A Stone that Kills two Birds: How Pantothenic Acid Unveils the Mysteries of Acne Vulgaris and Obesity

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Abstract

Acne vulgaris is the most common disease of the skin. Obesity is arguably the commonest of a clinical entities in the affluent society. The pathogenesis of these disorders is far from clear cut and they appear to have little in common. In the present paper it is hypothesized that the pathogenesis of both acne vulgaris and obesity is largely due to a relative deficiency of the same agent, pantothenic acid, a vitamin that is hitherto quite unknown to cause any deficiency syndromes in man. Furthermore, the evidence suggests that surprisingly large doses of pantothenic acid are required to overcome deficiency states as illustrated in the treatment of acne vulgaris and weight reduction.

Introduction

In reviewing the numerous studies that deal with the pathogenesis of acne vulgaris, and one gets the impression of reading a detective story. There is the victim. The facts are all there. There are all the clues, as well as the suspects. But the culprit cannot be identified. The identification is made the more difficult because the clues seem all tangled up. At times, they fit in with the suspects very well, other times however, the same clues are contradictory, and appear to lead to a hopeless situation. In the same way, it is quite a mystery that an over-weight person, with an abundance of energy deposited as fat depot, cannot efficiently use this stored fat in times of need as during dieting when food intake does not meet the energy demand. Not only is this precious stored unavailable,in some cases it is actually squandered.

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In two previous articles[1,2] the author reported that both of these two conditions are related largely to a deficiency in dietary pantothenic acid. It is the aim of this present article to expand and to describe in greater detail the reason and logic behind the hypothesis.

The Pathogenesis of Acne Vulgaris: a Hypothesis

Over the years, the pathogenesis of acne vulgaris has been extensively studied[3,4,5] including, the structure and function of the pilosebaceous follicle,[6] the physiology of sebum secretion[7,8,9] the composition of sebum[10-13] microflora in acne vulgaris,[14] and abnormal follicular keratinization[15,16] considered to be one of the earliest events in acne formation. Despite the concerted effort of many scientists, internists, pathologists and dermatologists, the pathogenesis of acne vulgaris remains largely elusive.

In this paper, I would like to approach this problem from a different perspective. My clinical observations suggest that acne vulgaris may be closely related to the consumption of diets which are rich in fat content. This impression, however, is by no means novel. Textbooks do briefly mention this correlation[17,18,19] though, more often than not, it is dismissed as irrelevant. However, my observations have led to quite the contrary conclusions. Not only is the fat content of food closely related to acne vulgaris, but it forms some sort of linear relationship with the disease process. The more fat the patient consumes, the more severe will be the acne process. This observation is in line with the opinion of many dermatologists that chocolate, which is composed mainly of the creamy

part of milk, and has a high degree of fat content, and is bad for acne.[20-23] Significantly, in this group of patients, any deliberate attempt in trying to avoid a fatty diet over a period of weeks, if not days, will often result in an improvement of the clinical condition. This observation forms the basis of my hypothesis that the disease process may be connected with fat metabolism–or a deficiency of it.

Other arguments also support this hypothesis. There is the composition of the sebum secretion which consists mainly of lipid material.[10,11,13] When lipids are deposited in the sebaceous glands and excreted as sebum secretion, it does suggest some abnormality is going on and hint that some form of fat metabolism may be at fault. These fatty materials, after all, are energy-rich compounds. Under normal circumstances, they should be stored away in fat depots. To have them excreted with a concomitant wastage of energy is not nature's way of handling excess energy. One possibility the body behaves in such a manner is that it is simply unable to cope effectively with all the fat that is being absorbed, resulting in some being dumped through some unusual venue. This perhaps helps to explain the observation that an increase in fat content of food appears to worsen acne.

Furthermore, there is the involvement of the sex hormones. The sex hormones, the androgens in particular, have long been recognized as important causative factors in the pathogenesis of acne vulgaris. A tremendous amount of very thorough work has been done in relation to this subject, and the conclusions of these studies are most intriguing. The findings, however, are often in conflict with one another, and no reasonable explanations can be provided for all the observations that are made. The sex hormones, aside from their established relationship with acne vulgaris, are of interest in another respect. This is their close relationship with the important compound cholesterol. It has long been established that the sex hormones are derivatives of cholesterol, whose synthesis has much to do with lipid metabolism. A hypothesis, therefore, which relates the acne process to lipid metabolism becomes something that is worthwhile looking into.

Before detailing such a hypothesis in any depth, it is relevant to recapitulate very briefly some of the main actions of the sex hormones relating to the acne process, and some of their apparent conflicting effects. Although the proposed hypothesis has little to do with the functional aspect of the hormones, it bears important association to these hormones as a whole. And remarkably enough, some of the conflicting hormonal effect lend strong support to the hypothesis.

The effect of Sex Hormones on Acne Vulgaris

1. The androgens

Androgens have their effect on the acne process on several fronts. For a long time, it has been shown that androgens exert great influences on sebum secretion,[24,25] which preceeds acne formation. Equally significant is the observation that the severity of clinical acne is directly related to the rate of sebum excretion.[26] Many studies have also revealed that the development of the sebaceous glands is influenced by androgens. Castrated men have smaller sebaceous glands and a much lower level of sebum secretion as compared to a normal man.[27,28] That the sebaceous gland is a target-organ of androgens can be shown by administration of testosterone to subjects that have very low levels of testosterone in their blood, like children and post- menopausal women, when there is prompt increase in sebaceous gland activity.[29,30]

2. The Estrogens

The consensus is that estrogens at physiological dosage have little effect on sebaceous activity. Doses in excess of this dosage will reduce sebaceous gland activity, hence sebum secretion.[31]

3.The Progestogens

It is generally agreed that progestogens have little effect on sebum production. It seems that things look quite straight forward with these observations and conclusions, androgen is to be the predominant factor in the pathogenesis of acne. Or is it? It is here that things start to look complicated and pose many problems.

The Controversies and Contradindications

1.Sex Distribution

Controversies abound in the realm of acne vulgaris and sex hormones. One of the fundamental questions to ask is perhaps, if androgen is so closely related to sebaceous gland activity, why is the sex distribution of the disease process equal? With androgen level so much higher in the male than in the female, one would expect the disease process should largely occur m the males. This is not true. This is something of a riddle that proves difficulty to solve.

Some workers offer to explain this by saying that it is not the amount of androgens in the blood that matters, but the sensitivity of the target-organ, the sebaceous glands, towards androgens that counts.[33] With this explanation, a few questions inevitably follow. The question of sensitivity is an issue. Little is known about the nature of this sensitivity. With the incidence of the disease process divided between male and female. it carries with it the implication that the female sebaceous glands have to be much more sensitive towards androgens than the male glands. But apparently there is little supporting evidence for this.

Even more puzzling is the clinical condition of premenstrual flare, in which female patients have much more prominent acne eruptions premenstrually. For the explanation to hold true. the sebaceous glands have to be particularly sensitive to androgens premenstrually. Again. there is no evidence for this.

2. Exogenous and Endogenous Androgens

There is another observation concerning the relationship of acne and androgens that is difficult to explain. Administration of testosterone in prepubertal boys increases the size of the sebaceous glands, but not so in the adult. Here, the glands would appear to be under stimulation by endogenous androgens rather than exogenous androgens.[28,29,32,34] This is an interesting phenomenon. The same compound, but with a different origin, will carry with it a different response in the adult body.

In trying to provide an answer to this observation, it is important to look beyond the relationship of androgens and acne, and perhaps look into other aspects relating to the androgens. The synthetic production of androgens, or the sex hormones as a whole, for example, may be worthwhileto examine, because the only difference between the two hormones is that one is synthesized in the body, whereas the other is not.

There is another reason for looking into the synthesis of hormones. It has been shown that pubertal boys with or without acne have about the same blood levels of testosterone.[35,36] On the face of it, there is no basic difference between these two groups of boys. However, at this stage of their life, one particular feature stands out: They all need to start synthesizing androgens, probably a good amount of it, to cater to the development of the sex organs. One possible reason that subsets within these two groups of boys may have some subtle differences in synthetic processes. Of course, the actual synthetic process will be the same, requiring the same enzymes, coenzymes and basic building blocks for the purpose. What constitutes the possible difference here is not so much as the nature, or quality, of these components, they should be the same, but rather some other factors. One possibility is the quantity of the dietary components may differ. One group may be provided with a good

supply of all the components and the other with varied degrees of shortages. This difference could be significant and provide the logical basis for looking into the synthetic process.

The essential steps in the synthesis of androgens and the other sex hormones are well known. They are all derived from the important compound cholesterol, which in turn is basically synthesized from units of acetyl-CoA. That is to say, the basic constituents or building blocks of the sex hormones are acetyl- CoA. In the synthetic process, the body naturally is always trying not only to reach for a normal level of androgens, but an optimal level., so as to allow the body to function at its best. However, this does not always possible, and the normal level reached may not represent the optimal level. This is nature's flexible way of dealing with shortage of essential dietary elements in any form–to achieve a level that is just enough to manage the present situation, leaving a variable degree of shortage from the optimal level. In the present instance, in the two groups of boys, one group may have a normal level of androgens that is falling short of the optimum. One possible explanation for this is that there is a lack of basic building blocks, the acetyl-CoAs, which deter the body from operating at peak efficiency. If this is a viable possibility, it suggests that a plentiful supply or a deficiency of acetyl-CoA in the body may play a role in the acne process. This is certainly possible. For, aside from its role in the synthesis of the sex hormones, acetyl-CoA, of which coenzyme A is the important component, is also important in fatty acid metabolism-as an acyl carrier in the lengthening and degradation of long chain fatty acids by adding or removing acyl groups in the metabolic process.

To sum up the events, the situation is such that acne vulgaris is related to lipid metabolism as well as the sex hormones, both of which have a lot to do with Coenzyme A. This relationship provides a reasonable ground to link up the acne process to Coenzyme A and to investigate the pathogenesis of acne vulgaris along this line.

The Importance of Coenzyme A

In trying to link up acne vulgaris to Coenzyme A, it is important to have a hypothesis supporting some basic facts. A closer look at Coenzyme A may provide the evidence.

1.A Sharing Scenario

As a coenzyme active in both fatty acid metabolism and sex hormone synthesis, Coenzyme A is shared between two different metabolic processes. This is not uncommon in biochemical reactions in metabolism, where a coenzyme is often shared among a number of reactions. But with Coenzyme A, it is somewhat different. With its involvement in more than one hundred reactions.[37,38] Coenzyme A is arguably the most important coenzyme in the body, and when a coenzyme is involved in the metabolic process to such an extent as this, it becomes legitimate to ask if a shortage and deficiency is possible. To answer this, a brief look at the structure of Coenzyme A is warranted.

2. Pantothenic Acid

Coenzyme A is formed from adenosine triphosphate, cysteine, and pantothenic acid. Of these pantothenic acid is the only component that is a vitamin, and must be provided from our dietary intake. Can there be an insufficient intake of pantothenic acid resulting in a deficiency in Coenzyme A which would leave the body unable to cope with all the reactions that it has to perform with that all important coenzyme? Conventional wisdom does not think so. It is suggested that pantothenic acid, being ubiquitous, enough can be had from whatever kind of food that is taken in, and that there is no question as to its deficiency in our body. However, a deficiency is still possible. After all, when so many reactions are dependent on the same agent, its demand must be tremendous. Shortage under such cir-

cumstances is not entirely impossible.

3.The Crucial Question and the New Theory

If the question of deficiency of Coenzyme A does come up, how does it affect acne, knowing its importance in fatty acid metabolism and sex hormone synthesis? This is the crucial question. This is where the new hypothesis on the pathogenesis of acne vulgaris is based, and this is where it diverges from conventional medical ideas. The author's proposed hypothesis for the pathogenesis of acne vulgaris is that the disease process is not caused by androgens, or any other sex hormones. But rather, the disease process results from a defects in lipid metabolism that is secondary to a deficiency in pantothenic acid, hence Coenzyme A. Coenzyme A, in carrying out its function efficiently both as an agent in fatty acid metabolism and an agent in androgen and sex hormone synthesis, has to be present in sufficient amounts, and anything that is less than sufficient will result in some compromise of the work.

4.Mother Nature's Choice

Facing with the dilemma of a shortage of Coenzyme A, the body will tend to make a choice that is to the best advantage of the individual. The body does by largely maintaining the functionally more important reaction, while at the same time slowing down the lesser important one. The choice here is a relatively simple one. Nature will seek to take care of the synthesis of hormones first, because continuation of the species depends on the development of the sex organs. Fatty acid metabolism is for the time being at least in part halted, Lipid in the sebaceous glands starts to accumulate, sebum excretion is increased, and acne begins to appear. When there is enough pantothenic acid in the body, however, both reactions will be well taken care of. There is enough sex hormones for the sex organs to develop. The lipids in the sebaceous glands are completely metabolized by sufficient Coezyme A, and there will be no unwanted lipid in the glands and little sebum will be excreted to cause acne vulgaris.

The Mystery Revealed

The mechanism proposed above may be the reason why two groups of adolescent boys–both with a normal blood level of androgen–may exhibit differences in the incidence of acne. The group with acne is the one that has not enough of pantothenic acid in the body, whereas in the other group, pantothenic acid levels are not deficient.

This new theory seems to work well here, and can be tested in other metabolic situations. In the case in which endogenous androgen stimulates acne, whereas exogenous does not, the reasoning for the observation is the same. Any endogenous androgen synthesis will require the participation of extra amount of pantothenic acid. This will channel off some of those that are doing the work of fatty acid metabolism. Consequently, fatty acid metabolism becomes less efficient and the individual is more prone to have acne. Exogenous androgen, on the other hand, does not affect the pantothenic acid pool (which is a term used to represent the total pantothenic acid in the body) in any manner, hence no effect on acne. This explains the seemingly mysterious nature of this observation.

What about premenstrual flare? In the luteal phase of the menstrual cycle, progesterone in is secreted abundantly by the corpus luteum. This naturally will take up a lot of pantothenic acid in the body's pantothenic acid pool, leading to a re-distribution of the vitamin and putting enormous pressure on fatty acid metabolism. When this metabolic process is not performing satisfactorily, lipid begins to accumulate in the sebaceous glands, an increase in sebum is excreted, and acne follows. That is why, even though progesterone has no effect on sebaceous gland activity, an increasing level of progesterone in the late stage of the luteal phase leaves the acne patient with a prominent flare.

A similar explanation may why eunuchs rarely exhibit acne.[27,28] This may be because so few sex hormones are secreted, the pantothenic acid pool can deploy a more significant portion of its reserve to metabolize fatty acids. When the job is efficiently done, little sebum is excreted, and no acne is formed.

This theory will also serve to explain the paradoxical problem of equal sex distribution of acne incidence. It is not the male hormone androgen that is important, but rather the absolute amount of sex hormones that counts. Both males and females will need sex hormones for the development of sex organs and the secondary sexual characteristics. The only difference is that in the male, androgens predominates, whereas in the females, the female sex hormones. Apparently the synthesis of sex hormones, which probably ranks high up in the various reactions served by pantothenic acid, takes away a rather big portion of the pantothenic acid pool, leaving a relative shortage of it to efficiently metabolize fatty acids. The result is that acne starts to erupt, right at the time the sex organs begin to develop—at puberty. The reason acne first erupts at puberty is not, therefore, endocrinological, but rather secondary to the deployment of a substantial amount of pantothenic acid for the purposes of synthesis of sex hormones, leaving a relative deficiency for fatty acid metabolism. The size of this pantothenic acid pool and the ability with which the individual can deploy any reserve from the common pool probably varies in different individuals and is likely to be influenced by genetic and dietary factors. That is why, in some individuals with little pantothenic acid in reserve, acne begins to appear early on at puberty, whereas in some others, those with a large reserve, have their acne to appear relatively late, or not at all.

This hypothesis thus offers an explanation as to the relationship of the sex hormones and acne. It is suggested that sex hormones and androgens are not important factors. What is important is the availability of extra pantothenic acid to discharge the function of fatty acid metabolism on top of the synthesis of the sex hormones. That is why, in conditions in which there is an increase in secretion of any hormone whose synthesis requires the participation of pantothenic acid, acne may erupt This is frequently seen with those hormone secreting tumour of the ovary, testis and the adrenals. The rapid decline in incidence of acne after adolescence, say in the late teens and early twenties, can also be explained. After the sex organs are fully developed, probably not as much sex hormones are required, leaving an adequate supply of pantothenic acid to serve the function of fatty acid metabolism. When this function is cleanly accomplished, sebum secretion dries up, and acne starts to fade.

Deficiency in Lipid Metabolism

In linking the pathogenesis of acne vulgaris to a deficiency in lipid metabolism and pantothenic acid, it is worthwhile to remember that fatty acid metabolism is not the sole domain of pantothenic acid. There are some other essential dietary factors that are also of importance in the same process. Together they form a system that will make the whole metabolic process as efficient as possibly. Preliminary studies by the author suggest that, together with pantothenic acid, biotin as well as nicotinamide help to further improve the therapeutic results. By themselves alone, they are far less effective in helping acne patients than pantothenic acid, and this, in a way, serves to support the suggestion that pantothenic acid plays a central role in lipid metabolism. Lipid metabolism is a complicated process, and is often intertwined with other metabolic processes, sharing with them common coenzymes in widely different reactions. When there is an increase in level of some of these coenzymes, there may be a shift in the directions of some on-going reactions, and

may affect lipid metabolism as a result. This can manifest clinically as acne vulgaris. To illustrate this, there are reports[39,40] saying that acne may be induced by administration of large doses of vitamin B 12 alone or in combination with B6. Cessation of the administration of these vitamins will bring a halt to the acne eruptions. This may also be explained. If the body is in a relative deficiency state in B6 and B12, administration of the vitamins will enhance the reactions that involve the participation of these vitamins. This will set up a chain of events, some of which will likely to entail the participation of pantothenic acid. With the total pantothenic acid pool fixed relative to an increase in other vitamins, emphasis of any reaction involving pantothenic acid will automatically mean a cutting back on other reactions that require the same vitamin as a coenzyme. This will often include those involving lipid metabolism, resulting in a certain degree of deficiency in that metabolic process, hence the increased incidence of acne vulgaris in these studies. It is probably the same reason that in clinical practice, it is not uncommon to find acne patients developing a flare when given muti-vitamin tablets.

Stress Related Acne

It is perhaps relevant here to consider another common factor–stress–that is known to affect acne adversely. Stress in many forms poses as an aggravating factor in acne lesions. Lack of sleep at night, pre-examination tension, and any psychological problem that may worry the patient will bring on new acne lesions.33 To explain this, one should recall that in combating stress, the body will secrete glucocorticoids from the adrenal glands as a means to adapt to stress, what is commonly known as the fight-or-flight reaction. The glucocorticoids, like the sex hormones, are derivatives of cholesterol, and increased demand for this hormone will draw on the pantothenic acid pool. Lipid metabolism may therefore be compromised, rendering the body more prone to acne.

If pantothenic acid deficiency is indeed the main causative agent in the pathogenesis of acne vulgaris, it is logical to ask how much pantothenic acid patients are lacking in absolute amounts.

Deficiency syndromes

For decades, the medical profession has tied their hands with a fiction of their own device. They held, contrary to the facts, that nutritional requirements can be met through a well balanced diet, and that dietary supplements, including vitamins, are not required. It is the belief of the medical profession that vitamins, though essential to life and not synthesized in the body, are not required in great amounts. To them, the importance of vitamins lies mostly in ridding patients of deficiency syndromes. To keep individuals in good health does is not accepted as the major role of vitamins. This view was challenged, notably by Linus Pauling. In his book, How to live longer and feel better, Pauling provided vigorous proof, through comparative studies in animals and from an evolutionary point of view, that vitamin C supplements are needed if an optimal state of health is to be achieved. Not only is supplementation necessary, but the amount required is far greater than most people believe, as with the case of vitamin C where the optimal dose is 10 or more grams a day.[41]

This issue was a point of heated debate in the 70s and 80s. Though Pauling has quite a large following, by and large, the issue was dismissed by the mainstream medical profession,[42] because of a lack of theoretical support and a general bias against nutritional and vitamin therapy. But, in view of the new evidence suggested in this paper, it seems appropriate that the issue be raised again.

How Much Pantothenic Acid?

In trying to determine the actual amount of pantothenic acid necessary to relieve acne patients of their symptoms, Linus Pauling's experience with vitamin C provides a good guideline. Pauling had for a long time recommended vitamin C in high dosages to achieve optimal health. Radically different from what is recommended by the Food and Nutrition Board of the National Research Council (who recommended 60 mg daily), Pauling's recommended daily intake of vitamin C amounts to several grams a day. The recommendation was stepped up to 15-20 grams a day in his later years. Using these recommendations as a background, it becomes somewhat easier to arrive at a proper dosage for pantothenic acid in the treatment of acne vulgaris.

Pantothenic acid, which acquires its name from the Greek word meaning ubiquitous, is present in all tissues. Its universal presence is an indication of its importance. This is further reflected by the many reactions that it catalyzes. Given all these, it should not come as a surprise if the amoumt of pantothenic acid required to for optimal health is of the same order of that of vitamin C. Based on this argument, the dose of pantothenic acid administered to the acne patients was up to 10 gm a day, and the result of these studies were first reported in Medical Hypotheses.[1]

The Effect of Pantothenic Acid on Acne Vulgaris

One hundred patients of Chinese descent were included in the study, 45 males and 55 females. The age ranged from 10-30, and with about 80% between 13 and 23. The severity of the disease process varied. They were given 10 g of pantothenic acid a day in 4 divided doses. To enhance the effect, the patients were also asked to apply a cream consisting of 20% by weight of pantothenic acid to the affected area, 4-6 times a day. With this treatment regimen, the response is as prompt as it is impressive. There is a noticeable decrease in sebum secretion on the face usually 2-3 days after initiation of therapy. the face becomes less oily. After 2 weeks, existing lesions start to regress while the rate of eruption of new acne lesions begins to slow down. In cases with moderate severity, the condition is normally in complete control in about 8 weeks, with most of the lesions gone and new lesions only to erupt occasionally. In those patients with severe acne lesions, complete control may take months, sometimes up to six months or longer. In some of these cases, in order to get a more immediate response, it may even be necessary to step up the dose to 15-20 grams a day. In any event, the improvement is normally a gradual and steady process, with perhaps minor interruptions by premenstrual flare or excessive intakes of oily food. With this form of treatment, another striking feature is the size of the facial skin pore. The pore size becomes noticeably smaller within 1-2 weeks, very often much sooner. Like sebum excretion, the pores will continue to shrink until the skin becomes much finer, giving the patient a much more beautiful skin.

This decrease in skin pore size is presumably related to sebum excretion. When an acne lesion is formed, there is in the epithelial cell of the hair follicle an accumulation of lipids, leaving the epithelial cells bulky and the lumen of the gland narrowed. When there is a concomitant increase in sebum flow, the follicle has no choice but to hypertrophy to accommodate the changes, resulting in an enlarged skin pore and coarse skin. With the administration of pantothenic acid, the whole process is reversed Lipid metabolism becomes normal and efficient. The epithelium is no longer laden with fat droplets, there is a decrease in sebum excretion, the hypertrophy process is not required. The skin pore reverts to a much smaller size The skin becomes smooth and fine.

Is a Maintenance Dose Necessary?As acne lesions tend to subside spontaneously after puberty, technically speaking, most patients do not need a maintenance dose. But, if a patient is in his mid-teens, when the sexual characteristics are yet to fully develop, it becomes necessary that a replacement therapy be implemented. This maintenance dose, though, can be lowered, or be titrated with the clinical symptoms. It is, however, a good idea to put all patients on a maintenance dose. This will not only act as a Preventive measure against sporadic eruption, but the extra pantothenic acid will help to ease the relative deficiency state, hopefully improving the general heal th of the patient.

Pantothenic Acid and Weight Reduction

With pantothenic acid so closely related to lipid metabolism, it raises the question if it has anything to do with obesity, and hence weight reduction. In the rest of this article, the author will try to explore the problem of weight reduction which is equally, if not a more mysterious problem, than acne vulgaris.

Regarding negative calorie balance and dieting, the only guiding principle behind weight reduction is that the calorie intake must be less than the calorie output, so that there is a negative calorie balance. The body will try to make up for this negative balance by burning the fat that is stored in the fat cells, the so-called depot fat. With such a process, fat in the body is consumed, and the individual loses weight. This sounds rather simple, and the goal should therefore easily be achieved. In practice, however, this is quite a different story. By taking in less than what is actually needed, the dieter in fact faces two hurdles that may prove too difficult to overcome. There is the problem of hunger. It takes enormous self- restraint and determination to keep the appetite in check, and when hungry, there is the constant temptation to satiate this primitive instinct by grabbing whatever is available. To keep this situation in check is difficult, but not insurmountable with a conscious effort, conviction and perseverance. But more troublsome and difficult to manage is the weakness, sweating, dizziness and fainting episodes that follow the sensation of hunger. Under such circumstances, the dieter will have little choice except to start eat ing again, gaining back the weight that he has tried so hard to shed.

The Paradox

The key question to the whole problem of weight reduction is why is one hungry and compelled to eat when one has enough of stored fat in the body? In other words, why is one not able to convert, freely, one's storage fat into energy? Storage fat, as the story of evolution will tell, is meant as an energy reserve in t me of need. Famine is a typical example of such a needy time. So, why can't one make use of the storage fat at a time when one needs it most? Or can one do it? This is the key question which needs to be examined very carefully,

It is not strictly true to say that the body is not able to utilize its stored fat when the situation warrants it. Not only can ti burn fat stores, but it can do it with great efficiency, initially at least. The trouble is that this ability does not last. When the body is deprived of its food and energy is not forthcoming from the external source, glycogen that is stored in the liver is first called on to furnish the energy deficit. Unfortunately, the glycogen store is very limited, and very soon, even before the glycogen store is totally depleted, the body will have to mobilize its stored fat from its fat depot to supplement its energy requirement

For a short time, the body can freely derive its energy from its stored fat All the fat that is mobilized will be completely burnt with no wastage. But very soon, very occasionally within hours, for unknown reasons, the body can no longer maintain this rate of functioning. It can still burn

its mobilized fat, but no longer as effectively and as efficiently as before, with ketone bodies representing partially burnt fatty acids appearing in the blood stream and urine. With time, if food is still not forthcoming, the accumulation of ketone bodies will significantly increase, an indication that the power to metabolize stored fat is further being eroded. The individual begins to feel hungry, with the concomitant symptoms of weakness, dizziness, sweating emerging.

It has been recognized that the time taken from the start of fasting to the onset of ketosis varies, sometimes to a considerable extent among different individuals. While some may become weak within a matter of hours, others can get on very well without food for more than one to two days. In laboratory animals, it is not uncommon for some to stay active and yet free of ketosis for 2-5 days after the onset of fasting.[43,44]

Ketosis and the Loss of Energy

Here, two most important points are raised. Why is it that some people can tolerate fasting better than the others in the sense that they can go on with their activity without ketosis for a much longer period of time? And more important, why is the body, with the development of ketosis, losing precious stored energy at a time when the body needs it most? It appears that the body, resisting the onslaught of fasting, has installed a mechanism whereby fat can readily be converted into energy. But this mechanism is far from perfect, and fails to keep engaged for very long in some individuals, although in others the mechanism can maintain its function for several days. Still, the mechanism gets blunted with time, and is unable to efficiently perform its function-to completely burn off all the mobilized fat and provide the body with energy, with no ketogenic wasting of stored energy. This eventual blunting of the metabolic mechanism applies to every individual, without exception. In time, if fasting is prolonged, this mechanism will become even more inefficient and more ketone bodies will build up as the body loses more of its precious stored energy through the urine and the breath.

Judging from what actually happens after the onset of fasting, there is little doubt that the body is empowered with a mechanism to metabolize mobilized fat. The only question is why this mechanism fails to last. If only one can identify the problem, and prolong the mechanism of fat burning, then weight reduction will be simple. One can just fast or semi-fast the individual, and set the mechanism at work, then all the calorie deficit will be provided by energy converted from the body's stored fat. The stored fat will be steadily depleted, and the individual will gradually and slowly lose weight.

The New Hypothesis of Ketone Body Formation

It seems that the crux of the matter rests on the formation of ketone bodies. So long as mechanism is working efficiently, no ketone bodies will emerge, and the first sign of failure of the mechanism is the appearance of ketone bodies in the blood stream. What then, is the reason for the failure of the mechanism that leads to the formation of ketone bodies? There is no conclusive answer, but there are some clues. It is known that ketone bodies only appear when the body is asked to catabolize a large amount of fat, as when the energy requirement of the body is largely provided by its stored fat.[45,46,47] At the point where the body can no longer cope with efficiently breaking down this large amount of fat, ketone bodies appear. To understand ketone body formation, it seems pertinent to have a good look at the catabolism of fat and fatty acids.[48,49] Briefly, fat catabolism is a process in which the stored fat in the form of triglycerides is first broken down into glycerol and long-chain fatty acids. These long-chain fatty acids are then serially broken down by a process called

B-oxidation in which the long carbon chain is fragmented into units containing two carbon atoms each. Before this can happen, the long-chain carbon has to be activated into its high-energy Coenzyme A ester by reacting the acid with ATP and Coenzyme A. A subsequent cleavage at the B carbon atom of this long carbon chain by reacting with another molecule of Coenzyme A will spin off a molecule of acetyl-CoA, leaving the original long carbon chain with 2 carbons less but still as a CoA ester. The whole process is then repeated again and again. with each process consuming one molecule of Coenzyme A, until the whole long chain is totally broken down into many fragments of acetyl CoA.

Take for example, palmitic acid, a l6-carbon saturated fatty acid, which is broken down by this process of B oxidation into 8 fragments of acetyl-CoA. It is to be noted that in converting palmitic acid into 8 units of acetyl-CoA, a total of 8 molecules of Coenzyme A is taken up from the body's pool of Coenzyme A molecules. All these units of acetyl-CoA will be metabolized via the citric acid cycle, releasing energy in the form of ATP, leaving carbon dioxide and water as the final end products. This is how the body gets its energy from its stored depot fat. And this is what is supposed to happen in an ideal situation, when all the mobilized fat is metabolized completely, with no wastage of energy. For very obscured reasons, when fat is broken down in large quantities, as in fasting, not all the units of acetyl-CoA will go into the citric acid cycle. Some of these units will choose to combine with each other. In the process, 2 molecules of acetyl-CoA will yield one molecule of acetoacetyl CoA and one molecule of Coenzyme A. The acetoacetyl- CoA molecule is very unstable, and will rapidly decompose itself into one molecule of acetoacetic acid and another molecule of Coenzyme A Then, through a process of decarboxylation, which is an irreversible process, acetoacetic acid is turned into acetone, better known as a ketone body. The accumulation of any significant amount of ketone bodies in the body results in a certain degree of acidosis. To off set such acidosis, the body will try to eliminate the ketone bodies in the urine as well as in the breath. This is effectively a wastage of precious stored energy that is originally intended for emergency use.

Coenzyme A Deficiency

It is baffling that 2 molecules of acetyl-CoA should start combining with each other to form acetoacetyl-CoA, part of which is ultimately lost to the exterior in the form of ketone bodies at a time of crisis. In an effort to understand the process, it is useful to remember the situation in the fasting state. In a bid to provide sufficient energy, the body is scrambling to produce a large amount of long chain fatty acids from its fat depot that will meet the calorie requirement. These long chain fatty acids are then broken down, all at the same time, into units of acetyl-CoA. The body sees it proper to do it this way. because, only by so doing, can it be in a position to provide itself with enough energy by burning these units of acetyl-CoA through the citric acid cycle. But, it has to be remembered, for every 2-carbon unit, it is necessary to attach one molecule of Coenzyme A to it. Here, one must ask the all important and very practical question: Has the body, in its total pool of Coenzyme A, enough of such molecules to handle this?

The body may be able to do this for a short period of time, but with an increasing portion of the body's energy needs provided for by fat, the call for extra Coenzyme A will sharply increase. The point will be reached in which the body will no longer be able to cope with the demand, and under these conditions the body will, within its scope of capability, try to generate more Coenzyme A to deal with the situation. The easiest way to do it is for 2 molecules of acetyl-CoA to condense to form a molecule of acetoacetyl-

CoA, generating one molecule of Coenzyme A along the way. This in fact also obeys the physical law of concentration of a chemical reaction. When the concentrati on of acetyl-CoA is getting so high, the direction of the reaction will be driven towards the formation of acetoacetyl-CoA and an molecule of Coenzyme A. To provide the body with more Coenzyme A, which the body urgently needs in this state, the acetoacetyl-CoA molecule is quickly transformed into acetoacetic acid, generating another molecule of Coenzyme A in the process. This is perhaps nature's way of handling a dire situation in which generating energy to sustain life is of overriding importance. This serial event, the author would suspect, is the basis for the generation of ketone bodies. The subsequent event, which is the loss of ketone bodies through their excretion from the kidneys and lungs, is a desperate attempt of the body to counter the acidosis following the build up of ketone bodies, as well an attempt to maintain a relatively normal pH of the body fluid. To maintain life, therefore, the body has no choice but to compromise by sacrificing some of its precious energy stores.

Overcoming CoA Deficiency with Pantothenic acid

If this postulation is true, it would mean that, by providing the body with a high concentration of Coenzyme A, the acetyl-CoA molecules, instead of condensing with each other to form acetoacetyl-CoA, will stay as they are. They will all eventually go into the citric acid cycle and be completely metabolized. The way to provide the body with a high concentration of Coenzyme A is rather simple. As explained earlier, the only one component of Coenzyme A that is an essential dietary factor is pantothenic acid. If the body be provided with a large amount of pantothenic acid, an equivalent amount of Coenzyme A will be formed To ensure that the concentration of Coenzyme A is really high, a huge dose of pantothenic acid can be administered.

The New Concept of Weight Reduction

This is the author's concept of a new way to achieve weight reduction, in away in which one can overcome the tricky and difficult part of weight reduction—to rid the dieter of the sensation of hunger and at the same time allow them to have sufficient energy to see them through their daily activites. This is done with a diet that is low in calorie, deliberately creating a situation in which there is an energy deficit To make up for this, pantothenic acid is administered so that any mobilized fatty acids can be converted to fully utilized energy

A clinical study was carried out in 100 individuals of Chinese descent, 40 males and 60 females The age range was 15- 55, with even distribution. The participants were given a carefully designed diet containing about I000 calories a day, together with all the essential nutrients. To go along with this diet, about 10 gm of pantothenic acid a day, in 4 divided doses with each dose taken 4 hours apart, is administered. In practice, there are alternative ways of doing it The idea is to give pantothenic acid in between meals and when symptoms of hunger arise. The dieters have varied goals which range from losing less than 5 kg to more than 30 kg. Approximately half of them aimed at shedding 10-20 kg The average weight loss was about 1.2 kg per week. Ketone bodies in urine were monitored and were found absent in most instances. Occasionally, small amounts were present, indicating that in some individuals, an amount of pantothenic acid larger than 10 gm is required. The patients exhibited no weakness. Often, there was the desire to eat, but no actual hunger. Daily activites could be carried out normally. With determination and perseverence, this process can be continued day after day, week after week, until the desired weight is achieved. The rate of weight loss can be

regulated if the calorie deficit is made larger by eating very little, or it can be slowed down by eating more, keeping the calorie deficit to a very low level. However, it is not a good idea to lose weight too quickly for health reasons.

The Salient Features

In choosing to reduce body weight with this method, there are 3 salient features to be noted. One is the unusually high successful rate, which is understandable. To ensure success, the only prerequisite here is to maintain a calorie deficit through dieting. There is no hunger to worry about, and weakness will not be a problem. With these 2 hurdles removed, extended dieting should not present a major problem. The other feature, of course, is the significance of exercise, which is the mainstay of most conventional methods for weight reduction. What is necessary is the presence of a large amount of pantothenic acid in a semi-fast state, so that stored fat will be burnt slowly and steadily. If the dieter does exercise, it certainly will help to hasten the process.

The third feature, of course, is the absence of side effects with such therapy. This is quite unlike the conventional drug therapy with stimulants and appetite suppressants in which unpleasant side effects are common. Pantothenic acid, being a food, and important component of the body, is non-toxic.50 No toxicity has been observed by the author with anyone taking pantothenic acid in doses of 10-20 or more grams a day over a prolonged periods, in some cases of more than a year.

Not only is there no toxicity, there is actually improvement of the general state of health for those taking in large amount of pantothenic acid every day. This too is not difficult to understand since Pantothenic acid plays so many important and diverified roles in the body as a coenzyme. Any supplement which will help the body to accomplish important reactions that it previously was unable to carry out, is evidence of a prior deficiency state. Such reactions are important to the optimal health state as well as the general well-being of the individual When a relative deficiency state is rectified, many of these important reactions can go on, helping to improve the general well being of the individual.

Pantothenic Acid and Weight Reduction

It seems that, aside from its other functions, pantothenic acid is important in keeping a stable body weight An individual has to have enough of it to stay away from getting overweight if there is a deficiency, just missing a meal may bring on a certain degree of ketosis, reflecting clinically as hunger, weakness, and perhaps giddiness. All these are signals that urge the individual to have food immediately. This will make any attempt to reduce body weight not only very difficult, but almost impossible. It is not that the dieter is lacking in will power, but rather in pantothenic acid, and it is unfair to label him as somebody who lacks perseverance and motivation. He does not really have a choice under such circumstances other than to eat

And it is in these people that whenever they overeat, all the extra energy deriving from that meal will be put safely away in the fat depot. It seems that, in the body, this primitive instinct of storing food away in the fat cells for future needy times is retained, despite a deficiency in pantothenic acid. This leaves this group of people, who already have difficulty in reducing their body weight. particularly prone to put on weight. What a Herculean task it must be for those people without enough pantothenic acid in their bodies to achieve weight reduction! Failure to supplement dieters with pantothenic acid is perhaps the main reason for the very high failure rate of diets which use conventional methods.

Further Supporting Evidence

With the same principle, it is possible to explain many of the commonly observed phenomena that occur around us.

For example, it can be explained why females have a higher fat ratio in their bodies and that they are more prone to gain weight than their male counterparts when they reach their middle age. It is not the direct role of female hormones, as conventional wisdom postulates. One has to remember that the monthly menstrual cycle, which requires plenty of pantothenic acid to synthesize estrogens and progestogens to support the cycle, is continually drawing on the pantothenic acid pool that is very often quite deficient from the start. This makes pantothenic acid deficiency particularly common in the females, especially at a time around their mid-30s. This is the time when the cumulative effects of 20 years or so of reproductive cycles, with each cycle soaking up some pantothenic acid from the body's total pool, begins to take shape. Added on to this is pregnancy. This requires even more female hormones to see it through, allowing the deficiency to go even more severe. With another pregnancy, and another, the situation gets from bad to worse. That is why, even though some women with I or 2 children may still be able to retain their slim figure with a carefully watched diet, many more are gain a significant amount of weight. For those with many children, few women can manage to stay slim, no matter how hard their dieting attempt may be. Their pantothenic pool is dwindling.

There are probably more reasons for obesity than a deficiency in pantothenic acid alone, the most obvious of which is overeating. But judging from what has just been described, it appears that pantothenic acid must play a significant role in obesity as welll as weight loss. The body has a natural tendency to store away any excess calorie intake in its fat depot. Pantothenic acid is the key that unlocks this fat depot and is the agent that converts the mobilized fat into energy. With plenty of pantothenic acid in the body, this conversion is always simple and easy, allowing the body to retrieve as much energy from its depot as is necessary. On a low calorie diet, the amount of pantothenic acid that is required to keep ketone bodies at a minimum level can actually be titrated with the calorie intake. The lower the calorie intake, the larger an amount of pantothenic acid is necessary. Within a certain range, the amount of pantothenic acid required forms almost a linear relati onship with the calorie intake. In such cases, it can be seen that 10 gm a day, or even more, is in fact, necessary. To maintain one's body weight after ones goal is reached can be achieved by supplying the body with a liberal amoumt of pantothenic acid, in the region of 2-3 gm a day to enable the body to freely convert mobilized fat into energy, and the individual will appear active, agile, and full of energy.

The More Important Message

The relationship of pantothenic acid with acne vulgaris and weight reduction is important and carries a message that is of greater significance regarding the use of megadoses of vitamins. The war of words between the Linus Pauling camp and the mainstream medical profession serves to illustrate the opposing views of the two sides.41,42 This debate went on for more than 2 decades, with the mainstream medical profession maintaining their view that vitamins in huge doses are not necessary and until further proof is forthcoming, the idea of mega-dosage is quite wrong. It is believed that this proof is now available, though not coming from ascorbic acid, but from another vitamin— pantothenic acid.

This conclusion leaves us pondering another important corollary: What is the position of vitamins other than pantothenic acid and ascorbic acid? Does one need huge doses of these vitamins as well? There are already hundreds of papers on vitamin C over the last 20 years that provide evidence that large doses of the vitamin do help in various clinical conditions. With pantothenic acid, the situation is

probably very much the same, Already. there is evidence that those who take in large doses of pantothenic acid, either for acne vulgaris or for weight reduction, feel a lot better, and do not tire as easily. Their skin remains supple and taut, even after losing more than 20-30 kg of body weight. This is quite unlike other method of weight reduction in which excess looseness of skin normally follows any significant weight reduction. In the future, other diverse conditions, including conditions that are not very well defined clinically, may be helped with large doses of pantothenic acidas will likely be true with most other vitamins and nutrients.

Conclusion

I would like to conclude this paper with another question: Why is it that vitamins are needed in such a large dosage? Are they not supposed to work as catalysts which can be recycled? To assume that coenzymes work in the way that textbooks portray them—as a catalyst that will not perish—is perhaps unrealistic. Not only are they perishable, but the substrates in the citric acid cycle, or for that matter, probably any substrate in biochemical cycles in the body, may share the same fate. The following observation helps to illustrate this. In the course of weight reduction, a few dieters chose to hasten their progress. They ate very little, sometimes nothing at all for more than 2 days, surviving only on water and a huge dose of pantothenic acid. Theoretically, these people have more than enough of fat stored in their body to see them through for many days if not weeks. Since they have so much pantothenic acid in their body, they should be able to generate enough energy without experiencing ketosis. But this is not the case. Usually, in less than 2-3 days, they too develop ketosis regardless of how much pantothenic acid is given. Under such circumstances, the body's many acetyl CoA units cannot go into the citric acid cycles to be burnt—not because of a lack in pantothenic acid, but a lack in the substrates. This is evidenced by the fact that the situation can readily be reversed by giving the dieters a small amount of carbohydrates. Therefore we see how substrates of a biochemical cycle can be worn out, and need be replaced constantly. The same probably applies to other coenzymes of the body.

Although this observation does not fully answer the question as to why large doses of vitamins are needed, but does throw some new light on previous concepts about vitamins and coenzymes. With the present clinical results of pantothenic acid on acne vulgaris and weight reduction, it is perhaps time to focus more attention on how high doses of vitamins and nutrients can be used in the prevention and treatment of diseases.

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