Alkylglycerols and Cancer

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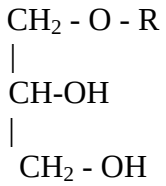
The ratfish *(Chimera monstrosa)*, like the dogfish and the shark, is a member of the elasmobranch class of fish which are characterized by their distinctive lamellate gills. The oil from its liver is an ancient remedy among the fishermen along with west coast of Norway and Sweden. In addition to using it for the treatment of general debility, it had several specific applications. These included wound healing, and the treatment of irritations of the respiratory and alimentary tracts. Of particular interest, the oil was used to treat what was referred to in those days as glandular disease, and nowadays would be called lymphadenopathy.

Over time, the medicinal use of ratfish liver oil became less popular and, by the early nineteenth century, the practice had only survived in a few fishing communities in the region. It was not until the early part of this century that biochemists discovered substances in the oil that may have accounted for its traditional uses - namely the alkylglycerols.

The liver oil from the ratfish and other elasmobranch fish is particularly rich in alkylglycerols. These substances were discovered in 1922 by Tsujimoto and Toyama[1] and were first synthesized in 1930 by Sir Robert Robinson, a Nobel laureate. In natural sources, they are always found esterified with fatty acids. Their chemical structure consists simply of a backbone of glycerol attached with a ether link to an alkyl group (Figure 1). Thus the alkylglycerols can also be referred to as alkyl ether lipids or as alkyl glycerol ethers.

Figure 1. Structure of Alkylglycerols



The glycerol ethers are widely distributed in animal tissue, although the liver oil of elasmobranch fish remains the richest known natural source (Table 1). A comparatively high content of non-substituted glycerol ethers along with traces of methoxy-substituted compounds are found in the human bone marrow. In experiments conducted between 1949 and 1960, these non-substituted glycerol ethers were shown to stimulate erythropoietic, thrombopoietic and granulopoietic activity.[2]

Table 1
Percentage Of Glycerol Ethers In Lipids

Source	Glycerol Ethers in Lipids
Liver oil of elasmobranch fish	10 - 30%
Human bone marrow	0.2%
Human milk	0.1%
Human spleen	0.05%
Cow milk	0.01%

(Source: Hallgren B, Larsson S. The glyceryl ethers in man and cow. J *Lipid Res* 3(1):39-43, 1962)

In 1952, Astrid Brohult, a young Swedish doctor, hypothesized that a bone marrow extract made from fresh calf bones may stimulate white blood cell production in leukemic children with leukopenia. Her initial results were uneven, but improvements in white count and energy were promising enough for her to ask her husband, a professor of biochemistry at a Swedish university, to analyze the calf bone marrow to see if he could determine what factor was responsible for stimulating white cell production. After several years, he established that the immune stimulants were alkylglycerols.

The Brohults brought their results to AB Astra Pharmaceuticals in Sweden in order to produce a commercial product. As it proved difficult to obtain sufficient quantities of concentrated of alkylglycerols from bone marrow, the company searched for a better commercial source and decided on using the liver oil of the Greenland shark (Somniosus microcephalus) as up to 50% of this oil consists of alkylglycerol esters.[3] Similar to human bone marrow, glycerol ethers in Green-

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land shark liver oil are non-substituted with the exception of roughly 4% that are methoxy-substituted.[4]

In the 1970s, evidence started to accumulate that the alkylglycerols had application in the treatment of solid cancers. One team of investigators reported that the small methoxy-substituted fraction of Greenland shark liver oil was active against tumor growth in cultured cells[4] as well as against experimental tumor growth and metastasis formation in animals.[2] Meanwhile, the Brohults began to publish a series of retrospective studies reviewing their results in providing a shark liver oil-derived alkylglycerol product to patients with invasive cancer of the uterine cervix who were receiving radiation therapy.

They initially described a series of 849 such patients who were given 200 mg three times daily of alkylglycerols derived from shark liver oil in conjunction with their radiotherapy. About half of the patients received the mixture prophylactically one week prior to radiation, while the rest only received it during radiation treatment. Radiotherapy began with two series of intracavitary radium applications separated by a three week interval. After a three week hiatus, external radiotherapy using either roentgen rays or cobalt irradiation was given over three to four weeks.

Since the duration of radiation treatment varied between two and 11 weeks, there was a considerable variation in the amount of alkylglycerols given. The Brohults took advantage of this situation by ranking patients in the prophylactic group according to the total dosage they received and dividing them into two equal-sized groups, with the high-dosage sub-group receiving an average of 95 grams and the low-dosage sub-group receiving an average of 65 grams. The mortality rates of the differently treated groups were compared with those of two control groups. One of these consisted of 1968 patients treated during the previous four years, and the other consisted of 938 patients treated during the three years following the experiment. True mortality rates for the patient groups due to cervical cancer were calculated by subtracting normal mortality rates obtained from the Swedish Bureau of Statistics from the observed mortality.

The administration of alkylglycerols prophylactically prior to radiation treatment was found to markedly affect the mortality rate. After three years, the group that only received radiation treatment had a mortality of 29.6%, while the group that was also treated prophylactically with alkylglycerols had a mortality of 19.6%. This difference is even more pronounced for the high-dosage subgroup, which had a mortality of only 13.7%. No significant difference was found between the group that only received alkylglycerols during radiation treatment and the controls, suggesting that alkylglycerols were ineffective if not started prior to radiation treatment.

According to the Brohult team, the evidence suggests that the reduction in mortality was due to a shift in the distribution of the stages of the cancer even before radiation treatment was begun. Specifically, following the period of prophylactic alkylglycerol administration and prior to the start of radiation treatment, a larger percentage of patients treated with alkylglycerols was found to have tumors in less advanced stages. This finding was reported to be statistically significant, although no statistics were given.[3]

Since their initial report, the Brohult team has published retrospective data from the entire series of cases of invasive carcinoma of the uterine cervix treated in their hospital's department of gynecology between 1958 and 1975. 4403 patients given radiotherapy alone were compared to 841 patients given radiotherapy along with prophylactic alkylglycerols. Patients given prophylactic alkylglycerols began their administration seven days prior to the start of radiation treatment. Administration was continued during radiation treatment and one to three months afterwards. The clinical stage of each cancer was determined just prior to radiation treatment. At the time of staging, the percentage of alkylglycerol-treated patients whose cancers were in advanced stages was 12.1% lower than that of the controls. This difference is highly significant ($p<0.001$) .[5]

In response to the argument that the shift in stage in the patients who received prophylactic alkylglycerols could be due to an unequal distribution in ages between patients in the two groups, patients were divided into four age groups. Based on the radio of patients with early stage cancers to those with advanced stage cancers, a substantial decrease in advanced stages was found for all four prophylactic groups as

compared to the controls (Table 2).

There was also other evidence that this increase in the early to advanced quotient was due to alkylglycerol administration. During the years when patients were treated with radiotherapy alone, there was no systematic change in the percentage of patients with early versus advanced stages. Only when prophylactic administration of alkylglycerols became part of the treatment protocol did the distribution shift towards earlier stages.[5]

In comparing patients who received alkylglycerols to controls, there was a relatively small increase in mortality for patients with early-stage cancers and a relatively large decrease in mortality for patients with late-stage cancers. The Brohult group attributes the small increase in mortality for patients with early-stage cancers to the shift in the distribution of alkylglycerol-treated patients towards less advanced stages prior to radiation treatment - though the results seem to suggest that alkylglycerols are ineffective and may even be contraindicated for the treatment of early-stage cancers (Table 3).

Table 2. Effect Of Alkylglycerols On Cervical Cancer Stages: Early/Advanced Quotient (Prophylactic, Concurrent And Subsequent Administration)

	Total #	**<40**	**41-50**	**51-60**	**>60**
Untreated	4403	3.84	1.87	1.05	0.75
Treated	841	7.33	4.15	2.81	0.87

(Source: Brohult A, Brohult J, Brohult S, Joelsson I. Reduced mortality in cancer patients after administration of alkoxyglycerols. *Acta Obstet Gynecol Scand* 65:779-85, 1986.

Table 3: Effect Of Alkylglycerols On Five-Year Mortality (Prophylactic, Concurrent And Subsequent Administration)

	Total #	**<40**	**41-50**	**51-60**	**>60**
Early Stages (IA-IIA)		14.7%	11.1%	12.6%	13.2%
Radiotherapy alone	558	15.3%	12.7% +	13.4%	14.6%
Radiotherapy & Alkylglycerols	116	+0.6%	1.6%	+0.8%	+1.4%
Difference					
Advanced Stages (IIB-IV)		14.6%	21.8%	31.2%	41.5%
Radiotherapy alone	1186	6% -8.6%	13.4% -	14.3%	33.5% -
Radiotherapy & Alkylglycerols	145		8.4%	-16.9%	8.0%
Difference					

(Source: Brohult A, Brohult J, Brohult S, Joelsson I. Reduced mortality in cancer patients after administration of alkoxyglycerols. *Acta Obstet Gynecol Scand* 65:779-85, 1986).

Alkylglycerol administration only reduced long-term mortality when given prior to radium implantation as well as during and after the procedure. Five-year mortality rates for each age group (D_T) were plotted against the percentage of patients with early-stage cancers (E). DT as a function of E was the same for both the prophylactic alkylglycerol groups and the control groups; thus no decrease in mortality was observed for the alkylglycerol groups once the difference in staging (which was done just prior to radiotherapy) was controlled for.[6]

In 1979, the Brohult team detailed their clinical experience to date concerning the effect of alkylglycerols on radiation injuries among patients with invasive carcinoma of the uterine cervix using the Kottmeier criteria (Table 4).

For analyses, Grade I injuries were excluded

as they were considered to be merely acute radiation reactions rather than true injuries. Under the category of total injuries, the authors included complex injuries - namely, injuries due either to tumor growth alone or to a combination of tumor growth and radiation treatment - as well as injuries that were clearly due to radiation treatment. Injuries that appeared any time within five years after the start of radiation treatment were included, while injuries that appeared within three months of surgery plus radiotherapy were excluded as were injuries that were not clearly related to radiation treatment or tumor growth (Table 5).

Table 4. Injuries Following Radiation Therapy

Grade I	Injuries producing mild subjective symptoms accompanied by minimal objective changes to the mucosa.
Grade II	Injuries which are composed of moderately severe objective changes, such as areas of necrosis, ulcers or moderate stenosis.
Grade III	Bladder and ureter injuries comprising fistulas, and rectal and intestinal injuries comprising stenoses that require colostomy.
Grade IV	Rectal and intestinal fistulas.

(Source: Kottmeier HL. Complications following radiation therapy in carcinoma of the cervix and their treatment. *Am J Obstet Gynecol* 88:854, 1964)

Table 5. Total Injuries Following Radiation Therapy: Effect Of Alkylglycerols

	# of patients	Grade II	Grade III	Grade IV
Radiation only	648	24.1%	7.1%	6.5%
Alkylglycerols only during Radiation	380	12.6%	7.6%	4.2%
Alkylglycerols prior to & during Radiation	454	9%	5.7%	3.5%

(Source: Brohult A, Brohult J, Brohult S, Joelsson I. Effect of alkoxyglycerols on the frequency of fistulas following radiation therapy for carcinoma of the uterine cervix. *Acta Obstet Gynecol Scand* 58(2):203-7, 1979)

The Brohult team noted that, while radiation-induced injuries are usually healed in 6 to 12 months, almost all patients with complex injuries die within five years. They found that complex injuries were reduced to one-third when alkylglycerols were given prophylactically and during radiation treatment as compared to when patients were given radiation treatment alone. This finding is statistically significant ($p<0.001$).l It is also in accord with the results of another, similar group of 279 of their patients that was treated under double-blind conditions and followed for three and a half years. For this group, the total number of injuries was reduced by one-half from 52.1% to 26.3% by the administration of alkylglycerols before and during radiation treatment.[7,8]

Mechanism of Action

The mechanism of action of the alkylglycerols to explain their efficacy in cancer treatment is unclear. Neoplastic tissues have high levels of alkylglycerol esters, together with characteristic abnormalities of ether-lipid-synthesizing and

degrading enzymes,[9] suggesting that alkylglycerol administration may somehow impede cellular metabolism. The Brohult team has theorized that the alkylglycerols or their esters form liquid crystals which rigidify the cell membrane, thus reducing the cell's ability to divide.[10]

There is experimental evidence that the alkylglycerols are immune stimulants. In 1978, the mixture of glycerol esters isolated from Greenland shark liver oil administered orally to mice was shown to stimulate immune reactivity. The evidence presented suggests that this effect was due specifically to the methoxy-substituted glycerols ethers which, as I noted earlier, constitute only about 4% of the total alkylglycerol content in both human bone marrow and Shark liver oil.

Data suggesting that immune stimulation may be relevant to cancer treatment comes from the Brohult team. They vaccinated 54 of their patients with cervical cancer against typhus-paratyphus the day before and the day after the initial radium implantation. In addition, every second patient was given 300 mg of alkylglycerols daily for three weeks immediately after the first vaccination. Samples for serological analysis were taken before the vaccination and about three weeks later before the second radium implantation. As a measure of immune response, the agglutination effect for six different Salmonella antigens was determined for all patients. The average number of agglutination reactions per patient for the 26 patients who had received alkylglycerols was 2.2 compared to 1.5 or the 28 controls, a significant difference ($p<0.02$), suggesting that the administration of alkylglycerols activated immune responsiveness.[11]

After three years, 21 of the 54 patients had died. Review of the data revealed that the patients who had died had earlier failed to react to an average of 2.4 antigens, while the 33 survivors had only failed to react to an average of 1.5 antigens. This difference was statistically significant ($p<0.01$), suggesting that surviving patients had a greater ability to form antibodies against typhus-paratyphus, and consequently that the administration of alkylglycerols may combat cancer by activating immune responsiveness. A comparison of treated patients versus controls provides further evidence of the immune-enhancing effect of alkylglycerols[11] (Table 6).

Table 6. Serological Reactions As Related To Mortality

		Average # No Reactions	
	# Patients	**Controls**	**Treated**
Deceased	21	2.7	1.7
Surviving	33	2.4	1.4

(Source: Brohult A, Brohult J, Brohult S. Effect of irradiation and alkoxyglycerol treatment on the formation of antibodies after Salmonella vaccination. *Experientia* 28:954-5, 1972)

The alkylglycerols also appear to reduce radiation-induced leucopenia and thrombocytopenia. Experiments with rats have suggested that this may be due to their protective effect on the bone marrow where they inhibit the decrease in both megakaryocytes and nucleated cells following radiation exposure.[12] For example, 75% of a group of 100 cancer patients responded to treatment with shark liver oil-derived alkylglycerol esters with an increased leucocyte count in spite of continued radiation treatment, 15% had no change, and only 10% sustained a further decrease.[13]

An interesting case study concerns a nurse who had been occupationally exposed to radium had a baseline leucocyte count of about 2000 for more than a year. After three days' treatment, her leucocyte count had risen to 3600. Subsequent treatments of three to five days' duration were successfully able to maintain the higher leucocyte count.[13]

In a prospective, controlled study of 250 patients with cervical cancer, Astrid Brohult administered alkylglycerol esters to every second patient prior to radiation treatment.[13] Initially, both groups had an average leucocyte count of 6000. Following the two courses of radium implantation, the controls had a white count of 4000 compared to 4700 in the alkylglycerol group. Following x-ray treatment, the white cell count was 3200 for the controls compared to 3900 for the alkylglycerol group. The mean value during x-ray treatment was 3450 for the controls and 4000 for the alkylglycerol group, a highly significant difference ($p=0.0001$).

A dose-response effect was found, with evidence that, for reducing radiation-induced leucopenia, the optimal dosage of alkylglycerol esters during x-ray treatment is about 1200 mg a day. Moreover, dosages in excess of about 2200 mg daily actually promoted leucopenia. This danger of excessive dosing confirms animal toxicity studies in which a synthetic methoxy-substituted glycerol was found to be toxic to the lymphatic system when administered orally in massive doses to rats and dogs.[4]

Similar results were found in respect to thrombocytes, with the average platelet count during radiotherapy of 155,000 in controls versus 190,000 in patients receiving 1200 mg alkylglycerol esters daily. The ability of alkylglycerols to reduce radiation-induced leucopenia and thrombocytopenia made it possible to complete the course of radiation treatment when otherwise the deteriorating blood picture would have forced its premature termination.[13]

Alkylglycerols may also benefit cancer patients receiving radiation therapy by protecting them against protein breakdown. Ornithine carbamoyl transferase (OCT) is synthesized in the liver, where it is involved in the synthesis of urea. Its levels rise with liver injury and with increased protein degradation, such as in conjunction with radiation. The Brohult group compared serum OCT values prior to and one, four, six and eight days after the start of radiation treatment of their cervical cancer patients with radium implants and found that the rise in OCT due to radiation treatment was reduced by giving prophylactic alkylglycerols eight days prior to the start of the treatment protocol[14] (Table 7).

Table 7: Serum Ornithine Carbamoyl Transferase As Related To Radiation Treatment (Geometric Means)

	Days after start of radiation treatment				
	Baseline	**1**	**4**	**6**	**8**
Radiation only	**1.1**	**1.2**	**2.7**	**2.2**	**1.3**
Radiation plus Alkylglycerols	**1.0**	**1.0**	**1.4**	**1.4**	**1.0**

(Source: Brohult A, Brohult J, Brohult S. Effect of alkoxyglycerols on the serum ornithine carbamoyl transferase in connection with radiation treatment. *Experientia* 28:146-7, 1972)

To summarize, there is preliminary evidence that alkylglycerols from natural sources may be beneficial in cancer treatment:

1. When given alone for one week, alkylglycerols appear to promote regression, or at least a lack of progression, of the cancer. *(The dosage utilized for the later clinical studies was 600 mg daily of alkylglycerols.)*
2. When given for one week prior to a course of radiation treatment as well as during and after radiation treatment, alkylglycerols appear to reduce the long-term mortality rate for patients with advanced cancers. Apparent effects that could account for this reduction include:

a. reduced tissue injuries due to radiation treatment.
b. reduced tissue injuries due to the growth of the tumor.
c. improved immune response to antigenic stimulation.
d. reduced radiation-associated leucopenia and thrombocytopenia.
(The optimal dosage for this effect appears to be 1200 mg daily of alkylglycerols.)
e. reduced degradation of proteins.

3. While administration at customary dosages appears to be safe, higher dosages are toxic to the lymphatic system.

Discussion

If the data presented to date is evaluated on the basis of scientific merit, the methodology utilized was seriously flawed, and thus these findings,

though intriguing, are far from conclusive. For example, only a minority of the patients studied were involved in a prospective, double-blind experiment; the data from this small double-blind study were merged with data from other studies using patients from the same cohort - namely patients undergoing the same treatment at the same location for the same diagnosis - but data that resulted from the use of different, less rigorous, methodologies. Moreover, what data there is needs further statistical analysis.

Regrettably, the cancers were not staged prior to alkylglycerol administration, but only just before radiation treatment, so we are unable to confirm directly whether alkylglycerol administration was associated with tumor regression. Does the small increase in mortality in each age group mean that alkylglycerols are contraindicated in early-stage cancers? We have no additional data to enlighten us - not even a study in which alkylglycerols were administered to patients with cervical dysplasia - a condition that, for some women, is a transitional stage to the development of cervical cancer. Evidence that alkylglycerols reverse cervical dysplasia would extend their potential clinical applications and provide some reassurance concerning their use in early stages of cervical carcinoma.

Many other questions remain to be answered. The possibility that alkylglycerols have similar effects upon other neoplasias has not been explored. Alkylglycerols were only provided as an adjunct to radiation treatment, so we lack data concerning their efficacy when other forms of concurrent treatment are selected. This is particularly unfortunate as alkylglycerols only appeared to reduce long-term mortality if they were given for a week prior to the start of radiation, suggesting that they may be more effective when given without radiotherapy for a longer period of time. Finally, especially since the Brohult group is closely tied to the major commercial source of natural alkylglycerols, we need independent confirmation of the Brohults' clinical work.

Current Research

In recent years, investigators have focused on synthesizing new ether lipids, particularly the alkyl-lysophospholipids, with the goal of developing therapeutic agents that are more potent than the natural ones. Synthetic ether lipids have been shown to change the invasive and differentiative behavior of tumor cells and to induce a selective destruction of neoplastic cells. They have potent anti-tumor activity in experimental animal models of cancer and, currently, controlled human trials of these agents are underway.[15]

An exciting finding related to these investigations has recently opened up a new direction in cancer research. While the alkyl-lysophospholipids being developed for cancer treatment are synthetic, it just so happens that platelet-activating factor (PAF) was found to be an alkyl-lysophospholipid, and its structure has turned out to be nearly identical to that of the most potent of these new compounds.[16]

Like the eicosanoids, PAF has been found to be an important mediator of inflammation and appears to be involved in a great variety of membrane-dependent processes" that play a fundamental role in the maintenance of homeostasis.[17] Its many potent biological activities, which are mediated through stimulatory effects on target cells and tissues, are known to play a role in the development of the degenerative diseases,[18] and it has been found to be elevated in malignant tumors.[19] We can expect that investigators will soon clarify the relationship between PAF and tumor growth and better elucidate the relationship between PAF and the alkylglycerols.

Because I believe that, in general, supplementation with nutrients that naturally play a beneficial role in our metabolic processes have a better risk/benefit ratio than foreign substances, I would very much like to see studies attempting to confirm the clinical efficacy of natural alkylglycerol mixtures. Evidence of the toxicity of the most popular of the synthetic methoxy ether lipids has already come from a phase I trial. In that trial, while three out of 16 patients showed a partial response, treatment resulted in grade 2-4 toxicity with the development of pulmonary edema and impairment of liver function.[20] Given the evident safety of the natural alkylglycerols, I believe they deserve more adequate clinical trials before their synthetic cousins are further tested.

References

1. Tsujimoto M, Toyama Y. Ueber die unverseifbaren Bestandteile (hoheren Alkohole) der Haifish- und Rochen-leberole. I. *Chemische Umschau* 29:27-9, 1922.
2. Boeryd B,Hallgren B,Stellberg G. Studies on the effect of methoxy-substituted glycerol ethers on tumour growth and metastasis formation. *Br J Exp Path* 52:221-30, 1971.
3. Brohult A, Brohult J, Brohult S. Biochemical effects of alkoxyglycerols and their use in cancer therapy. *Acta Chem Scand* 24:730, 1970.
4. Hallgren, Stellberg G, Boeryd B. Occurrence, synthesis and biological effects of substituted glycerol ethers. *Prog Chem Fats Other Lipids* 16:45-58, 1978.
5. Brohult A, Brohult J, Brohult S. Regression of tumour growth after administration of alkoxygylcerols. *Acta Obstet Gynecol Scand* 57(l):79-83, 1978.
6. Brohult A, Brohult J, Brohult S, Joelsson I. Reduced mortality in cancer patients after administration of alkylglycerols. *Acta Obstet Gynecol Scand* 65:779-85, 1986.
7. Brohult A, Brohult J, Brohult S, Joelsson I. Effect of alkoxyglycerols on the frequency of injuries following radiation therapy for carcinoma of the uterine cervix. *Acta Obstet Gynecol Scand* 56:441-8, 1977.
8. Brohult A, Brohult J, Brohult S, Joelsson I. Effect of alkoxyglycerols on the frequency of fistulas following radiation therapy for carcinoma of the uterine cervix. *Acta Obstet Gynecol Scand* 58(2):203-7, 1979
9. Snyder F. *Ether Lipids. Chemistry and Biology.* New York, Academic Press, 1972.
10. Brohult A, Brohult J, Brohult S, Joelsson I. Alkoxyglycerols in cell membranes stop tumour growth? *Proceedings of the Third International Conference on Surface and Colloid Science.* Stockholm, August, 1979.
11. Brohult A, Brohult J, Brohult S. Effect of irradiation and alkoxylglycerol treatment on the formation of antibodies after Salmonella vaccination. *Experientia* 28:954-5, 1972.
12. Brohult A. Nature 181:1484, 1958.
13. Brohult A. Alkoxyglycerol-esters in irradiation treatment. Advances in Radiobiology: *Proceedings of the Fifth International Conference in Radiobiology*, Stockholm, August, 1956. 1957, pp. 241-7.
14. Brohult A, Brohult J, Brohult S. Effect of alkoxyglycerols on the serum ornithine carbamoyl transferase in connection with radiation treatment. *Experientia* 28:146-7, 1972.
15. Andreesen R. Ether lipids in the therapy of cancer. *Prog Biochem Pharmacol* 22:118-31, 1988.
16. Benveniste J, Tence M, Varenne P, et al. [Semi-synthesis and proposed structure of platelet-activating factor (P.A.F.): PAF-acether an alkyl ether analog of lysophosphatidylcholine.] *C R Seances Acad Sci D* 289(14):1037'-40, 1979.
17. Koltai M, Hosford D, Guinot P, et al. Platelet activating factor (PAF). A review of its effects, antagonists and possible future clinical implications (Part I). *Drugs* 42(l):9-29,1991.
18. Kroegel C, Kortsik C, Kroegel N, Matthys H. The pathophysiological role and therapeutic implications of platelet activating factor in diseases of aging. *Drugs Aging* 2(4):345-55, 1992.
19. Nigam S, Muller S, Benedetto C. Elevated plasma levels of platlet-activating factor (PAF) in breast cancer patients with hyperclacemia. J *Lipid Mediat* l(6):323-8, 1989.
20. Berdel WE, Fink U, Rastetter J. Clinical phase I pilot study of the alkyllysophospholipid derivative ET-18-OCH3. Lipids 22(11):967-9 1987.