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Influence of the Environment on Asymptomatic Human Disease

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INFLUENCE OF THE ENVIRONMENT ON ASYMPTOMATIC HUMAN DISEASE

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THE CONCEPT of altering the incidence and the effect of a disease by a change in the *external* or *internal* environment of the patient is well established. The incidence of insect-borne disease (e.g., malaria, yellow fever) has been reduced by the elimination of the mosquito vector, a change of the *external* environment. The survival of patients with pneumonia has been increased markedly by the use of antibiotics (a change of the *internal* environment). A relatively recent medical concept is the unmasking of a disease heretofore asymptomatic or "occult," as a result of a change in the environment. The disease may be either inherited or acquired, but in both cases, the patient and the physician are unaware of an underlying abnormality until a specific environmental change produces overt symptoms.

INFLUENCE OF ENVIRONMENT ON INHERITED ABNORMALITIES

The inheritance of man is determined by the information that is carried on forty-six chromosomes located in the nucleus of each cell. Each chromosome consists of thousands of genes that have been intermixed during the evolution of man through a variety of mechanisms: (a) mutation of a gene, which is a change in a specific inherited character; (b) recombination of chromosomes in which separate chromosome strands are exchanged; and (c) random distribution of chromosomes in reproduction. The consequence of these alterations is a human that is biochemically unique, yet amazingly similar to other members of his species.

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The expression of each inherited characteristic is modified by other inherited characteristics and by the environment. For example, the inheritance of high intelligence is not expressed if the patient also inherits the gene for phenylketonuria, a disease that is characterized by mental deficiency. Therefore, abnormalities in the inherited constitution of an individual have a great variability in the degree of expression:[1]

(a) *Asymptomatic and without consequences.* These inherited abnormalities are without known human disease and are laboratory curiosities (e.g., the inability to taste thiourea compounds, hereditary webbing of toes).

(b) *Symptomatic to a moderate or lethal degree.* Such inherited abnormalities are overtly symptomatic during the life span of the patient. The inherited disease may be expressed at infancy (e.g., phenylketonuria, mongolism), or as an adult (e.g., gout, diabetes mellitus).

(c) *Asymptomatic except for environmental alterations.* Changes in the internal or external environment result in the overt expression of a previously asymptomatic inherited disease, occasionally resulting in death. This category represents the largest and, unfortunately, the most poorly understood group.

ALTERATION OF INTERNAL ENVIRONMENT

The term "pharmacogenetics" was introduced by Vogel in 1959[2] to indicate a study of genetically determined variance which is revealed by an altered response to specific drugs. A classical example of pharmacogenetics is the severe hemolytic anemia induced in certain patients by drugs. Destruction of red blood cells, hemolytic anemia, by drugs is a well-known clinical event that has been observed by physicians for centuries. Since drugs are used in patients suffering from disease, some of which can cause anemia, the importance of the drug, as a cause of anemia, was not appreciated until the 1940's. During World War II, a large program for the testing of antimalarial drugs in human volunteers was launched. These volunteers were without

[1] STANBURY, WYNGAARDEN & FREDRICKSON, THE METABOLIC BASIS OF INHERITED DISEASE 3 (2d ed. 1966).

[2] Vogel, *Moderne Probleme der Humangenetik*, 12 ERGEBN. INN. MED. KINDERHEILK 52 (1959).

disease and it was noted that in some of the patients an acute hemolytic anemia occurred.[3] Subsequent studies of the biochemistry of the sensitive red blood cells have shown that the major abnormality is a deficiency of an enzyme in sugar metabolism called glucose 6 phosphate dehydrogenase (G6PD).[4] A deficiency of this enzyme results in a cell that can not maintain itself in an environment of certain drugs (antimalarials, sulfonamides, etc.). Certain agents such as aspirin can induce hemolysis of G6PD-deficient cells, but only in huge doses. The patient who is sensitive to this type of drug reaction has an entirely normal life expectancy unless exposed to an ordinarily harmless drug. The erythrocyte abnormality is asymptomatic or "occult," and is only expressed when the internal environment is altered.

A similar abnormality that has been reported recently is an inherited deficiency of pseudocholinesterase, an enzyme in the body that is important in nerve conduction.[5] In 1952, a drug, Suxamethonium, was introduced as a rapid acting, short duration muscle relaxant to be used during surgery. Several patients exhibited a marked sensitivity to the drug. Normally, the drug causes muscle relaxation of two to three minutes; in a few patients, a marked sensitivity to the drug was found with extreme muscle relaxation and associated lack of respiration (apnea) for as long as three hours. This unusual reaction is the result of a deficiency of pseudocholinesterase, an inherited enzyme. A number of families with this abnormality have been studied and the patients are entirely healthy with a normal life expectancy unless exposed to an ordinarily harmless drug during the course of surgery.

Physicians always have recognized a rare, "idiosyncratic" reaction that can occur with drugs. An idiosyncratic reaction is an unusual reaction that is totally dissimilar to the expected pharmacologic reaction of the drug. A typical example of this type of reaction is illustrated by the drug Chloramphenicol (Chloromycetin^{R}). This drug is an effective antibiotic and has been used in millions of patients for infectious diseases. The pharmacologic property of the antibiotic is to kill bacteria by interference with the metabolism of the infecting organism.

[3] Dern, Weinstein, LeRoy, Talmage & Alving, *The Hemolytic Effect of Primaquine*, 43 J. LAB. CLIN. MED. 303 (1954).

[4] Beutler, *Glucose-6-Phosphate-Dehyrogenase Deficiency and Nonspherocytic Congenital Hemolytic Anemia*, 2 SEM. IN HEMAT. 91 (1965).

[5] Lehmann & Liddell, *Pseudocholinesterase Deficiency and Some Other Pharmacogenetic Disorders*, in THE METABOLIC BASIS OF INHERITED DISEASE 1356 (2d ed. 1966).

The normal cells of the body are influenced to a slight degree by the drug and a mild depression of the normal red cell and white cell count occurs.[6] Rarely, an idiosyncratic reaction occurs and all of the bone marrow cells of the patient are destroyed, a condition called aplastic anemia. This condition has a mortality of nearly one hundred per cent and Chloramphenicol is currently the major recognized cause of aplastic anemia in the United States. The occurrence of aplastic anemia in these patients is not related to the dosage of Chloromycetin or the condition of the patient at the time the drug is given. In addition, there is no way for the physician to identify the patient in whom this dread reaction will occur. The reaction has an estimated frequency of one in 10,000 patients; a frequency similar to the frequency of phenylketonuria, an inherited abnormality. The rarity of the idiosyncratic reaction suggests an inherited abnormality in the patient is made manifest by the drug.

With the discovery of new drugs for human disease, many pharmacogenetic abnormalities will be identified. The problem of causation of disease is difficult to evaluate when the reaction to the drug is a manifestation of a pre-existing inherited disease. Informed consent from patients for the use of all drugs that may cause idiosyncratic reactions would place an impossible burden on the physician and the patient, would seriously interfere with medical practice, and would not significantly reduce the frequency of this type of reaction.

ALTERATION OF EXTERNAL ENVIRONMENT

The role of the external environment in manifesting an inherited disease is graphically illustrated by the role of trauma in the patient with hemophilia, an inherited disease that causes bleeding. The role of the environment in this abnormality was recognized as long ago as the sixth century A.D. when it was stated in the Tract Yebamoth of the Babylonian Talmud that all boys whose brothers had bled following circumcision were exempted from this rite. Today, the inherited pattern of this disease is well established. An abnormal gene is carried on the sex chromosome and is transferred from the asymptomatic, carrier mother to fifty per cent of her sons. The affected male can

[6] Ward, *The Effect of Chloramphenicol on RNA and Hemesynthesis in Bone Marrow Cultures*, 68 J. LAB. CLIN. MED. 400 (1966).

expect a long-term survival unless the external environment (i.e., trauma) supervenes.

Another interesting example of the influence of the external environment on an inherited disease is illustrated by patients with an abnormal hemoglobin, the protein in red cells that carries oxygen. The structure of hemoglobin is inherited and the majority of the white race carries the same form of hemoglobin, called hemoglobin A. In certain areas of Africa, a different form of hemoglobin called hemoglobin S (sickle hemoglobin) is carried in the population. This type of hemoglobin probably has survived the influence of natural selection because a red cell with hemoglobin S is more resistant to infestation with malaria, an obvious survival advantage in Africa. A patient with one hundred per cent hemoglobin S, a homozygous S inheritance, has a shortened natural survival because of the propensity of red cells with this type of hemoglobin to spontaneously adopt a "sickle" shape instead of the normal round form. The sickled red cells aggregate in small clots, blocking circulation to vital organs, and, eventually, causing death. Individuals with the heterozygote or carrier form of sickle cell disease have fifty per cent S hemoglobin and fifty per cent A hemoglobin. The amount of normal A hemoglobin is sufficient to prevent spontaneous sickling and a normal life survival is expected. In World War II, many Negro troops transported in non-pressurized airplanes had the sudden onset of severe, diffuse pain, anemia, and occasionally, death. An intensive study of this problem showed that these soldiers had heterozygote sickle cell disease, the asymptomatic trait. Further investigation established that low oxygen tension (e.g., high altitude) causes red cells with fifty per cent S hemoglobin to "sickle." The asymptomatic, occult inherited disease becomes symptomatic and a threat to life by a change in the external environment. The following case is an example of this problem:

A 34-year-old Negro was admitted to Colorado General Hospital for a two-hour history of severe, left upper abdominal pain and shortness of breath that occurred at the top of Pikes Peak, an altitude of approximately 14,000 feet. The patient had been in excellent health all of his life and had gained national fame as a high school athlete, an All-American football player, a national record holder in track and field events, and a professional football player. He was currently employed by a major corporation as a sales representative and was in Colorado for a sales meeting at the time of his trip to Pikes Peak. On admission, the physical examination was remarkable for severe, left upper abdominal pain and splinting of the left chest with respirations. Laboratory evaluation showed a mild anemia with obvious sickle-cell heterozygote state. Subsequent studies demonstrated that this

patient had suffered an infarction or a blood clot in the spleen and had a mild left lower lung pneumonia because of his inability to take a deep breath due to severe splenic pain. The patient improved during the following seven days and was discharged from the hospital without further therapy. He was advised to avoid environments with a low oxygen tension because of the sickle cell trait.

The influence of the environment on asymptomatic inherited mental diseases is speculative at this time. A possible link between an abnormal chromosome number and criminal behavior was suggested in 1965 when an XYY chromosome complement was detected in nearly four per cent of the inmates at a maximum security prison in Scotland. Several recent chromosome surveys of newborns indicate that the XYY karotype may occur in as many as one in three hundred males. If this high frequency is confirmed by additional studies, the role of the environment in the cause of criminal behavior and the role of a protective environment as a therapy for the genetically-fated criminal must be re-evaluated by society.

INFLUENCE OF ENVIRONMENT ON ACQUIRED DISEASE

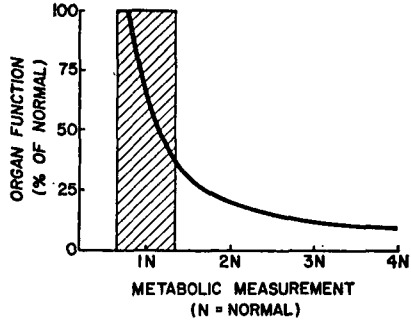
The natural history of acquired disease has a predictable pattern. All of us have observed the syndrome of the "flu" with a short, asymptomatic incubation period of three to seven days; initial, sharply demarcated symptoms of fever, chills and stuffy nose; a symptomatic duration of three days; and complete recovery. The majority of human disease follows this simple pattern but with a greatly expanded scale. The asymptomatic or incubation period may be measured in decades instead of days and resembles the hidden portion of an iceberg. Recent evidence suggests that even leukemia[7] and cancer[8] may have a long asymptomatic period. The ability of the physician to diagnose a disease during the incubation period is poor primarily because of the limitations of current diagnostic methodology and the functional reserve capacity of all organs of the body.

Methods of diagnosis in human disease have advanced rapidly in the past fifty years. Although the physician is still highly dependent upon a history and a physical examination of the patient, a large armamentarium of blood, urine, X-ray and radioisotope methodology

[7] Ward & Block, *Myeloid Metaplasia—A Reevaluation* [to be published in SYMPOSIUM ON MYELOPROLIFERATIVE DISORDERS OF ANIMALS AND MAN (Battelle Memorial Institute)].

[8] Garland, Coulson & Wollin, *The Rate of Growth and Apparent Duration of Untreated Primary Bronchial Carcinoma*, 16 CANCER 694 (1963).

is available. The value of a routine yearly physical examination is based on the ability of medical science to diagnose disease in the asymptomatic period. Advances have been made, but a normal physical examination and laboratory evaluation does not exclude significant disease. Unfortunately, a patient may have a heart attack within minutes or days of a normal electrocardiogram. This does not indicate failure of the electrocardiogram, but only demonstrates that the electrical impulses recorded by the electrocardiogram are normal until the death of heart muscle. The process that causes the death of heart muscle is atherosclerosis (hardening of the arteries), a process that takes decades. The electrocardiogram is unable to detect the progression of atherosclerosis and only detects the end result, a myocardial infarction. A similar limitation in diagnostic methodology is demonstrated by reliance on the chest X-ray to exclude lung disease. An abnormality in the chest must reach a significant size before it can be separated from the mottled background of the normal lung. Studies in several medical centers have shown that cancer of the lung may exist for as long as twelve years before the diagnosis can be established in the chest X-ray.[9]



The relationship between the total function of an organ and the measurement of a common metabolic product of the organ. For example, kidney function and level of urea in the blood; liver function and level of bilirubin in the blood.

The functional reserve capacity of an organ is a fundamental, biological feature of all organs of the body. The relationship is hyperbolic. An analysis of the properties of a hyperbolic function shows that organ function can be reduced to greater than fifty per cent of normal before standard methods of measurement detect a significant abnormality. This has obvious importance in survival; an individual can lose one kidney (reduction of 50% of kidney organ

[9] *Supra* note 8.

function) and have a normal urea (a metabolic measurement of the kidney). This biological law forms the basis for renal transplantation. The donor, who is left with one kidney, and the recipient, who receives one kidney, are entirely normal without symptoms of uremia.

The same hyperbolic relationship is found with the heart, lung, or liver. A serious degree of impairment, as much as seventy per cent in some organs, can exist without symptoms in the patient and without routine laboratory measurements indicating a disease. When the functional reserve of an organ has reached a critical level, minor changes in the internal or external environment that would be insignificant to a normal organ may result in overt clinical manifestations of the occult disease.

ALTERATION OF INTERNAL ENVIRONMENT

A change in the internal environment in a patient with asymptomatic acquired disease may lead to explosive and sometimes fatal reactions. The reactions can be divided into two major categories: (1) increased sensitivity of a deceased target organ to drugs, and (2) failure of normal breakdown or excretion of drugs due to disease in a nontarget organ.

A diseased organ frequently has an increased sensitivity to the action of a drug. The increased activity may represent increased entry of the drug into the diseased cell or accentuation of the action of the drug on a biochemical process within the diseased cell. The heightened effect of the drug occurs at a dosage level that is easily and safely tolerated by a normal cell or organ. A common example of this problem is illustrated by the drug digitalis. This drug has been used for over one hundred fifty years in the treatment of congestive heart failure and remains today the most effective method of therapy for this common disease. A standard dosage of therapy has been determined in medical practice that provides a wide safety margin, the difference between a toxic level and a therapeutic level. Patients with certain forms of heart disease (e.g., primary myocardiopathy, cor pulmonale) are exquisitely sensitive to the effects of this drug and the usual drug dosage may cause a toxic level and result in death.

The majority of drugs used in medical practice are metabolized or excreted by the liver or kidney. These drugs may be used for a

target organ elsewhere in the body, but because the level of the drug depends upon its metabolism within the body, a toxic level of the drug results from disease in the nontarget organ. The antibiotics streptomycin, kanamycin and polymyxin are excreted by the kidneys and in normal patients these antibiotics are virtually nondetectable in the blood four hours after injection. When the kidney is diseased, the excretion of these drugs is impaired and a significant level of streptomycin may be measured in the blood twenty-five to thirty hours after injection.[10] The elevated level of streptomycin is toxic and side effects such as ototoxicity (deafness) can occur. Unless the physician is aware of significant renal disease, a standard therapeutic dose level in this type of patient is a toxic level.

A similar problem is encountered when using a drug that is metabolized by the liver in a patient with asymptomatic occult liver disease. The liver is the major site of metabolism of several of the barbiturates. A diseased liver, but a liver not producing symptoms, is unable to excrete barbiturates and a high level is produced by an innocuous dosage. A barbiturate sleeping pill given to a patient with liver disease may result in a state of unconsciousness for several days and cause death.

A recent group of drug problems has been described that represents cross interference between two drugs. This problem has been recognized previously but an explanation has not been apparent. Recently, a large number of drugs have been found to stimulate their own metabolism or the metabolism of other compounds. The stimulation of metabolism represents an increase of specific enzymes in the cell induced by the drug. This phenomenon is referred to as "enzyme induction"[11] and will be an important medical field of the future. An example of enzyme induction in man is the observation that barbiturates accelerate the metabolism of dicoumarin anticoagulants. A patient receiving dicoumeral has a decreased level of anticoagulant activity when barbiturates are given. This effect requires that the dosage of dicoumeral be increased to achieve an adequate level of anticoagulation. Serious toxicity results if the enzyme stimulator (e.g., phenobarbital) is withdrawn and the anticoagulant is continued at the same dose that was used when phenobarbital was being given.

[10] Weinstein & Dalton, *Host Determinants of Response to Antimicrobial Agents*, 279 N. ENG. J. MED. 580 (1968).

[11] Conney, *Pharmacological Implications of Microsomal Enzyme Induction*, 19 PHARM. REV. 317 (1967).

ALTERATION OF EXTERNAL ENVIRONMENT

An occult, acquired disease is frequently manifested by a change in the *external* environment. A common problem in medical practice is the discovery of cancer in a bone at the time of accidental fracture of the bone. A primary or metastatic tumor of the bone can reach an enormous size before the weakened framework spontaneously breaks. However, trauma may fracture the bone at the tumor site before the disease is apparent and problems of legal responsibility for the fracture, and, occasionally, questions of causation of a cancer by the trauma are raised. Single, isolated trauma is never a cause of cancer, but repeated trauma to the same area can be a cause of cancer. A nevus, the common pigmented mole, may become malignant (malignant melanoma) by repeated injury to the surface of the mole. For this reason, all moles located over pressure areas of the body should be removed. Repeated and intense exposure to sunlight, a type of trauma, is a cause of skin cancer. It is rare to see a basal cell carcinoma of the skin in any area of the body that is covered commonly from the sun.

A common medico-legal problem is the effect of *external* environmental change on the cardiovascular system. The relation of such factors as occupational stress, or emotional alteration to the occurrence of a myocardial infarction (heart attack) is unclear. Evidence supporting a causal relationship is confused by the multiple factors of racial incidence, inherited familial predisposition, dietary and exercise habits, and coexisting disease. In addition, the concept of prolonged asymptomatic disease is illustrated strikingly in the majority of these patients: postmortem studies invariably show a severe degree of atherosclerosis in multiple arteries of the body, indicative of a generalized disease of long duration.

SUMMARY

A change in the *internal* or *external* environment of the patient may cause a heretofore unrecognized asymptomatic disease to become overt and symptomatic. The disease may be inherited or acquired but in both cases the physician and patient are unaware of its presence until an environmental change occurs.

Limitations imposed on medical science by the sensitivity of current

diagnostic methodology and the biological law of organ reserve capacity make it difficult to diagnose disease in the asymptomatic stage. The medico-legal assumption that an alteration of environment, such as drugs or trauma, has a simple causal relation to the resultant reaction should be re-evaluated when the reaction represents an unmasking of a hidden disease and is dependent upon the presence of the asymptomatic disease.