36 Coenzyme Q_{10} and Neoplasia: Overview of Experimental and Clinical Evidence

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Illness is nothing else than a break of body's harmony that has the endogenous tendency to reconstitute itself, an endeavor that the physician can only support by appropriate measures.

Hippocrates, 460–377 B.C.

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36.1 THE INTEGRATION OF CANCER, IMMUNE SYSTEM, AGING, AND COENZYME Q

36.1.1 The View from Afar

Over millions of years of evolution, organisms have developed immune systems. The human immune system has evolved from a primitive state to a highly sophisticated, very complex, efficient, interrelated host-defense system. Immunological thinking was and still is considerably influenced by the phenomenon of protective immunity to infections. This feature was already well known to the ancient Greeks and has been impressively described by Thucydides in his report on the casualties during the Peloponnesian war (431–406 B.C.).

The idea that the immune responses are the body's principal defense mechanisms has deeply influenced cancer research during the past decades. This idea, although suggested by Paul Ehrlich

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in 1909, remained dormant until it was reformulated and crystallized as a general theory of "immunologic surveillance" by Frank McFarlan Burnet in 1959. An extensive review of the earlier publications on this subject was compiled by Stutman in 1975 [1]. The main contention of immunologic surveillance is that the immune functions have evolved, in part, as a mechanism to prevent the emergence of cancer cells. Burnet [2] regarded neoplasia as "not self," and postulated that a major function of the immune system is to seek out and destroy new cancer cells as they arise. This revolutionary view of cancer as "nonself" gained wide acceptance, and substantial effort has gone into the development of practical applications. In a way, as suggested by Stutman [1], an established advanced tumor would represent an actual failure of the immune surveillance mechanism. Furthermore, individuals with immune disorders have an increased likelihood of being diagnosed with cancer, and those with congenital immunodeficiencies develop cancer at 200 times the expected prevalence [3].

The current definition of the immune system in general and immune surveillance in particular is, as expected, subject to persuasive genuine as well as fictitious criticism, based on biomedical, philosophical, and theological rationale, despite the vast practical accomplishments. A thought-provoking and an intriguing personal perception of several "classical" concepts ruling contemporary immunology is debated in a recently published review by Thiele [4], where the "accepted" definitions of self and nonself discrimination, immune surveillance, the network theory, and others are discussed and criticized. In an earlier review, Fuchs and Matzinger [5] proposed an alternative assessment of immune surveillance. According to a new concept, the immune system reacts to disruption of tissue integrity, allowing its renewal; thus the immune system protects the integrity of tissues [6].

The current doctrine governing the morphology and the function of the immune system is the subject of numerous comprehensive reviews. The immune system, through a complex interplay of highly specialized cell lines and seemingly endless number of newly defined soluble mediators, contends to ensure protection from the potentially harmful endogenous and exogenous insults that we encounter throughout our lifetimes. There are two major divisions of the immune system, namely the phylogenetically older innate and the acquired. The cellular components (macrophages, eosinophils, natural-killer lymphocytes) and the molecular components (complement, antibacterial peptides, diverse cytokines) of the innate immune system provide multiple signals for activation of the acquired immune system. The innate system has evolved to recognize common potentially pathogenic structures. The recognition of insulting agents by the acquired immune system involves specific interactions between antigen receptors on B and T cells and specific sites on foreign molecules (antigen determinants). The B and the T cells represent the decisive armament of the immune system. According to earlier classification, T cells represent the cellular immune response (operating in neoplasia), and the B-cell compartment is the source of all antibodies (IgG, IgM, IgA, IgD, and IgE). The major features of acquired immunity are specificity and memory [7]. However, an efficient immune response requires the synchronous operation of all components of the immune system. The critical effective players in neoplastic cell elimination, prevention of metastatic tumor cell dissemination, and immune response facilitation (also against viruses) are the natural killer (NK) cells [8]. They represent a segment of the lymphoid cell population accounting for only 10 to 20% of the peripheral blood lymphocytes [9].

It is not unexpected that the immune system is not a totally autonomously existing entity. The interactions between the immune and the nervous systems at all levels, including the brain, pituitary, peripheral nervous system, and the immune cells, was the subject of an international conference in 1998 entitled "Neuroimmunomodulation: Molecular Aspects, Integrative Systems, and Clinical Advances," organized by the New York Academy of Sciences [10]. Anecdotal and, occasionally, hyperbolized reports on this interaction are also abundant. The interrelationship between the endocrine and the immune systems was well recognized much earlier.

It should be emphasized that the developing malignancy is not entirely defenseless and possesses mechanisms capable of overwhelming, overriding, or evading the host's attack, referred to as the

"sneak-in" [8]. Postulated mechanisms include changes in the immunogenicity of the tumor cells and alteration of the tumor-specific antigen; production of blocking antibodies "masking" the neoplastic cells; intervention by inhibitory T cells; or overwhelming the host immune functions by the tumor's rapid, destructive growth (blockade). Of special interest here is the profound immunosuppression associated with the progression of some viral infections, particularly retroviral, in animals (murine Friend leukemia virus) and in humans (HIV/AIDS virus).

In order to understand both the development and differentiation of normal tissues and to develop therapies for tissues that have exhibited abnormal growth patterns such as hyperplasia, dysplasia and neoplasia, it is imperative to comprehend the nature and the regulation of the normal cell cycle. Persuasive evidence indicates that the growth of tissues in both health and disease is a perfect balance between cell division and programmed cell death (apoptosis). Most often undefined, minute, generally long-lasting exogenous or endogenous impacts can tip this delicate balance in favor of the intruder, with the development of overt clinical neoplastic manifestations or in favor of the host, erroneously designated as spontaneous cancer regression. Established clinical events in the evolution of neoplastic disease include the loss of proliferative control, the failure to undergo apoptosis, the onset of neoangiogenesis, tissue remodeling, invasion of tumor cells into surrounding tissue, and finally, metastatic dissemination of tumor cells to distant sites [11]. A major promising future therapeutic aspect of neoplastic (and viral) disease progression will be the regulation of apoptosis. This and other fast-advancing areas in cancer research have led to four conferences on cancer during the past eight years under the auspices of the New York Academy of Sciences, covering subjects such as immune system, aging, genetics, prophylaxis, and therapy. The domain of clinical cancer research representing an integration of the natural defense mechanisms of the host, augmented by the use of pharmacotherapeutic agents including nutritional modalities, deserves high priority, in our opinion, in the development of new and more physiological approaches to cancer prevention and treatment [12].

New data recently released by the American Cancer Society (February 2003) corroborate that for the year 2000, the U.S. leading causes of death (as percent of total deaths) still are heart disease (No. 1, 29.6%) and cancer (No. 2, 23.0%). Unlike the mortality from cardiovascular diseases, which is declining in people of all age groups, the mortality due to cancer, notwithstanding the declared "war against cancer," is still rising for older individuals (Figure 36.1). Approximately 50% of all neoplasms occur in the 12% of the population aged 65 or older, and this number will increase with the projected expansion of the older population [12]. Of particular interest is the swift increase in the incidence of certain neoplasms in older individuals that has become evident during the past 20 years (Figure 36.2). These neoplasms include nonmelanoma skin cancer, non-Hodgkin's lymphoma, and malignant brain tumors. This phenomenon cannot be ascribed solely to improved diagnostic techniques. According to a meritorious hypothesis that has both experimental and clinical support, older people may develop cancer earlier than younger individuals when exposed to the same dose of a carcinogen [12]. This is an important phenomenon in light of the current life-extension programs, further strengthening our position concerning the interplay between cancer, aging, and the immune system.

36.1.2 Coenzyme Q, Mitochondria, and Bioenergetics

All biochemical processes involve energy production, transformation, and utilization; thus the term *bioenergetics* could validly be applied to the whole of life sciences. Bioenergetics as a well-defined discipline rose to prominence in the 1950s. In this complex process, the source of energy is adenosine triphosphate (ATP), which is generated by oxidative phosphorylation in the inner membrane of the mitochondria. This evolved and adapted biological system converts energy in the most efficient manner for events such as biosynthetic processes, transport of molecules across cell membranes, and muscle contraction. Our knowledge has advanced dramatically during the past 15 years, as evidenced by the explosion of investigations and the elucidation of molecular

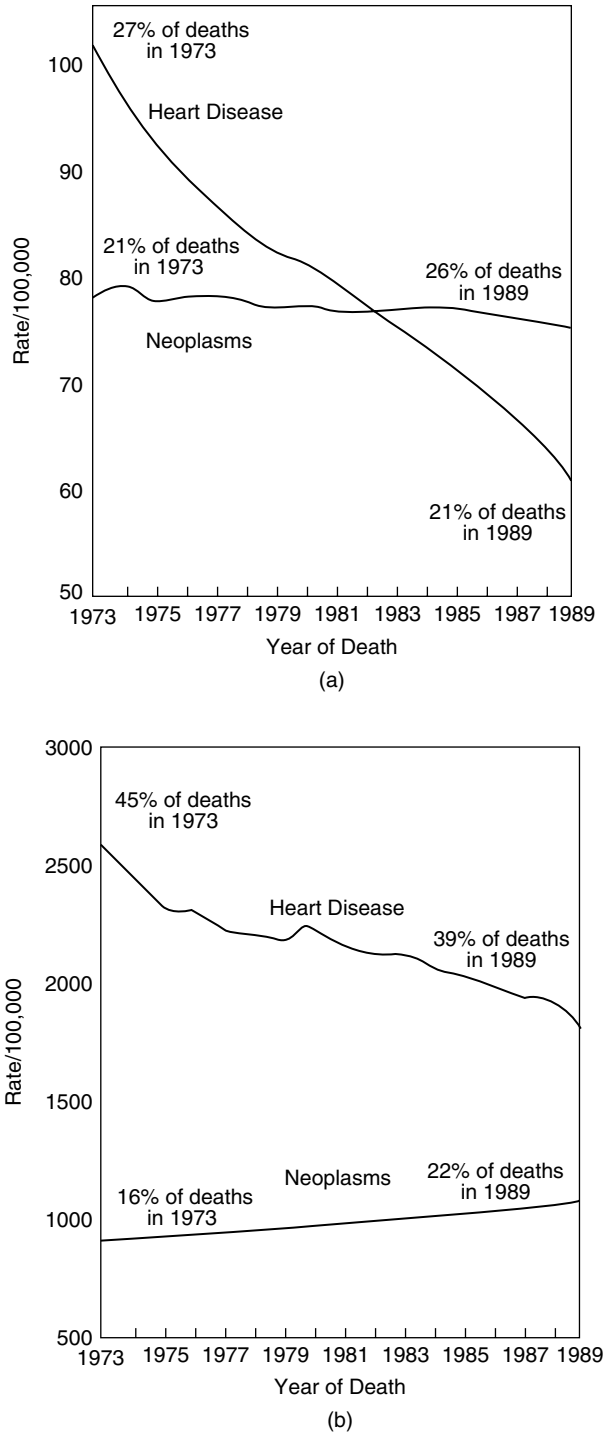

FIGURE 36.1 Variations in causes of death for younger (A, under 65 years) and older (B, over 65 years) individuals over time. (From Berlin, A., *Cancer Invest.*, 13, 540, 1995. Reproduced with permission.)

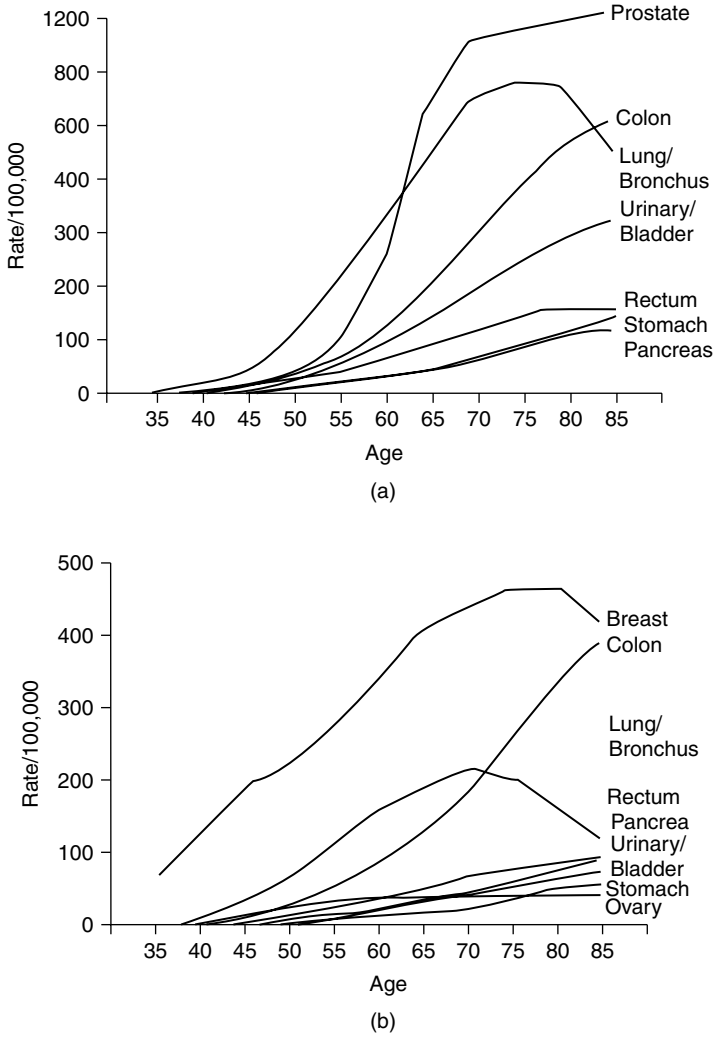

FIGURE 36.2 Age-related incidence in different neoplasms: A, male; B, female. (From Yanick, R. and Ries, L.A. [12]. Reproduced with permission.)

mechanisms of mitochondrial physiology and pathology, bringing a better understanding of the role of mitochondria in health and disease. The mitochondrion was once thought to be stable and reliable, and its possible dysfunctions were not even considered. It is now revealed to be a primary intracellular structure operating close to its design limits and extremely prone to damage, with potential disastrous consequences for the organelle itself and for its host cell. Many disorders, particularly the chronic neurodegenerative and cardiovascular diseases, neoplasia, diabetes, and others, are now considered to involve, to greater or lesser extent, mitochondrial dysfunction and therefore impaired energy production. More than 75 disease states are now linked to this pathologic process [13]. The outburst of activity in this area necessitated the creation of a new nosological entity, "diseases of bioenergetics." A testimonial for this productive research effort is the Nobel prize awarded to Peter Mitchell in 1978 for his elucidation of the "Q-cycle" in the electron transport chain, and to Paul Boyer and John Walker in 1997 for their work on ATP synthase enzyme. A comprehensive review of the current advances in bioenergetics has been compiled by Nichols and Ferguson [14].

It is now well established that mitochondria are critical targets in many, if not most, events of apoptotic cell death. The concept of a mitochondrial basis for eliminating tumor cells has been advanced since the early part of the last century, built upon general differences in metabolic control between neoplastic and cancer cells [15]. In 1956Warburg postulated that mitochondrial oxidative phosphorylation was defective in tumor cells, and that the initial insult led to increase in glycolytic ATP production as the central event of cell transformation. He predicted that treatment producing mitochondrial injury of a general nature would strike a greater blow against cancer cells than against normal cells. Furthermore, aerobic glycolysis (the Warburg effect) in cancer cells may compete for ADP and phosphate, with oxidative phosphorylation resulting in a mitochondrial shift to a non-phosphorylating state. Another possibility suggested by Hockenberry [15] is that high rates of glycolysis may suppress respiration, known as the Crabtree effect.

ATP, the purine ubiquitously responsible for the storage and resupply of metabolic energy in biological systems, has sprung a new intriguing surprise on scientists working in this area. Recent studies indicate that ATP, in addition to its well-recognized intracellular functions, has unrealized diverse extracellular functions [16] such as:

- Neurotransmitter (or a cotransmitter) function in the central and the sympathetic nervous system, thus transmitting signals across the synapse
- Modulation of the immune system
- Trophic effects in the development and regeneration of the nervous system
- Inhibition of platelet aggregation
- Cytotoxic and apoptotic effects

It is premature at this time even to speculate on the paramount role of this new player in the fast-evolving area of research involving the link between disease, aging, and coenzyme Q, but the potential pharmacological and clinical implications are immense.

Coenzyme Q is well defined as a crucial component of the oxidative phosphorylation system in the mitochondria, where energy derived from the products of fatty acids and carbohydrates is converted into ATP to drive cellular machinery and biosynthetic processes (Figure 36.3). Coenzyme Q (also known as ubiquinone) was discovered by Fred Crane and his colleagues in 1957 in beef heart mitochondria [17]. Karl Folkers and his associates elucidated its chemical structure in 1958 [18]. Coenzyme Q is composed of a homologous series of compounds differing in the length of the isoprene side chain, and coenzyme Q_{10}, the homologue present in humans and several other species, has 10 isoprene units with the structure 2,3-dimethoxy-5-methyl-6-decaprenyl-1,4-benzoquinone (Figure 36.4). Coenzyme Q is a ubiquitous, naturally occurring, fat-soluble molecule with characteristics similar to those of vitamins and is essential for the sustenance and functioning of most organisms.

Crane [19, 20] has concisely summarized the currently recognized functions of coenzyme Q as:

- Needed for energy conversion (ATP production)
- An essential antioxidant
- Regenerates other antioxidants
- Stimulates cell growth and inhibits cell death
- Decreased biosynthesis may cause deficiency

The normal content of coenzyme Q in mitochondrial membranes has been reported to be below that required for kinetic saturation [21]. This finding strongly suggests that coenzyme Q may be the rate-limiting component in the respiratory chain, especially in the mitochondria of compromised or incapacitated tissues.

Coenzyme Q_{10} is of dual origin in humans, partly exogenously derived (food) and partly synthesized in the body. The dietary intake of coenzyme Q_{10} is likely to be much lower these days

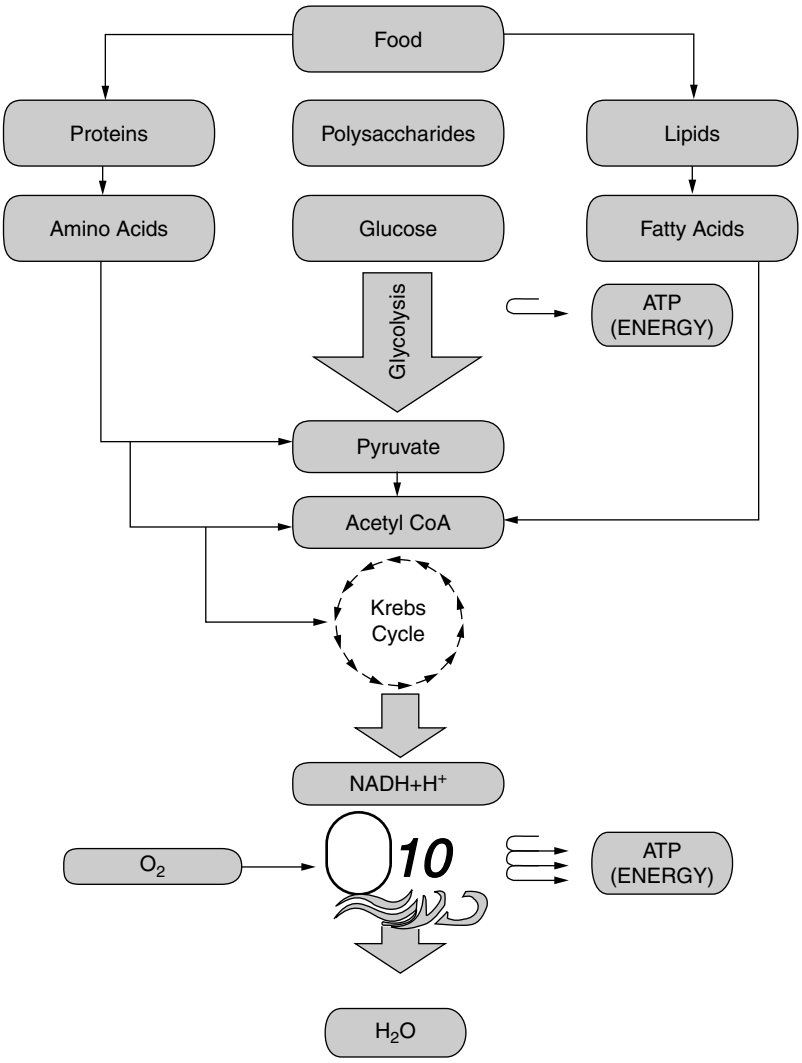

FIGURE 36.3 Role of coenzyme Q_{10} in mitochondrial ATP (energy) production. (From Littarru, G.P., *Energy and Defense*, Casa Editrice Scientifica Internazionale, Roma, Italy, 1995. Reproduced with permission.)

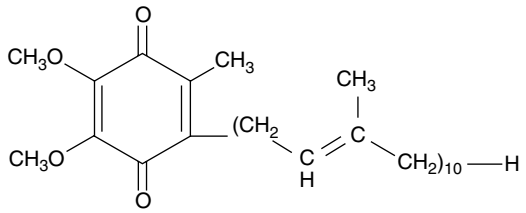

FIGURE 36.4 Structure of coenzyme Q_{10}.

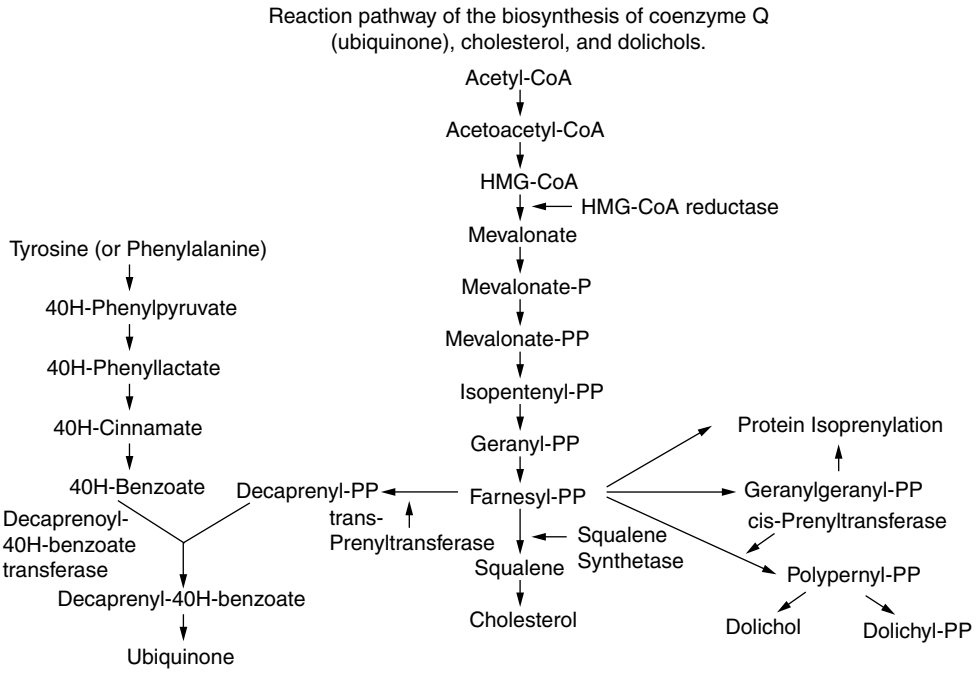

FIGURE 36.5 Reaction pathway of the biosynthesis of coenzyme Q_{10} (ubiquinone), cholesterol, and dolichols.

due to avoidance of foods high in fat, which for the most part also contain higher amounts of coenzyme Q_{10} [22]. This has an effect on other nutrients as well. During gastrointestinal uptake, dietary coenzyme Q_{10} is efficiently reduced to the antioxidant-active ubiquinol form that enters the circulation within the lipoproteins for potential uptake by tissues [23]. The endogenous synthesis of coenzyme Q_{10} is an elaborate process first described by Folkers [24] that depends on the availability of several vitamins and minerals (Figure 36.5). Deficiencies in any one of those building blocks will impair its biosynthesis and result in coenzyme Q_{10} deficiency, thus compromising coenzyme Q-dependent vital functions. Furthermore, the age-dependent decline in the coenzyme Q_{10} content of various tissues in humans and animals, to be discussed later, is postulated to be responsible, at least in part, for the "diseases of aging" [25]. Bioenergetic degradation affects first and most intensely the cardiovascular and immune systems as well as the brain, tissues with the highest energy needs. As a consequence, a cascade of functional impairment begins in these systems followed, if not corrected, by overt clinical manifestations. Not surprisingly, cardiovascular, neoplastic, and neurodegenerative diseases are the most common causes of morbidity and mortality in the elderly. Furthermore, as a potent and versatile antioxidant, coenzyme Q blocks oxidative injuries to DNA, lipids, proteins, and other essential structures. This well-documented function prevents or retards the development of many diseases, particularly the "diseases of aging."

In this context, it is interesting to note that in his book on coenzyme Q_{10}, Littarru [26] devoted over 70% of the content to coenzyme Q_{10} prevention of oxidative damage. The rationale and the benefits of coenzyme Q_{10} and idebenone use in the treatment of respiratory chain diseases were reviewed recently [27]. Summing up the practical aspect, data from numerous experimental studies as well as clinical trials demonstrate the strong relationship between coenzyme Q_{10} deficiency, progression of many disease states ("diseases of bioenergetics"), and the beneficial effects of coenzyme Q_{10} supplementation.

Since 1960, the biochemistry, physiology, and clinical effectiveness of coenzyme Q_{10} have been presented at 17 specialized international symposia, with a total of almost 5000 published pages.

Most coenzyme Q_{10} clinical research is focused on the large, heterogeneous group of cardiovascular diseases. The published results of 34 controlled clinical trials and several open-labeled and long-term studies were critically reviewed [28]. The evaluation reveals that out of 58 early and current trials involving 5727 patients with various forms of cardiovascular diseases, only three trials reported negative results (1.7%) experienced by 110 participants (1.9%). A testimonial for the heightened interest in the biomedical and clinical functions of coenzyme Q_{10} is the recent increase in publications on this subject, particularly the two books edited by Kagan and Quinn [29] and Ebadi et al. [30] that contain comprehensive reviews covering all aspects of coenzyme Q.

One issue that needs to be addressed here and is rarely considered by most physicians is the question of bioavailability of coenzyme Q_{10} products intended for oral use. Being somewhat fat-soluble (and insoluble in water), its absorption and bioavailability are very limited and depend on food fat intake to some extent. Commercially available preparations of coenzyme Q_{10} in the U.S. and elsewhere are generally based on the pure crystalline material (as powder-filled capsules or tablets) and oil suspensions (in soft gel capsules), and these forms have limited bioavailability [31]. A recently introduced product that is "hydrosoluble" (called Q-Gel, Tishcon Corp., Westbury, NY) has been shown to have superior bioavailability (about three-fold higher than the other products) in clinical testing [31–34]. There have been numerous experimental and clinical studies using this product. Previous data based on animal experiments using coenzyme Q_{10} in the powder form had not provided clear evidence that coenzyme Q_{10} could be incorporated into tissue mitochondria. It is therefore noteworthy that in a recent study, Kwong et al. [35] demonstrated conclusively that in rats supplemented with Q-Gel in the diet, coenzyme Q_{10} content of tissues and isolated mitochondria showed a significant increase along with an increase in the antioxidative potential and a decrease in protein oxidative damage. This study thus confirms not only the improved bioavailability of Q-Gel, as shown by its concentration in blood, but also the ability to increase the intracellular and mitochondrial uptake of coenzyme Q_{10} in various tissues, including the brain.

The Food and Drug Administration (FDA) recently granted an "orphan drug" designation for UbiQ-Gel for the treatment of mitochondrial cytopathies. In Europe and in Japan, a synthetic analogue of coenzyme Q_{10} called Idebenone (Takeda Chemical Industries, Osaka, Japan) is also available with claims that it has improved bioavailability, but it cannot be legally sold in the U.S. until it has been tested and approved as a "new drug" by the FDA. Another new development in this area is the introduction of stabilized ubiquinol, the reduced and the predominant form of coenzyme Q_{10} in blood circulation (Q-Nol, GelTec/Tishcon Corp., Westbury, NY). Human and animal data have shown that Q-Nol has even higher bioavailability [33, 34]. The clinical efficacy of both Q-Gel and Q-Nol are currently being evaluated in several clinical trials.

An intriguing subject is the production and availability of coenzyme Q_{10} for commercial purposes. In the late 1960s and early 1970s, coenzyme Q_{10} was available only in minute amounts for use as an analytical standard. Slowly, with increased demand, the production increased, first using beef heart as the source, then horse heart, and the product was marketed in the U.S. by the meat-packing industry and not by pharmaceutical companies. At that time, the Swiss giant Hoffmann-La Roche ventured that the limited demand for coenzyme Q_{10} would eventually explode and, after enormous effort initiated in 1958, developed and patented a very long, complicated, and expensive synthetic method for its industrial production. The demand slowly increased, but at that time, Japanese scientists developed and patented a much simpler and cheaper method by way of fermentation. Then the price dropped from $1000 per gram to $17 to 20 per gram, and it is down to between $1 to 2 per gram today. Coenzyme Q_{10} is produced exclusively in Japan, and extremely high-quality material is available in large quantities from Kaneka Corp., Osaka (yeast fermentation process, initiated in 1977), Nisshin Flour Milling Co., Tokyo (semisynthetic process using plant cell culture, initiated in 1974), and Mitsubishi Gas and Chemical Co. (bacterial fermentation process). The Nisshin process for industrial coenzyme Q_{10} production qualifies the product as a phytopharmaceutical. Estimates put the combined annual production of coenzyme Q_{10} by the three companies in Japan to between 150 and 200 metric tons.

36.1.3 Tumor–Host Interplay

36.1.3.1 General Setting

Tumorigenesis is a multistage process that has been classified into initiation, promotion, and progression phases, and each stage involves both genetic and epigenetic alterations, functional as well as morphological. These changes can be caused by chemical or physical factors and frequently involve the formation of reactive oxygen species (ROS) and other highly reactive molecules. These agents can damage DNA and other essential cellular components, modify gene expression, alter the cellular antioxidant defenses, and thus affect cell growth and differentiation [36].

During metabolism of oxygen to water in the mitochondria, a small fraction of the oxygen is reductively converted into superoxide as a by-product. Superoxide may be further converted into various ROS, i.e., hydroxyl radical, hydrogen peroxide and others. However, the majority of the cells possess intracellular antioxidant defense mechanisms against the potentially harmful effects of the ROS. A second defense mechanism at the DNA region is the base excision and strand-break repair enzymes, which remove the damaged segments in order to maintain the integrity of the genome. However, deleterious genetic alterations, particularly poorly repaired oxidative damages, may accumulate in cells with age through errors in repair, replication, and recombination. Furthermore, the level of repair may decrease with the aging of the cell. Recent reviews have addressed the role of oxidative damage to the DNA [37] and its implication in carcinogenesis, atherosclerosis and AIDS [38], and the inhibition of intracellular oxidative stress by anticarcinogenic antioxidants [39].

Experimental and epidemiological data validating the concept that most tumors are associated with mutagens and mitogens suggest an empirical therapeutic approach, searching for agents that inhibit or reverse the cellular transformation elicited by these substances. Since 1987, over 1000 compounds have been screened for their anticarcinogenic potential under the National Cancer Institute Chemoprevention Testing Program, and a few such as tamoxifen, retinoic acid, vitamin E, selenium, and calcium have been further evaluated in large-scale intervention trials [40].

Cancer chemoprevention is defined as the use of specific compounds or agents to prevent, inhibit, or reverse the progress of carcinogenesis [40]. Human cancer development requires 20 to 40 years or more in many major target tissues, and the scope of chemoprevention actually encompasses all phases of this process — from healthy subjects exposed to "normal" risk; to populations at intermediate risk due to environmental and lifestyle factors, genetic predisposition, and precancerous lesions; and then to previous cancer patients at high risk for other primaries. Clearly, the distinction between cancer prophylaxis and cancer treatment (primary, regrowth after treatment, or distant metastasis) is blurred or overlapping and thus is not practical. For this reason, we will assess the options for therapeutic intervention at all stages of tumorigenesis in this chapter.

The early clinical literature is replete with ample anecdotal verification of the potential role of the immune system in the surveillance, elimination, and the "cure" of cancer. The factors most commonly associated with the spontaneous regression have been fever, concurrent bacterial infections, administration of bacterial vaccines, or the removal of at least some portions of the tumor. The occasional regression that accompanied bacterial infections did not go unnoticed by physicians. This technique, referred as "nonspecific cancer immunotherapy," dates back to at least 1774, when a Parisian physician injected pus into the leg of a patient with inoperable breast cancer. As the induced infection worsened, the patient's cancer disappeared. More than a century later, Coley, noting the apparent beneficial effect of erysipelas infection on cancer regression, formulated a well-publicized preparation based on soluble toxins from erysipelas. More recently, local application of the tuberculosis BCG vaccine has proven to be effective therapy for certain cancers in randomized clinical trials. It is interesting to note here that in 1971, Laborit and his colleagues [41] reported an improvement in mouse Ehrlich ascites cancer by treatment with isolated mouse hepatic mitochondria. They speculated that the improvement resulted from an increase in the "defense system" activity. This study perhaps represents the first step in our understanding of the interrelationship

between cancer, immune system, and coenzyme Q. Following a review of these findings, Fuchs and Matzinger [5] suggested that these "nonspecific" immune stimulants may be providing the necessary signals to stimulate local cells to initiate an immune response to tumor-specific antigens.

A comprehensive evaluation of current cancer chemotherapy status was outlined by Davis [42] and Agarwala [43]. A more specialized novel area of research with practical applicability is the effect of immune reactivity, expressed as an inflammatory process, on angiogenesis and thus on tumor growth [44]. It as appropriate to recall here that the direct effect of cholesterol on the immune system, more specifically on phagocytosis, was observed as early as 1914 [45]. Furthermore, McMichael et al. [46] accumulated epidemiologic data suggesting that low serum cholesterol is associated with increased risk of cancer of the lung or colon. Klurfeld [45] concluded his review, stating emphatically that "cholesterol interactions with cells of the immune system are potentially some of the most important in the area of nutrition and immunity." This serious concern and the implications for cancer and other diseases are hotly denounced by today's anticholesterol crusaders.

36.1.3.2 Coenzyme Q: Animal Studies

In the early 1960s, we established our then-called "host defense program," representing a search for a physiologic stimulant of the immune system with applicability to humans. (The term *stimulant* was later replaced by the technically more precise term *modulator*). Many compounds were evaluated for activity based on a battery of animal tests, measuring their response upon stimulation of various parameters of the immune system. Satisfactory activity was first demonstrated by coenzyme Q_6 and then by coenzyme Q_{10}. For the first time, our results suggested the capability of the coenzyme Q group of compounds to stimulate *in vivo* two fundamental parameters of the immune system response: the phagocytic process in rats and the antibody production in mice, and the preliminary results were published in 1970 [47]. Subsequently, studies were carried out using more complex test systems measuring the total host response to *Plasmodium berghei* infection in mice (causing a fulminate malaria infection) treated by coenzyme Q_{10} in combination with chloroquine [48]. This model exemplifies the effectiveness of a nonspecific stimulation of the immune system (coenzyme Q_{10}) plus a specific antimalarial drug. The combined treatment resulted in increased number of survivals, prolonged survival time, and reduced intraerythrocytic parasitemia. The involvement of the immune system in protozoan infections, particularly in malaria, has long been recognized but never fully demonstrated, and our study contributed significantly in enhancing our knowledge in this area.

Chemically induced tumors are still considered a good model for human neoplasia, and we evaluated the effectiveness of coenzyme Q_{10} in mice with dibenzpyrene-induced tumors. A second test system in this study was a retroviral infection in mice (Friend leukemia virus), a model used in the evaluation of new drugs for HIV/AIDS. Our findings and conclusions could be summarized as follows [49].

- Treatment with coenzyme Q_{10} reduced the percentage of mice with tumors, increased the number of survivors, and reduced tumor size in mice with tumors induced by 3,4,9,10-dibenzpyrene.
- Treatment with coenzyme Q_{10} decreased splenomegaly and hepatomegaly (critical early symptoms in the progression of the infection) and increased the number of surviving mice infected with Friend leukemia virus.

In a joint program with Karl Folkers at the University of Texas in Austin, TX, we evaluated the changes in coenzyme Q_{10} levels in blood and other tissues following infection with murine Friend leukemia virus. The data revealed a significant coenzyme Q_{10} deficiency in blood and spleen (mitochondria) as the infection progressed. On day 20 after the infection, the coenzyme Q_{10} was reduced to 36% in blood and to 62% in spleen mitochondria (spleen being a major immune

TABLE 36.1
Coenzyme Q_{10} and Leukemia Experimental Infection in Mice

Treatment	Spleen wt.	
	Body wt.	%
1. FLV infection (alone)	50.28	100.0
2. FLV + cyclophosphamide	47.61	94.7
3. FLV + cyclophosphamide + coenzyme Q_{10}	23.72	42.7
1. FLV infection (alone)	50.29	100.0
2. FLV + hydrocortisone	28.61	56.9
3. FLV + hydrocortisone + coenzyme Q_{10}	17.43	34.7

Note: FLV = Friend leukemia virus. Mice were treated on day 20 after infection.

Source: Bliznakov, E.G., in *Biomedical and Clinical Aspects of Coenzyme Q,* Folkers, K. and Yamamura, Y., Eds., Elsevier, Amsterdam, 1977, p. 73. With permission.

system organ). Our conclusion at that time was that the limiting factor in the resistance to retroviral infection in mice appeared to be the intracellular availability of coenzyme Q_{10}.

We presented a review of our earlier studies on experimental infections and neoplasia along with some new data at the International Symposium on Coenzyme Q_{10}, held at Lake Yamanaka, Japan, in September 1976 [50]. These are summarized in Table 36.1. Consequently and in confirmation of our earlier published results, Folkers et al. [51] reported that coenzyme Q_{10} administration in patients increased the blood count of T4 lymphocytes and the blood level of IgG antibody. More recently, Barbieri et al. [52] demonstrated that coenzyme Q_{10} increased in a dose-dependent manner the antibody response to hepatitis B vaccine. In this single-blind, placebo-controlled and randomized clinical study, 21 volunteers per study group were supplemented with coenzyme Q_{10}, 90 mg/day or 180 mg/day, for 14 days prior and for 90 days after the vaccine administration. At day 60 after the vaccination, the antibody titers were increased by 135% for the 90-mg coenzyme Q_{10} and by 155% for the 180-mg coenzyme Q_{10} groups. It is interesting to note that the authors of this Swedish study offered an alternative and intriguing speculation. According to this group, the immunomodulating coenzyme Q_{10} activity is associated with its antioxidant effectiveness, which minimizes the oxidative stress and cell membrane turnover, thus improving antigen recognition and antibody production. They proposed that "the immunoenhancing coenzyme Q_{10} effect can be of certain importance for elderly people with lower endogenous production of coenzyme Q_{10}."

36.1.3.3 Coenzyme Q_{10}: Clinical Studies

The encouraging results from our extensive animal studies on the coenzyme Q–neoplasia link, discussed earlier, led many scientists to test further the validity of this link in limited clinical trials. Two reviews, one being short and popular and the other extensive and technical, were published recently on this still-neglected subject by the National Cancer Institute dated June 12, 2002 [53, 54]. The latter report traces the interest in coenzyme Q as a cancer therapeutic agent as early as 1961, when coenzyme Q_{10} deficiency was detected in patients with breast and other forms of cancer. A subsequent study showed a statistically significant relationship between the degree of coenzyme Q_{10} deficiency and the progression of breast cancer. Yet, these findings on the encouraging and potentially successful approach to cancer management have been largely overlooked and even forgotten over the years. Back in 1987, Eggens et al. [55] had reported that in humans with hepatocellular carcinoma, the coenzyme Q_{10} content in liver dropped to one-half that found in control tissue.

There has been some sporadic activity in this area during the past few years. Recently, Portakal et al. [56] published data on the relationship between oxidative stress and breast cancer development

in 21 patients, and their results showed a decrease in the coenzyme Q_{10} content in the tumor tissue and an increase in the oxidative stress as compared with that in the surrounding normal tissue. They construed that administration of coenzyme Q_{10} may afford protection against increased oxidative stress and its consequences in breast tissue. In another study involving 28 untreated patients with lung and breast cancer, increased oxidative stress and reduced levels of lipid-soluble antioxidants, in particular reduced coenzyme Q_{10}, were found in blood and bone marrow plasma as compared with those of controls [57]. This, according to the authors, represents an imbalance between oxidant generation and antioxidant defense in favor of the former in cancer patients. In a study with 80 breast cancer patients, plasma coenzyme Q_{10} level was found to be significantly lower, and this reduction was more pronounced in patients with larger tumor volume [58]. Similar results have been reported in 116 patients with myeloma and breast cancer [59]. Mikhail et al. [60] examined the association between plasma coenzyme Q_{10} and α-tocopherol in cervical cancer patients and found that the mean plasma levels of both antioxidants were significantly lower than those in controls. They concluded that this reflected increased utilization of the antioxidants due to oxidative stress and that both coenzyme Q_{10} and α-tocopherol might play a role in the pathogenesis of cervical neoplasia.

Three small-scale clinical trials with cancer patients undergoing standard treatment along with coenzyme Q_{10} supplementation indicated a tumor suppressive effect [61–63]. A study by Lockwood et al. [61] in Denmark involved 32 breast cancer patients. In six of them (18.8%), signs of remission were reported following treatment with antioxidants that included coenzyme Q_{10} at a relatively low dose (90 mg per day). All the patients also reported a decreased use of painkillers, absence of weight loss, and improved quality of life. The survival rate at 18 months was 100% against an expected rate of 87.5%, and at 24 months the survival rate was still 100%, whereas the expected rate was 81.2%. In a follow-up study, one new patient and one previously treated patient exhibiting cancer remission were given higher doses of coenzyme Q_{10} (300 mg and 390 mg per day) for three to four months. Both patients showed complete regression of the tumors following this treatment. In another study by the same group [62, 63], three breast cancer patients were treated with a high dose of coenzyme Q_{10} (390 mg per day) and followed for three to five years. Two showed complete regression of cancer and metastases, and the third had no microscopic evidence of cancer after mastectomy. One of the clinicians participating in this study stated ardently that he had seen around 200 cases of breast cancer a year, but he had never seen a spontaneous complete regression of 1.5- to 2.0-cm tumor, and had never seen a comparable regression following any conventional antitumor therapy in his 35 years of oncology practice.

In extension of the previously reported murine retroviral–coenzyme Q_{10} link studies, two preliminary clinical observations deserve notice. In a blinded study, Bui et al. [64] found that plasma coenzyme Q_{10} levels were significantly lower in HIV-positive patients than in healthy individuals and even lower in more advanced stages of the infection (level 4 or 5). In an early open-label study, coenzyme Q_{10} (200 mg/day) increased the ratios of T lymphocytes (T4 helper to T8 suppressor cells) in AIDS patients [65]. This ratio is used as a sensitive indicator for evaluation of immunologic parameters and is depressed in HIV infections and in cancer. The explosion of AIDS infections in some parts of the world mandates a concentrated effort to evaluate the involvement of coenzyme Q_{10} in the progression of this debilitating infection.

Admittedly, many of the clinical trials reported in the literature on coenzyme Q_{10} and cancer link have design flaws, often accentuated by the critics. Another limiting factor in the earlier trials was the very low dose of coenzyme Q_{10} employed along with too short a treatment period, both factors reflecting the insufficient supply of coenzyme Q_{10} and the high price of the product at that time. Nevertheless, the results of these studies, as well as anecdotal reports of increased survival of patients with various types of cancer (pancreas, lung, colon, rectum, and prostate) treated with coenzyme Q_{10} [63, 66], suggest the therapeutic potential of coenzyme Q_{10} in cancer therapy and also possibly in its prophylaxis, as demonstrated in the more extensive animal studies. Additional support for this optimistic outlook is provided by the simultaneous achievements in the neoplasia-related domain of research: immunology and aging, and their dependence on coenzyme Q_{10} availability.

There are numerous reports on the efficacy of coenzyme Q_{10} as a protective agent in preventing cardiotoxicity in cancer patients treated with anthracycline drugs, as previously shown in animal studies. This was discussed in a short review published recently [67]. Published studies indicate that inclusion of coenzyme Q_{10} in the treatment regimen of cancer patients does not compromise the antitumor effect of Adriamycin™. On the other hand, an additive or even a synergistic therapeutic effect of combined treatment with anthracyclines and coenzyme Q_{10} in cancer patients could be expected. Treatment of cancer patients with doxorubicin and coenzyme Q_{10} was shown to lower the incidence of cardiac dysfunction [68]. This was followed by a study by Tsubaki et al. [69] showing that 18 of 25 patients (72%) with malignant lymphoma treated with Adriamycin and daunorubicin and 20 of 50 patients (40%) also treated with coenzyme Q_{10} developed abnormal ECGs. The coenzyme Q_{10}-treated patients also showed significant improvements in diarrhea and stomatitis. In a longer-term study, the same authors reported that while 11 of 12 patients (91.7%) treated with anthracyclines developed abnormal ECGs, only 11 of 17 (64.7%) also treated with coenzyme Q_{10} manifested ECG problems. A study by Karlsson et al. [70] established that patients on doxorubicin have lower concentrations of coenzyme Q_{10} in heart, skeletal muscle, and blood as compared with healthy subjects. The authors concluded that the lower the heart muscle coenzyme Q_{10}, the more impaired is the cardiac function. A randomized clinical trial with 10 cancer patients treated with Adriamycin and coenzyme Q_{10} (100 mg, twice daily) also demonstrated the ECG evidence for the protective effect of coenzyme Q_{10} [71].

The results of numerous uncontrolled clinical trials, although often dismissed as not being rigorous enough, lend further support to the effectiveness and protective effect of coenzyme Q_{10} in cancer patients [reviewed in 66, 72]. The differences in the response to coenzyme Q_{10} in the various studies could be attributed to dosage, duration, and bioavailability factors.

More than a quarter century has passed since Karl Folkers postulated that coenzyme Q_{10} could have therapeutic potential for the treatment of cancer [73]. He argued then that, as coenzyme Q_{10} was essential for normal cell respiration and function, any deficiency in its availability or biosynthesis could disrupt normal cellular functions. This could lead to abnormal pattern of cell division that, in turn, might induce an oncogenic response. Today, it is unequivocal that additional clinical evidence evolving from larger, well-designed, state-of-the-art trials will bring us closer to the prophetic assertions of Karl Folkers. While the pharmaceutical industry has shown little interest in the past, further progress in this important area cannot be made without the participation of foundations, scientific organizations, academia, and the government.

36.1.4 The Burden of Aging

36.1.4.1 Pandemic Relevance

Another domain of scientific quest in which information from three areas of exploration sometimes collide and sometimes complement each other is the merger of immunologic, cancer, and aging research. The parallel increase in cancer risk with advancing age is well recognized [74], as evident from the very low occurrence in the first decade of life, which rises to an incidence of about 30% in the seventh decade (Figure 36.2). In this regard, cancer may be considered a disease of the elderly, although from another point of view, the multistep nature of carcinogenesis indicates that the disease actually originates much earlier in life. Several pathophysiologic mechanisms common to all three areas of exploration have been proposed to explain the increased incidence such as genetic defects; exposure to environmental, physical, or chemical carcinogenic agents; and even infections. Additionally, many neoplastic alterations develop spontaneously as a result of accumulated random damage to genetic material and to other critical cellular structures, and the resulting functional dysfunctions not infrequently bear a resemblance to those associated with aging. For this and other reasons, cancer and other pathological states, i.e., cardiovascular and neurodegenerative diseases, are contemplated as "diseases of aging." In particular, ROS and oxidative stress with

damage to critical biomolecules indicate another common mechanism underlying the progressive cellular functional insufficiency, characteristic of all three areas.

The replication of mitochondrial DNA mutations eventually leads to impairment of cellular function. The resulting ATP deficit and increased redox stress cause cell senescence and eventually cell death. Among the systems affected by this cellular disintegration are various compartments of the immune system. This overwhelming cellular functional erosion justifies proposed strategies aimed at reducing oxidative and other noxious tissue damages in an attempt to delay the aging process and to compress the time frame of chronic disease advent, thus enhancing the quality of life and ameliorating the social burden on the community [12, 75].

"Probably no subject so deeply interests human beings as that of the duration of life," wrote Raymond Pearl in his classic *The Biology of Death*. Ancient societies attributed to their gods, whether in Valhalla or on Mount Olympus, magical ways of postponing old age forever. Today's multifaceted research on aging based on scientific principles, rather than the magical *Fountanus Juventus* of Ponce de Leon and Columbus followers, began with the 1955 formulation of the "free radical theory" of aging by Denham Harman, a theory that is now supported by extensive experimental data [76]. His earlier studies had shown an effect of vitamin E on immune function, resulting in increased antibody-forming capacity of old mice by 189% [77]. As expected, some criticism is voiced on this now-accepted "theory of aging" [78, 79].

Aging is both a complex scientific predicament as well as a human event of universal concern. A recent publication by the New York Academy of Sciences entitled "Towards Prolongation of the Healthy Life Span" was based on a conference to address this issue [80]. The genetic approach is a novel and a fashionable mode of exploration employed by gerontological science. The dichotomy of this is well conveyed by Martin [81], who asks, "Do senescent phenotypes and their associated increased vulnerability to organismal death result from a relatively simple program of gene action or is it exceedingly complex, modulated by allelic variants at hundreds or thousands of loci?" The answer to this enigmatic question would provide a rationale (or the lack of it) for the development of interventions for the extension of our own life spans.

Overall, there is profusion of evidence that mitochondrial function and bioenergetic capacity deteriorate during normal aging, especially in postmitotic tissues such as brain, heart, and skeletal muscle [82]. Furthermore, Nicholls and Budd [83] recently reviewed mitochondrial function and dysfunction in cells and their relevance to aging and aging-related disorders. Additionally, Bruce Ames and his colleagues [84] have demonstrated that mitochondria from old rats can be "rejuvenated" and memory improved with a diet supplemented with acetyl-L-carnitine and α-lipoic acid, again confirming the participation of the mitochondrial energy and antioxidant processes in aging. In line with this and other similar observations, the Mitochondria Research Society recently published well-grounded recommendations for the design of clinical trials evaluating not single, but a combination of compounds that target two or more of the final common pathways of energy dysfunction [85].

36.1.4.2 Coenzyme Q Implications

One segment of our host defense system program explored some of the modern aspects of aging and their links with the immune system and with some disease states emerging with accelerated frequency during aging. Our objective was not to discover the proverbial "fountain of youth," but to develop the means to delay or to ameliorate the clinical symptoms of the so-called diseases of aging, more specifically the diseases that accompany aging, and thus improve the quality of life.

The immunological senescence in mice and its reversal by coenzyme Q_{10}, further supporting its role as a potent immunomodulating agent, has been discussed previously [86, 87]. In one set of experiments, old mice 16 to 18 months of age were treated with weekly injections of coenzyme Q_{10}. This resulted in a significant reduction in overall age-related mortality as compared with control mice of the same age (Figure 36.6). Furthermore, the mean survival time of the coenzyme

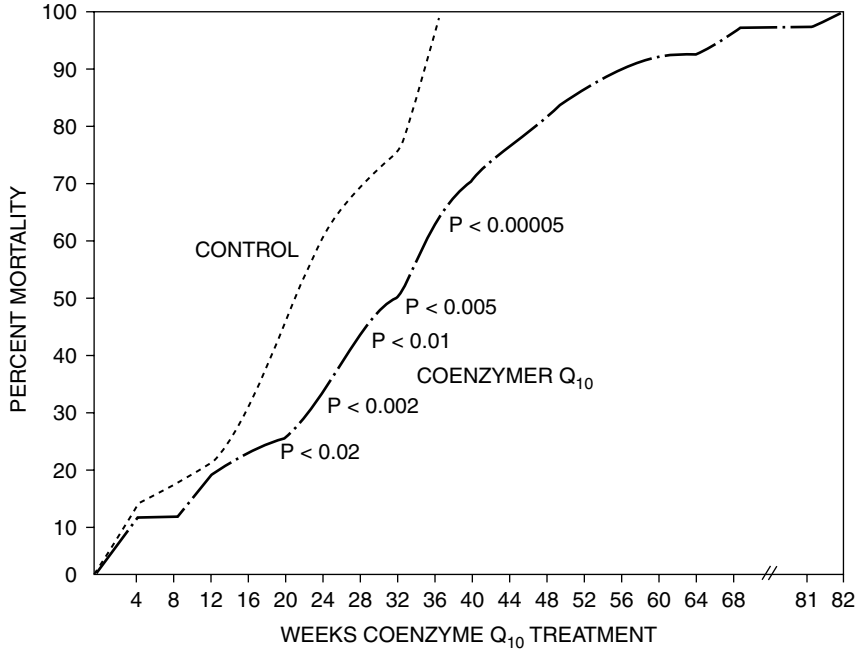

FIGURE 36.6 Modification of overall age-related mortality in old mice (CF1 female) by coenzyme Q_{10} treatment. Coenzyme Q_{10}: 50 μg/mouse (i.p.), administered as an emulsion weekly for 81 weeks starting at age 16 to 18 months (50 mice per group). (From Bliznakov, E.G., in *Biomedical and Clinical Aspects of Coenzyme Q*, Vol. 3, Folkers, K. and Yamamura Y., Eds., Elsevier/North-Holland Biomedical Press, Amsterdam, 1981, p. 311. Reproduced with permission.)

Q_{10}-treated group was significantly increased (Table 36.2). These findings have been presented at several conferences and were also recently reviewed [87–90].

A well-known event associated with the decline of the immune function with aging is the involution of the thymus, regulated tightly by the brain and by the hormonal system. A predominant immunologic change observed in aging individuals is a decline in T-cell (thymus derived) function, affecting both subsets CD4 and CD8. Because of strong T-cell–B-cell interactions, this decline affects the function of both T and B cells, although the B cells themselves remain reasonably intact

TABLE 36.2
Survival of Old Mice Treated with Coenzyme Q_1

	Mean Survival Time after Treatment	
Treatment	**Weeks**	**%**
Control	20.0	100.0
Coenzyme Q_{10}	32.2	156.0 [a]

Note: Duration of coenzyme Q_{10} treatment was 81 weeks starting at age 16 to 18 months.

[a] $p < 0.001$

Source: Bliznakov, E.G., in *Biomedical and Clinical Aspects of Coenzyme Q*, Vol. 3, Folkers, K. and Yamamura Y., Eds., Elsevier/North-Holland Biomedical Press, Amsterdam, 1981, p. 311. With permission.

during aging. Furthermore, the process of T-cell maturation is determined by the degree of age involution of the thymus. The development of new therapies that can be used to enhance thymic regenerative capability in humans with T-cell-depletion states such as aging, cytotoxic chemotherapy, and infections (HIV/AIDS) are urgently needed [91]. Our studies have confirmed the age-dependent involution of the thymus. Old mice aged 24 months retained only 25% of the thymus weight as compared with young mice 10 weeks of age. In a recent issue of the popular *Health and Healing* newsletter (February 2000), it was reported that the thymus in infants is 70 g and shrinks to an incredible weight of just 3 g after age 50. Furthermore, in a joint study with Karl Folkers and his group, we extended the thymus involution study and established that the coenzyme Q_{10} deficiency index of old mice at age 24 months reached 80% [92].

Normal human cells reach senescence after dividing around 50 to 90 times in cell culture. Recent studies show that they have a "molecular clock" that informs them of their limited life span. This clock is the telomere, a structure at the end of each chromosome that shortens with each cell division and thus reminds a cell how many times it has divided before reaching the stage of "replicative senescence" [93]. The involvement of telomeres not only in the aging process but also in cancer progression is evident but unexplored.

Following the publication of our aging studies, some groups of scientists ignored them, while others confirmed our then-unconventional concept. The oft-cited, now classical publication by Kalen et al. [94] verified that in humans 77 to 81 years old, the coenzyme Q_{10} content of heart is only 43% of that present in subjects 19 to 21 years old. A similar pattern was observed in rats. In a small study, Fahy [95] was able to confirm our results, noting the extension of mean survival time in a group of mice receiving coenzyme Q_{10} in their diet. In another publication, Coles and Harris [96], as a part of a general survey, screened "promising single agents for anti-aging properties" using a long-lived strain of mice. At 39 months, 50% of the mice on coenzyme Q_{10}-supplemented diet were still alive compared with only 25% of the control animals. The average life span of the control mice was 30.8 months as opposed to 37.0 months for the coenzyme Q_{10}-supplemented group, a statistically significant difference. The "most spectacular" difference between the two groups, however, was the far greater level of activity in the coenzyme Q_{10}-treated mice. In a study by Lonnrot et al. [97] with rats and mice, treatment with coenzyme Q_{10} did not prolong or shorten their life span. Yet, in a subsequent publication [98], they reported that extended treatment of senescent rats with coenzyme Q_{10} ameliorated the age-associated deterioration of the arterial vasodilatation, frequently the cause of increased mortality due to myocardial infarction and stroke. The authors stressed the possibility that dietary coenzyme Q_{10} would protect arteries against the age-related pathological changes. In a recent article very pointedly entitled "Human aging and global function of coenzyme Q_{10}," Linnane et al. [99] concluded much more generally, "In this paper we asked the question whether coenzyme Q_{10} can ameliorate the rate of tissue aging. The results suggest that this may indeed be possible." In a recently published communication, Wouters-Wesseling et al. [100] evaluated the effect of a "complete nutrition supplement" that also contained coenzyme Q_{10} on the antibody response to influenza vaccine in elderly subjects. The author concluded that the nutritional supplement might have a beneficial effect on the antibody response in the elderly population.

36.2 INTERFERENCE BETWEEN COENZYME Q BIOSYNTHESIS AND DRUGS COMMONLY USED IN CLINICAL PRACTICE

The endogenous synthesis of coenzyme Q in the body is a very complex process requiring numerous substrates and cofactors. A number of commonly used drugs have been shown to cause coenzyme Q deficiency, either by inhibiting its synthesis or by interfering with its transport via blood circulation. This phenomenon has been described adequately during the past 20 years, but it is still ignored or not recognized by the majority of medical professionals and, most importantly, by the

pharmaceutical industry. Furthermore, it is interesting to note that coenzyme Q deficiency is involved in the initiation and progression of the side effects of many drugs. Of particular importance in this group are the widely prescribed lipid-lowering drugs known as statins (HMG-CoA reductase inhibitors). Their use has been shown to cause significant reductions in coenzyme Q and ATP in blood. The reasons are obvious. Cholesterol and coenzyme Q share a common biosynthetic pathway, and an inhibition of cholesterol synthesis at the HMG-CoA reductase step results in an unintended inhibition of coenzyme Q, leading to a deficiency of coenzyme Q as well as other end products in the same pathway.

Coenzyme Q deficiency is implicated at least in part in the development of many of the side effects of statins, such as myopathies and rhabdomyolysis with renal failure, increased incidence of neoplasia, cataracts, peripheral neuropathies, and also some psychiatric disturbances. Despite this long list, the medical literature describes statins as "well tolerated" drugs, and their use in some cases is indiscriminate. *Health News* (September 2001), a publication of the Massachusetts Medical Society, recently sponsored a shocking editorial entitled, "A statin in every medicine cabinet." Another publication in the *American Journal of Cardiology* [101], authored by its editor, is entitled, "Getting more people on statins." It is interesting that the popular magazines such as *U.S. News & World Report* (October 7, 2002) are more critical of this trend than the medical professionals. Notwithstanding this optimistic stand, the German pharmaceutical giant Bayer AG announced on August 6, 2001, the voluntary withdrawal from the market of their statin drug Baycol (Lipobay), also known as cerivastatin. The reason for this swift withdrawal, proclaimed in the German publications as the "Baycol Katastrophe," was the unacceptable high number of fatal side effects following treatment with this drug.

The multiplicity of effects resulting from treatment with statins has been the center of attention, frequently overstated, during the past few years. Referred to as pleiotropic effects, statins influence a wide range of physiologic functions. One of the newly described effects declared as a beneficial capability is immunosuppression [102, 103]. Surely, it might be beneficial in patients with organ transplantation, but it could also explain the increased incidence of infections, neoplasia, and other side effects after long-term statin treatment, events well recognized by clinicians. Since the normal immune response provides surveillance against neoplastic transformation, it is not unexpected that the immunosuppressed host is at higher risk. Statistical evidence indicates that the chance of lymphoma developing in the immunosuppressed transplant recipient is increased 35-fold, with reticulum cell sarcoma occurring at 300 times the expected frequency [104].

Of particular interest is the significant increase in the incidence of breast cancer in one of the clinical trials with statins (designated, regrettably, as CARE) that has been disregarded by most clinicians. Muldoon [*New York Times*, September 5, 2000] set forth this controversy as follows: "We have studies that show statins don't cause cancer within a five year period. Of course, neither does smoking." We have reviewed the literature on the relationship between statin treatment, side effects, and coenzyme Q deficiency, considering the medical [22, 105, 106] as well as the ethical aspects [107], and we advocate the concomitant administration of coenzyme Q_{10} during statin treatment, especially in older patients, to prevent coenzyme Q_{10} deficiency and to support the impaired cellular bioenergetics. It should be stressed here that in addition to statins, there are numerous other clinically useful drugs that interfere with the biosynthesis of coenzyme Q_{10} or its transport. The list of drugs included in this roster contains 49 drugs [108]. Another name was just added to the list based on the observation that long-term corticosteroid administration (the routine treatment for autoimmune and allergic diseases) induces oxidative stress-mediated mitochondrial injury with oculoskeletal symptoms, including myopathy [109].

Adriamycin is an antibiotic of the anthracycline family, and it is a major drug in cancer therapy. Its clinical application, however, has been limited by its often lethal cardiotoxicity in the form of cardiomyopathy. Ultrastructurally, this is characterized by necrosis and degeneration of the mitochondria, resulting in inhibition of respiratory activity. Adriamycin is accumulated within the macrophages, causing loss of cellular function. This contributes to its strong immunosuppressive

TABLE 36.3
Coenzyme Q_{10} Treatment and Humoral Antibody Response in Mice

Treatment	Hemolytic Antibody Units	Percent
1. SRBC (alone)	127.5	100.0
2. SRBC + cyclophosphamide	80.1	62.8
3. SRBC + cyclophosphamide + coenzyme Q_{10}	113.3	88.9

Note: SRBC = sheep red blood cells.

Source: Bliznakov, E.G., in *Biomedical and Clinical Aspects of Coenzyme Q,* Folkers, K. and Yamamura, Y., Eds., Elsevier, Amsterdam, 1977, p. 73. With permission.

effect, associated with a significant reduction (over 50%) in thymus and spleen weights in mice. A single dose of this drug almost completely suppressed the hemolytic antibody production in mice, and coenzyme Q_{10} administration led to a partial but significant reversal [88]. These findings justify consideration of coenzyme Q_{10} as an adjunct to the current treatment regimen with Adriamycin in cancer patients. Similar results have been obtained with the use of cyclophosphamide, another well-known anticancer drug. Data from one study with mice is shown is Table 36.3 [50].

Cancer chemotherapy is certainly effective in the treatment of various forms of neoplasia. Yet, this effectiveness is generally associated with a profound immunosuppression that is well recognized by the medical professionals. It is for this reason that some of the same drugs are used in the treatment of autoimmune diseases, such as lupus erythematosus. Nevertheless, there was a publication in *Cancer Research* many years ago entitled, "Are the cancer drugs self-defeating?" This is a very relevant question that still has not been answered.

The foregoing discussion illustrates the importance of coenzyme Q as a critical component for the optimal function of the immune system at the mitochondrial level. Furthermore, we established the role of coenzyme Q as an active immunomodulating agent using animal models to evaluate various parameters of the immune system (phagocytic rate, circulating antibody levels, neoplasia, viral and parasitic infections). This capability is further enhanced if coenzyme Q_{10} is administered in combination with other specific drugs, i.e., chemotherapy.

36.3 COENZYME Q_{10}: SAFETY CONSIDERATIONS

Coenzyme Q_{10} has an excellent safety profile. No significant side effects have been observed in clinical testing involving thousands of patients on long-term high-dose coenzyme Q_{10} treatment other than mild GI symptoms in a few cases. Parallel with our studies on the effectiveness of coenzyme Q_{10}, we carried out extensive toxicological evaluation, first as preclinical and then as FDA Phase I clinical trial in terminal cancer patients at the Yale Medical School (New Haven, CT) during 1972–1974, and our results on the lack of any significant adverse effects of coenzyme Q_{10} have been confirmed by others. In one recent clinical trial in patients with Parkinson's disease, high-dose coenzyme Q_{10} (up to 1200 mg a day for 16 months) was found to be safe and well tolerated [110]. Chronic toxicity testing using rats at doses up to 1200 mg per kg per day for 1 year has not revealed any adverse changes [111]. Thus, the safety of high-dose coenzyme Q_{10} is well documented. Furthermore, the *Physicians Desk Reference* (1999, p. 3286) categorically states, "Adverse effects — none reported."

Another observation that is relevant to the clinical applicability of coenzyme Q_{10} is that the enhancement of the immune functions established in our program did not result from hyperplastic alterations of spleen, liver, and other organs directly involved in immune system responsiveness. These would be considered as undesirable side effects. Accordingly, the described effects most likely result from an increased activity of existing cells via improved bioenergetic balance.

36.4 REFLECTIONS AND CONCLUDING THOUGHTS

Despite the many advances in both the basic and clinical areas of bioenergetics, and particularly the critical role of coenzyme Q_{10}, progress can be characterized as slow-paced and sometimes disorganized. There are several underlying reasons for this unfortunate situation. The most important ones are as follows:

The pharmaceutical industry continues to have a negative attitude, despite convincing evidence of the therapeutic potential of coenzyme Q_{10}, and it shows a lack of interest in developing products based on coenzyme Q_{10}. The obvious reason, and perhaps a pragmatic one, is that there is no patent protection. A secondary reason may be that the supply of the bulk material is totally dependent on a few producers in Japan, with no alternative sources.

The U.S. government agencies have provided limited financial support for the clinical evaluation of coenzyme Q_{10}, with the exception of three major recent clinical trials funded by the NIH on three neurodegenerative diseases.

Although our understanding of the origin and pathogenesis of neoplasia is far from complete, substantial knowledge has been gained with respect to possible mechanisms and potential therapeutic agents to justify large-scale clinical trials with coenzyme Q_{10} in selected forms of cancers such as prostate and breast, alone or in combination with other therapeutics, as discussed earlier.

A more philosophical point that needs to be emphasized is that coenzyme Q_{10} is a nutrient and not a drug, and therefore it should not be treated as such. Being labeled as a nutrient hinders its acceptance as a potentially useful therapeutic agent by the pharmaceutical industry as well as by mainstream physicians. In this context, we need only to look at the status of carnitine. It is an important nutrient essential for cellular functions like coenzyme Q_{10}, and it is available as a nutritional supplement. Since its therapeutic efficacy has been well established in certain genetic disorders and also in kidney disease, carnitine is also approved and marketed as a drug in the U.S. Coenzyme Q_{10} should be viewed exactly in the same light.

In addition to continuing to explore the efficacy of coenzyme Q_{10}, research is also warranted on the therapeutic potential of derivatives of coenzyme Q_{10}. It is possible that we might identify a molecule that is perhaps more versatile and potent.

Notwithstanding these paramount and rather grim obstacles, data presented in this review indicate that coenzyme Q_{10} is an appropriate candidate for future clinical applications in the "diseases of bioenergetics" and, more specifically, in disease states with impaired immune system function. The incorporation of coenzyme Q_{10} in our, as of now, confined armament in the "war against cancer" should be intensified and facilitated.

In closing, it is appropriate and timely to quote Arthur Schopenhauer (1788–1860), an authority on the philosophy of pessimism, who wrote prophetically, "All truth passes through three stages: First, it is ridiculed; second, it is violently opposed; and third, it is accepted as self-evident."

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