The Present Status of Topical Chlorophyll Therapy

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Now that the hysteria associated with the extravagant and largely unjustified promotional claims relating to chlorophyll derivatives in the deodorant field has largely subsided, it seems an appropriate time to review impartially and critically the other side of the picture, that associated with the legitimate, ethical, therapeutic use of chlorophyll derivatives in medical practice. Only in this way can we as physicians arrive at any honest opinion as to whether or not "chlorophyll" has any place in our therapeutic armamentarium.

While this article is in one sense a review of a not inconsiderable segment of the literature on chlorophyll as it relates to medicine, in another sense it attempts to point the way to further research in its future therapeutic application and to bring out certain of the errors which have become apparent as to our earlier understanding of the problem. Obviously in a brief critique of this nature it is possible to mention individually the work of but a comparatively few of the investigators in this broad area of research. Their very numbers are impressive, and their names in the majority of instances rank high in the scientific world. The accompanying bibliography gives the original source references for the material presented in this review for those readers not already familiar with it. Certainly the problem of "chlorophyll" as it applies to human economy is a challenge to scientists of every discipline the world over, and with its ultimate solution many fundamental biologic problems will have been cleared away.

In the somewhat restricted field to which this review is limited, i.e., the topical application of chlorophyll derivatives and particularly as this relates to wound healing, it is interesting to note that although earlier studies by Buergi and his associates[1,2] had suggested that chlorophyll derivatives might prove to be of therapeutic value, it was only with the publication of a paper on the use of "chlorophyll," especially the water-soluble chlorophyllins, in the treatment of suppurative lesions by Gruskin[3] in 1940 that interest in this fundamental concept was aroused in this country.

Since Verdeil's[4] discovery of the similarity in structure of chlorophyll and hemoglobin in the middle of the nineteenth century, chemists have been seeking to understand the role of chlorophyll in nature, especially as it applies to photosynthesis. For the first fifty or sixty years following Verdeil's studies all efforts were aimed at identifying the molecular structure of chlorophyll. These culminated in the publications of Willstaetter and Stoll[5] and others in the decade from 1910 to 1920. Since then some 800 chlorophyll derivatives have been prepared, the great majority of them of academic interest only.[6] Very few of these derivatives have been investigated from a clinical standpoint, and of those which have, many are totally inert. Evidence is accumulating, however, to suggest that certain other derivatives or modifications of existing derivatives may well be developed in the future to enhance the therapeutic usefulness of currently available "chlorophyll" preparations. It would be strange if this should not prove to be true in the case of "chlorophyll," just as has occurred in the case of most chemotherapeutic agents employed today, including even the sulfas and antibiotics. For example, scientists have come a long way in scarcely more than a decade from the days of high cost, low yield, crude, dirty brown amorphous penicillin to its present pure, white, crystalline salts and esters and correspondingly greater beneficial clinical results, even though from the very outset penicillin was recognized as a "miracle" drug.

In the same way therapeutic "chlorophyll" products have been undergoing a similar continuous program of improvement but at a slower pace than has been true of the sulfa drugs and antibiotics. Indeed, the very intensiveness of the program in the development of these latter strictly antibacterial agents during the war years has tended to delay the program in the case of "chlorophyll" in spite of its established position of importance in the field of wound healing. The talent required for this kind of research was largely diverted to the sulfonamide and antibiotic programs, and save for a very few specially skilled workers conversant with chlorophyll chemistry, studies in this direction were sadly

restricted. However, with the ever-increasing interest of the medical profession in the outstanding advantages of chlorophyll therapy in the treatment of ulcerative lesions of any etiology, and especially in chronic recalcitrant cases associated with circulatory disturbances, the research and development program in the chlorophyll field once again is rapidly extending.

Much of the early work in this country with "chlorophyll," both in the laboratory and clinically, was open to the criticism that the material employed was of poorly defined composition, and as a result many of the experiments were inadequately controlled. However, regardless of this legitimate scientific criticism, the fact emerged that empirically these relatively crude chlorophyll preparations *did* have therapeutic activity in promoting more rapid wound healing. Gradually, with more uniform standardization of products and more adequately planned experiments, the original observations on the clinical effectiveness of chlorophyll derivatives have been repeatedly confirmed and chlorophyll therapy established on a sound basis.

While even today our knowledge regarding the pharmacodynamic mechanisms of chlorophyll activity is far from complete, we have learned considerable regarding its mode of action. We know that "chlorophyll" in the form of the sodium or potassium salts of chelated, water-soluble chlorophyllins possesses bacteriostatic activity in varying degrees. We know that these same chlorophyllins exert a growth-stimulating effect on connective tissue cells, both in tissue culture and in wound healing, producing healthy granulations and cutting down the total elapsed healing time of experimentally induced lesions. We know that these chlorophyllins have shown remarkable deodorizing effects in the case of infected wounds and that the major part of this deodorization is dependent upon the action of the "chlorophyll" on bacterial metabolism. We know that these activities reside in the tetrapyrrolic nucleus of the molecule and that the phytol portion of the total molecule can be removed chemically by saponification without changing the clinical effectiveness of the remaining structure. Indeed, on a weight basis the remaining tetrapyrrolic nucleus shows proportionally greater activity.

It is interesting that from the phytol portion of the molecule it is readily possible to synthesize vitamins E and K. Experimental work with the pyrrolic nucleus suggests that certain of its pharmacologic functions can be similarly modified by substituting various side chains and by chelating with various metals.

The fundamental precursor that gives rise to the tetrapyrrolic nucleus of chlorophyll is porphin, exactly the same precursor from which is derived the red coloring matter of the blood and the prosthetic groups of several indispensable respiratory pigments including catalase, peroxidase, and the cytochromes. Some or all of these respiratory pigments are involved in the oxidation-reduction phenomena without which life in any form is impossible. It was the recognition of this fact that early prompted study of oxidation-reduction behavior of bacteria treated in the test tube with chlorophyll derivatives. From these studies it was suggested as the most likely explanation that in the case of anaerobic organisms, chlorophyll is bacteriostatic by reason of its interference with oxidation-reduction mechanisms, although at that time the precise nature of this interference had not been determined.[7]

One of the most striking characteristics of chlorophyll, as of hemoglobin, is the centrally bound or chelated metal, completely encompassed and protected by the tetrapyrrolic ring structure. In nature the metal in chlorophyll is magnesium, just as it is iron in the case of hemoglobin. In either instance the metal can easily be removed chemically from its central, sheltered position and replaced by almost any other metal. Indeed, chlorophyll represents one of the classic illustrations of the chelation phenomenon. When such chelation exists, the complex containing the metal fails to give the common inorganic ion reactions for the particular metal involved and behaves more like a single but complex organic substance.

From this fundamental concept certain facts with respect to the pharmacodynamic potency of chlorophyll and chelation have emerged. For maximum effectiveness, either from the antibacterial or growth-stimulating viewpoint, a metal must be present in the molecule. For example, pheophytin and pheophorbide are both relatively inert in either capacity. The different metals seem to modify appreciably the action of the molecule as a whole. Studies on various chelates of chlorophyll, including copper, nickel, cobalt, zinc, cadmium, iron (ferrous), manganese, magnesium, and other metals, suggest that the magnesium chelate is the least stable and possesses essentially no hematopoietic activity.[8]

The copper compound has been the one most generally employed and has been demonstrated to have to a very adequate degree the antibacterial cell growth-stimulating, and hematopoietic activity needed for clinical effectiveness.

The dependence of life on traces of metals is once again emphasized, and with it develops an old controversy in new form—the relative value of "inorganic" versus "organic" metals, likening chelated metal forms to "organic."

No purpose is to be served in this discussion in elaborating upon the more general chemical features of chlorophyll. These are readily available in a number of encyclopedic monographs by the greatest authorities in the field[6,9–13] (see also various reviews in the *Annual Review of Biochemistry*). However, certain salient points might appropriately be brought to light by way of demonstrating that the generic term "chlorophyll" has been used in the loosest possible sense with little or no scientific meaning.

On the basis of even our current knowledge of "chlorophyll," it is apparent that the various relatively impure chlorophyll derivatives employed in many of the so-called deodorant products commercially promoted during the past few years could not possibly be so effective as certain manufacturers attempted to claim. This statement does not necessarily apply to all preparations for which reasonable deodorization claims have been advanced. Among this latter group should be included toothpastes, chewing gums, lozenges, and even oral tablets where the beneficial action is not entirely dependent upon contact deodorization, but also results from the antibacterial activity of the "chlorophyll." In general, however, "chlorophyll" is not a particularly effective contact deodorant. Even Hainer[14] in his recent report brings out the fact that "chlorophyll" is limited in its adsorptive deodorant capacity, tending to show some selective action in the case of the mercaptans and sulfides, neither of which offer any problem in wound healing.

Even the lay public rejected many of the ridculous products carrying the magical green color, such as insoles, toilet paper, diapers, bed linens, and other similar preparations wherein the crude degradation products of "chlorophyll" were added without rhyme or reason. Much of the claimed efficiency of "chlorophyll" as a deodorant in these products was based on speculative implication because of its recognized value in the deodorization of infected wounds. In this latter instance the principal mechanism involved is interference with bacterial metabolism. To a limited extent contact adsorption may also play a minor role.

After the Gruskin report appeared, it became obvious that there was need for "standardizing" the chlorophyll preparations used in the clinic. Based on the fragmentary but sound evidence then in existence from Europe and America, an ethical pharmaceutical company was formed* to refine such "chlorophyll" as was commercially available and to convert it to the form then believed to be the most effective for the treatment of wounds and burns.[3] The crude chlorophyll was freed from phytol, cleared of most of the nondescript degradation products of chlorophyll decomposition, and properly rechelated. These refined water-soluble chlorophyll preparations were prepared as solutions or ointments for clinical use and were marketed under the trade name Chloresium. In that form they were accepted by the Council on Pharmacy and Chemistry of the American Medical Association.[15]

The Temple University studies gave new impetus to the study of how "chlorophyll" aids in the healing of wounds and burns. A series of reports from that institution were published over a period of the following two or three years.[16–18] None of these reports furnished a complete or final answer to the problem, but each pointed more and more to certain facts which, since that time, have been more fully integrated by others. What was of greatest importance in the decade following the issuing of the Temple University report was the almost universal corroboration of the original clinical findings. Some of the results were exceptional. These clinical reports have continued to appear in the medical literature and have continued to show uniformly outstanding results. Criticism has been raised from time to time that the effectiveness of these "chlorophyll" products has been based on empiricism, that they have not been adequately controlled, and that no satisfactory explanation as to the mechanism has been propounded. If these arguments are tenable, then similar arguments could have been raised validly in respect to many of our most useful drugs and would still hold today for a smaller number. It would appear that the *clinical value of "chlorophyll" therapy has been established* in the treatment of wounds and burns whether or not accompanied by infection. It

* Rystan Company, Mount Vernon, New York.

would also appear to be incontrovertible that Council-accepted, ethically marketed "chlorophyll" products have an unusual degree of safety.

So far as the criticisms are concerned, the one most constantly and justly raised questioned the uniformity of composition of the chlorophyll derivative being employed, both in the early animal studies and later in clinical use. For this reason, in this review reference is made only to reports in which the so-called water soluble chlorophyllins have been the material used. In this way one variable, that incident to chlorophyll composition, has been reduced to a minimum, and the results can be better compared. These compounds will hereafter be referred to as "chlorophyll."

Deodorization of Wounds

One of the most gratifying features of "chlorophyll" therapy in the treatment of foul-smelling, secondarily infected, ulcerative lesions has been its ability to deodorize promptly such conditions as chronic osteomyelitis, infected compound fractures, sinus tracts, ulcerative carcinomas, and chronic decubitus and leg ulcers.[19-24] Criticism has been raised from time to time that such reports have been on a purely arbitrary, empiric basis. But interference with the malodorous putrefactive process in these cases is a dramatic reality, attested to by patient, nurse, physician, and visitors alike, regardless of the various interpretations offered as to the mechanism involved.

Certainly it has been shown on innumerable occasions, both in the test tube and clinically, that "chlorophyll" possesses definite antibacterial activity of a relatively low order of magnitude. Thus it does interfere with bacterial metabolism and stops the further breakdown of tissue by proteolytic organisms.[24] As has been stated previously, this appears to be the major mechanism involved, although some adsorption of odors undoubtedly contributes to the rapidity of the deodorization.[14,25-27]

As Bowers[19] states after commenting that it is his belief that chlorophyll therapy has been the means of saving several limbs from amputation, "even if chlorophyll did nothing in these cases but to stop odor, decrease suppuration...its use would be amply justified." This deodorization of foul-smelling lesions by "chlorophyll" therapy has been an almost universal experience and undoubtedly has been one important reason for the continuously increasing demand for "chlorophyll" medication.

Absence of toxicity has been another outstanding feature throughout more than a decade of clinical use, and agreement on the following clinical opinions is common to all the reports:

1. "Chlorophyll," whether in the form of ointment or solution, promotes the growth of healthy granulation tissue.
2. It is conducive to the production of a clean, granulating wound base.
3. Itching, pain, and local irritation, which so frequently are the outstanding symptoms associated with ulcers, burns, wounds, and dermatoses, are usually relieved promptly, and this relief is gratefully ackowledged by the patient.
4. Normal repair and epithelization proceeds more rapidly under "chlorophyll" treatment of burns and dermatoses than with other agents.
5. Malodorous lesions are deodorized (an action not to be confused with mere contact deodorization as implied by certain less accurate promotional claims in some instances).
6. Blandness of action, freedom from tissue damage, and lack of toxicity as well as comforting, soothing relief are almost invariably characteristic of "chlorophyll" therapy.

Tissue Stimulation Action

From the early experimental studies by the Temple University group it was shown conclusively that even the relatively impure "chlorophyll" preparations which were available at that time were highly effective in stimulating fibroblastic proliferation, both in tissue culture and in various types of induced skin lesions. These studies were carefully controlled except in respect to the absolute purity of the particular water-soluble sodium copper chlorophyll preparations employed. The results accordingly were strictly comparable insofar as these laboratory prepared products were concerned. Of particular interest perhaps were the studies by Smith and Sano[18] on the effect of these chlorophyll derivatives on the growth of fibroblasts in tissue culture. It was shown that the addition of as little as 0.05 per cent of the above-mentioned "chlorophyll" produced an almost complete elimination of the usual lag period before growth ordinarily could be observed. These observations were confirmed by Dunham[28] entirely independently. The obvious implication of this biologic activity in the

clinical application of such "chlorophyll" derivatives in wound healing requires no elaboration.

Clinical Application

It was not long before clinical reports on the use of these "chlorophyll" preparations in the treatment of a wide variety of conditions began to appear. These included various types of ulcers, particularly those of the chronic, indolent type associated with circulatory deficiencies, such as those of arteriosclerotic, diabetic, varicose vein, and decubitus etiology,[3,19–21,23,29–34] as well as cases of radiation origin.[35]

Similarly "chlorophyll" was reported as being highly effective in the treatment of wounds in general, including traumatic injuries of the soft tissues, compound fractures, chronic osteomyelitis, postoperative wounds, sinus tracts, fistulas, amputation stumps, and gunshot injuries to mention but a few typical examples.[3,19–21,23,29–38]

Likewise several authors reported the successful use of "chlorophyll" in burns both experimentally in animals[16,17] and clinically, including those due to thermal and chemical sources such as dry heat flash burns, moist heat scalding burns, sunburn, and various chemical or acid burns.[39–41] Holmes and Mueller[35] found "chlorophyll" of inestimable value in controlling postirradiation erythema. They state, "a check-up examination of the patients...showed the healing process to be better than any we had previously obtained... As a matter of fact we have rarely had an opportunity to see a severe radiation reaction since we began the use of chlorophyll early and routinely."

Haughton,[40] Bowers,[19] Lowry,[42] Carpenter,[20] and others all uniformly report that because of the action of "chlorophyll" in producing a healthy granulating base to the lesion, it is a useful agent both for preoperative preparation of patients for grafting and for successful maintenance of skin grafts.

No particular purpose would seem to be served by more detailed discussion of these clinical reports as such. They exhibit an amazing uniformity as to the effectiveness of "chlorophyll" therapy in topical therapy, especially in the case of chronic, infected lesions. They all emphasize the complete lack of toxicity, the relief of pain and itching, the deodorizing action in cases of foul-smelling infected lesions, the stimulation of healthy granulation tissue formation, and accordingly the relative acceleration of healing in such cases. Nowhere is this better brought out than in Pollock's paper[34] on the treatment of decubitus ulcers in which a comparative study was made with ten other well-recognized agents: (1) soap and water, (2) hydrogen peroxide, (3) ultraviolet radiation, (4) zinc oxide ointment, (5) nitrofurazone ointment, (6) sulfathiazole ointment, (7) iodochlorhydroxyquin U.S.P. (Vioform) ointment, (8) petrolatum U.S.P., (9) thiomerosal N.F. (Merthiolate), and (10) bacitracin ointment. These authors conclude "the least effective agent was found to be sulfathiazole, and the *most effective* agent is generally agreed to be chlorophyll ointment and liquid." It is perhaps of more than passing interest that Smith and Livingston[16,17] made essentially the same comment nine years earlier, namely, that the sulfa preparations alone caused actual delay in healing, whereas there was "acceleration of healing...in 71 per cent of the chlorophyll topically treated lesions" in guinea pigs.

Antibacterial Activity

Clinicians in general are not concerned with *how* a product works so long as it *works*, but the more strictly scientifically trained man is not satisfied with this approach. He must search for a reason to explain the *how* and *why* some particular product has such irrefutable beneficial activity, while another preparation very similar in character is virtually of no clinical value.

In some of the early studies from Temple University, Spaulding, quoted by Smith,[7] reported that water-soluble sodium copper chlorophyllin showed definite antibacterial activity against both gram-positive and gram-negative bacteria, including certain of the more common anaerobes. They postulated the theory that such chlorophyllins interfered with the oxidation-reduction mechanism of bacterial respiration to account for the marked bacteriostatic and even bactericidal effect under optimal environmental conditions. In general, their observations pointed toward a greater effectiveness against gram-positive organisms than against gram-negative bacteria.

Daly and his associates[43] had found that "chlorophyll" derivatives were even more active against both avian and human type tubercle bacilli. Certain specifications concerning such active in vitro "chlorophyll" derivatives became matters of patent.[44,45] Actually it requires but very low concentrations of certain selected water-soluble "chlorophyll" derivatives to inhibit the growth of

avian or human tubercle bacilli in the test tube.[46] On the other hand, the effect of chlorine on retarding the growth of the organisms is virtually nil.

More recent studies on the effect of chlorophyll as an inhibitor of tubercle bacillus growth strongly suggest that the effectiveness may be enhanced by the preservation of the fifth ring in the molecule, making it operative in gamma dosage.[47] Another point of interest in this connection is the apparent similarity of action of such dicarboxylic "chlorophyll" derivatives and streptomycin in certain respects. The initial bacteriostatic requirements of each are of about the same order of magnitude. However, in successive transplants there is a striking difference in their effectiveness. In the case of streptomycin the tubercle bacilli become increasingly resistant to its action, whereas in the case of the "chlorophyll" derivatives the organisms become increasingly sensitive so that diminishing doses are able to bring about prolonged bacteriostasis and even at times a bactericidal effect.

Another evidence of the importance of "chlorophyll" as an antimetabolic agent is seen in the case of Bacillus prodigiosus which normally produces a tripyrrolic pigment, prodigiosin, having marked antibiotic activity but unfortunately associated with a rather high order of toxicity, so as to render it of very little practical value therapeutically.[48,49] If, however, B. prodiogiosus is grown in the presence of certain "chlorophyll" derivatives, the pigment fails to develop, and extracts of the dried organisms are devoid of toxic effect.

The action of even relatively impure water-soluble "chlorophyll" derivatives has been demonstrated repeatedly to alter the metabolism of colon bacilli in the intestinal tract. There have been numerous clinical observations that indol and skatol formation are lessened after feeding "chlorophyll," such as those of Weingarten[50] and Joseph.[51] One practical application of this antimetabolic action has been the use of "chlorophyll" in the treatment of colostomy wounds. Laboratory evidence likewise confirms the lessened indol and skatol production by Escherichia coli in the test tube in spite of the fact that the growth of the organisms themselves is not inhibited by the "chlorophyll." Parenthetically in this connection it is interesting to note that colon bacilli grow profusely in the presence of bile pigments which likewise are porphin derivatives with the same basic pyrrol nuclear structure as that of "chlorophyll."

A few paragraphs back we commented briefly on certain streptomycin or antibiotic-like characteristics of "chlorophyll." We would be remiss, indeed, if we did not call attention to various other contributions which tend to emphasize this common denominator feature of "chlorophyll" and streptomycin. Some five years ago Provasoli and his associates[52] observed that streptomycin inhibited the development of "chlorophyll" in the growth of certain algae (Euglenophyta), although *not* interfering with their multiplication.[53] Lwoff and his collaborators[54] confirmed these observations and likewise demonstrated the analogous structural relationship of "chlorophyll" and streptomycin. Van Niel[55] had commented some three years previously that the so-called "purple" sulfur bacteria tended to be inhibited in their growth by the presence of streptomycin, but in this instance no interference with pigment production is noted. This of course suggests that metabolic interference by streptomycin with the transsulfuration mechanism of bacteria is involved. Further corroborative evidence of this relationship is found in the report of the German investigators, Erbring, Niedner, and Wulf.[56]

Since the porphin nucleus which may ultimately produce either "chlorophyll" or hemoglobin is derived from simple amino acids, including glycine in particular, coupled with acetic acid,[57–62] the reports of the antagonism between streptomycin and "chlorophyll" immediately suggested that an isosteric resemblance between the two could explain the clinical findings and the isolated experimental findings that had accumulated up to that time. The next question was how to establish such isosteric antagonism on an experimental basis. Research work in progress but as yet unpublished[63] tends to confirm this suspected antimetabolic activity in relation to transsulfuration, namely, the prevention of the appearance of mercaptan sulfur in the urine following the feeding of asparagus along with certain "chlorophyll" derivatives. Further evidence[63] is to be found in data obtained from an extensive clinical study in which suitable "chlorophyll" derivatives were given orally to a series of women in an attempt to learn whether such preparations would interfere with transsulfuration mechanism during the menstrual period to suppress mercaptan, acetylcholine, and trimethylamine secretion in the

apocrine sweat. There is objective and subjective correlation of the data which tends to indicate that such oral "chlorophyll" therapy does suppress such odoriferous secretions about three times more frequently in the experimental group than in the control group who were given "chlorophyll"-free placebo tablets.

We have dealt at some length with the reports in the literature regarding the antibacterial features of "chlorophyll" and its points of similarity and disparity to streptomycin, another rather more limited type of antibiotic, primarily to emphasize that it is our conviction from a review of the literature and from our own personal experimental, laboratory, and clinical experience that "chlorophyll," when further developed, will prove to be *one* of the most important, if not *the* most important pharmaceutic "materia prima" from which new antibacterial derivatives tailored to specific jobs will be developed by the biochemist for our needs. All of the published data point toward its antibacterial activity as being its most important function so far as the treatment of acute or chronic suppurative lesions topically is concerned. The key to this mechanism lies in the direction of a metabolic antagonism wherein "chlorophyll" modifies the growth pattern and functional capacities of the infecting bacteria. This modification is primarily in the direction of decreasing or destroying the toxicity of the bacterial metabolic products, while at the same time promoting or stimulating normal cell proliferation which in turn accelerates comparatively the healing process. Wasielewski and Albrecht[24] emphasize the importance of such alteration of metabolism in the case of B. proteus in the presence of "chlorophyll."

This concept in turn raises the whole problem of host resistance (immunity) or sensitivity to bacterial invasion. This is still one of the most important biologic mysteries to be solved. Perhaps the streptomycin-"chlorophyll" relationship discussed above will serve as a signpost toward its solution. In the meantime the work of a number of investigators in the general field of immunology and tissue response offer theoretic approaches toward answering the problem.

Barnes[64–66] has developed an ingenious technic whereby he can measure the electrical potential developed at the injured site following the production of a standard abrasion of the skin by means of coarse sandpaper. This method lends itself particularly well to carefully controlled studies using a variety of agents and determining not only the actual time required for healing to take place objectively but also the time required for the electrical potential to become restored to its former negative phase. In a series of studies Barnes found that healing was accelerated when "chlorophyll" was applied topically to such experimental abrasions and that the measurement of decline of the electrical potential served as a very accurate index of the rate of healing. He obtained this index by subtracting the per cent loss of positive potential in the control wound from that noted in the experimental lesion. The index with "chlorophyll" ran as high as 1.30, indicative of a marked shortening of the healing time. This differential was much higher than that of his control preparations, including sulfanilamide powder, scarlet red, penicillin, and vitamin D ointment, as well as the ointment base itself in which the "chlorophyll" was incorporated.

In a recent paper on the biometric method of measuring the rate of healing of wounds Barnes[67] reports that statistical analysis of his data in 76 wounds in man treated with Chloresium shows that the increased healing rate produced by such preparations is statistically significant. These studies would seem to support further the hypothesis advanced earlier in this discussion that "chlorophyll" exerts a direct growth-stimulating effect upon tissues. Incidentally, it is of more than passing interest to note that this growth-stimulating action might properly be termed physiologic in nature. Only rarely has granulation tissue formation been reported as going on to a pathologic hyperplastic state and then only under rather notably adverse conditions. It is almost as if there were a teleologic element involved, as so often appears to be the case with other natural phenomena. While these experiments of Barnes have little to do with the concept of the infectious aspects of the immunologic phenomena in man, they do lend support to that phase of the hypothesis which deals with cell resistance to injury generally.

In line with the immunity approach to the problem, Barnard[68] has recently come forward with some very broad hypothetic views, backed up by a limited amount of preliminary experimental laboratory data. He has felt, as others have, that while the clinical benefits of "chlorophyll" therapy have been validated repeatedly, the mechanism by which these effects have been produced has *not* been precisely defined.

Barnard has been particularly interested for more than ten years in those phenomena of the blood associated with hemolysis and agglutination. He and his associates[69–72] have shown that as little as 0.01 to 0.1 per cent of "chlorophyll" derivatives will delay or even prevent red cell hemolysis in oxalated or citrated blood samples stored under the usual temperature precautions. On the basis of previous work they were of the opinion that spontaneous hemolysis is caused by the presence of mucoproteins and that the so-called Rh "blocking antibodies" responsible for many transfusion reactions and for fetal deaths in Rh-sensitized mothers are also mucoproteins, so that it was simple to set up a series of tests incorporating the same "chlorophyll" derivatives in varying concentrations to determine whether the "chlorophyll" would act in a similar manner in this analogous system. It was found that agglutination was definitely inhibited or abolished if the concentration of "chlorophyll" was sufficiently great. Following these preliminary experiments "chlorophyll" was tested against a wide range of specific hemagglutinins including mucoproteins from the blood of patients with leukemia, hemolytic anemia, vaccinia, and other infections. Other agents such as Dextran, gamma globulin, partially depolymerized hyaluronic acid, and Menkin's necrosin failed to yield the same results.[73]

The studies with necrosin are of particular interest in that this material, isolated from the exudate of wounds, produces necrosis with the development of nonhealing ulcerations when injected subdermally in rabbits. If "chlorophyll" is added, the phenomenon is prevented. Barnard feels that these two properties of "chlorophyll"—preventing hemagglutination and protecting the tissue cells from the necrotizing action of toxic substances in the inflammatory exudate—go far toward explaining one aspect of action of the "chlorophyll" in promoting healing. He supports his contention with both laboratory and clinical data of cases from whom such "aggressins," as he terms them, have been isolated and checked for activity. He notes that serial samples of exudate from cases under "chlorophyll" treatment show a progressive quantitative decrease in these substances. His studies open up a comparatively unexplored approach to the entire problem of wound healing. As he states in conclusion, "there is no doubt... that it (chlorophyll) is a highly active substance and it will be very surprising if broader and more important therapeutic applications are not found for chlorophyll derivatives than have been even preliminarily investigated to date."[68]

There is need of course for a great deal more study of the pharmacodynamic potentialities of the "chlorophyll" molecule. This review of the literature has attempted to bring out such knowledge as has accumulated during the past quarter of a century to help explain the underlying mechanisms involved in the uniformly effective clinical applications of "chlorophyll" therapy. Each new advance in our knowledge will bring continuing improvement to the form in which "chlorophyll" can be most advantageously used in ethical medical practice.

Summary

Meanwhile, a summary of the clinical and experimental research with "chlorophyll" over this twenty-five-year period reveals that:

1. As a porphin derivative involved in the fundamental mechanism of oxidation-reduction, "chlorophyll" ranks with the red coloring matter of the blood, catalase, peroxidase, and the cytochromes. All are of deep significance and of indispensable importance to life in any form.

2. Over 800 derivatives of "chlorophyll" have been described. Even the earliest impure ones made commercially have proved their therapeutic value. There is every indication that other, newer, improved derivatives will be of even greater scientific interest and therapeutic importance.

3. We are gradually learning about the properties that must be conserved in the molecule of "chlorophyll" to exert effective pharmacodynamic activity. The side chains are of tremendous importance. The preservation of the fifth ring appears to be of considerable advantage. Chelation with various metals other than magnesium or copper holds promise of even greater therapeutic application.

4. Twenty-five years of laboratory and clinical experience have proved consistently that certain water-soluble "chlorophyll" derivatives are effective in the treatment of acute and chronic suppurative disease, as well as in both infected and noninfected wounds and burns. More spectacular treatments have developed during this period in respect to many of the *acute* infections, especially during the past decade with increasing use of the antibiotics. Despite the advent of these invaluable new drugs clinicians return re-

peatedly to the use of "chlorophyll" alone or in combination with such drugs, especially in the treatment of chronic, stubborn, ulcerative lesions.

5. The vast amount of research invested in the sulfonamides and antibiotics has taught us what to look for in our attempts to conquer bacterial infection. The newer thinking is in the direction of nutritional antagonism or competition, in which the antimetabolic agent tends to inhibit the action of a specific enzyme indispensable to the life of the bacterium, but nonessential to the life of the host's tissues. This is essentially the extension in terms of modern chemical and pharmacologic knowledge of Ehrlich's basic postulate. Its significance is being realized more and more each day.

6. The clinical use of "chlorophyll" preparations, notably Chloresium, in the past has been completely justified on the basis of the generally excellent therapeutic results obtained empirically and even more rationally today on the further basis of objectively demonstrable mechanisms in line with those whereby all respiratory pigments carry on their functions.

7. The indications are that "chlorophyll" may well prove to be a "materia prima" from which the chemist can synthesize antibiotic-like preparations against specific infectious agents. As in the case of vitamin B_{12}, their pharmacodynamic power may be enhanced because of the chelation which is common to the green coloring matter of plants, the red coloring matter of blood, and the prosthetic groups of catalase, peroxidase, and all the cytochromes. Studies exploring the effect of "chlorophyll" on certain aspects of the serologic and immunity factors in wound healing open up a new approach to the problem which requires further development and confirmation.

Conclusion

In conclusion, a review of the literature as it relates to ethical "chlorophyll" therapy, particularly over the past decade, gives every justification for its widespread acceptance in the field of burns and wound healing in particular.

In the deodorization of such secondarily infected, ulcerative lesions its position is secure. The mechanism of this deodorizing property has been clearly shown to be dependent principally on the antibacterial action of "chlorophyll" and *not* on its capacity as a contact adsorbent.

New laboratory evidence indicates certain points of similarity between at least one major antibiotic, streptomycin, and specific "chlorophyll" derivatives, suggesting a vast future research program with the development of selective antibacterial agents using "chlorophyll" as the starting "materia prima."

Preliminary experimental work with many new chelated "chlorophyll" compounds likewise promises to expand the fields of usefulness for "chlorophyll" therapy, especially in the geriatric chronic degenerative diseases.

All in all, a careful review of the literature reawakens one's enthusiasm as to the tremendous possibilities for the development of "chlorophyll" derivatives which can be just as revolutionary in the future, although probably not so spectacular, as the antibiotics have been during the past decade.

119 EAST 26TH STREET

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How much we suffer from failure to convey our wishes correctly to our patients. Listening to one's colleagues shows how much time and effort are wasted by lack of liaison.

Lie on our back on the couch—No, on your back, please.

Show me where the pain comes—No, on your own back please.

Please stand up—now, raise your right leg—thank you, and now your left leg—thank you, and now get up off the floor.

There is clearly an urgent need to revise the technic of medical questioning, and at the next twelve unselected outpatient clinics we are giving a trial to the following phrases:

Lie on the couch with your tummy upwards.

Show me on your own back where the pain is.

Bend your knee crooked—and now bend it straight.

I would welcome suggestions how to avoid the inevitable contraction of the calf muscle just as I withdraw the tendon hammer from my pocket. "Relax," "Pretend you're asleep," "Don't bother about me," "Go loose," and "Pretend you're dead" have been tried and found wanting.—*The Lancet, May 7, 1955*