood (4) in his rationalization of Sydenham's doctrine of generic or epidemic constitutional factors said: "But it no longer seems that we should regard the basis of an epidemic constitution as beyond the compass of human intellect." In considering intrinsic and extrinsic factors, he acknowledged that variations of natural resistance and environmental conditions, such as diet, do greatly influence the severity of some epidemic diseases (3). But upon reviewing the then available evidence from animals, he regarded it as overly optimistic to accept as experimentally proved "that the amount and severity of infection can be *controlled* by varying diet and race." Appraised by such a pragmatic criterion, he concluded, neither is of primary importance.

Rather, among the factors conducing to continuation of an epidemic, he assigned a potent influence to admission of nonimmunes to a herd in which infection was already prevalent. Recognizing both the immunization resulting from chance sublethal infection and the innate power of resistance with its individual variation, he believed that experimental evidence on their relative effectiveness for survival of animals favored immunization over selection.

During the same period Webster, likewise from studies in experimental epidemiology, reached the opposing view that inborn resistance to infectious disease is a primary factor in determining the fate of an individual during an epidemic (9). Further evidence indicated, according to him, that the level of resistance which is inherited can be altered by environmental factors, not the least of which is diet (10). By sharpening and defining the experimental approach (11, 12, 13) Schneider found an answer to the question (13): "What are the requisites

for a demonstration of the influence of diet on an infection?" In his opinion it is necessary to differentiate genotypes in both host and pathogen; in that way he was able to demarcate the area in which diet has its maximum effect on resistance to infectious disease. It was characterized by genetically heterogeneous hosts being infected by mixed virulent and avirulent strains of pathogenic bacteria, a situation simulating that of man in his natural setting.

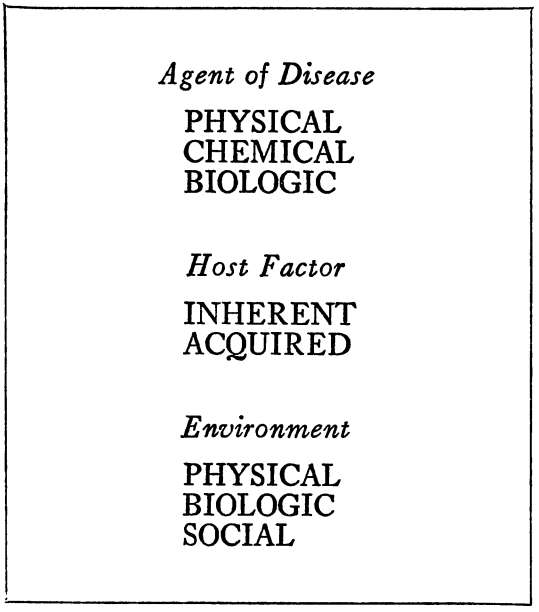


Fig. 1. Schema showing the three elements of the ecologic complex that determine disease, according to Gordon.

One of the present-day exponents of the epidemic constitution, Galdston, has defined (14) its telluric and cosmic influences in more precise and comprehensible terms as "the entire physical environment of the people and in addition, their cultural, industrial and economic status." Moreover, he suggests that the identity of part of the unknown factors of the epidemic constitution is the concept of disease from deficiency or deprivation. Certainly, there is a wealth of evidence to support the view that deficiency states can affect susceptibility to infectious disease (15). In all this Galdston recognizes, of course, that the presence and operation of noxious agents conduce to the production of disease; but he argues that the absence of essential factors, the status of the host, and environmental influences must also be taken into account in any examination of etiology.

Subscribing to this concept of causation, Gordon (16) has placed it in a simple schema (Figure 1). Disease is viewed as

the interaction of the triad: the agent, the host, and the intricate complex of environment. Included under agents of disease are substances of physical, chemical, and biological nature. Disturbance may come about by the presence of some in excess, by a deficiency of others. The host may contribute to the occurence of disease through his inherent characteristics which are of anatomic, physiologic, genetic, or developmental nature. Age, race, sex, and other attributes are indices of them. Also through acquired characteristics, including specific immunity, metabolic and morphologic changes consequent to previous illness, and adaptations, the host participates in the interaction leading to health or disease. Environmental influences may be divided into three broad categories: physical, biological, and social. To name a few environmental conditions: food supply, housing, sanitation, and health and medical services.

These three components—agent, host, and environment—are regarded as the determinants of disease. According to this tenet, the problem of ascertaining the cause of a disease is not solved by identifying the agent. The complete solution comes only after also examining the qualities of the host and environmental influences. This viewpoint is one example of what is sometimes called the doctrine of multiple causation.

In tracing the evolution of thought on the causation of disease, especially infectious disease on an epidemic scale, with noxious agents as the starting point, it may be noted that for completeness in accommodating all the facts, stress and deprivation were brought in as factors. In the latest form of the thesis, as manifested in the views of Galdston and Gordon, many of the influences exerted within the host and by external environment may be recognized as falling in the category of conditions creating stress, although they were not so designated specifically. In addition to noxious agents with their connotation of a positive mode, deprivation with its minus aspect is also incorporated into the formulations. Indeed, Galdston, Webster, and Schneider conceive of both in joint

operation in the production of epidemic infections. In effect, then, stress and deprivation are placed in association with noxious agents as conducive to occurrence of such diseases.

If the production of disease be next examined in association with stress, it is found that Claude Bernard, the eminent physiologist, laid the foundations for this approach (17). Actually, he was thinking in terms of the body's wonderful panoply of protection against the vicissitudes of the external environment, therefore not the engenderment but rather the prevention of disease.

He pointed out that "in animals with complex organization the living parts exist in fluids bathing them, such as blood and lymph, which constitute the internal environment." This environment is fabricated and controlled by the organism itself. As organisms become more independent, more free from changes in the outer world, they do so Bernard said, by preserving uniform their own inner world in spite of shifts of outer circumstances. He wrote: "All the vital mechanisms, however varied they may be, have only one object, that of preserving constant the conditions of life in the internal environment." It was his profound conclusion that: "It is the fixity of the internal environment which is the condition of free and independent life." For, he explained, it is this fixity "which enables an organism to cope with a new or changing environment." According to him, the conditions which must be maintained constant in the fluid matrix of the body in order to favor freedom from external limitations are water, oxygen, temperature, and nutriment (including salts, fat, and sugar).

This concept was further elaborated in scope and detail in 1926 by Cannon (18, 19, 20). To the internal environment, that arrangement in the organization of the body by which all living tissue has intimate contact with fluid, he gave the name fluid matrix. Like Bernard, he regarded its stability as its outstanding feature. The body, being in constant relationship with its surroundings, may undergo internal disturbances from environmental changes. "But," he said, "ordinarily such

HOMEOSTATIC CONDITIONS

A. Material supplies for cellular needs.
   1. Material serving for the exhibition of energy, and for growth and repair—glucose, protein, fat.
   2. Water.
   3. Sodium chloride and other inorganic constituents except calcium.
   4. Calcium.
   5. Oxygen.
   6. Internal secretions having general and continuous effects.

B. Environmental factors affecting cellular activity.
   1. Osmotic pressure.
   2. Temperature.
   3. Hydrogen-ion concentration.

Fig. 2. Cannon's classification of homeostatic conditions.

disturbances are kept within narrow limits because automatic adjustments within the system are brought into action, and thereby wide oscillations are prevented and the internal conditions are held fairly constant." To this steady state of the fluid matrix, Cannon gave the name homeostasis. It is equivalent to Bernard's designation, fixity. However, it should be emphasized that it is not a static state but variation within limits. This homeostatic regulation is exercised over both bodily supplies and processes. Extending Bernard's list, Cannon (18) gave a classification of supplies and processes which exhibit homeostasis but cautioned that undoubtedly it was incomplete (Figure 2).

Homeostasis, according to Cannon, arises from coordinated physiological reactions which through their regulatory action maintain the internal environment in a steady state. The sympatho-adrenal system is the coordinating agency and principal regulator of the internal environment and preserver of homeostasis; the effector organs by which it performs its functions are the second component in the protective system. The signal for bringing this corrective system into action is some change in the internal environment. But it is the role of the protective system to resist such an alteration and preserve the fluid matrix in a stable state.

To the external and internal conditions placing stress upon the regulators of homeostasis and tending to disturb the steady state of the fluid matrix, Cannon gave the name stresses (20). Among them he included: cold, oxygen deficiency, loss of blood, and low blood sugar.

One example from Cannon will set forth his principle concretely. Oxygen is needed to burn non-volatile acid constantly produced by cells. Exposure to high altitude with its lessened oxygen supply brings about a sequence of regulatory and protective reactions: an increase in the heart rate and constriction of blood vessels in strategic areas raise the arterial pressure which in turns hastens the blood flow and thereby accelerates the delivery of oxygen. Contraction of the spleen, the third reaction, mobilizes corpuscles from reserve into active service as carriers of oxygen.

So long as living parts and body fluids are protected from extreme change and maintained in a steady state, the body is spared the peril of serious consequences from these stresses. Cannon emphasizes how extensive is the damage when constancy fails. The effect of homeostasis is, then, to confer freedom from disease, injury, or death arising from stress.

But, as Cannon explains, homeostasis as a state is not absolute and immutable; it may be overcome or weaken and fail. For one thing, there are limits to the ability of the regulatory system to withstand stress and preserve a steady state in the fluid matrix. If stress is increased in intensity or duration, a point is reached beyond which the regulatory system is under too great a strain and is overwhelmed, even though it is performing to its fullest its function of resisting change in the fluid matrix. Then the state of the internal environment is significantly, if not seriously altered. An excessive stress may even induce a breaking strain in the homeostatic regulators. To return to the previous example: if the supply of oxygen fails, acidosis with coma supervenes and even death may occur.

Quite apart from the magnitude of the stress, the functional capacity of the regulatory system may vary over the life span

under influences, both normal and pathogenic, that are accounted to be ordinary vicissitudes and exigencies. Among the conditions that affect the regulatory processes which determine homeostasis are: infection, inactivity, worry, dissipation, loss of sleep.

Finally, homeostasis fails to operate and injurious consequences ensue when the body is entirely deprived of its regulatory system. When the sympatho-adrenal system is removed, a stress that had previously been successfully met now produces a breaking strain.

In this concept which in its entirety goes under the name of physiological homeostasis, the emphasis is on protection from harm through stability of the body's internal environment which is achieved by highly effective regulatory reactions. Nevertheless, although not underscored, noxious states, stress, and deprivation appear in the scheme; and therefore *ipso facto* come into association with serious implications for production of disease. Infections from pathogenic microorganisms as noxious agents are visualized as diminishing the reactive capacity of the homeostatic regulatory system. Stresses are specifically mentioned. Those conditions which elicit the initial change in the internal environment and thereby set off the sequence of protective reactions through the homeostatic regulators are designated as stresses. If sufficiently potent, these stresses may have highly pathogenic, if not fatal consequences. Deprivation or deficit appears in two parts of the concept. Some of the stresses are pictured as arising from deficiency of essential substances; e.g., lack of oxygen and loss of blood. They are adverse and potentially productive of injury. Again, the deficient performance of the homeostatic regulatory processes or actual deprivation of its principal member, the sympatho-adrenal coordinator, has decidedly pathological consequences. Despite the orientation of the concept of homeostasis towards protection of health and life, it is not difficult to discern in it the lines of association between noxious agents, stress and deprivation in the engenderment of disease.

Further developments in the concept of the body's reaction to stress have come from Selye in his general adaptation syndrome (21, 22, 23). He pointed out that various noxious agents produce the same systemic changes. The aggregate of nonspecific systemic reactions which occur upon exposure to stress, he named the general adaptation syndrome. Here adaptation, used in its physiological rather than its evolutionary sense, means a modification in the organism from exposure to environmental conditions which makes it react less to them. It will be noted that in this view the general adaptation syndrome resulting from encounter with stress is apart from and in addition to homeostasis with its maintenance of a steady state in the internal environment. As an emergency adjustment to changes in the environment, homeostasis presents many specific defense reactions. In contrast the general adaptation syndrome with its nonspecific manifestations is an adaptive reaction comprising acquisition of defense against future exposure to stress and maintenance of this acquired state of adaptation. The reaction is general, that is systemic, affecting large portions of the body, adaptive and syndromic; hence, its name.

The general adaptation syndrome evolves in three distinct stages: alarm reaction, resistance, and exhaustion. The alarm reaction is the composite of nonspecific systemic phenomena elicited by sudden exposure to stress to which the body is not adapted. The stage of resistance represents the group of nonspecific systemic reactions evoked by prolonged exposure to stimuli to which the organism has acquired adaptation by that experience. The stage of exhaustion presents a complex of general reactions which occur upon over-exposure to stimuli to which adaptation and resistance have been developed but can no longer be maintained.

In this concept stress is regarded as the factor that elicits the general adaptation syndrome. But it also is an effect as well as a cause. Drawing a proper distinction, Selye uses the term alarming stimuli or stressors to denote agents which pro-

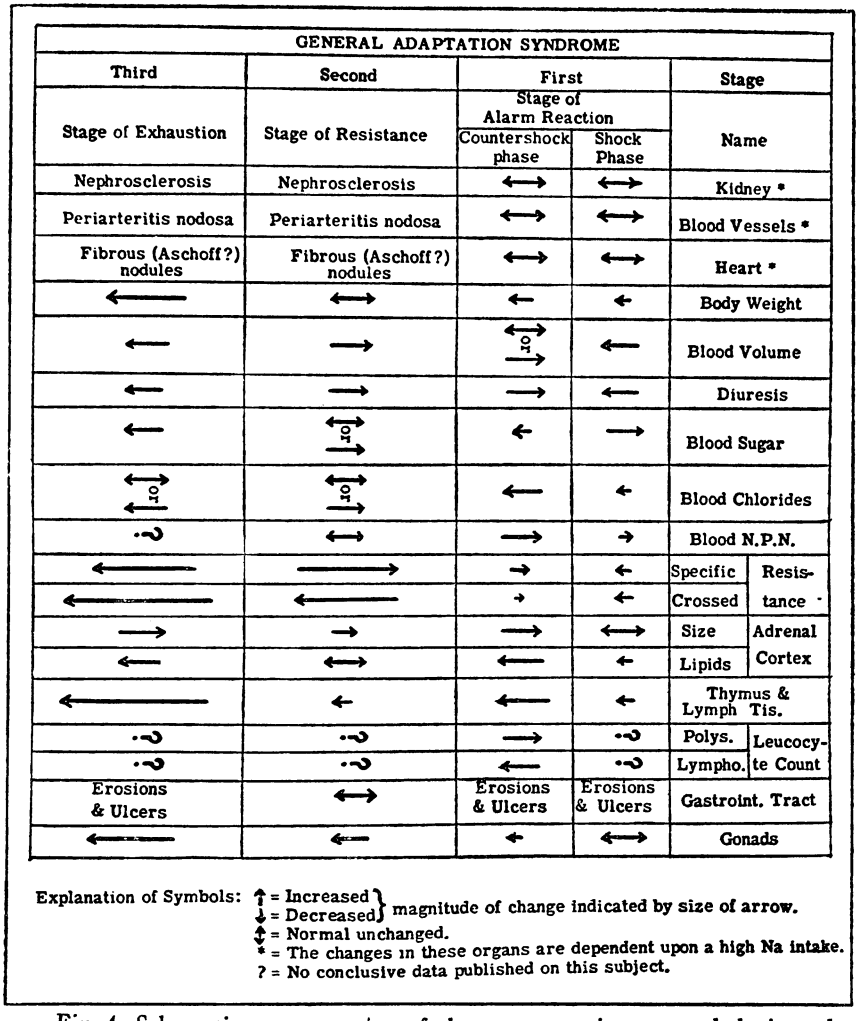
ALARMING STIMULI

- Trauma
  - Surgical Interference with Vital Organs
  - Fractures
  - Crushing of Tissue
- Infectious Diseases
- Bacterial Toxins
- Hemorrhage
- Exposure to Cold and Heat
- Obstetric Shock
- Gravity Shock
- Nervous Stimuli
  - Spinal Transection
- Emotional Stimuli
  - Rage, Fear
- Deep Anesthesia
- Temporary Blood Vessel Occlusion
- Reduced Oxygen Tension
- Burns
- Drugs
  - Colchicine
- Hormones
  - Natural and Synthetic Folliculoids (Estrogens)
- Diet
  - Fasting
  - Overfeeding
  - Vitamin Deficiencies
- X-rays or Radium Rays
- Solar Rays

Fig. 3. Selye's listing of alarming stimuli.

duce systemic stress, that is, affect large portions of the body (Figure 3). Under suitable intensity and duration, an alarming stimulus is capable of bringing about all three stages of the general adaptation syndrome.

Because of the circumstances surrounding their origin the manifestations of the general adaptation syndrome are said not to be readily separated and identified. Agents acting as stressors create stress which operating through the general adaptation syndrome produces both damage and defense. Manifestations of passive nonspecific damage are intermingled with those of active defense; these changes of damage and defense—and only these changes—are integral parts of the general adaptation syndrome. But in addition to creating stress with its nonspecific effects of damage and defense, stressors also have their specific actions. "Hence," Selye asserts (23), "the general adaptation syndrome never occurs in its pure form but is always complicated by superimposed specific actions of the stressors." As a consequence in analyzing "a biologic response"—whether it be intoxication or disease—it is difficult to identify individual manifestations as being due, respectively, to damage, defense, or specific action of the pro-



GENERAL ADAPTATION SYNDROME					
Third	Second	First		Stage	
Stage of Exhaustion	Stage of Resistance	Stage of Alarm Reaction		Name	
		Countershock phase	Shock Phase		
Nephrosclerosis	Nephrosclerosis	↔	↔	Kidney *	
Periarteritis nodosa	Periarteritis nodosa	↔	↔	Blood Vessels *	
Fibrous (Aschoff?) nodules	Fibrous (Aschoff?) nodules	↔	↔	Heart *	
⟵	↔	←	←	Body Weight	
←	→	↔ or →	←	Blood Volume	
←	→	→	←	Diuresis	
←	↔ or →	←	→	Blood Sugar	
↔ or ←	↔ or →	←	←	Blood Chlorides	
·ᔓ	↔	→	→	Blood N.P.N.	
⟵	⟶	→	←	Specific	Resistance
⟵	⟵	→	←	Crossed	
→	→	→	↔	Size	Adrenal Cortex
←	↔	←	←	Lipids	
⟵	←	←	←	Thymus & Lymph Tis.	
·ᔓ	·ᔓ	→	·ᔓ	Polys.	Leucocyte Count
·ᔓ	·ᔓ	←	·ᔓ	Lympho.	
Erosions & Ulcers	↔	Erosions & Ulcers	Erosions & Ulcers	Gastroint. Tract	
⟵	⟵	←	↔	Gonads	

Explanation of Symbols: ↑ = Increased, ↓ = Decreased } magnitude of change indicated by size of arrow.
↕ = Normal unchanged.
* = The changes in these organs are dependent upon a high Na intake.
? = No conclusive data published on this subject.

Fig. 4. Schematic representation of the most prominent morphologic and metabolic changes during the general adaptation syndrome and the diseases of adaptation. (After H. Selye: *Journal of Clinical Endocrinology*, 6, 117, 1946.)

vocative agent.

The nonspecific changes which appear during the course of the general adaptation syndrome are of functional, metabolic and morphological nature. A representative list is shown in Figure 4. It should be reiterated that they are nonspecific since they are producible by various agents; furthermore they are systemic or general, that is, not localized or topical. In the

course of the general adaptation syndrome, these manifestations undergo change with stage.

On the basis of experimental evidence, Selye has set forth his view in some detail about the channels through which stress operates to evoke the general adaptation syndrome. The coordinating and integrating pathways for mustering defense are believed to be through the nervous and endocrine systems. A noxious agent is viewed as directly or indirectly stimulating the anterior pituitary to discharge ACTH. This in turn acts upon the adrenal cortex to produce an excess of corticoid hormones which help to raise the resistance of the body. Thus in adaptation as in homeostasis, the adrenal gland is visualized as playing a controlling part with this difference—its function is described in very much more extent and detail out of the greater present knowledge of its chemistry and physiology.

The pattern and course of the general adaptation syndrome are under the influence of conditioning factors which operate in two ways. In one, the specific action of the individual stressors produces a modifying effect. For example, if insulin is the stressor, the blood sugar curve deviates from the characteristic pattern. In the other, peripheral conditioning at various intermediate points of the general adaptation syndrome or in the target organ increases or decreases the activity there. To illustrate, the production and effectiveness of hormones during stress are influenced by diet and metabolic changes. In this, sodium, protein, and carbohydrate are particularly important. In consequence of its modifiability by conditioning factors, the essentially stereotyped defense pattern of the general adaptation syndrome can manifest itself in widely different ways.

From further observations Selye propounded the view that during the general adaptation syndrome some of the anterior pituitary and adreno-cortical hormones are produced in excess. This defensive endocrine response is useful since it raises resistance to stress. But the endogenous hormonal overproduction also has its harmful aspects since it can induce cardiovascular, renal and joint diseases (Figure 5). Thus the

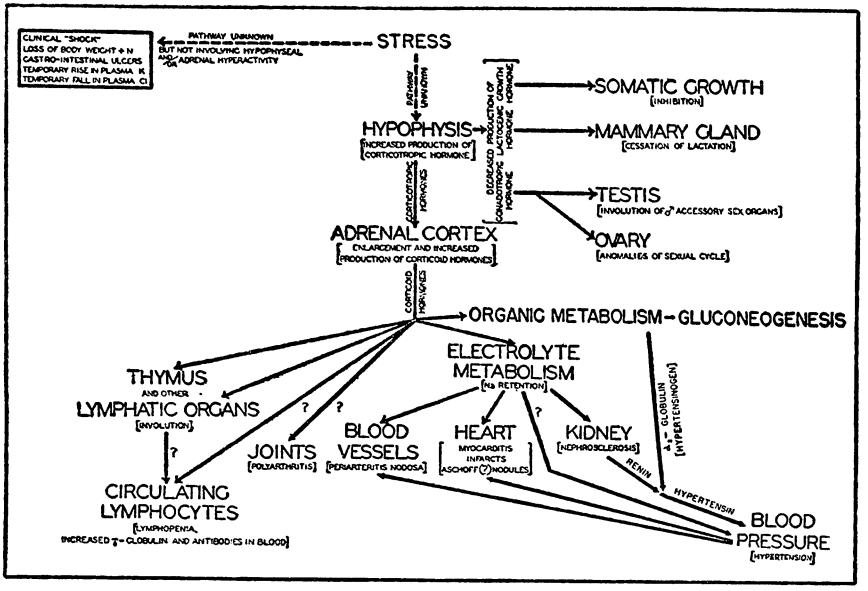


Fig. 5. Functional interrelations during the general adaptation syndrome. (After H. Selye: *Journal of Clinical Endocrinology*, 6, 117, 1946.)

by-products of these excessive or abnormal adaptive reactions to stress are the so-called diseases of adaptation. They include some of the diseases that most frequently afflict man.

Conditions which by their effect on the production and activity of hormones modify the course of the general adaptation syndrome, also influence the production of diseases of adaptation. Indeed, it is postulated that conditions conducive to diseases of adaptation operate by augmenting the production and action of both corticotrophin and corticoids. According to Selye, acceptance that conditioning factors lead to polymorphic symptom complexes in the general adaptation syndrome is basic to understanding the production of diseases of adaptation. Unless conditioning factors could alter considerably the reaction pattern to stress, it would be impossible to ascribe various disorders to the same causative agent, systemic stress.

Even from this barest outline of the general adaptation syndrome and its diseases, a relationship between noxious agents, stress, and deprivation may be visualized. As used by Selye

the term noxious agent is not limited to toxic substances or germs; rather it is almost synonymous with stressor. Stress, created by the stressor, elicits the general adaptation syndrome. As examples of deprivation, vitamin deficiencies, loss of blood, and anoxia are regarded as forms of stressors. But deprivation also appears in a different relation. Removal of the pituitary and adrenals diminishes resistance to all types of stressors; the body becomes ill-equipped to acquire or maintain a state of adaptation. Certainly the responsibility of the general adaptation syndrome for producing disease is emphasized. And its origin is traced to stress. A common, though not reciprocal relationship between noxious agents, stress, excess, and deprivation is recognized, in which excess looms larger than deprivation.

Finally, we come to the concept of deprivation as a producer of disease, which in its original version dates back to the latter half of the last century. Early prospectors among the endocrines and diet unearthed this nugget. At the time when the relation of bacteria to infectious disease was being established and the fixity of the internal environment was being announced, Kocher (24) and Schiff (25) showed that removal of the thyroid led to disease. About twenty years later, Grijns (26) enunciated the doctrine of deficiency diseases arising from lack of an essential nutrient in the diet.

Long after deprivation had been recognized to be a basic mode of etiology, it was regarded as an independent causative, complete and sufficient unto itself and outside the sphere of influences. Indeed, in many minds, such is the position today. Far from relating deprivation and noxious agency in the origin of disease, the prevailing view set the two in contradistinction. It was reasoned that the one leads to disease by a lack, an absence of something, a negative state; the other by a malign presence, the effect of a positive agent. Once again, the design of experiment and technic completely determined the nature of the result, colored the interpretation, and dominated the thinking on etiology of disease. Just as the bacteriological ap-

proach held such complete sway over the interpretation of the causation of infectious diseases that the role of bacteria was magnified to the neglect of associated conditions and etiology was reduced to the overly simple formula, bacterium produces infectious disease; so experimental production of deficiency diseases by inadequate rations so overemphasized diet and disregarded all else that it was regarded as the sole cause of deficiency states. To add to the confusion, for some time the terms diet and nutrition have been used synonymously. This was and is the preponderant way of thinking about the causation of deficiency states, with only a voice or two raised in dissent. Such a view, while wonderfully neat and pat, unfortunately does not accord with the facts. To be sure, this view did regard particular periods, episodes and activities of life as stressful and requiring greater dietary allowances. To that extent stress was recognized, but it was not accorded a place in etiology.

It was already known that factors other than inadequate diet could lead to deficiency disorders. Some students attempted to resolve the complexity, as well as the confusion, of the situation, by retaining the causal thesis of diet in its original form in all its primacy and to dispose of deficiency states from other causes by patchwork amendment, so to speak, that placed them in a separate and subordinate category. Deficiencies arising from an inadequate diet were called primary; those from other causes, secondary. Thus there were two unrelated causations; and the effects, despite their identity, were regarded as two unrelated types.

I have developed a concept of the etiology of deficiency states in which the various aspects previously treated as unrelated and divergent are harmonized and consolidated (27, 28). It contains the three principles of noxious agents, stress, and deprivation, as well as excess, and, what is most important, their interrelationships. It is not relevant to the present topic to retrace the steps, to put together piece by piece the evidence that went into its formulation. Rather on this occasion the

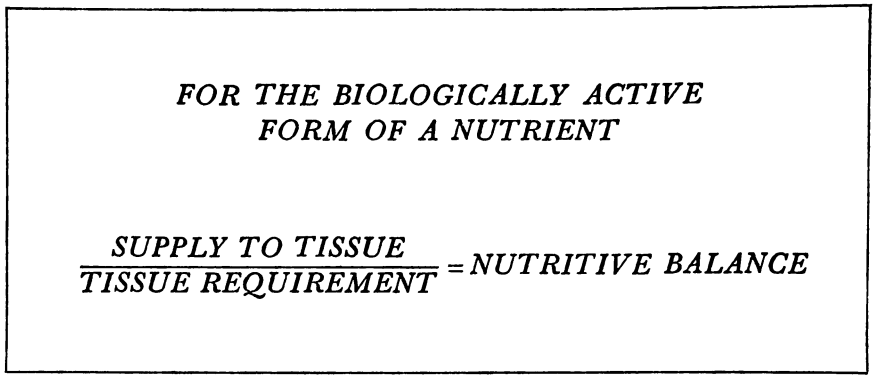


Fig. 6. Ratio determining nutritive balance of a tissue in respect to the biologically active form of a nutrient, according to Kruse.

concept must be presented didactically and then only in skeleton form.

Preparatory to its presentation, a definition of terms is fundamental to clarity. In many minds diet is so closely associated with nutrition that often the terms are used interchangeably with consequent confusion from lack of distinction between them. Nutrition is a bodily process; diet refers to a regimen of food which supports nutrition. This distinction is basic to separating effect from cause; for deficiency states are in reality tissue not dietary deficiencies.

For its nutrition, tissue must have essential nutrients supplied to it to meet requirements for structure and function. Whether nutrition of the tissue proceeds in a favorable or unfavorable direction turns upon the relation between the supply of nutrients to it and its requirements. Tissue nutrition in respect to the biologically active form of a nutrient depends upon this relationship which may be most simply expressed as a ratio (Figure 6).

The ratio takes into account both terms, requirements as well as supply, and their relationship in producing a favorable or unfavorable balance; it summarizes the resultant of this relationship as a causal force for good or poor nutrition. Thus when supply equals or exceeds requirements, the bodily processes operate toward good nutritional status. But when the

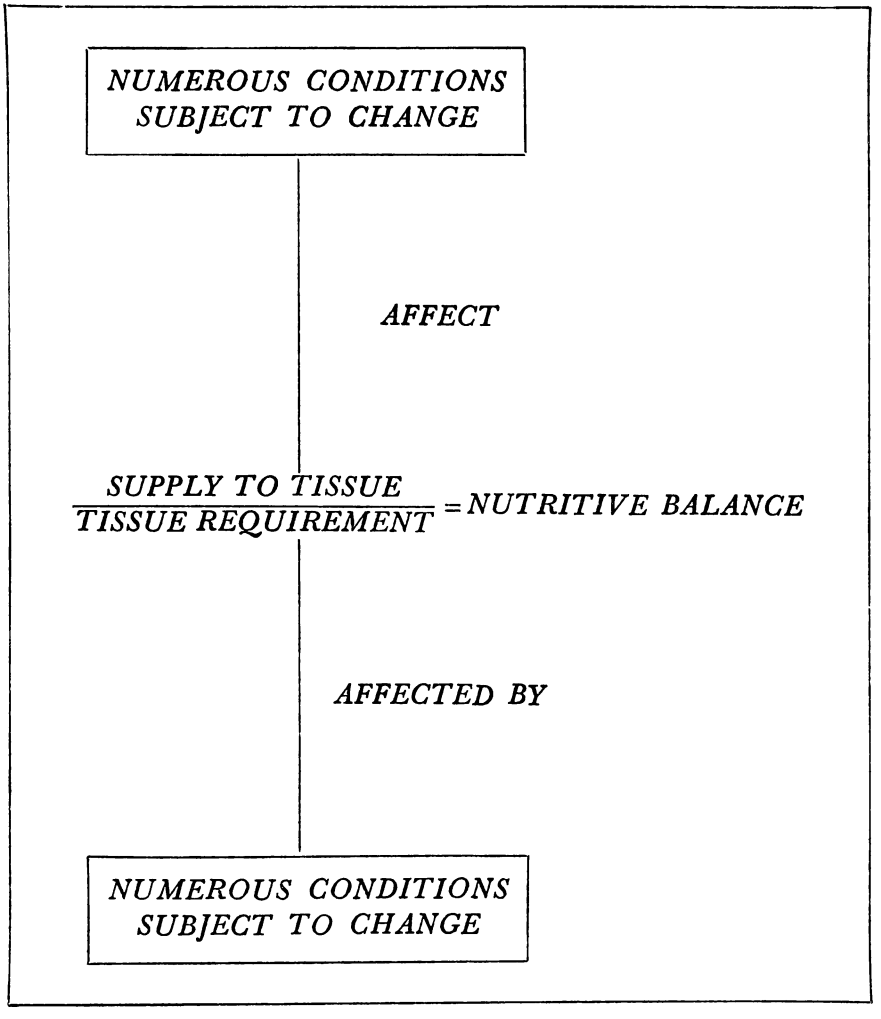


Fig. 7. Schema to show the action of conditions on members of the ratio determining nutritive balance. (After Kruse: Milbank Memorial Fund *Quarterly*, 26, 41, 1948.)

quotient is less than one through need exceeding supply because the former is high or the latter is low or both, it is adverse on an absolute scale. It represents a deficit or deficiency and the bodily processes operate toward poor nutritional status. This deficiency expressed by an unfavorable ratio conduces to the creation, maintenance, or progression of pathological changes in the tissue which constitute a deficiency disease.

CLASSIFICATION OF CONDITIONS

1. *External Environment*

a. *Socio-Economic*
- Living conditions
- Working conditions
- Available foods
- Ability to seek them
- Income
- Education

b. *Physical and Chemical*
- Radiant energy
  - Light infra-red
  - Ultra-violet, x-ray
  - Radioactive
- Temperature
- Mechanical
  - Trauma
  - Physical movement
  - Pressure; irritation; friction
  - Occlusion
  - Dentures
- Toxicants

c. *Time*

d. *Dietary*
1) Form of nutrient
   - Provitamin: analogue
   - Potential or intrinsic biological activity
2) Level
3) Imbalance—
   - Disproportion
4) Interrelations
   - a. Protein-Carbohydrate-Fat
   - b. Vitamin-Vitamin
   - c. Vitamin { Protein, Carbohydrate, Fat }

2. *Bodily Environment*

a. *Digestive and Metabolic Channels*
- Functional form of nutrient
- Appetite
- Ingestion
- Digestion
- Absorption
- Transport
- Formation of enzyme
- Breakdown of enzyme
- Elaboration, Utilization } Metabolism
- Storage
- Metabolic level
- Excretion
- Biosynthesis
  - Intestinal synthesis
- Biodegradation
  - Intestinal destruction

b. *Functions and Reactions*
- Disease { Degenerative, Neoplastic, Organic, Toxic, Infectious }
- Chemotherapy
- Endocrine relationship
- Nutritional status
  - Morphology and physiology of tissue
- Growth
- Pregnancy
- Lactation
- Work
- Psychobiology
  - Food habits
  - Psychosomatic reactions

c. *Time*

5) Inhibitors—Antagonists
   - Anti-vitamins
6) Enzymatic destruction
7) Autoxidation-rancidity
   - Oxidants-autoxidants
8) Processing of foods
9) Availability of nutrients
   - Precipitation
     - Phytic acid—Iron
     - Oxalic acid—Ca
10) Acceptability—
    - Palatability

3. *Genetic Patterns*

Fig. 8. Classification of conditions affecting the ratio according to their natural location and character. The list is not exhaustive. (After Kruse: Milbank Memorial Fund *Quarterly*, 26, 41, 1948.)

Parenthetically, it should be noted that for some, if not all, nutrients the ratio has an optimum zone above which as well as below which it is adverse. For example, a supply of lipogenic nutrients in excess of requirements would be conducive to obesity.

One of the most significant features of the ratio is its dynamic behavior. It reflects the continuous operation of its terms with the capacity to undergo change at any time. The terms and ratio may change in either direction, decrease or increase. Thus by a decrease in supply or an increase in requirements, or both, a satisfactory ratio may be lowered to the point of indicating a deficiency which sets into operation the bodily processes in an adverse direction. Oppositely, by an increase in supply or a decrease in requirements, or both, a low ratio reflecting an unsatisfactory balance increases thereby setting into operation the bodily processes in the more favorable direction. Certainly the ratio can undergo change at any time, and probably does change frequently or continually, if only to a slight extent. Evidence from persons of all ages indicates a long-term trend over a lifetime with seasonal cycles and intercurrent fluctuation.

But change is not a spontaneous, inherent property of the terms of the ratio. It is brought about by influences upon the terms. These influences affect both terms, i.e., supply and requirements: some act on one; some on the other; some on both. They may change the terms favorably or unfavorably and may likewise change the ratio. These influences are conditions, a precise yet shorter term than conditioning factors (Figure 7). Conditions exert their effects by their presence or absence, and by their excess or deficit.

All the external and internal environmental as well as hereditary factors that influence either or both members of the ratio in whatever direction are conditions. They are manifold (Figure 8). Diet, growth, pregnancy, lactation, work, sunlight, climate, toxic material, and disease are just a few of those included in the list. It is to be noted particularly that conditions

embrace those of a dietary as well as a nondietary character.

Not only are the conditions numerous, but they are multiple in operation. In any instance several or many conditions are affecting the ratio and it is their resultant which determines its balance. Furthermore, these conditions are dynamic in nature. They are capable of change and are constantly exerting their influence on the ratio. According to their nature or circumstances, conditions differ in their schedule of activity or influence. Some are continuous through life, constantly in action. Others, impermanent, may occur frequently, occasionally, or only once; and may last a very short or very long time.

These multiple conditions act upon the ratio by influencing both of its terms; some affecting supply, some altering requirements, some modifying both. Conditions that increase the numerator or decrease the denominator tend toward making the ratio favorable; those that operate oppositely conduce to an adverse ratio. When untoward conditions predominate and the ratio tends to a decline, counteracting conditions operating in a favorable direction are brought into action. It is a homeostatic reaction, an attempt at adjustment. As another means of protection, particularly offending or adverse conditions may be removed, controlled, or diminished. Despite preservative reactions, the adverse conditions may preponderate; then the ratio moves towards, enters or sinks deeper into the pathological zone.

It is the net effect of the aggregate of conditions that determines the quotient. Never is one solely responsible for an adverse ratio. Since not only the cast of conditions but also the degree of activity of any condition may change from time to time, the proportional influence of each adverse condition in the composite may vary. Hence, the etiological complex exhibits relativity.

An adverse ratio and the combination of conditions responsible for it comprising a complex can be regarded as the cause of the resulting deficiency state in the tissue and its ensuing pathology. But in the interest of clarity and precision in delv-

ing into the etiological system, a distinction should be drawn between the ratio and the conditions. The adverse ratio is the primary, direct, immediate cause of the tissue deficiency process; while the combination of conditions influencing the ratio to that end are secondary, indirect, mediate causes. Most simply and accurately designated, the adverse ratio expressing deficiency is the cause; factors responsible for its unfavorable level are adverse conditions. But it should be reiterated that not only the adverse ratio but also the conditions which brought it about are a fundamental and integral consideration in the etiology of deficiency states.

To clarify what is meant by conditions and how they influence the ratio, it might be helpful to cite a few familiar examples of them and their effect on the development or accentuation as well as on the subsidence of deficiency states. A gastrointestinal disorder may impede absorption and transport of nutrients and thereby interfere with supply to the tissues. Decrease in supply diminishing the quotient of the ratio tends to a deficiency state.

Acting on the other member of the ratio, growth, pregnancy, and physical labor are conditions conducing to deficiency states by raising the level of requirements. It is a commonplace in experimental studies with deficient diets that animals must grow if they are to develop acute deficiency states. In pregnancy the incidence of deficiency disease in exacerbated form has been repeatedly observed. And bed rest is a highly effective therapeutic measure for abating deficiency disease. In all three examples, growth, pregnancy, and work, the recognition of increased requirements associated with them is evidenced by larger recommended dietary allowances. The attempt is to increase supply to counterbalance the increased requirements. But to repeat, although each of the three conditions may precipitate an aggravation of deficiency states, it should not be concluded that any of them alone can bring it about. Unless other adverse conditions, such as inferior diet, disease or pre-existing poor nutritional status prevail, growth, preg-

nancy, or physical exertion does not set off deficiency signs. Of the aggregate of adverse conditions contributing to an unfavorable ratio, one is usually decisive in the sense that it adds enough to tip the scale. It is, however, not necessarily the major adverse force; rather its timing attracts disproportionate attention to it.

At the risk of seeming to minimize diet, whereas the intent is to bring the ensemble of conditions into proper perspective in which neglected members are elevated to their rightful place, it should be pointed out that poor diet is not the cause of a deficiency state but a condition conducive to it. Poor diet alone cannot produce a deficiency state; for it is never the sole condition in operation—other conditions intrinsically participate. Deficiency states may even occur when diet is satisfactory and therefore operating favorably on the ratio. True, in many, if not most, instances of deficiency disease, poor diet is the major adverse condition; but in other instances, it is a minor condition. Sometimes deficiency disease occurs when diet is not an adverse condition.

Two of the most influential adverse conditions are infection and existing poor nutritional status. An infectious disease may lower food consumption and interfere with absorption and utilization. As a condition, not a cause, it conduces to pathology of deficiency. Also especially noteworthy among the list of conditions is existing nutritional status. If the tissue is already the site of deficiency pathology, usually chronic, its requirements obviously are raised.

It has been demonstrated that many conditions, among them growth, pregnancy, and disease, affect nutrition. But whether there is a reverse relationship, a reciprocity of nature, in which nutrition influences these functions of life has been a transcendent question. Studies with animals on these relationships have yielded a decisive and convincing affirmation. Evidence on man is naturally less abundant. But certainly reciprocity has been fully established for nutrition and growth. Data from four separate human studies have put the favorable

effect of improving nutrition on pregnancy beyond the questionable stage. And even in the far more complex and difficult matter of ascertaining in man whether nutrition confers any benefit in combatting noxious states, definite results of a positive nature have been obtained. From these lines of evidence the conclusion is inescapable that nutrition and some of its conditions, particularly bodily conditions, are interrelated in a two-way action.

In this concept, all three members—noxious agents, stress, as well as deprivation—are to be found among the conditions. Noxious agents represent one type of conditions which tend to depress the ratio. As for stress, the term may be applied to the action or effect that imposes a burden, adversity, or strain when a force or influence is exerted within or upon the body. In this sense, it is a generic term for a broad class and is an effect as well as a causal component. Conditions, such as deficient diet, growth, and pregnancy, that operate towards lowering the ratio produce stress. In sum and substance, then, stress is the effect of conditions which in turn is exerted upon the tissue ratio. Deprivation not only represents a type of condition, but also appears as an expression of the resultant state of tissue nutrition as manifested by ratio. Deficient diet, for example, is a condition of deprivation; it contributes to nutritional deprivation of the tissue.

Actually all three terms—noxious agents, stress, and deprivation—are generic; that is, they represent types or classes. Besides, as categories they are not mutally exclusive. For example noxious agents and deprivation itself, when it is an inimical condition, are sources of stress. On the other hand, in the interest of completeness, excess which has already been mentioned as having a place in the concept, should be added here as the fourth category. In this light two points emerge out of the concept that are more important than identifying examples of these categories among conditions.

It may be noted that each condition, according to its character, operates pathogenically in one or more of these cate-

gories. Indeed, these categories have been used to connote types of disease-production. But unfortunately some of these categories—stress in particular—are not homogeneous: their members do not have a pathogenic action that is the same in principle. For example, noxious agents, excess, and deprivation can produce stress. It would seem desirable, therefore, to have categories of pathogenicity based on their own common characteristics. Such a system might include the following four classes of pathogenic states: presence, excess, deficit, absence. Accordingly, the first point is that each condition operates by virtue of one of these states. It follows, then, that the status of each condition may be expressed by its own ratio. To differentiate it from the ratio of tissue nutrition it may be called condition ratio. If the condition be of the noxious agent type, a plus indicative of presence or excess has pathological significance. If it be of a type applicable to nutrients and hormones, absence, deficit, or excess has pathological significance. The state as well as the nature of the condition is, therefore, of consequence. There is then a coalition of conditions, some noxious and positive through their presence or excess, others depriving and negative through absence or deficit, each with its adverse ratio, each conducive to disease.

Against this group of conditions with the aggregate of their ratios tending to depress the ratio of tissue nutrition, other conditions by virtue of their presence, excess, deficit, or absence support it. The effect of all conditions with their individual ratios, adverse and favorable, is expressed by the ratio of tissue nutrition. In the event of an adverse change in this ratio, there is a reaction of opposition in which new counter conditions are called into action, existing favorable conditions are intensified and adverse conditions are lessened to bring a more favorable turn to the ratio or hold its adverse shift to a minimum. Viewed as a whole, the concept takes cognizance of an aggregate of adverse, counter, and favorable conditions, each operating by virtue of its presence, excess, deficit, or absence, and each having its individual ratio, whether adverse

or favorable. The resultant of all these ratios is reflected in the ratio of tissue nutrition.

The other significant point in the concept is that noxious agency, stress, and deprivation are interrelated, that presence, excess, deficit, and absence as states of conditions interact in the engenderment of disease. Of course, adverse conditions whatever their mode of pathogenicity are related in so far as they have a common action on the tissue ratio. But more than this, the bodily conditions exhibit interplay. A condition acts upon tissue nutrition with its ratio; in turn there is a reaction upon not only the same but also other conditions. Here are a few examples: Infection creates a tissue deficiency; a tissue deficiency predisposes to infection. With a deficient diet, growth is one of the conditions necessary in order to produce an acute deficiency state in healthy, young animals. On the other hand, deficiency states retard or suspend growth. Pregnancy may be accompanied by deterioration in nutrition; conversely, subnormal nutritional status may impair pregnancy. Between these conditions and nutrition there is an interaction. Furthermore, infection through its effect on nutrition may interfere with growth or pregnancy. The reverse is equally true: growth or pregnancy may exacerbate an infection. It is concludible, therefore, that through the medium of nutrition, one bodily condition is related reciprocally to another in pathogenesis. Indeed, to use the very words of the subject, there may be seen an interplay of noxious agents, stress and deprivation in the engenderment of disease. Since such condition has its own ratio and the resultant of all conditions is expressed by a ratio, there is an interrelationship expressible by ratio. It may be noted that the positive ratio representing presence of infection is one condition contributing to a negative nutrition ratio which in turn reacts to further the positive ratio of infection yet at the same time lessens the ratio of growth.

In this concept originally designed for tissue nutrition, the ratio pertained to any biologically active form of a nutrient and emphasis fell on deprivation as a pathogenic principle. But

as previously mentioned, it also covers excess and presence. Furthermore, the pivotal ratio with its constellation of conditions is equally as applicable to a noxious agent or hormone as to a nutrient. Hence, it is useful in conceptualizing the etiology of noxious states and endocrine disorders. For example, it should be noted that Selye in elaborating on the general adaptation syndrome has emphasized the importance of the $\frac{\text{gluco–corticoid}}{\text{minerals–corticoid}}$ ratio in the pathogenesis of arthritis (29) and hypertension (30). Indeed, the pivotal ratio would appear to be adaptable even to psychiatry, whether in its psychodynamic, psychosomatic, or somatopsychic aspects. For in this category of disease the same battery of pathogenic principles—presence, excess, deficit, and absence—again appears. The association of mental disorder with infection and the experimental production of psychotic states by drugs are well-known examples of the action of noxious agents. Liddell has stated that the incorporation of the concept of stress situations has given new life and meaning to the conditioned reflex which already included an element of deprivation (31). Social stress, economic stress, and various other types of stress are today common terms in psychiatry. And striking indeed are Spitz' observations on the effects of deprivation of maternal affection, a familiar theme in present-day discussion of emotional and behavior problems (32).

I have approached the consideration of etiology of disease by presenting concepts in which noxious agents, stress, and deprivation, respectively, appeared to be the prime factor; but in each instance the other modes were always found to have a part and in some were inextricably interwoven. It is striking how well the various concepts fit together and fill out in broad outlines the expanse of pathogenesis. It was as if we were looking at one map from first one and then another direction. In sweeping across it from whatever direction, ultimately the eye came upon the same familiar markings and connecting pathways—noxious agents, stress, excess, and deprivation.

I have not attempted a comprehensive critique of the various concepts, only an examination of them for their components and relationships. From this examination one point which they have in common stands out: there are multiple factors that operate in the production of disease. Three other points appear with varying degrees of recognition, becoming increasingly prominent in the more recent concepts: (1) among the etiological factors are noxious agents, stress, excess and deprivation; (2) they operate through their presence, excess, deficit or absence; (3) and between them there is an interrelation.

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