Systemic Lupus Erythematosus: A Combined Deficiency Disease

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Abstract

For more than 150 years, the pathogenesis of Systemic Lupus Erythematosus (SLE) continues to hide its secretive face. In this article, by critically analyzing clinical facts and laboratory data, the author has developed a new theory. It would explain most of the facts and controversies that revolve around the subject. The article begins by linking the cause of drug induced lupus erythematosus (DILE) to a deficiency in coenzyme A (Co A). This theory is then applied to explain the high incidence in females, the role played by the sex hormones, and the reasons for having a flare in SLE. The action of anti-malarials and steroids are also explained–all linked to the same deficiency. The protean clinical presentation of SLE is attributed to the co-existing deficiencies of various dietary factors other than pantothenic acid. These deficiencies may not necessarily reflect an insufficient intake, but rather an increased demand of these substances as a result of gene mutation. For replacement, a high dose of pantothenic acid, together with other essential nutrients, is given. This theory is supported by recent work that suggests the low activity of an enzyme can be remedied by raising the concentration of cellular coenzyme level by administering high doses of the corresponding vitamin that is hundreds of times larger than that of the normal Dietary Reference Intake (DRI).

Abbreviations: SLE, systemic lupus erythematosus; DILE, drug induced lupus erythematosus; DRI, dietary reference intake; Co A, coenzyme A; M.W., molecular weight; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate.

Key words: lupus, coenzyme A, sex hormones, pantothenic acid.

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Introduction

The name Systemic Lupus Erythematosus (SLE) was coined in 1851.[1] Since then, an untold amount of work was done in an effort to find out its pathogenesis. Despite the strides that were made all these years in revealing the various aspect of the disease process, the cause still eludes us. However, there are certain aspects of the disease process that are so uncommon and unusual that, by approaching them from a different perspective, new conclusions might be drawn. One of these is Drug Induced Lupus Erythematosus (DILE). By examining the clues that lie therein, this article makes an attempt to elucidate the pathogenesis not only of DILE, but also SLE. The first part includes an analysis of some of the important clinical data that are available and the conclusions that can be drawn from there. The second part is a discussion on the management scheme.

The Pathogenesis of DILE: A Hypothesis

Ruling out the Impossibilities

It is indeed a unique phenomenon. Seventy odd drugs, all structured differently, with different chemical and pharmacological properties, would give rise to identical symptoms when taken by an individual with a tendency to having the disease process.[2] Not only do these drugs have their respective actions, they also have their own metabolic by-products and elimination fates. The way through which they give rise to the same symptoms is a complete mystery. Attempts had been made to explain this inexplicable phenomenon. None is convincing enough to survive close examination. The more recent suggestion that these drugs might bind themselves to DNA and form new antigens that might stimulate the

immune system in an unknown way also finds little support in experimental and clinical studies.[3-5] If anything, such suggestions would only throw matters into more confusion. We will then need to explain the peculiar properties of these few dozens of drugs that would enable them to form new antigens without the rest being able to do so. Furthermore, there are clear differences among these DILE agents. Some seem to be able to cause symptoms much more easily than the others. It is patently clear that it is not possible to reconcile the clinical observation in this disease process with the present day knowledge and understanding of pharmacology, immunology and medicine. All these arguments point to just one possible conclusion: These drugs simply cannot, by their action, direct or otherwise, be the cause of DILE.

Looking for a Common Thread

To solve this mystery, the logical approach would be to look for something that is shared among these drugs, for the simple reason that only common properties will give rise to symptoms that are the same. For simplicity's sake, it is easier to narrow down the list of 70 odd drugs to the three drugs that carry the majority of cases of DILE: procainamide, hydralazine and isoniazid. On close examination, they do have just one thing in common from the point they enter the body to the time they are eliminated. It is the acetylation process by which they are metabolized. The acetylation process is not the commonest process for drugs to be metabolized, and it is quite extraordinary that all three are metabolized in the same manner. This coincidence alone is revealing enough that the metabolic process should deserve greater attention. The crucial question here: Is it acceptable, against traditional teaching, to incriminate a metabolic process as the culprit in this mysterious disease? It was Sir Arthur Canon Doyle who once said, "When you have eliminated the impossible, whatever remains, however improbable, must be the truth (The Sign of Four)." Since this is the only material clue, it is worthwhile to give it a close scrutiny and a detailed analysis.

The course, or fate, of a drug after it is ingested is relatively simple. It is absorbed, and even as it is distributed to its final destination, the elimination process begins. At the target sites, the drug exerts its action. This is what is commonly understood about drug actions. Little attention is paid to the elimination process, which usually, but not always, involves some enzymatic metabolic breakdown of the drug, of which the acetylation process is one.

A Deficiency Theory: Deficiency in Coenzyme A

The acetylation process is relatively simple. It involves the transfer of the acetyl group in acetyl-Co A to the molecule that is to be metabolized, leaving Co A in its thiol form. This will in turn combine with pyruvate and return back to its original form of acetyl-Co A. With this newly formed molecule, the acetylation process can again go on, and on, in like manner, in a cycle, or so it seems. It is generally held that this process of acetylation by acetyl-Co A can go on continuously forever. This is based on the belief that a coenzyme, which often includes a vitamin as a component, is not perishable. With this concept of a coenzyme deeply ingrained in the mind, it is small wonder that any thought that trouble could come up from there is readily dismissed. It is fundamentally important to remember that there is no proof that this cyclical event, as it is pictured in the mind, is absolutely true.

There is another way of looking at this supposedly cyclical event. It no doubt is a cyclical event, but it is unlikely to be a

perfect cyclical system that incurs no loss of the coenzyme at all times. If such were the case, it would not have been necessary to take in a certain amount of vitamin everyday, for the sake of replenishment. What is likely to happen is that there is always some form of a loss in this cyclical process. A wear and tear process, if you will, that would need maintenance. Depending on the individual's ability to handle this process and other factors, the need for replenishment would differ. In those whose replenishment could barely maintain a positive balance, any additional work that would require more of such replenishment, as when any one of the three drugs is taken, would push the balance into negative territory. Short of additional intake, this negative balance would build up, and in due course a deficiency would occur. It is obvious that, no matter which one of the three drugs is taken, the outcome would be the same. The clinical manifestation of DILE amounts to no more than a shortage of the coenzyme.

The long observed phenomenon that the onset of DILE is typically delayed now finds an easy explanation. It has a lagged period that varies from patient to patient. What it really amounts to is that every individual, aside from having his own pool of reserve of the coenzyme, also has a different capability of managing the wear and tear process. Anytime when the pool of reserve is exhausted, when not enough of the coenzyme is left to serve its various functions in the body, symptoms begin to set in. When the drug is stopped, when things revert back to its former state, when extra demand is no more needed, there is a gradual replacement, and symptoms slowly disappear. This behavior again correlates well with clinical experience.

This theory in essence relates the workload of the metabolic process to the symptoms. The more work that needs to be done, the more will be the loss, the sooner and the more severe are the symptoms. The workload is necessarily directly proportional to the number of molecules taken, which is dependent on the dosage and the molecular weight of the drug.

It is interesting to note that patients on isoniazid, a drug that has a smaller molecular weight (M.W.=137.1) and requires a bigger dosage for its effectiveness than either procainamide (M.W.=271.8) or hydralazine (M.W.=196.6), are less prone to have DILE than the other two. But this offers no contradiction to the present theory. Unlike procainamide and hydralazine, whose main metabolic breakdown pathway is the acetylation process alone, isoniazid has at least two main pathways for its breakdown.[6] There is the hydrolysis process in addition to the acetylation process. In the body, all metabolic processes are in a state of dynamic equilibrium. A drug's metabolic pathway, if found inefficient or ineffective due to a deficient enzyme, will shift to an alternative route whenever possible, one that is next best in doing it. With its ability to do so, isoniazid's chance in causing DILE is reduced. It is well known that the metabolism of any drug, while there is a general pattern for it to follow, shifts and varies all the time, depending on the overall biochemical environment. And that is exactly the reason why some of those seventy odd drugs that cause DILE may not seem to have anything to do with acetylation at all. It is likely that in the metabolism of these drugs, a series of interconnected reactions are involved, and in the course of which the acetylation process is called into play, and shortage of the coenzyme sometimes ensues. Admittedly this is something uncommon. But so are the incidences of many of those drugs that are reported to cause DILE.[7,8]

It is perhaps appropriate here to add a few words on how the human body handles a deficiency state. It is important

to recognize that the internal environment of the human body is a hugely complicated system that is in constant dynamic biochemical equilibrium where metabolic pathways may shift from one route to another possible route when it is required to do so. The body always does this with its best interest in mind. The metabolism of isoniazid is a good example. When Co A is deficient, the acetylation pathway is partly diverted to hydrolysis. This delays, and avoids as it sometimes does, the onset of an otherwise unavoidable disease process. This is obviously a move that will benefit the body as a whole. In a situation where not enough of a coenzyme is available to carry out all the work that it needs to do in various tissues, the same principle applies. The body has to figure out a way to distribute or re-distribute its resources in such a situation. In short, it is a rationing process that the body has to take. The fundamental law of natural selection will rule that the more important an organ is, the more ration it is going to get. This is nature's way of prolonging the life of the organism. It is not surprising then, that, in all deficiency diseases, the first manifestations are skin and joint and connective tissue lesions. The vital organs are only involved much later on. There are many examples illustrating this point in what is to follow in this article.

So far, this initial evidence relating a deficiency of Co A to symptoms of DILE provides a prima facie case that it is, like scurvy, a deficiency disease. It is logical to ask if the same argument can be extended to SLE, a disease that is closely linked to DILE? To make such a case, it is of first importance to show that there are other instances where the same correlation exists. Failing this, the theory would be just another speculation that cannot live up to the tests that are applied to it. The fact is such examples abound. I will go through some of the more important ones.

Systemic Lupus Erythematosus

The Sex Hormones: Amounts Secreted Do Matter

SLE is a disease that mainly involves women of childbearing age. The incidence is highest in those who are between 20-40 years of age. In this age group, the female and male ratio is roughly 10:1.[9] Incidence of the disease is relatively rare before puberty, and the sex ratio is a lot smaller. Then, beginning at puberty, there comes a change. While incidence of the disease process in both sexes goes up, in the female, it is a big jump over the male. The disparity of the sex ratio becomes very obvious. It continues on throughout the reproductive years until around the menopausal period when the ratio starts to narrow down again.[10] There has never been any satisfactory explanation for this phenomenon, which represents one of the most baffling and mysterious aspects of the disease process.[11-14] Any new theory as to its pathogenesis will need to explain this very unusual phenomenon.

The newly proposed theory suggests that this is the logical event to occur. At puberty, the sex organs and secondary sexual characteristics begin to mature, a process that needs a lot of sex hormone. As an individual enters puberty, the blood levels of sex hormones actually increase by a magnitude of some several dozen folds.[15] This poses a heavy demand for Co A, which is essential for the synthesis of all sex hormones and their precursor cholesterol. In most instances, the body can cope with this. But in a few, this proves to be just a bit too much, and symptoms of deficiency begin to appear. Among these few, the females predominate. This is by no means a random event. It has everything to do with the usage and consumption and replenishment of Co A, which is closely tied to the difference in the absolute amount of sex hormones produced in the male and female.

Female Predominance

Both the male and the female secrete a host of sex hormones that includes androgens and estrogens and their analogues. It is well known that there is a difference in the proportion of hormones between the two sexes. In the male, androgens predominate. While in the female, they are the estrogens and progestogens. However, there is in the literature not a single paper that actually compares the amount of sex hormones that is secreted by the male and the female respectively over a designated time frame. This reflects that no one thinks that this is of any significance. But it is of tremendous importance in order to explain the very unusual sex distribution of the disease process. Independent studies of sex hormones secreted by the female over a period of 28 days, the length of a menstrual cycle, and the sex hormones secreted by the male over the same period of time, showed that there is a definite difference in the amount. The males secrete their hormones in a relatively constant manner with little day to day variation in the amount secreted. In the female, it is different. Every menstrual cycle represents the building up of the uterine endometrium that prepares for the reception and implantation of a fertilized ovum followed by its menstrual flow, when the anticipated event does not occur. There is clear evidence to suggest that such a building up and dismantling process needs more sex hormones than in the male whose only need is for the maintenance of the sex organs alone. The secretion of estrogens and progesterones during each cycle rises and falls according to the demand, and is graphically represented by a curve that is not unlike that of a typical sine curve, with crests and troughs. A careful analysis of the total sex hormones secreted by the two sexes during this period supports this viewpoint

The male is estimated to secrete about 7mg of testosterone, the main sex hormone that he secretes, per day all through this period.[16] In the female, just in the luteal phase alone, the amount of progesterone secreted is more than 25 mg per day.[17] This amount is already more than the total testosterone produced by the male in the 28-day period. Take into account the 17-hydroxyprogesterone and the various estrogens, the production is much more. This would mean that the rate of usage, and hence the wear and tear of Co A in the female is far greater than that in the male. This obviously increases the chance of a female going into a relative deficiency state. With every passing cycle, every passing year, this relative deficiency adds up, and the chance for her to actually going into a deficiency gets bigger by the day as she grows older into womanhood, when symptoms begin to appear. In clinical practice, this translates into more cases of SLE with every passing year as the females go from puberty into adulthood and continue well into their middle age years, and the sex ratio widens. The basis of this explanation again holds true when it is extended to post-menopausal years. The females stop to menstruate and the incidence of the disease process narrows.

Adaptation to a Deficiency State

Low Sex Hormone Levels

As this deficiency is brewing, the body is quickly adapting itself to this changing and challenging environment. The initial effort will be through a process of retrenchment that would have far reaching effects. All systems need to cut down their Co A usage. This is in a manner that is tied to their importance to survival. The sex hormones, important as they are to the sex organs and to the propagation of life, also are forced to respond. Studies in sex hormone levels in SLE patients seem to support this proposition. Estrogen concentrations in most studies are typically low to normal in these patients.[18-22]

Progesterone levels are also lower than the controls.[22-26] Even in pregnancy, where the expectant mother needs more female sex hormones to support her pregnancy, SLE patients show abnormally low progesterone and estrogen levels.[20,24] Similarly, both female and male lupus patients have lower androgen levels than normal.[27-31] Meanwhile, both the follicular stimulating hormone (FSH) and the luteinizing hormone (LH) in both female and male SLE patients are elevated, and in some instances significantly so.[32-34] All these data suggest that the body, without enough of the coenzyme at its disposal, is unable to cope with a normal demand of essential hormones. This is even at the prompting of both FSH and LH, more of which are secreted in response to callings of low levels of estrogens and progesterones. This is a feedback mechanism that in normal circumstances maintains the proper levels of these hormones. But in the absence of enough of the coenzyme, it is a failed attempt. The gonads and the adrenals are simply incapable of secreting more despite their being urged to do so.

These low levels of sex hormones have often surprised investigators. This is contrary to what they suspect to be the role played by sex hormones in SLE. Though no conclusions have been drawn, estrogen is often seen as a promoter of the disease process, and its low levels in these instances do not seem to support this view. Androgens, when it is seen as a protector, should have a higher blood level than normal to carry out its role. Instead, the levels are also low. When this deficiency theory is applied, all the paradox falls into place. The part played by the sex hormones is largely misunderstood. The low level of these hormones is but a reflection of a limited supply of an essential part of the raw materials that is necessary for the synthesis of such hormones. The inability on the part of the body to provide a sufficient amount of the coenzyme causes it to have no choice but to cut back on its hormone production. This is the reason for the body to have sex hormone levels that are lower than in normal individuals.

This postulation finds support from other relevant data. One of the more commonly observed manifestations in connection with this is the flare that occurs premenstrually and during pregnancy.[35,36] In these instances, in which extra supply of sex hormones is required, the already stressed reserve is extended beyond its limits. It can no longer meet its demands, and an exacerbation occurs. This is in contrast to situations where the secretion of sex hormones is curtailed dramatically, such as when there is ovarian failure, or when the ovaries are removed, with improvement of the clinical condition.[37] Irregular menstrual cycles and amenorrhea are common symptoms in SLE patients, as are late menarche and early menopause.[36-41] The attempt made by the body here is perhaps obvious. It is an effort to conserve the coenzyme by slowing down, delaying, or shutting off the production of female hormones altogether. After menopause, when there is a dramatic decline in the secretion of the sex hormones, the disease process becomes quiescent and flares much less frequently.[42] The present theory provides a simple and yet logical explanation to correctly observed phenomenons that are previously proved difficult to understand.

Low Corticosteroid Levels

The sex hormones are not the only hormones that are affected by this supply and demand process. All the corticosteroids, which are built on the same cholesterol backbone, behave similarly as the sex hormones do. The many parts they play are more important in maintaining life than are the sex hormones. The body cuts back on their production as well. In SLE patients, serum levels of dehydro-

epiandrosterone (DHEA), DHEA sulfate (DHEAS) and cortisol are all significantly lower as compared to controls.[43,44] At a time when the body is under the influence of the stress of a disease process, one would have expected the body to churn out more of these essential hormones to combat stress, which is one of the more important functions of these hormones. However, shortage of this coenzyme does not allow this to happen. The best it can do under this difficult environment is to keep a low level of cortisols. When compounded by psychological and emotional stress, situations in which more cortisol is needed, these patients frequently go into a flare.[45)]

Role of Steroids

Taking into account the part CoA plays in steroid synthesis, together with the low levels of cortisol in SLE patients, it is not difficult to understand the action of steroid in its treatment in this disease process. Steroid treatment in such a condition has always been empirical, and there is no reasonable explanation to suggest how the medication might work. The side effect arising from its therapy is severe enough to prevent physicians prescribing the drug as a first line of defense. It is only used when other drugs have failed and the disease process is in a rather advanced state. Aside from what is normally claimed to be its anti-inflammatory and anti-immunity properties, there are other good reasons for the initial prompt response of steroid therapy when the whole situation in seen in the context of a deficiency in the coenzyme. The body is often severely affected by the disease process when the physician decides that steroids be administered. Its shortage of the coenzyme is no longer mild, as evidenced by the low serum levels of the corticosteroids, which, no doubt, contribute significantly to the clinical condition. On top of this, the steroids have some peculiar properties of their own that would aggravate the deficiency. They are not stored in the body in any significant amount. They have to be synthesized as a continual process by the adrenals. That is to say, even when the deficiency is at its worst, if life is to go on, some of the very little amount of the coenzymes that is still left with the body system needs to be directed to this end. This may mean a production rate that is far below normal levels, nevertheless, an amount that needs to sustain life has to be provided for. Steroids administered at this difficult time will serve at least two purposes. It serves to supplement the very low levels of corticosteroids that are barely enough to keep the body processes going. In addition, it also exercises a coenzyme sparing effect, allowing other slightly less vital mechanisms to claim their shares of the coenzyme that are denied to them previously.

In administering a steroid hormone, aside from the side effects that are all too familiar to physicians, there is a distinct disadvantage. It upsets the homeostasis of the finely balanced ratio of the different steroidal hormones that are in various stages of synthesis, one that is dictated by the auto-regulatory mechanism. Such interference is obviously not wanted. The body would do much better if enough of essential raw materials were supplied. This is the clear advantage of administering essential nutrients over synthetic exogenous hormones. The much-talked about DHEA and DHEAS in the treatment of lupus patients can be seen doing very much the same thing. They are in a way prefabricated hormones that are in readiness to convert largely into testosterone and estrogen, which again provide a coenzyme sparing effect by skipping a few steps in the synthesizing process.[46-48] However, they also upset the balanced levels of different analogous steroidal hormones, which can be extremely undesirable.

Action of Antimalarials

The coenzyme sparing effect is not limited to steroids with a cholesterol structure. Consider Plaquenil and its other quinine derivatives, the anti-malarial drugs. It is as unlikely as any other drugs that Plaquenil, a highly effective drug against the erythrocytic form of the malaria parasite but by no means non-toxic, should have a beneficial effect on SLE patients. Its treatment here is again empirical and restricted to milder forms of SLE. Its use does not seem to bear any relationship to steroid synthesis either. But studies have shown that it has a property that it shares with CoA in lowering serum lipid and cholesterol levels.[49-54] It is this property that spares some of the coenzyme, allowing it to engage in other reactions that are already under duress. This alleviates the deficiency a little and helps the clinical condition. Admittedly, this is not an important property when the coenzyme is grossly deficient and survival is threatened. That is exactly why the anti-malarials are only of use when the condition is of a mild or moderate nature when CoA still has a share in lowering the lipid and cholesterol levels. In serious conditions, the dire condition is such that the body can care little for the serum level of cholesterols, nor lipids, which poses no immediate question of survival. In such instances, as is again borne out by clinical experiences, these drugs are not of much value.

Circumstantial Evidences: Symptoms of Deficiency Syndromes

Classical Deficiency Syndromes

All these instances provide what I would call the more important material proofs that SLE is indeed closely tied to a deficiency in CoA. They illustrate the ingenious way the body adapts itself under such desperate and trying conditions so as to allow it to suffer the least damage. There are other evidences that I would call circumstantial to support this proposition.

The response of the body to nutrition depletion has always followed a certain pattern. As has been suggested, natural selection dictates that those organs that are less important to an organism's immediate survival are affected first. The description of scurvy, beriberi, pellagra, rickets and other similar diseases in the 1911 edition of the *Encyclopedia Britannica,* at a time when vitamins were not even known to exist, can attest to this. The initial stages of what we now know to be deficiency diseases had many features in common. They all had a chronic character with an insidious onset and were seldom recognized initially. They all had constitutional symptoms that included tiredness, feeling unfit for work, headache, low-grade fever, loss of appetite with weight loss, numbness in the extremities and muscle pain. Skin lesions that include some kind of a rash were common, as were mucosal lesions of the gastro-intestinal tract, noticeably the buccal mucosa.

Comparing SLE Symptoms to Classical Deficiency Syndromes

In SLE, the sequence of events unfolds in a similar manner. It is typically difficult to diagnose the disease in the initial stage, and it is not uncommon to take months, if not years, before the diagnosis is made. It has constitutional symptoms that are not unlike those that suffer from scurvy or beriberi. Fatigue, which is quite characteristic of lupus, stands out as the commonest symptom. Then, there is the fever, which is common in those patients with an active disease process. There is loss of appetite and weight. Arthritis, arthralgia, and myalgia are common. Here, one may venture to suggest that the appearance of these symptoms are steps taken by the body to limit activity as a means of conserving the deficient factors, and that raising the body temperature has the ef-

fect of increasing enzyme efficacy. Then there are the skin and mucosal changes. Even when important organs like the lungs and heart are involved, often later, it is the relatively unimportant pericardium and pleura that are involved in the beginning. It is quite uncommon for the myocardium and the lung tissue proper or the kidneys or the brain to be involved at an early stage.

Symptoms in DILE patients add further credence to this argument. These patients, before the onset of symptoms, are already at the brink of deficiency. When they do experience the first symptoms, the predominant clinical presentation is often symptoms of the musculoskeletal system while involvement of the renal and central nervous system is rare or absent.[55] Like all deficiency diseases, which mainly affect people of lower social economic classes, SLE is more prevalent in third world countries, and has a much lower incidence in wealthier families.[56-58]

The list here that suggests SLE has all the elements of a dietary deficiency syndrome is by no means complete. For the purposes of this article, it is enough to say that a lot of what is known of the disease fits well with a deficiency of the coenzyme. This is in essence a deficiency in pantothenic acid, the only component of the coenzyme that is an essential dietary factor. There is, however, one aspect of the disease process that does not fit with a theory that suggests the deficiency involves a single essential dietary factor. The unusually wide array of symptoms and signs can hardly be explained on such a theory alone. Indeed, the protean symptoms and signs shown in SLE patients are without parallel in medicine. It is not uncommon for a SLE patient who goes into relapses to have symptoms and signs that are quite unlike those of previous attacks. If it were a single factor deficiency, one would have expected the symptoms to remain very much the same. It is a condition that requires other explanations, aside from deficiency of pantothenic acid alone.

A Combined Deficiency Syndrome

A diverse genetic variation nowadays is no longer seen as an array of infirmities, but rather a broadening concept of what is accepted as normal, and individuals may require nutrients in widely varying quantities to satisfy their daily needs.[59] In this context, it can hardly be expected that a patient, who has a deficiency in one dietary element, either due to an elevated demand or an actual deficient intake, should have his deficiency limited to that particular element alone and be immune to other deficiencies. What is more likely is that he would have other deficiencies as well. The deficiency may range from vitamins to minerals and trace elements and from essential amino acids to fatty acids and phospholipids. It is important to remember that the magnitude of deficiency in each of these various nutrients can vary through a wide range, from a slightly to a grossly deficient state. Putting these two variables together, there will form a combination of variations that is virtually limitless. Translated into clinical terms, the presentation can vary through a spectrum that is so large as to pose no limit to it. This is what is seen in SLE.

It is reasonable then to hypothesize that SLE is a disease that arises from combined dietary deficiencies, the main deficiency of which is pantothenic acid. These other deficiencies vary with the physical state as well as the environment, resulting in a clinical picture that is totally unpredictable but familiar to those who have extensive experience of the disease process. It is now up to the medical community to investigate the other dietary factors that may be associated with each and every of these patients. What are the factors that are more commonly involved in these patients, and the dosages required

to replenish their deficiencies? These are the goals to achieve, and will need the combined effort of many, in fields that include nutrition and medicine.

Discussion

Replenishment

Once it is determined that SLE is a deficiency disease, it may seem a simple matter to institute treatment, but it is not. For the purposes of discussion, it is perhaps easier to forget all the other deficiencies and concentrate on its main deficiency, that of pantothenic acid. It should be stressed that orthomolecular therapy with vitamins and essential dietary factors have long been tried in the management of SLE, without success. A failure in response in such an instance does not necessarily mean that the hypothesis is without ground, and that there is no deficiency after all. Rather, it could mean that the dosage given as replacement is not the right one. It is far too small to be effective. It has to be admitted that these previous attempts in using dietary factors to treat SLE are all empirical. Without any basis for doing so, the treatment is apt to be half-hearted and the dosage administered in line with the DRI. Now, circumstances have changed. There is overwhelming evidences to suggest that it is a disease that is deficient in pantothenic acid. It is only when the replacement is not enough that the replacement therapy fails. Given a large enough dosage, if the reasoning prevails, it will work.

The Proper Dosage

I now turn to this very important question: What is a large enough dosage? What is the proper dosage to administer? In view of what I have just discussed, one of the possible answers will be that their nutrient requirements are very different. They are not deficient in these nutrients by normal standards. However, in conditions where they need much more, it is an entirely different problem. There are several reasons to support the viewpoint that their requirements may indeed be quite different.

Biochemical Individuality

About fifty years ago, Roger Williams introduced the idea of biochemical individuality.[60] He essentially said that biochemical variations among individuals can be very large, particularly the requirements of essential nutrients. The vitamin that forms part of an enzyme/coenzyme system is a good example here. From the time it is ingested, it needs to go through many processes that include digestion, absorption, transportation and assimilation before it is incorporated into the system. The effectiveness of the structures and mechanisms that are involved in each and every step in these different processes, probably genetically determined, can vary. These many steps, when taken together, can alter the requirements of some of these essential dietary factors by many, many folds among individuals.

On the same issue of biochemical individuality, Pauling, in his work on vitamin C, arrived at a conclusion that suggested the requirements for vitamin C in humans might vary through an eighty-fold range in a large population, from 250 mg per day to 20 g a day.[61]

Mutations and Single-Nucleotide Polymorphism

The recent studies by Ames[62] probably gave the strongest support to these viewpoints. He showed that there are enzymes whose Michaelis constant increased with a decreased binding affinity for their coenzyme as a result of mutation of genes, a common form of presentation of which is single-nucleotide polymorphism. He cited many such polymorphisms, in each of which the variant amino acid changes the configuration of the binding site for a coenzyme. This reduces coenzyme binding and thus enzymatic activity by up to

as much as 150-fold. The activity of the enzyme is likely to be remedied by raising the concentration of cellular coenzyme level by administering high dose of the corresponding vitamin. He is of the opinion that such a concept, with a lengthening list of single nucleotide polymorphism everyday, may present a rationale for high dose vitamin-therapy, perhaps hundreds of times the normal DRI in some cases. He then quoted Pauling, who in 1968 wrote, "The still greater disadvantage of low reaction rate for a mutated enzyme with K[m] only 0.01 could be overcome by a 200-fold increase in substrate concentration to [S] = 400. This mechanism of action of gene mutation is only one of several that lead to disadvantageous manifestations that could be overcome by an increase, perhaps a greatly increase, in the concentration of a vital substance in the body. These conclusions obviously suggest a rationale for megavitamin therapy." In SLE, whether such single-nucleotide polymorphism exists, or indeed is the main cause for the clinically expressed coenzyme deficiency, remains to be seen.

Acne Vulgaris and Megadose Pantothenic Acid

Finally, there is my own experience with pantothenic acid in the treatment of acne vulgaris, whose pathogenesis I ascribe to a deficiency in the vitamin.[63] Based on Pauling's work on vitamin C, I chose to use a dosage of 10 g a day of pantothenic acid. It turned out to be a good choice. Since the paper was published, and the concept spread through the medium of the internet, more people are using the vitamin to treat their acne. The picture has now become clearer. There were those with a moderate degree of acne who started on an initial dosage of 1-3 g of pantothenic acid a day. While there were some who showed response with that dosage, a good proportion had found little or no improvement of their condition for up to two or three months. By increasing the dosage to 5-10 g, the improvement was noted much sooner. I would say that those with a moderate degree of acne, the rapidity of the response's onset is almost proportional to the dosage given. The bigger the dosage, the sooner will be the response. Those with severe acne, even given a dosage of 10 g a day, may take anything from 4-8 weeks to get a definite initial improvement. There were patients in this category who stepped up the dosage to 15-20 g a day on their own accord after the initial response of 10 g a day did not meet their expectations. In these instances, the response is always better with a higher dosage. All these observations suggest that the requirement of an essential dietary factor, in this case pantothenic acid, varies considerably from individual to individual.

Based on these arguments, I have decided that the appropriate replacement to be used in SLE patients should be 10 g of pantothenic acid a day, the same dosage as used for treating acne patients. This dosage is large by conventional standards, but it is a safe dosage.[63,64] This is not supposed to be a standard replenishment dosage. It is a dosage that is pending revision, one that is dependent on future research efforts to determine the needs of individual patients. The medical and scientific community may find this an urgent mission to accomplish in view of the importance of the disease process and the number of sufferers afflicted by the disease and the mortality carried with it each year.

It is not immediately clear what leads to a pantothenic acid deficiency in SLE. One of the possibilities is that this can be a manifestation of a single-nucleotide polymorphism in which a very large amount of the vitamin, and its coenzyme, is required to fill all the binding sites of the enzyme-coenzyme complex that has been distorted by this polymorphism. In such an event, the deficiency really rep-

resents a relative deficiency in which the demand for the coenzyme is simply a lot higher than those with a normal binding site. This can be the reason for SLE to occur in neonates and in children. However, for most patients, the mechanism leading up to the deficiency may not be severe enough as to cause symptoms until the requirement of the vitamin is greatly increased, as when they go into puberty and beyond. For the unfortunate few who start to have symptoms in childhood, the mechanism leading up to the deficiency process is perhaps more severe. Unless cared for properly, these cases would have a poorer prognosis. This is quite consistent with available clinical data.[65]

To end this article, I would like to include a small series of twelve SLE patients who were given supplementation of nutrients. These were all proven cases of SLE, being followed up in local rheumatology clinics for at least two years. They were all females with age ranging from 18 to 43. They were all on medications that included non-steroidal anti-inflammatory drugs (NSAID), Plaquenil and steroids. They were asked to continue their follow-up in their respective clinics. The only difference was that they were given supplementation of nutrients. This is in the form of 10 g of calcium pantothenate, 2 g of vitamin C, 500 mg of B_1, 200 mg of B_6, 2 mg of B_{12}, and two tablets of Super B and two tablets of multivitamins with minerals per day. In designing the supplementation, the author freely admits that it was arbitrary. It was based on the personal experience of the author with vitamins and certainly would have to be revised in the future according to the needs of the patients. There probably are many other nutrients that may need to be replaced, and at different dosage range. But to straighten out all these, it would be a tremendous effort that requires the cooperation of nutritionists and research scientists and physicians alike. For the present purpose, the author just concentrates on pantothenic acid, and some of the vitamins that he feels are of help to these patients. Their nutritional therapy was followed up at 4-6 week intervals for 1 to 2 years. The results were more than encouraging. Within four weeks, they all showed a varying degree of improvement. They all felt better, with particularly noticeable improvement of their symptoms of fatigue. Later follow-up showed that the incidence of fever was much less. There were no major flares during the follow up period. In most cases, they also had their other symptoms and signs improved, sometimes significantly so, and were able to have their original medications reduced.

Conclusion

We can say that, all through these years, we have accumulated a wealth of clinical information about SLE. Unfortunately, all these are isolated facts that cannot be strung together for want of a tenable theory as to the cause of the disease process. However, with this newly proposed theory, many of the mysteries and controversies that revolve around the subject can now have a rational explanation, suggesting that it may well be the cause of the disease process. The question of orthomolecular therapy again is raised. It is interesting to see if conventional medicine, having so much bias against the idea that large doses of vitamins are required by many, is going to change its view point and position. Perhaps. It is because this time around, things are a little different. And I'll tell you why.

When Pauling started to champion large dose vitamin C therapy for the common cold, cancer, and a host of other diseases, there was much controversy. The many studies that showed the benefits of large doses of vitamin C were very often challenged by studies showing unimpressive results. No conclusions could

be reached because of these conflicting reports. The main reason for this is that there is not a single parameter that one can measure to show vitamin C's benefit. I will give an example to illustrate my point.

When we say that vitamin C has much to do with connective tissues and collagens, all that one can do is to show the swelling of such tissues in cases of deficiencies, as in scurvy. With replenishment, the swellings are gone. But because there is not a parameter to measure the deficiency, nor the swelling, nor the strength of the collagen, there is no way that we can tell how healthy or how poor is the collagen tissue, before the treatment and after the vitamin is administered. The failure to make such measurement will invariably lead to arguments that are so familiar to us. People begin talking about good health as different from a state that is just short of overt deficiency. There can be no agreement on this, and the debate will go on and on, and will never end.

This is distinctively different from say, iron deficiency anaemia where one can actually measure the severity of the disease process, many a time, not by the level of serum iron, but by the haemoglobin level. This haemoglobin level is the parameter that I am referring to. It is a parameter that we can use to measure the degree of deficiency that the patient has with iron. By administering iron, we can actually quantify the response by measuring the haemoglobin level. This is something we have not been able to do with ascorbic acid, or any other vitamins. There is not any such parameter that can be attached to all the vitamins that we have studied. Until now. In SLE, we have low sex hormone levels, we have low cortisol levels, and we have low levels of DHEA and a lot other steroidal hormones. If we were to administer pantothenic acid in such instances, measurement of these hormones will provide us a guideline as to how much of the vitamin that the patient actually needs. I am sure a large-scale study will settle this very sensitive as well as extremely important issue. And we can tell, once and for all, if vitamins are required in large doses in at least some individuals.

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