VITAMINS AND HORMONES

ADVANCES IN RESEARCH AND APPLICATIONS

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EDITORS' PREFACE

The Editors take pleasure in presenting this sixteenth volume of *Vitamins and Hormones*.

In planning each volume an attempt is usually made to include contributions from colleagues in a variety of countries. However, in the present volume it has not been possible to achieve this international representation, primarily because it has been necessary to postpone articles by several authors abroad. These will appear in subsequent volumes.

The standards of breadth of coverage and critical judgment shown in the nine articles in this volume are, we feel, of the same high quality as those in previous volumes of this series. The companion chapters on the relation of vitamins and of hormones to cardiovascular disease are of especially timely interest. The review of gonadal function also takes up some of the interrelationships between vitamins and hormones, and indeed envisages them in a fresh light. The article on vitamin B_6 summarizes well its numerous functions and the mechanisms of its action which have been brought to light in recent years. Of special interest to workers in tropical areas is the chapter on parasitic infections, which is complementary to that written by Dr. Smith for Volume XIII. The articles on glucagon and secretin both relate to the physiology of digestion, one of the earliest fields of endocrinology to become active; it is worth recalling, perhaps, that it was for Secretin that the term "hormone" was coined more than half a century ago. Finally, the thorough treatments of the thyroid-stimulating hormone and of synthetic corticoids should be of interest both to biochemical and to clinical workers.

This volume contains a cumulative subject index for Volumes XI–XV which is shorter and more compact than the two previous cumulative indexes (see Volumes VI and XI) due to the elimination of unnecessary and overlapping entries. We believe this slightly abbreviated index will be no less useful than its predecessors.

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August, 1958

CONTENTS

Hormonal Aspects of Coronary Artery Disease

M. F. Oliver and G. S. Boyd

The Physiology of Secretin

Morton I. Grossman

Chemistry and Physiology of the Thyroid-stimulating Hormone

Martin Sonenberg

Glucagon

Otto K. Behrens and William W. Bromer

Synthetic Derivatives of Cortical Hormones

Nutritional Effects of Parasitic Infections and Disease

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I. Introduction

The statement by Chandler (1953) that "Diet exerts profound influences on the course of parasitic infections" can be amply supported by data from studies with viruses, rickettsia, spirochetes, and fungi, as well as with animal parasites. The general concept that malnutrition leads to an increase in infections and parasitic disease in a population has to be qualified by the statement that the production and severity of the specific disease is determined by the kind of nutritional deficiency that exists. During World War II, deficient dietary protein in central and western Europe led to increased tuberculosis but greatly reduced the incidence and mortality figures for typhus, typhoid fever, diphtheria, scarlet fever, rheumatic fever, and bacillary dysentery (Kühnau, 1955). As Kühnau further points out, protein starvation may deprive the host of essential building blocks for antibody formation but may at the same time deprive the invading parasite of food necessary for growth and multiplication. Helweg-Larsen *et al.* (1952) stated in a comprehensive study of famine and disease in German concentration camps that infectious diseases are very prevalent under such conditions but that the nature of the diseases will vary with the circumstances. In 1955, D. A. Smith published a review

on "Parasitic Infections and Nutrition" for this series of publications and examined the thesis that "malnutrition tends to favor increased parasitization, and parasitization tends to increase malnutrition."

Parasitologists (using biochemical techniques), biochemists, and pharmacologists are discovering extensive material for study in the field of animal parasitology and are starting to fill the great gaps in our knowledge about the fundamental principles and facts that enable cells to live a parasitic existence and adapt themselves to a variety of environmental changes necessary to complete their life cycles.

In this paper, an effort will be made to review the physiological and metabolic behavior of animal parasites as affected by nutritional factors and to point out the status of our knowledge about the mechanisms involved in the production of disease, with emphasis on animal parasites infecting man and the diseases they produce.

The point of view about parasitism to be followed is well expressed by the words of Elton (1927):

"To imagine that parasites are unique in exploiting the activities and food-products of their hosts is to take a very limited view of natural history. It is common to find parasites referred to as if they were in some way more morally oblique in their habits than other animals, as if they were taking some unfair and mean advantage of their hosts. If we once start working out such 'responsibilities' we find that the whole animal kingdom lives on the spare energy of other species, or upon plants, while the latter depend upon the radiant energy of the sun. If parasites are to occupy a special place in this scheme we must, to be consistent, accuse cows of petty larceny against grass, and cactuses of cruelty to the sun. Once we take a broad view of animal interrelations it becomes quite clear that it is best to treat parasites as being essentially the same as carnivores, except in their smaller size, which enables them to live on their host. In other words, the resemblances between the two classes of animals are more important than the differences."

A similar point of view was expressed again by Theobald Smith (1934) in his oft-quoted book, "Parasitism and Disease." Parasitism is considered a normal, common, and natural phenomenon. To become established as a parasite in a host the organism must (1) gain entrance into or invade the host; (2) multiply within the body of the host, (3) be excreted or discharged, or it must migrate, and, finally, (4) develop a mechanism of transmission, either active or passive, to another host. If we examine these different categories or critical stages that are essential for the continued existence of a parasite, we discover that nutrition of the parasite must be maintained or food reserves stored throughout its life cycle if the parasite is to survive. In this connection, the food-chain concept of

Elton (1927) serves very well in helping us to understand and explain parasitism. Numerous parasites find their way by means of contaminated food and water into new hosts. They can invade the host by means of their own movements or secretions, or they can be introduced into the host by an infected arthropod seeking a blood meal, or mechanically when seeking body fluids. Once the parasite is within the host its survival, growth, and multiplication are entirely dependent on the physical and biochemical make up of the host tissue environment. Although the physical characteristics of such an environment must be compatible with life, food for growth and multiplication must be available for direct ingestion or absorption from the environment, or it must be obtained in competition with host tissues for the available supply. If the foreign organism becomes established in the host, complex mechanisms of transmission to other hosts once again involve food products and food cycles. Predatory animals, ingesting infected animals or animal products for food, or individuals, eating raw or partially cooked infected meat, likewise become infected. Thus we see that food cycles of animals are definitely involved with the continuation of parasitism.

Little by little, information is beginning to accumulate about the metabolic differences that exist between host and parasite. As we shall see, the processes are in many cases highly complex, far from the simple loss of superfluous structures or degeneration of system function. In other words, the physiology of parasites generally increases in complexity and specialization if the organism is to survive in the host environment and be transmitted for the continuity of its existence.

A parasite in the best position to survive is an organism that is living in balance with its host. In his paper on "The Efficient Parasite," Swellengrebel (1940) illustrated this point in a colorful way by comparing his own acute malaria in a new environment with the chronic malaria of natives who had acquired immunity during their lives in the same environment. If the balance is disturbed in favor of the host, the parasitic infection might die off, but if the parasite produces progressive tissue or biochemical lesions, the host develops disease and might possibly succumb to the infection. Inherent in this concept of the host-parasite relationship is our understanding of the word pathogenic, or capacity of the parasite to cause disease, and the resistance of the host to the invasiveness and lesion-producing characteristics of the parasite. The virulence of each strain of parasite is determined for each host and comparisons are made between efficient parasites for the same host or the same parasite for different hosts. The measures of virulence involve parasite and host effects (Miles, 1955) and will not be detailed here other than to indicate that the end points for the assessment of host effects are becoming more

highly refined. The production of detectable gross or microscopic tissue lesions, or the death of the host by a given parasite or combination of parasites—the classic methods devised to determine pathogenicity—are now being supplemented by methods of biochemistry and biophysics for the detection of host and parasite effects. In fact, the sensitivity of these newer methods will undoubtedly aid in showing host effects by parasites that are now labeled nonpathogens.

II. The Parasitic Habitat

The diversity of tissues parasitized in man and animals by animal parasites is evidence for the degree of specialization of each parasite and its attribute of finding the environment most suitable for growth and multiplication. The affinity of *Leishmania donovani*, causing leishmaniasis, for the viscera; of the morphologically similar *L. tropica* for cutaneous tissue; of human malaria sporozoites for liver tissue; and malaria trophozoites for erythrocytes; of larvae of *Trichinella spiralis*, a nematode, for muscle fibers; of *Schistosoma mansoni* for the portal circulation, illustrates that certain animal parasites seek precise biochemical environments for their development and metabolism just as do bacteria and viruses (*Hemophilus pertussis* on the epithelial surface of the upper respiratory tract, and the virus of mumps in the glands and occasionally in the central nervous system). The alternate occurrence of adult *Trypanosoma cruzi* of Chagas' disease in the blood stream, and then the invasion of host muscle fibers, has some similarity to the initial blood invasion in leptospirosis, with later invasion of the liver and kidneys. Although the parasites just mentioned are quite fastidious in the tissue environment they seek, there are parasites that adapt themselves readily to different environments and invade a wide range of host cells. *Toxoplasma gondii* of toxoplasmosis is such a parasite, with properties that enable it to parasitize a wide range of hosts and to invade the central nervous system, muscle cells, and reticuloendothelial cells—in fact, the parasites have been isolated by animal inoculation from a wide variety of tissues at autopsy where a careful search is made (Kass *et al.*, 1952).

The narrow or broad adaptability of animal parasites is also the basis for host susceptibility and specificity. That this phenomenon has a biochemical and biophysical explanation is becoming more evident as analysis of host environments and nutritional and metabolic pathways of parasites become known. The subtle species differences in the composition of their blood plasma and tissue fluids (Albritton, 1952, 1953), cellular metabolism, oxygen tension, temperature, and even anatomical structures as barriers to invasion determine the environment needed by the parasite, or to which it must adapt its needs if it is to survive.

Although we say that man is susceptible to infection by a virus, species of bacteria, or animal parasite, we forget that not all individuals who are exposed develop infection or disease. In a thought-provoking and stimulating book on "Biochemical Individuality, the Basis for the Genetotrophic Concept," Williams (1956) points out that medical sciences are concerned almost entirely with normal man and his reactions and then proceeds to advance the hypothesis that each individual (man and animal, presumably) is a "deviate" in susceptibility to disease. Available evidence that is presented to test the validity of the hypothesis is impressive, and the chapters on "Individuality in Composition," and "Individuality in Nutrition" seem particularly pertinent to our discussion. The variation of body water from 15.6 to 70.2% in eighteen "normal" males and eleven "normal" females, up to a threefold range in concentration of blood electrolytes, and up to a tenfold range in organic constituents of blood, to mention a few examples, certainly supports the concept of biochemical individuality. The evidence for certain components in given individuals suggests the requirement of distinctive nutritional needs and suggests the maintenance of distinctive tissue composition patterns over periods of time which could be of extreme importance to parasites seeking to invade and establish infection. The evidence for distinctive amino acid secretion, salivary and duodenal juice patterns in individuals is of particular importance to parasitism because these nutrients are the building blocks for parasite protein as well as host protein.

The difference then in the nutrient supply available in the host and required for his metabolism and the nutritional demands by the invading pathogen and its progeny could determine the sequence of events that will determine the course of the infection and development of disease.

In considering the hypothesis of biochemical individuality, and what it might mean to parasite susceptibility by man, the major portion of the data was obtained from subjects in countries where adequate diets are the rule rather than the exception. In those underdeveloped countries of the world where different races live and where levels of parasitic infection are higher, are the ranges of biochemical individuality still greater? Does the diet of the Oriental in Indonesia, the Bantu in South Africa, or the Arab in Saudi Arabia provide a better tissue environment for the development of parasitic infection? The accumulation of data about dietary habits in relation to the incidence of coronary disease (Portman and Hegsted, 1957) showing different plasma levels of cholesterol in individuals from geographically different racial groups represents a method that could be of considerable value in adding to our knowledge

about susceptibility to parasitic diseases in relation to dietary habits and their effects on biochemical host tissue environments.

III. Clinical and Pathological Effects of Parasitism

Information about parasites is slowly being obtained that enables us to explain the fundamental phenomena that are involved in the invasion of a host or of cells by an animal parasite. In very few cases, however, are we in a position to explain precisely how animal parasites invade host tissues and cells and how they produce disease, regardless of whether we accept the definition of disease given by Webster as "a condition in which bodily health is impaired," or the definition of Stetten (1956) as " . . . the manifestation of alterations in metabolic processes." Parasitologists cannot match the position of bacteriologists who have determined the cause and defined the biochemical mechanisms for the production of disease by the toxin of the diphtheria bacillus (Pappenheimer, 1955), the effects of tubercle bacilli on host cells (Dubos, 1954), and the production of lesions and the biochemical characteristics of the toxins of the *Clostridium* species that cause botulism, tetanus, and gas gangrene, and the death of the host (Wright, 1955; Macfarlane, 1955).

Before proceeding with the pathological manifestations in man of certain species of animal parasites as examples, we need to understand that parasitic infections do not always mean parasitic disease. Very often an individual may be infected, but the degree of infection is insufficient to cause illness or demonstrable tissue damage. Thus disease in many parasitic infections is a function of the dosage, or a function of the multiplication of parasites in the host. Moreover, when we speak about disease, our criteria for the diagnosis are dependent upon disturbed organic function with resultant clinical signs and symptoms, or the detection of gross or microscopic pathological changes in host tissues. The ability to determine the effects of parasites on hosts is now being greatly extended with the advent of such new tools as chromatographic procedures and the use of radioactive isotopes in studies of host-parasite nutrition and metabolism.

When one speaks only of clinical symptoms caused by animal parasites, attempts at diagnosis by this evidence alone are hazardous. The symptoms caused by the animal parasite are the result of the same basic biological and pathological principles that are involved with infections caused by viruses, bacteria, spirochetes, and fungi. Specific effects on the host or host tissues by the animal parasite, of course, are dependent on the characteristics inherent in the biology of the organism involved, the host defenses repelling the invader, and the environment. The ability of the organism to penetrate unbroken tissues can be a function of motility or the production of enzymes (Lewert and Lee, 1954, 1957).

enabling the parasite to gain entry; or the parasite can find its way into the host tissues as a result of contaminated food, water, or air.

If the infection is produced by the bite of infected arthropods seeking a blood meal, infective stages of parasites find their way into the blood stream or tissue fluids, either to migrate or be passively carried to the organ or tissue suitable for growth and multiplication. Once inside the body, in cavities, in the gastrointestinal tract, or in the vascular system, cellular invasion by intracellular parasites again is dependent on mechanical or biochemical penetration of the gastrointestinal mucosa or the endothelial lining of the blood vessels, or phagocytosis by the reticuloendothelial cells or cells of the lymphoid-macrophage series.

It has already been inferred that the mere introduction of the parasite by whatever means does not always produce disease. There are certain parasites that do not multiply when introduced into the human host because of peculiarities in their life cycle (*Wuchereria bancrofti*). On the other hand, there are parasites that can overwhelm their host by multiplication in the tissues (*Plasmodium falciparum* and *Leishmania donovani*). The numbers of injected or ingested parasites, then, as well as their ability to multiply, are determining factors in setting the stage for the production of tissue reaction and detectable lesions.

For the sake of convenience, animal parasites in the host may be arbitrarily divided into three different categories: (1) Cavity or lumen dwellers in the human or animal host, with or without local tissue reaction. Examples are: *Trichomonas vaginalis*, the cause of trichomonas vaginitis, and *Ascaris lumbricoides*, a nematode that parasitizes the intestines of man and animals, with occasional migration to the liver or other tissues. (2) Tissue invaders that remain extracellular but are capable of producing lesions. Examples for this group are two species of trypanosomes causing African sleeping sickness; the dysentery ameba, *Entamoeba histolytica;* the blood, lung, and liver flukes; the larvae of tapeworms causing cysticercosis; nematodes causing filariasis; and the itch mite causing scabies. And, (3), intracellular parasites that produce the death of host cells, along with the production of lesions. In this group are the parasites causing malaria; three species of *Leishmania* causing visceral and cutaneous leishmaniasis; *Toxoplasma gondii*, causing toxoplasmosis; species of trypanosomes, causing Chagas' disease; and *Trichinella spiralis*, causing trichinosis.

1. Cavity or Lumen Dwellers

In this group of animal parasites, found in both man and animals, a wide variety of effects are produced on the host. These effects are seldom discernible in terms of specific tissue damage. The host may be invaded

by a single adult *Ascaris*, or the intestines may be parasitized by as many as 120 adult worms weighing 200 gm. (Jelliffe, 1953). The damage then to the host by lumen-dwelling *Ascaris* appears to be the result of competition for host nutrients and the secretion of toxic metabolic products. Even when this parasite migrates into the liver by way of the bile duct, or invades the appendix, or causes fistulas and peritonitis, there is little tissue reaction to be detected around the parasite other than mild focal inflammatory reactions, or pressure atrophy of the epithelial lining of the bile ducts (Ash and Spitz, 1945). In the case of trichomonas vaginitis, the causative organism, *Trichomonas vaginalis*, belongs both to category 1 and category 2 because the parasite can invade the vaginal wall or the cervix with the production of hemorrhagic petechiae. Biopsy specimens of such areas have revealed the flagellates in the center (Kessel and Gafford, 1940).

Infections of children and adults by the dwarf tapeworm (*Hymenolepis nana*) and the rat tapeworm (*H. diminuta*) are common in various parts of the world. Positive statements about the production of considerable irritation in the small bowel, the presence of generalized toxemia following the absorption of metabolic wastes by these tapeworms (Faust and Russell, 1957) and, "There are no characteristic pathological changes," (Mackie *et al.*, 1954) are now being tested experimentally to determine the actual host-parasite relationship. These studies are reviewed below.

2. Tissue Invaders That Remain Extracellular

This group of animal parasites causes a variety of host tissue changes when the parasites gain access to the tissues. Each parasite has its own sequence of stages, biological characteristics, and tissue responses from the host. In the production of amebic dysentery, the active stage, or trophozoite of *Entamoeba histolytica* gains access to the tissue as a result of mechanical penetration and proteolytic action. The amebas with the aid of proteolytic enzymes destroy the tissue cells with which they come in contact; they migrate into the submucosa, ingest erythrocytes if they are available, and multiply, with the result that the host tissue is eroded with the production of a typical flask-shaped ulcer. There is little cellular host response to the parasites unless secondary bacterial invaders become involved. The lesions, then, of uncomplicated amebic dysentery (Faust and Russell, 1957; Koppisch, 1953) include ulceration of the colon and rectum with minimal inflammatory reaction, bleeding as a result of mucosal erosion, and associated disturbances of intestinal physiology leading to the secretion of fluids and the production of dysentery. Once the organisms are in the tissues, they can gain access to the liver by way

of the portal circulation and in this organ produce amebic hepatitis or amebic abscesses. In a typical amebic liver abscess, necrotic tissue occupies the center, which is surrounded by a partially degenerated zone of liver tissue and debris that has undergone coagulation and necrosis. Fibrous tissue, and liver tissue which are infiltrated with lymphocytes and plasma cells, delimit the margin of the abscess. For our purpose, the presence of the parasite in the edge of an advancing intestinal lesion and in the outer layer of recognizable liver tissue rather than in the necrotic center of the abscess is an important point in the host-parasite relationship of this infection and will be discussed in greater detail below.

African sleeping sickness caused by two species of trypanosomes, *Trypanosoma gambiense* and *T. rhodesiense*, falls within this category also because the parasite primarily invades the blood and the lymphatics. As the infection progresses, these parasites penetrate the central nervous system and the parenchyma of the brain and spinal cord. However, these two species do not invade cells as does *T. cruzi*. Initially, *T. gambiense* and *T. rhodesiense* are found in the regional lymphatics, giving rise to proliferation of lymphoid tissue and enlargement of lymph nodes, particularly the cervical lymph nodes. Splenomegaly and hepatomegaly, cardiac symptoms, and muscle paralysis, associated with fever, can occur at this stage. After invasion of the central nervous system takes place and the development of the meningoencephalitic stage, physical activity and consumption of food decreases, somnolence develops, and finally death occurs (Napier, 1946). Dutton *et al.* (1905) in their early studies state that there was no relation between the numbers of parasites in the blood stream to the severity of the disease. As pointed out by Wenyon (1926) trypanosomes are to be found in greatest numbers in the lymphatic channels. The primary lesion in the central nervous system to be found at autopsy is a perivascular collar of endothelial, plasma, and neuroglia cells, and the brain and cord are congested with occasional hemorrhages. In essence, then, there are no dramatic tissue lesions at the time of death, even though the disease usually has a chronic course with ample time for extensive pathological tissue changes. This means, then, that biochemical lesions need to be sought to explain the cause of death. Von Brand (1938, 1951a) has reviewed the different theories advanced to explain the pathogenesis of trypanosomes and evidence in their support. Some comments about the current status of our knowledge are given below.

Another example of animal parasites that fits into this category are the larvae of *Ascaris* as they migrate through the lungs on their way to the intestines. These larvae pass into the pulmonary alveoli with the production of hemorrhage and tissue reaction involving neutrophiles and eosinophiles. If great numbers of migrating larvae are involved a fatal

Ascaris pneumonia can be produced. This type of infection is most commonly seen in children because they frequently receive heavier infections as a result of ingesting contaminated dirt, food, or water. In this case, the migrating ascarid larvae are responsible for the tissue reaction, again presumably caused by their existence as foreign bodies within the lungs or as a result of toxic metabolic products.

Filariasis of man is of interest to us under this category because the primary pathology in this disease is caused by adult worms in the larger lymphatic channels and sinuses of lymph nodes. Just as long as the adult worms remain alive by obtaining their required nutrients from the host, little pathology is demonstrable. However, either the host's defenses, or the failure of the worms to obtain sufficient nutrients, lead to the death of the worms, initiating a granulomatous inflammatory reaction. This reaction leads to interference with lymphatic circulation, the development of edema, progressive proliferation of fibrous tissue, and enlargement of the involved area to produce what is known as elephantiasis (Koppisch, 1953). The pathology, then, appears to be initiated by dead parasites, leading to blockage of lymphatic channels and regional lymph nodes, and superimposed secondary bacterial infection.

3. Intracellular Parasites

Lesions produced by this group of animal parasites include both helminths and protozoa, but the resultant diseases have little in common with each other except invasion of cells and in most cases multiplication within the host cell. In malaria, the parasites responsible for clinical symptoms invade erythrocytes; they grow and multiply by an asexual process and eventually rupture the host cell to free the progeny for reinvasion of other erythrocytes. This phenomenon leads to periodic destruction of red cells every 48 or 72 hours, depending on the asexual cycle of the species, and to the development of anemia if the malaria persists. Splenomegaly, caused by hyperplasia of the lymphoid-macrophage cells to free the blood plasma of cellular debris and pigment produced by the parasites, is a characteristic pathological feature of the infection. *Plasmodium falciparum*, the cause of malignant tertian malaria, changes the physical and chemical characteristics of the host cell after invasion, leading to rapid multiplication and spontaneous agglutination within the small capillaries, stasis of blood supply, and anoxia of surrounding tissues. If this occurs in the brain, coma and possible death result; if intravascular stasis occurs in the viscera, a protean variety of symptoms and complications can occur. With this basic mechanism of intracellular parasitism involving components of the entire vascular