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SPECIAL ARTICLE

THE NATURE OF SUFFERING AND THE GOALS OF MEDICINE

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Abstract The question of suffering and its relation to organic illness has rarely been addressed in the medical literature. This article offers a description of the nature and causes of suffering in patients undergoing medical treatment. A distinction based on clinical observations is made between suffering and physical distress. Suffering is experienced by persons, not merely by bodies, and has its source in challenges that threaten the intactness of the person as a complex social and psychological entity. Suffering can include physical pain but is by no means limited to it. The relief of suffering and the cure of disease must be seen as twin obligations of a medical profession that is truly dedicated to the care of the sick. Physicians' failure to understand the nature of suffering can result in medical intervention that (though technically adequate) not only fails to relieve suffering but becomes a source of suffering itself. (N Engl J Med. 1982; 306:639-45.)

THE obligation of physicians to relieve human suffering stretches back into antiquity. Despite this fact, little attention is explicitly given to the problem of suffering in medical education, research, or practice. I will begin by focusing on a modern paradox: Even in the best settings and with the best physicians, it is not uncommon for suffering to occur not only during the course of a disease but also as a result of its treatment. To understand this paradox and its resolution requires an understanding of what suffering is and how it relates to medical care.

Consider this case: A 35-year-old sculptor with metastatic disease of the breast was treated by competent physicians employing advanced knowledge and technology and acting out of kindness and true concern. At every stage, the treatment as well as the disease was a source of suffering to her. She was uncertain and frightened about her future, but she could get little information from her physicians, and what she was told was not always the truth. She had been unaware, for example, that the irradiated breast would be so disfigured. After an oophorectomy and a regimen of medications, she became hirsute, obese, and devoid of libido. With tumor in the supraclavicular fossa, she lost strength in the hand that she had used in sculpturing, and she became profoundly depressed. She had a pathologic fracture of the femur, and treatment was delayed while her physicians openly disagreed about pinning her hip.

Each time her disease responded to therapy and her hope was rekindled, a new manifestation would appear. Thus, when a new course of chemotherapy was started, she was torn between a desire to live and the fear that allowing hope to emerge again would merely expose her to misery if the treatment failed. The nausea and vomiting from the chemotherapy were distressing, but no more so than the anticipation of hair loss. She feared the future. Each tomorrow was seen as heralding increased sickness, pain, or disability, never as the beginning of better times. She felt isolated because she was no longer like other people and could not do what other people did. She feared that her friends would stop visiting her. She was sure that she would die.

This young woman had severe pain and other physical symptoms that caused her suffering. But she also suffered from some threats that were social and from others that were personal and private. She suffered from the effects of the disease and its treatment on her appearance and abilities. She also suffered unremittingly from her perception of the future.

What can this case tell us about the ends of medicine and the relief of suffering? Three facts stand out: The first is that this woman's suffering was not confined to her physical symptoms. The second is that she suffered not only from her disease but also from its treatment. The third is that one could not anticipate what she would describe as a source of suffering; like

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other patients, she had to be asked. Some features of her condition she would call painful, upsetting, uncomfortable, and distressing, but not a source of suffering. In these characteristics her case was ordinary.

In discussing the matter of suffering with lay persons, I learned that they were shocked to discover that the problem of suffering was not directly addressed in medical education. My colleagues of a contemplative nature were surprised at how little they knew of the problem and how little thought they had given it, whereas medical students tended to be unsure of the relevance of the issue to their work.

The relief of suffering, it would appear, is considered one of the primary ends of medicine by patients and lay persons, but not by the medical profession. As in the care of the dying, patients and their friends and families do not make a distinction between physical and nonphysical sources of suffering in the same way that doctors do.[1]

A search of the medical and social-science literature did not help me in understanding what suffering is; the word "suffering" was most often coupled with the word "pain," as in "pain and suffering." (The data bases used were *Psychological Abstracts,* the *Citation Index,* and the *Index Medicus.)*

This phenomenon reflects a historically constrained and currently inadequate view of the ends of medicine. Medicine's traditional concern primarily for the body and for physical disease is well known, as are the widespread effects of the mind–body dichotomy on medical theory and practice. I believe that this dichotomy itself is a source of the paradoxical situation in which doctors cause suffering in their care of the sick. Today, as ideas about the separation of mind and body are called into question, physicians are concerning themselves with new aspects of the human condition. The profession of medicine is being pushed and pulled into new areas, both by its technology and by the demands of its patients. Attempting to understand what suffering is and how physicians might truly be devoted to its relief will require that medicine and its critics overcome the dichotomy between mind and body and the associated dichotomies between subjective and objective and between person and object.

In the remainder of this paper I am going to make three points. The first is that suffering is experienced by persons. In the separation between mind and body, the concept of the person, or personhood, has been associated with that of mind, spirit, and the subjective. However, as I will show, a person is not merely mind, merely spiritual, or only subjectively knowable. Personhood has many facets, and it is ignorance of them that actively contributes to patients' suffering. The understanding of the place of the person in human illness requires a rejection of the historical dualism of mind and body.

The second point derives from my interpretation of clinical observations: Suffering occurs when an impending destruction of the person is perceived; it continues until the threat of disintegration has passed or until the integrity of the person can be restored in some other manner. It follows, then, that although suffering often occurs in the presence of acute pain, shortness of breath, or other bodily symptoms, suffering extends beyond the physical. Most generally, suffering can be defined as the state of severe distress associated with events that threaten the intactness of the person.

The third point is that suffering can occur in relation to any aspect of the person, whether it is in the realm of social roles, group identification, the relation with self, body, or family, or the relation with a transpersonal, transcendent source of meaning. Below is a simplified description or "topology" of the constituents of personhood.

"Person" Is Not "Mind"

The split between mind and body that has so deeply influenced our approach to medical care was proposed by Descartes to resolve certain philosophical issues. Moreover, Cartesian dualism made it possible for science to escape the control of the church by assigning the noncorporeal, spiritual realm to the church, leaving the physical world as the domain of science. In that religious age, "person," synonymous with "mind," was necessarily off limits to science.

Changes in the meaning of concepts like that of personhood occur with changes in society, while the word for the concept remains the same. This fact tends to obscure the depth of the transformations that have occurred between the 17th century and today. People simply *are* "persons" in this time, as in past times, and they have difficulty imagining that the term described something quite different in an earlier period when the concept was more constrained.

If the mind–body dichotomy results in assigning the body to medicine, and the person is not in that category, then the only remaining place for the person is in the category of mind. Where the mind is problematic (not identifiable in objective terms), its very reality diminishes for science, and so, too, does that of the person. Therefore, so long as the mind–body dichotomy is accepted, suffering is either subjective and thus not truly "real" — not within medicine's domain — or identified exclusively with bodily pain. Not only is such an identification misleading and distorting, for it depersonalizes the sick patient, but it is itself a source of suffering. It is not possible to treat sickness as something that happens solely to the body without thereby risking damage to the person. An anachronistic division of the human condition into what is medical (having to do with the body) and what is nonmedical (the remainder) has given medicine too narrow a notion of its calling. Because of this division, physicians may, in concentrating on the cure of bodily disease, do things that cause the patient as a person to suffer.

An Impending Destruction of Person

Suffering is ultimately a personal matter. Patients sometimes report suffering when one does not expect it, or do not report suffering when one does expect it.

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Furthermore, a person can suffer enormously at the distress of another, especially a loved one.

In some theologies, suffering has been seen as bringing one closer to God. This "function" of suffering is at once its glorification and its relief. If, through great pain or deprivation, someone is brought closer to a cherished goal, that person may have no sense of having suffered but may instead feel enormous triumph. To an observer, however, only the deprivation may be apparent. This cautionary note is important because people are often said to have suffered greatly, in a religious context, when they are known only to have been injured, tortured, or in pain, not to have suffered.

Although pain and suffering are closely identified in the medical literature, they are phenomenologically distinct.[2] The difficulty of understanding pain and the problems of physicians in providing adequate relief of physical pain are well known.[3-5]

The greater the pain, the more it is believed to cause suffering. However, some pain, like that of childbirth, can be extremely severe and yet considered rewarding. The perceived meaning of pain influences the amount of medication that will be required to control it. For example, a patient reported that when she believed the pain in her leg was sciatica, she could control it with small doses of codeine, but when she discovered that it was due to the spread of malignant disease, much greater amounts of medication were required for relief. Patients can writhe in pain from kidney stones and by their own admission not be suffering, because they "know what it is"; they may also report considerable suffering from apparently minor discomfort when they do not know its source. Suffering in close relation to the intensity of pain is reported when the pain is virtually overwhelming, such as that associated with a dissecting aortic aneurysm. Suffering is also reported when the patient does not believe that the pain can be controlled. The suffering of patients with terminal cancer can often be relieved by demonstrating that their pain truly can be controlled; they will then often tolerate the same pain without any medication, preferring the pain to the side effects of their analgesics. Another type of pain that can be a source of suffering is pain that is not overwhelming but continues for a very long time.

In summary, people in pain frequently report suffering from the pain when they feel out of control, when the pain is overwhelming, when the source of the pain is unknown, when the meaning of the pain is dire, or when the pain is chronic.

In all these situations, persons perceive pain as a threat to their continued existence — not merely to their lives, but to their integrity as persons. That this is the relation of pain to suffering is strongly suggested by the fact that suffering can be relieved, in the presence of continued pain, by making the source of the pain known, changing its meaning, and demonstrating that it can be controlled and that an end is in sight.

It follows, then, that suffering has a temporal element. In order for a situation to be a source of suffering, it must influence the person's perception of future events. ("If the pain continues like this, I *will be* overwhelmed"; "If the pain comes from cancer, I *will* die"; "If the pain cannot be controlled, I *will not* be able to take it.") At the moment when the patient is saying, "If the pain continues like this, I will be overwhelmed," he or she is not overwhelmed. Fear itself always involves the future. In the case with which I opened this paper, the patient could not give up her fears of her sense of future, despite the agony they caused her. As suffering is discussed in the other dimensions of personhood, note how it would not exist if the future were not a major concern.

Two other aspects of the relation between pain and suffering should be mentioned. Suffering can occur when physicians do not validate the patient's pain. In the absence of disease, physicians may suggest that the pain is "psychological" (in the sense of not being real) or that the patient is "faking." Similarly, patients with chronic pain may believe after a time that they can no longer talk to others about their distress. In the former case the person is caused to distrust his or her perceptions of reality, and in both instances social isolation adds to the person's suffering.

Another aspect essential to an understanding of the suffering of sick persons is the relation of meaning to the way in which illness is experienced. The word "meaning" is used here in two senses. In the first, to mean is to signify, to imply. Pain in the chest may imply heart disease. We also say that we know what something means when we know how important it is. The importance of things is always personal and individual, even though meaning in this sense may be shared by others or by society as a whole. What something signifies and how important it is relative to the whole array of a person's concerns contribute to its personal meaning. "Belief" is another word for that aspect of meaning concerned with implications, and "value" concerns the degree of importance to a particular person.

The personal meaning of things does not consist exclusively of values and beliefs that are held intellectually; it includes other dimensions. For the same word, a person may simultaneously have a cognitive meaning, an affective or emotional meaning, a bodily meaning, and a transcendent or spiritual meaning. And there may be contradictions in the different levels of meaning. The nuances of personal meaning are complex, and when I speak of personal meanings I am implying this complexity in all its depth — known and unknown. Personal meaning is a fundamental dimension of personhood, and there can be no understanding of human illness or suffering without taking it into account.

A Simplified Description of the Person

A simple topology of a person may be useful in understanding the relation between suffering and the goals of medicine. The features discussed below point

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the way to further study and to the possibility of specific action by individual physicians.

Persons have personality and character. Personality traits appear within the first few weeks of life and are remarkably durable over time. Some personalities handle some illnesses better than others. Individual persons vary in character as well. During the heyday of psychoanalysis in the 1950s, all behavior was attributed to unconscious determinants: No one was bad or good; they were merely sick or well. Fortunately, that simplistic view of human character is now out of favor. Some people do in fact have stronger characters and bear adversity better. Some are good and kind under the stress of terminal illness, whereas others become mean and offensive when even mildly ill.

A person has a past. The experiences gathered during one's life are a part of today as well as yesterday. Memory exists in the nostrils and the hands, not only in the mind. A fragrance drifts by, and a memory is evoked. My feet have not forgotten how to roller-skate, and my hands remember skills that I was hardly aware I had learned. When these past experiences involve sickness and medical care, they can influence present illness and medical care. They stimulate fear, confidence, physical symptoms, and anguish. It damages people to rob them of their past and deny their memories, or to mock their fears and worries. A person without a past is incomplete.

Life experiences — previous illness, experiences with doctors, hospitals, and medications, deformities and disabilities, pleasures and successes, miseries and failures — all form the nexus for illness. The personal meaning of the disease and its treatment arises from the past as well as the present. If cancer occurs in a patient with self-confidence from past achievements, it may give rise to optimism and a resurgence of strength. Even if it is fatal, the disease may not produce the destruction of the person but, rather, reaffirm his or her indomitability. The outcome would be different in a person for whom life had been a series of failures.

The intensity of ties to the family cannot be overemphasized; people frequently behave as though they were physical extensions of their parents. Events that might cause suffering in others may be borne without complaint by someone who believes that the disease is part of his or her family identity and hence inevitable. Even diseases for which no heritable basis is known may be borne easily by a person because others in the family have been similarly afflicted. Just as the person's past experiences give meaning to present events, so do the past experiences of his or her family. Those meanings are part of the person.

A person has a cultural background. Just as a person is part of a culture and a society, these elements are part of the person. Culture defines what is meant by masculinity or femininity, what attire is acceptable, attitudes toward the dying and sick, mating behavior, the height of chairs and steps, degrees of tolerance for odors and excreta, and how the aged and the disabled are treated. Cultural definitions have an enormous impact on the sick and can be a source of untold suffering. They influence the behavior of others toward the sick person and that of the sick toward themselves. Cultural norms and social rules regulate whether someone can be among others or will be isolated, whether the sick will be considered foul or acceptable, and whether they are to be pitied or censured.

Returning to the sculptor described earlier, we know why that young woman suffered. She was housebound and bedbound, her face was changed by steroids, she was masculinized by her treatment, one breast was scarred, and she had almost no hair. The degree of importance attached to these losses — that aspect of their personal meaning — is determined to a great degree by cultural priorities.

With this in mind, we can also realize how much someone devoid of physical pain, even devoid of "symptoms," may suffer. People suffer from what they have lost of themselves in relation to the world of objects, events, and relationships. We realize, too, that although medical care can reduce the impact of sickness, inattentive care can increase the disruption caused by illness.

A person has roles. I am a husband, a father, a physician, a teacher, a brother, an orphaned son, and an uncle. People are their roles, and each role has rules. Together, the rules that guide the performance of roles make up a complex set of entitlements and limitations of responsibility and privilege. By middle age, the roles may be so firmly set that disease can lead to the virtual destruction of a person by making the performance of his or her roles impossible. Whether the patient is a doctor who cannot doctor or a mother who cannot mother, he or she is diminished by the loss of function.

No person exists without others; there is no consciousness without a consciousness of others, no speaker without a hearer, and no act, object, or thought that does not somehow encompass others.[6] All behavior is or will be involved with others, even if only in memory or reverie. Take away others, remove sight or hearing, and the person is diminished. Everyone dreads becoming blind or deaf, but these are only the most obvious injuries to human interaction. There are many ways in which human beings can be cut off from others and then suffer the loss.

It is in relationships with others that the full range of human emotions finds expression. It is this dimension of the person that may be injured when illness disrupts the ability to express emotion. Furthermore, the extent and nature of a sick person's relationships influence the degree of suffering from a disease. There is a vast difference between going home to an empty apartment and going home to a network of friends and family after hospitalization. Illness may occur in one partner of a long and strongly bound marriage or in a union that is falling apart. Suffering from the loss of

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sexual function associated with some diseases will depend not only on the importance of sexual performance itself but also on its importance in the sick person's relationships.

A person is a political being. A person is in this sense equal to other persons, with rights and obligations and the ability to redress injury by others and the state. Sickness can interfere, producing the feeling of political powerlessness and lack of representation. Persons who are permanently handicapped may suffer from a feeling of exclusion from participation in the political realm.

Persons do things. They act, create, make, take apart, put together, wind, unwind, cause to be, and cause to vanish. They know themselves, and are known, by these acts. When illness restricts the range of activity of persons, they are not themselves.

Persons are often unaware of much that happens within them and why. Thus, there are things in the mind that cannot be brought to awareness by ordinary reflection. The structure of the unconscious is pictured quite differently by different scholars, but most students of human behavior accept the assertion that such an interior world exists. People can behave in ways that seem inexplicable and strange even to themselves, and the sense of powerlessness that the person may feel in the presence of such behavior can be a source of great distress.

Persons have regular behaviors. In health, we take for granted the details of our day-to-day behavior. Persons know themselves to be well as much by whether they behave as usual as by any other set of facts. Patients decide that they are ill because they cannot perform as usual, and they may suffer the loss of their routine. If they cannot do the things that they identify with the fact of their being, they are not whole.

Every person has a body. The relation with one's body may vary from identification with it to admiration, loathing, or constant fear. The body may even be perceived as a representation of a parent, so that when something happens to the person's body it is as though a parent were injured. Disease can so alter the relation that the body is no longer seen as a friend but, rather, as an untrustworthy enemy. This is intensified if the illness comes on without warning, and as illness persists, the person may feel increasingly vulnerable. Just as many people have an expanded sense of self as a result of changes in their bodies from exercise, the potential exists for a contraction of this sense through injury to the body.

Everyone has a secret life. Sometimes it takes the form of fantasies and dreams of glory; sometimes it has a real existence known to only a few. Within the secret life are fears, desires, love affairs of the past and present, hopes, and fantasies. Disease may destroy not only the public or the private person but the secret person as well. A secret beloved friend may be lost to a sick person because he or she has no legitimate place by the sickbed. When that happens, the patient may have lost the part of life that made tolerable an otherwise embittered existence. Or the loss may be only of a dream, but one that might have come true. Such loss can be a source of great distress and intensely private pain.

Everyone has a perceived future. Events that one expects to come to pass vary from expectations for one's children to a belief in one's creative ability. Intense unhappiness results from a loss of the future — the future of the individual person, of children, and of other loved ones. Hope dwells in this dimension of existence, and great suffering attends the loss of hope.

Everyone has a transcendent dimension, a life of the spirit. This is most directly expressed in religion and the mystic traditions, but the frequency with which people have intense feelings of bonding with groups, ideals, or anything larger and more enduring than the person is evidence of the universality of the transcendent dimension. The quality of being greater and more lasting than an individual life gives this aspect of the person its timeless dimension. The profession of medicine appears to ignore the human spirit. When I see patients in nursing homes who have become only bodies, I wonder whether it is not their transcendent dimension that they have lost.

The Nature of Suffering

For purposes of explanation, I have outlined various parts that make up a person. However, persons cannot be reduced to their parts in order to be better understood. Reductionist scientific methods, so successful in human biology, do not help us to comprehend whole persons. My intent was rather to suggest the complexity of the person and the potential for injury and suffering that exists in everyone. With this in mind, any suggestion of mechanical simplicity should disappear from my definition of suffering. All the aspects of personhood — the lived past, the family's lived past, culture and society, roles, the instrumental dimension, associations and relationships, the body, the unconscious mind, the political being, the secret life, the perceived future, and the transcendent dimension — are susceptible to damage and loss.

Injuries to the integrity of the person may be expressed by sadness, anger, loneliness, depression, grief, unhappiness, melancholy, rage, withdrawal, or yearning. We acknowledge the person's right to have and express such feelings. But we often forget that the affect is merely the outward expression of the injury, not the injury itself. We know little about the nature of the injuries themselves, and what we know has been learned largely from literature, not medicine.

If the injury is sufficient, the person suffers. The only way to learn what damage is sufficient to cause suffering, or whether suffering is present, is to ask the sufferer. We all recognize certain injuries that almost invariably cause suffering: the death or distress of loved ones, powerlessness, helplessness, hopelessness, torture, the loss of a life's work, betrayal, physical agony, isolation, homelessness, memory failure, and

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fear. Each is both universal and individual. Each touches features common to all of us, yet each contains features that must be defined in terms of a specific person at a specific time. With the relief of suffering in mind, however, we should reflect on how remarkably little is known of these injuries.

The Amelioration of Suffering

One might inquire why everyone is not suffering all the time. In a busy life, almost no day passes in which one's intactness goes unchallenged. Obviously, not every challenge is a threat. Yet I suspect that there is more suffering than is known. Just as people with chronic pain learn to keep it to themselves because others lose interest, so may those with chronic suffering.

There is another reason why every injury may not cause suffering. Persons are able to enlarge themselves in response to damage, so that instead of being reduced, they may indeed grow. This response to suffering has encouraged the belief that suffering is good for people. To some degree, and in some persons, this may be so. If a leg is injured so that an athlete cannot run again, the athlete may compensate for the loss by learning another sport or mode of expression. So it is with the loss of relationships, loves, roles, physical strength, dreams, and power. The human body may lack the capacity to gain a new part when one is lost, but the person has it.

The ability to recover from loss without succumbing to suffering is sometimes called resilience, as though nothing but elastic rebound were involved, but it is more as though an inner force were withdrawn from one manifestation of a person and redirected to another. If a child dies and the parent makes a successful recovery, the person is said to have "rebuilt" his or her life. The term suggests that the parts of the person are structured in a new manner, allowing expression in different dimensions. If a previously active person is confined to a wheelchair, intellectual pursuits may occupy more time.

Recovery from suffering often involves help, as though people who have lost parts of themselves can be sustained by the personhood of others until their own recovers. This is one of the latent functions of physicians: to lend strength. A group, too, may lend strength: Consider the success of groups of the similarly afflicted in easing the burden of illness (e.g., women with mastectomies, people with ostomies, and even the parents or family members of the diseased).

Meaning and transcendence offer two additional ways by which the suffering associated with destruction of a part of personhood is ameliorated. Assigning a meaning to the injurious condition often reduces or even resolves the suffering associated with it. Most often, a cause for the condition is sought within past behaviors or beliefs. Thus, the pain or threat that causes suffering is seen as not destroying a part of the person, because it is part of the person by virtue of its origin within the self. In our culture, taking the blame for harm that comes to oneself because of the unconscious mind serves the same purpose as the concept of karma in Eastern theologies; suffering is reduced when it can be located within a coherent set of meanings. Physicians are familiar with the question from the sick, "Did I do something that made this happen?" It is more tolerable for a terrible thing to happen because of something that one has done than it is to be at the mercy of chance.

Transcendence is probably the most powerful way in which one is restored to wholeness after an injury to personhood. When experienced, transcendence locates the person in a far larger landscape. The sufferer is not isolated by pain but is brought closer to a transpersonal source of meaning and to the human community that shares those meanings. Such an experience need not involve religion in any formal sense; however, in its transpersonal dimension, it is deeply spiritual. For example, patriotism can be a secular expression of transcendence.

When Suffering Continues

But what happens when suffering is not relieved? If suffering occurs when there is a threat to one's integrity or a loss of a part of a person, then suffering will continue if the person cannot be made whole again. Little is known about this aspect of suffering. Is much of what we call depression merely unrelieved suffering? Considering that depression commonly follows the loss of loved ones, business reversals, prolonged illness, profound injuries to self-esteem, and other damages to personhood, the possibility is real. In many chronic or serious diseases, persons who "recover" or who seem to be successfully treated do not return to normal function. They may never again be employed, recover sexual function, pursue career goals, reestablish family relationships, or reenter the social world, despite a physical cure. Such patients may not have recovered from the nonphysical changes occurring with serious illness. Consider the dimensions of personhood described above, and note that each is threatened or damaged in profound illness. It should come as no surprise, then, that chronic suffering frequently follows in the wake of disease.

The paradox with which this paper began — that suffering is often caused by the treatment of the sick — no longer seems so puzzling. How could it be otherwise, when medicine has concerned itself so little with the nature and causes of suffering? This lack is not a failure of good intentions. None are more concerned about pain or loss of function than physicians. Instead, it is a failure of knowledge and understanding. We lack knowledge, because in working from a dichotomy contrived within a historical context far from our own, we have artificially circumscribed our task in caring for the sick.

Attempts to understand all the known dimensions of personhood and their relations to illness and suffering present problems of staggering complexity. The problems are no greater, however, than those initially posed by the question of how the body works — a

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question that we have managed to answer in extraordinary detail. If the ends of medicine are to be directed toward the relief of human suffering, the need is clear.

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MEDICAL PROGRESS

APLASTIC ANEMIA

(First of Two Parts)

Pathogenesis, Diagnosis, Treatment, and Prognosis

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APLASTIC anemia was first described by Ehrlich in 1888. It is not a single disease but, rather, a group of disorders characterized by peripheral-blood pancytopenia, variable bone-marrow hypocellularity, and the absence of underlying malignant or myeloproliferative disease. "Aplastic pancytopenia" would be a more accurate name, but Chauffard's original term has persisted. This review summarizes current concepts of the pathogenesis, diagnosis, treatment, and prognosis of marrow aplasias. The interested reader is referred to several excellent monographs for further data and references.[1-5]

Normal Hematopoiesis

Normal hematopoiesis occurs within a specialized physical and functional microenvironment.[6] Thus, although fetal hematopoiesis originates in the yolk sac and liver, quantitatively important hematopoiesis is confined to the bone marrow after mid-gestation. Marrow-sinus endothelial cells are covered incompletely on their abluminal surface by adventitial reticular cells. Hematopoietic cells are supported in extravascular spaces by the reticular cells and reticular-cell-derived fibrils. Fibroblasts and fat cells (both of which are derived from reticular cells), lymphocytes, nerves, and endosteal surfaces complete the marrow microenvironment.

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Mature blood cells are derived from pluripotent precursors. Schofield suggests that these pluripotent stem cells self-replicate as long as they remain within their primary microenvironment.[7] After leaving this niche they gradually mature, becoming less capable of self-renewal. On encountering an appropriate secondary microenvironment, the stem cells become committed and develop along specific differentiation pathways.[8,9] In addition to cellular interactions, stem-cell self-replication, maturation, and differentiation are modulated by humoral factors.

Normally, hematopoiesis can be increased markedly in response to increased demands. This reserve capacity is usually more than adequate for a person's life span. Aplastic anemia occurs when hematopoiesis fails. Possible causes of this failure are listed in Table 1 and discussed below.

Pathogenesis

Animal Models of Aplastic Anemia

In the best-studied animal models of aplastic anemia, hematopoietic insufficiency may result from either stem-cell or microenvironmental injury. In mice treated with busulfan (5 to 20 mg per kilogram of body weight for four doses), marrow hypoplasia develops; the mice then apparently recover with minimal hematologic abnormalities in their peripheral blood.[10] However, residual quantitative and qualitative stem-cell defects are evidenced by the following factors: decreased numbers of pluripotent and granulocytic stem cells, poor growth of granulocytic stem cells, delayed repopulation of irradiated normal marrow by marrow from busulfan-treated animals, decreased numbers of pluripotent and granulocytic stem cells per spleen colony in irradiated normal mice given injections of busulfan-treated marrow, further de-

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