REVIEW ARTICLE: BIOLOGICAL ACTIVITIES OF CHLOROPHYLL DERIVATIVES

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The authors review the anti-inflammatory, wound healing, and malodor-reducing properties of chlorophyllin, a chlorophyll-related medicinal agent; the study includes plant-derived, chlorophyll-based compounds under study as useful anticancer, antiatherosclerosis, and antipsoriasis drugs.

Although chlorophyll generally is known as the major photosynthetic porphyrin pigment in plants, some of its chemical derivatives exhibit interesting biological activities in animals and humans. It has been at least 14 years since the last survey on this subject appeared.[1] The purpose of this article is to present a brief review of the older literature, the more recent publications, and some unpublished results of our ongoing studies. Selected aspects of the biological activities of chlorophyll derivatives, especially chlorophyllin copper complex (CCC), a centrally coordinated metal tetrapyrrole compound, with particular emphasis on stimulation of cell regeneration, influence on wound-healing retardation factors, toxicological characteristics, and the clinical application of CCC as a wound healing and deodorizing agent will be discussed. Furthermore, the possible utilization of these substances as therapeutic agents in some new, promising areas, also will be described.

PRECLINICAL STUDIES

Smith and Sano were among the first workers to investigate the effects of chlorophyll derivatives on cell growth using tissue culture methods.[2] The addition of 0.05 or 0.5 percent of CCC to cultured embryonic mouse heart fibroblasts resulted in a rapidly increased growth rate (40 percent) which was maintained by replenishing the CCC every 48 hours. Another tissue culture study demonstrated similar growth stimulating effects of chlorophyll derivatives. For example, these substances at concentrations of 2×10^{-4}M increased by 31 percent the neurite outgrowth in mouse neuroblastoma cells.[3]

The observations made on the tissue culture studies also were investigated in animal experiments. Ointments containing chlorophyll derivatives which were applied to guinea pigs and rabbits with induced skin wounds resulted in faster healing rates than those occurring with some other agents tested. "Chlorophyll" therapy initiated early appearance of clean granulation tissue, rapid epithelization, and acceleration of wound healing without inflammation.[4] Similar studies in various animals showed that CCC consistently displayed statistically significant effects, increasing the rate of healing by approximately 25 percent in about 68 percent of the cases of traumatic and thermal wounds.[5] Additional experiments using topical "chlorophyll" therapy supported the positive wound healing effects noted earlier.[6] Chlorophyll derivatives

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led to activation of fibroblasts, reduction of epithelization time, and marked increases in cell mitotic indices which accompanied accelerated wound healing. Also, it was observed that the number of blood vessels and the resultant circulation in the chlorophyll-treated wounds were increased.[7,8]

In connection with wound healing, one of the concerns among clinicians is the recognition that topical wounds and ulcers frequently are infected. Thus, even when treated by preparations which stimulate cell regeneration, infected areas heal poorly. Clearly, an ideal wound-healing agent should demonstrate dual actions: cell regeneration as well as antimicrobial properties. In a series of further investigations, it was shown that CCC[9-11] and other chlorophyll derivatives[12,13] were bacteriostatic in vitro, mainly against gram-positive microorganisms, some of which are wound pathogens. Also, these substances neutralized *Staphylococcus aureus* and *Clostridium perfringens* toxins[14] which may inhibit or prevent wound healing. The topical application of CCC abolished the undesirable hemagglutinating and inflammatory effects of one or more components of microbial and nonmicrobial origin present in wound exudates and thereby promoted healing.[15] Finally, CCC inhibited staphylococcal coagulase-induced clotting that otherwise may result in fibrin-coated bacteria which subsequently resist phagocytosis.[16]

Another approach taken for studying the cell regeneration activity of chlorophyll derivatives was to study the effect of these substances on formed blood elements. The administration of these agents alone or with iron-containing compounds, stimulated the production of hemoglobin and erythrocytes in anemic animals.[17] Anèmic rabbits fed a regular diet supplemented with chlorophyll derivatives recovered after 14 days, compared to 23 days for the controls.[18] Other studies in anemic animals treated with CCC (0.025 g/kg, intravenous or 0.05 g/kg, by mouth)[19] or with different chlorophyll derivatives (0.05 mg/kg, subcutaneously)[20] showed a 70.5 to 83 percent increase in erythrocytes and normalization of hemoglobin levels in 10 to 16 days. Oil-soluble as well as water-soluble chlorophyll derivatives exhibited antianemic effects.[21] Chlorophyll-iron complexes have been especially successful in managing anemic animals.[22] The utility of chlorophyll derivatives for treating various anemias also was described by other workers,[23] although it should be noted that in one study, these substances were ineffective.[24] In addition to erythrocytes, the regeneration of other blood cells can be stimulated by these substances. Thus, chlorophyll derivatives administered intraperitoneally reversed or prevented chemical and x-ray-induced leukopenia in several animal models.[25,26]

Morever, the regenerative and protective properties of chlorophyll derivatives were further substantiated by observing the effect of these substances on some internal organs. Thus, orally administered CCC-containing preparations showed antiulcer activities in animals.[27] Also, chlorophyll derivatives protected against carbon tetrachloride-induced liver damage in animals.[28] Finally, in in vivo models, these agents increased oxygen consumption, which is an indicator of cell regeneration.[29]

The potential of chlorophyll derivatives, particularly CCC, for therapeutic use, initiated toxicological studies on the latter. Thus, rabbits, dogs, cats, guinea pigs, rats, and mice were administered CCC by various routes. The doses, ranging from 100 to 300 mg daily, were given for periods of from five to eight days depending on the animal. At all of the doses administered, no animals were found to exhibit signs of toxicity, thereby attesting to the safety of CCC.[30] In mice the LD_{50} (lethal dose) values for CCC were: 285 mg/kg intravenously, 400 mg/kg intraperitoneally (ip), and 10 g/kg by mouth.[31] Harrison and colleagues using Swiss male mice reported the following acute toxicity data: LD_{50}, 7 g/kg by mouth (LD_0, 5 g/kg and LD_{100}, 12 g/kg) and 0.19 g/kg ip (LD_0, 0.13 g/kg and LD_{100}, 0.32 g/kg).[32] Moreover, during a ten-day period, Sprague-Dawley rats ingested a total of 10.2 g and 13.4 g of CCC, respectively, with no deaths observed (LD_0, 50 g/kg). These results point up the fact that CCC is an extremely safe substance from an acute and chronic toxicity point of view.

CLINICAL STUDIES

Wound healing. The cell regeneration effects of CCC in tissue culture and animal model studies, its influence on wound healing retardation factors, and its apparent lack of toxic properties led to clinical investigations which started actively in the United States in 1940. Ointments and solutions containing chlorophyll derivatives, including CCC*, were found to promote wound healing and to reduce malodors in various types of suppurative lesions.[33] In more than 400 hospital cases of suppurative disease, the topical application of CCC stimulated granulation tissue and epithelization better than several other agents.[34] Numerous clinical cases of chronic, refractory skin lesions, mainly dermal ulcers which failed to respond to conventional therapy, were treated successfully with CCC.[35] Marked improvement and healing following CCC therapy, with relief of itching and burning, were reported in various types of dermatological cases as well as in burns.[36,37] Indeed, numerous clinical studies have demonstrated the potential of CCC as a tissue stimulant and wound healing agent in managing a wide variety of burns, dermatoses, and skin and gingival lesions.[38-42] Objective methods to evaluate the effectiveness of CCC using comparative therapy with other agents in patients with bilateral lesions demonstrated CCC to be the wound-healing drug of choice.[43] Only a few reports have failed to show a therapeutic effect for CCC in the wound-healing process,[44] with one study indicating that CCC at least tended to improve wound appearance.[45]

Although CCC topical therapy generally gave acceptable clinical results, continued experience with CCC preparations revealed that some cases of especially chronic, slow-healing ulcers failed to respond satisfactorily.[33-45] Further investigations showed that these recalcitrant lesions exhibited decreased vascularization due to capillary occlusion by agglutinated erythrocytes. In addition, the occurrence of densely collagenized

*Most of the clinical studies in the United States employed ointments containing 0.5 percent CCC in a water-washable base or aqueous solutions containing 0.2 percent CCC (Chloresium®, Rystan Co., Inc.)

fibrous tissue, together with toxic products from tissue breakdown and necrosis within the ulcer itself, led to incomplete healing with frequent reoccurrences of healed tissue breakdown.[46] Therefore, a novel topical preparation* was developed which contained CCC as an antiagglutinating and wound-healing agent, the proteolytic enzyme papain as a debriding agent, and urea to render necrotic tissue and wound debris more susceptible to papain breakdown. This formulation was more effective (86 percent complete healing) than either papain or CCC alone in treating slow-healing wounds.[46] Twenty-three of 24 patients[47] and 26 of 27 cases,[48] all involving various foul-smelling skin ulcers and suppurative wounds, were effectively managed and, in many cases, completely healed[47] with the papain-urea-CCC(PUC) ointment. Different types of chronically infected wounds, many of which did not respond to antimicrobial therapy, and/or surgical debridement were effectively treated with PUC therapy.[49,50] Eradication of local infection and complete healing of chronic dermal ulcers were reported in 36 of 37 cases.[49] Application of PUC ointment in 18 of 22 cases of chronically infected wounds provided effective debridement prior to surgery, eliminated malodors, and avoided surgery in a few cases.[50] All these clinical reports indicated that the use of PUC ointment was safe, i.e. transient; mild local effects including burning, stinging, or itching were only rarely observed and generally did not warrant cessation of therapy, and were highly beneficial in managing slow-healing wounds complicated by necrosis and infection.

Internal Deodorization. In view of the many observations that CCC exhibited deodorizing effects as well as healed foul-smelling wounds, it was suggested that CCC might be helpful in controlling the odor problems of ostomy patients. Early reports showed that the deep insertion of chlorophyll derivatives by patients into their colostomies led to significant deodorization.[51] Subsequently, it was shown in several studies that the oral administration of CCC** in doses of about 100 to 200 mg daily to colostomy patients, was sufficient to control malodors without undesirable side effects.[52-54] Using the same dosage schedule, many studies also have been carried out on the use of CCC to control malodors in patients with urinary and fecal incontinence problems.[55-58] Except for one study which employed low, daily oral doses of CCC over relatively short periods of time,[58] these reports generally afforded evidence that odors were reduced markedly in about one week and continued treatment maintained good control consistently. CCC has been classified as being generally recognized as safe and effective as an internal deodorant by the U.S. Food and Drug Administration.[59]

MODE OF ACTION

The exact mechanisms whereby chlorophyll derivatives promote wound healing are not fully understood. Some possibilities include: a) the stimulation of protein synthesis[20] in a manner similar to that known for heme[60] and subsequent cell regeneration[2,3,12] with concomitant increased oxygen uptake;[29] and b) antimicrobial effects and/or direct neutralizing effects on toxins as well as other wound-healing retarding compounds present in wound exudates.[9-16, 61-68] Various mechanisms have been suggested to explain the deodorizing effect of chlorophyll derivatives. Thus, the absorptive properties of these substances for odorous compounds have been reported.[64] Chlorophyll derivatives were found to tightly bind and immobilize odorous microbial indolic compounds.[65] Also, these chlorophyll derivatives may induce metabolic changes in odor-causing microorganisms. For example, *P. vulgaris* grown in the presence of these agents produced lesser than normal amounts of hydrogen sulfide, ammonia, and methyl indole compounds.[66,67] It is tempting to speculate that at least one common general underlying molecular mechanism may account for the biological activities of chlorophyll derivatives. This mechanism may involve the affinity of these substances to form complexes with proteins. As a result, the normal biological activities of the complexed proteins are altered.

NEW AREAS OF APPLICATION

This review deals mainly with the use of chlorophyll derivatives as wound healing and deodorization agents. However, studies carried out in the last decade have suggested that new medical applications may be developed for these substances. For example, since several different enzymatic reactions were influenced by chlorophyll derivatives,[68,69] these agents were evaluated for treating experimental pancreatitis[70,71] which involves pathological changes induced by certain enzymes. The preclinical results were promising, and a few clinical studies have shown that chlorophyll derivatives may be useful in treating pancreatitis.[72]

Of great interest are reported studies on the antimutagenic effects of chlorophyll derivatives and plant extracts rich in chlorophyll. These preparations have demonstrated most activity against several carcinogens in the Ames Salmonella/mammalian microsome test as well as in other test systems.[73,74] If further investigations confirm that chlorophyll and its derivatives possess antimutagenic and/or anticancer properties, the inclusion of these agents in the human diet may provide a modicum of protection against cancer disease. Also, new attempts to investigate the action of chlorophyll derivatives on formed blood elements have been undertaken. Thus, orally administered, these substances were used successfully to increase the number of leukocytes in children suffering from leukopenia due to various causes. In some cases, these agents prevented leukopenia and, also, in combination with standard therapy, gave better results in treating thrombocytopenia of various origins than those obtained with the standard therapy alone.[75,76]

A new technique, photodynamic therapy (PDT), was recently introduced to treat cancer disease. It includes the parenteral administration of selected photosensitizing porphyrins, for example, hematoporphyrin derivative (HPD), to patients, followed by the application of long wavelength light to the area of tumor growth. This procedure results in the generation of singlet oxygen in the photosensitized cancer cells and

*Ten percent papain, 10 percent urea, and 0.5 percent CCC in a water-washable base (Panafil® Ointment, Rystan Co., Inc.).

**Tablets containing 100 mg CCC (Derifil®, Rystan Co., Inc.).

subsequent photodestruction of tumors.[77] PDT also may be useful for treating psoriasis,[78] atherosclerosis,[79] and certain infections.[80] Preclinical PDT studies using different chlorophyll derivatives have shown that these substances are active antitumor photosensitizers[81,82] and may prove to be better clinical candidates for PDT than HPD.

Chlorophyll derivatives also have been found to display immunological[83] and antioxidant[84] activities, but the practical application of these properties has not yet been developed.

CONCLUSIONS

Although one chlorophyll derivative, CCC, is enjoying an ever-increasing level of use as an internal deodorant, the wound-healing application of these substances, particularly to treat pressure sores and other skin ulcers, seems to have been neglected during the past 25 years. One possible explanation for this occurrence may be that much of the knowledge about the therapeutic applications of chlorophyll derivatives was forgotten because of the introduction in the 1960s of potent anti-inflammatory steroids and antimicrobial products intended for topical use (although steroids actually inhibit wound healing). Indeed, the management of patients with slow-healing wounds still presents problems today because the treatment is expensive and the rehabilitation time is prolonged.[85]

Based on many published reports on the wound healing properties of CCC and other chlorophyll derivatives, as well as a consideration of the relatively low cost of these substances, it now would seem to be an opportune time to take a new clinical look at these neglected medicinal agents. Biological and chemical studies on chlorophyll derivatives, aimed at some of the new areas of applications (anticancer, antiatherosclerosis, and antipsoriasis), currently are underway in several laboratories worldwide. One can anticipate new and important results relative to this interesting group of natural substances.

REFERENCES

1. Luk'ianenko IV, Fragina AI, Chernomorsky SA: Antimicrobial, regenerative and deodorizing properties of chlorophyll preparations. *Stomatologia* 52:95-97, 1973.

2. Smith LW, Sano ME: Chlorophyll: An experimental study of its water-soluble derivatives. *J Lab Clin Med* 29:241-246, 1944.

3. Ishii DN, Maniatis GM: Haemin promotes rapid neurite outgrowth in cultured mouse neuroblastoma cells. *Nature* 274:372-374, 1978.

4. Burgi E: Uber die wundheilenden wirkungen der porphyrine. *Schweiz Med Wochenschr* 8:239-242, 1942.

5. Smith LW, Livingston AE: Chlorophyll—an experimental study of its water-soluble derivatives in wound healing. *Am J Surg* 62:358-369, 1943.

6. Smith LW, Livingston AE: Wound healing—an experimental study of water-soluble chlorophyll derivatives in conjunction with various antibacterial agents. *Am J Surg* 67:30-39, 1945.

7. Krasnikova NA: The use of aqueous solution of sodium chlorophyllin for acceleration of healing of skin wounds under experimental conditions. *Eksp Khir Anesteziol* 5:19-22, 1972.

8. Krasnikova NA: Proliferation of epithelium surrounding a skin wound in hairless mice treated with sodium chlorophyllin. *Byul Eksp Biol Med* 76:99-102, 1973.

9. Mowbray S: The antibacterial activity of chlorophyll. *Br Med J* 5013:268-270, 1957.

10. El-Nakeeb MA, Yousef RT: Antimicrobial activity of sodium copper chlorophyllin. *Pharmazie* 29:48-50, 1974.

11. Segelman AB, Chernomorsky SA: Unpublished data.

12. Duma I, Baba I, Andronescu E, et al.: Experimental studies on the biological effects of some chlorophyll salts. *Cujul Medical* 48:279-281, 1975.

13. Chernomorsky SA: Prospects for using plant pigments as drugs, in Bukin VN, Gunar VI, Soschnikoff DYA, et al. (eds), *Vitaminnye Rastitel'nye Resursy i Ikh Ispol'zovanie*. Moscow, Moscow University, 1977, pp 335-336.

14. Kojima R: Effect of copper-chlorophyllin on the α-toxin of *Clostridium perfringens*. *Igaku to Seibutsugaku* 89:87-89, 1974.

15. Sack PW, Bernard RD: Studies on the hemagglutinating and inflammatory properties of exudate from nonhealing wounds and their inhibitation by chlorophyll derivatives. *NY State J Med* 55:2952-2956, 1955.

16. Miller JM, Jackson DA, Collier CS: The inhibition of the coagulase of the *Staphylococcus aureus* by the water-soluble derivatives of sodium-copper chlorophyllin. *Am J Surg* 97:321-323, 1959.

17. Burgi E: Das chlorophyll als blutbildendes und belebendes Agens. *Ther Mh* 1:1-11, 1918.

18. Kirkman NF: The effect of low-porphyrin diet on erythropolesis and haemoglobin regeneration. *J Physiol* 95:508-515, 1939.

19. Kelentei B, Fekete I, Kun F: Influence of copper chlorophyllin on experimental anemia. *Acta Pharm Hung* 28:176-180, 1958.

20. Borisenko AN, Sofonova AD: Hemopoietic effect of Na chlorophyllin. *Vrach Delo* 9:44-46, 1965.

21. Binet L, Strumza MV: Recherches sur l' anemie provoquee: Essais de therapeutique experimentale. *J Physiol Pathol Genet* 35:44-49, 1937.

22. Berestov VA, Petrova GG, Izotova SP, et al.: Feeding young minks. *USSR Pat* 733:617, 1980.

23. Levshin BI: Pharmacological characteristics of sodium chlorophyllin. *Farmakol Toksikol* 21:46-50, 1958.

24. Kohler GO, Elvenhjem CA, Hart EB: The relation of pyrrole-containing pigments to hemoglobin synthesis. *J Biol Chem* 128:501-509, 1939.

25. Frolov SF, Chernomorsky SA, Prozorovskii VB, et al.: Effect of pheophytin on leukopenia. *Nauchnye Trudy Leningradskoi Lesotekhnicheskoi Akademii* 119:95-97, 1969.

26. Novoselova GS, Frolov SF, Chernomorsky SA, et al.: Effect of pheophytin on the course of experimentally-induced radiation leukopenia. *Nauchnye Trudy Leningradskoi Lesotekhnicheskoi Akademii* 119:93-94, 1969.

27. Takagi K, Okabe S, Saziki R: Production of chronic gastric ulcer in rats and the effect of several drugs on its healing. *Jpn J Pharmacol* 19:418-426, 1969.

28. Frolov SF, Chernomorsky SA, Kurnygina VT, et al.: Effect of pheophytin on the functional state of the liver of animals poisoned with carbon tetrachloride, in Mednikov FA (ed), *Ispol'zovanie Biologicheski Aktivnyh Veshchestv Dereva*. Riga, Zinatne, 1973, pp. 111-113.

29. Borisenko AN: Biological activity of chlorophyllin sodium. *Byul Eksp Biol Med* 66:68-70, 1968.

30. Smith LW: Chlorophyll—an experimental study of its water-soluble derivatives. *Am J Med Sci* 207-647-654, 1944.

31. Heinrichs D, Rummel W, Schunk R: Zur pharmakologie des chlorophylls. *Arzneimittelforschung* 4:19-20, 1954.

32. Harrison JWE, Levin SE, Trabin B: The safety and fate of potassium sodium copper chlorophyllin and other copper compounds. *JAMA* 43:722-737, 1954.

33. Gruskin B: Chlorophyll—its therapeutic place in acute and suppurative disease. *Am J Surg* 49:49-55, 1940.

34. Bowers WF: Chlorophyll in wound healing and suppurative disease. *Am J Surg* 73:37-50, 1947.

35. Carpenter EB: Clinical experiences with chlorophyll preparations. *Am J Surg* 77:167-171, 1949.

36. Langley WD, Morgan WS: Chlorophyll in the treatment of dermatoses. *Pen Med J* 51:44-48, 1947.

37. Johnson HM: Dermatologic evaluation of yeast, tyrothricin, chlorophyll, and nitrofurazone. *Arch Dermatol Syph* 57:348-356, 1948.

38. Haughton H: Chlorophyll: A preliminary report of its use in two cases of second and third degree burns. *Med J Aust* 1:337-340, 1950.

39. Combes FC, Zuckerman R, Kern AB: Chlorophyll in

topical therapy. *NY State J Med* 52:1025-1026, 1952.

40. Edwards BJ: Treatment of chronic leg ulcers with ointment containing soluble chlorophyll. *Physiotherapy* 40:177-179, 1954.

41. Diamond OK: A study of the value of chlorophyll-derivative ointment in institutional practice. *Psychiatr Q* 29:193-196, 1955.

42. Larato DC, Pfau FR: Effects of a water-soluble chlorophyllin ointment on gingival inflammation. *NY Dent J* 36:291-293, 1970.

43. Morgan WS: Chlorophyll therapy. *Guthrie Clin Bull* 16:94-107, 1947.

44. Lam CR, Brush BE: Chlorophyll and wound healing. *Am J Surg* 80:204-210, 1950.

45. Moss NH, Morrow BA, Long RC, et al.: Effectiveness of chloresium in wound healing and deodorant effects. *JAMA* 140:1336-1339, 1949.

46. Garnes AL, Barnard RD: Histologic and pharmacologic studies on nonhealing dermal wounds. *Angiology* 8:13-18, 1957.

47. Miller Jr EW: Decubitus ulcers treated with papain-urea-chlorophyllin ointment. *NY State J Med* 56:1446-1447, 1956.

48. Burke JF, Golden T: A clinical evaluation of enzymatic debridement with papain-urea-chlorophyllin ointment. *Am J Surg* 95:828-842, 1958.

49. Carter CH: Chronic ulcers. *Med Times* 86:1382-1390, 1958.

50. Carpenter EB: Chemical debridement of infected wounds with a papain-urea-chlorophyll ointment. *Virginia Med Month* 85:22-24, 1958.

51. Astler VB, Morley GW: Deodorization of colostomies and leukorrheic conditions by means of chlorophyll preparations. *Univ Mich Med Bull* 17:112-114, 1951.

52. Golden T, Burke JF: Effective management of offensive odors. *Gastroenterology* 31:260-265, 1956.

53. Siegel LH: The control of ileostomy and colostomy odors. *Gastroenterology* 38:634-636, 1960.

54. Noonan L: Summary of Derifil® tablets trial, unpublished data, in OTC volume 170014 (exhibit Y), Docket No. 81N-0064. Dockets Management Branch, U.S.F.D.A.

55. O'Connel I: A useful adjunct for odor control in malodorous surface lesions and incontinence. *J Cent Islip State Hosp* 1:23-26, 1968.

56. Dory AE: The control of odor in urinary incontinence. *Nurs Homes* 20:28, 1971.

57. Young RW, Beregi JS: Use of chlorophyllin in the care of geriatric patients. *J Am Geriatr Soc* 28:46-47, 1980.

58. Nahata MC, Slencsak CA, Kamp J: Effect of chlorophyllin on urinary odor in incontinent geriatric patients. *Drug Intell Clin Pharm* 17:732-734, 1983.

59. Federal Registry 50:25162-25167, 1985.

60. Tomas NSB, Matts RL, London IM: The storage of globin mRNA during the inhibition of protein synthesis by heme deprivation. *Biochem Biophys Res Commun* 134:1048-1055, 1986.

61. Koser SA, Hodges EA: The effect of sodium copper chlorophyllin on growth and acid production of some oral bacteria. *J Infect Dis* 92:10-19, 1953.

62. Nevin TA, Bibby BG: The effect of sodium copper chlorophyllin on pure cultures of oral-type organisms. *J Dent Res* 33:571-579, 1954.

63. Miller JM: The interaction of papain, urea, and water-soluble chlorophyll in a proteolytic ointment for infected wounds. *Surgery* 43:939-948, 1958.

64. Hainer RM: Studies of copper chlorophyllin—odorant systems. *Science* 119:609-610, 1954.

65. Zirm KL, Kilches R, Oberrosler L: Die aufhebung der indikanamie und indikanurie durch perorale magnesium-chlorophyllingaben. *Wien Med Wochenschr* 103:898-900, 1953.

66. Wasielewski E, Albrecht A: Der wirkungsmechanismus des chlorophylls bei der desodoration. *Arzneimittelforschung* 2:448-449, 1952.

67. Wasielewski E, Albrecht A: Bakteriologischer beitrag uber den wirkungsmechanismus des chlorophylls bei der desodoration. *Zeitschr Hygiene* 136:141-158, 1953.

68. Chernomorsky SA, Fragina AI: Effect of chlorophyll derivatives on the activity of some digestive enzymes in vitro. *Biol Nauki* 3:29-31, 1978.

69. Kurnygina VT, Nikitina TV: Effect of metal-chlorophyll derivative complexes on pancreatic lipase activity. *Biol Nauki* 6:31-34, 1981.

70. Wiznitzer T, Orda R, Bawnik JB, et al.: Acute necrotizing pancreatitis in the guinea pig—effect of chlorophyll-a on survival times. *Am J Dig Dis* 21:459-464, 1976.

71. Mann SK, Mann NS: Effect of chlorophyll-a, fluorouracil, and pituitrin on experimental acute pancreatitis. *Arch Pathol Lab Med* 103:79-81, 1979.

72. Yokono O: Therapeutic effect of intravenously administered chlorophyll-a in the treatment of chronic relapsing pancreatitis. *Hepatogastroenterology* 27:220, 1980.

73. Kimm SW, Tchai BS, Park SC, et al.: Antimutagenic activity of chlorophyll to direct and indirect-acting mutagens and its contents in the vegetables. *Korean J Biochem* 14:1-7, 1982.

74. Ong TM, Whong WZ, Stewart J, et al.: Chlorophyllin: A potent antimutagen against environmental and dietary complex mixtures. *Mutat Res* 173:111-115, 1986.

75. Berlinson MY: Application of sodium chlorophyllin in children leukopenias. *Nauchnye Trudy Leningradskoi Lesotekhnicheskoi Akademii* 119:113-116, 1969.

76. Chernomorsky SA: Unpublished data.

77. Kessel D: Hematoporphyrin and HPD: Photophysics, photochemistry, and phototherapy. *Photochem Photobiol* 39:851-859, 1984.

78. McCullough JL, Weinstein GD, Douglas JL, et al.: Photosensitizers in dermatology. *Photochem Photobiol* 46:77-82, 1987.

79. Litvack F, Grundfest WS, Forrester JS, et al.: Effect of hematoporphyrin derivative and photodynamic therapy on atherosclerotic rabbits. *Am J Cardiol* 56:667-671, 1985.

80. Lombard GF, Tealdi S, Lanotte MM: The treatment of neurosurgical infections by lasers and porphyrins, in Jori G, Perria C (eds), *Photodynamic Therapy of Tumors and Other Diseases.* Padova, Libreria Progetto Editore, pp. 363-366, 1985.

81. Chernomorsky SA, Poretz R, Segelman AB: The photodynamic effect of chlorophyll derivatives on murine myeloma cells in tissue culture. *Photochem Photobiol* 39:49S, 1984.

82. Sakata I, Nakajima S, Koshimizu K, et al.: 9-desoxo-9-hydroxy-pheophorbide derivatives and alkaline salts thereof. US Pat 4,604,241, 1986.

83. Nagai H, Nishiyori T, Daikoku M, et al.: Immunopharmacological studies of sodium copper chlorophyllin. *Jpn J Pharmacol* 33:819-828, 1983.

84. Sato M, Konagai K, Kuwana T, et al.: Effect of sodium copper chlorophyllin on lipid peroxidation. *Chem Pharm Bull* 32:2855-2858, 1984.

85. Anthypas PG: Management of pressure sores. *Curr Probl Surg* 17:229-244, 1980.