CHAPTER VIII

BIOLOGICAL EFFECTS AND BIOMEDICAL APPLICATIONS OF ALKOXYLIPIDS

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I. Introduction

It is generally conceded that many questions concerning the biological significance of the naturally occurring alkoxylipids are unanswered. Why, for instance, is there such a striking difference between the contents of alkyldiacylglycerols in normal and neoplastic tissues? What are the functions of the high proportions of alk-1-enylacyl phosphoglycerides in the central and peripheral nervous system? Can the composition of the various alkoxylipids in a tissue be changed and how do such changes affect the organism?

In the last 25 years, numerous biological activities have been attributed to "chimyl alcohol," "batyl alcohol," and "selachyl alcohol," the 1-alkylglycerols that are the most common constituents of naturally occurring alkoxylipids. Investigators have claimed that these compounds have therapeutic value in a number of disease states. However, reports of the biological and therapeutic effects of the 1-alkylglycerols are at variance, and in the opinion of this author, none of these effects has been unequivocally proven. Obviously it is difficult to repeat the experiments reported from one laboratory in another, and it is particularly difficult to substantiate claims of biological effects, since the preparations used in some biological studies were rather ill-defined. In most cases, the alkoxylipids were isolated from animal tissues, usually shark livers. The alkoxylipid content and the composition of the alkoxylipid fraction were not determined, and it is more than likely that the preparations contained a large variety of compounds other than alkoxylipids. Thus, the biological effects of some of the preparations might have been due to the presence of fat-soluble vitamins.

In recent years, synthetic lipids containing alkyl groups or alk-1-enyl groups have become available, and methods for the characterization and analysis of these compounds have been developed. Experiments that have led to reports of biological activities and even therapeutic effects of various alkoxylipids should now be repeated using pure synthetic compounds. Such studies should also consider compounds that, as a rule, occur naturally in trace amounts only, such as alkoxylipids derived from polyhydric alcohols other than glycerol, and alkoxylipids containing polyunsaturated alkyl or alk-1-enyl moieties.

Glycerol-derived lipids containing one, two, or three alkyl groups instead

of acyl groups of comparable chain lengths resemble the glycerides closely in molecular size and shape, and also in their physical properties. However, the alkyl ethers are more stable, or even totally resistant to hydrolytic enzymes. Therefore, individual synthetic alkoxylipids are finding wide application as model substances in systems where lipids containing ester bonds cannot be used because of their relative instability. Alkoxylipids that contain more than one alkyl moiety are of particular interest, especially the trialkylglycerols. These compounds resemble the triacylglycerols ("triglycerides") in many respects, but are extraordinarily stable against enzymic action, and remarkably resistant to chemical attack.

In this chapter the various biological activities and therapeutic effects that have been ascribed to lipids containing alkyl or alk-1-enyl groups will be discussed, and an attempt will be made to present a balanced view of the many conflicting reports. However, since these aspects have been reviewed quite recently (Snyder, 1969), emphasis will be placed on the description of studies in which pure individual alkoxylipids were put to good use because of their relative stability.

II. Toxicity of Alkoxylipids

A. 1-Alkylglycerols and 1-Alkyl-2,3-diacylglycerols

1. *Toxicity in Animals*

Alkylglycerols and their esters have been administered orally to mice, rats, and dogs. Agduhr *et al.* (1934) reported that mice given small oral doses of batyl alcohol for several months developed lesions in their hearts, kidneys, livers, and adrenal glands. These observations could not be confirmed by later investigators. Thus, Alexander *et al.* (1959) reported that mice which had received a diet containing 18% alkyldiacylglycerols showed no ill effects, even after 2 years. And Brohult (1963) mentioned unpublished work by B. Melander, who fed large doses of alkylglycerols as well as alkyldiacylglycerols to mice. Melander reportedly found that mice could tolerate as much as about 4.4 g of alkyldiacylglycerols per kg of body weight per day, for 18 days. The weight gain of the mice was found to be normal, and pathological changes could not be observed. Thus, Brohult (1963) concluded that the toxicity of purified alkylglycerols and their esters to mice is low. But she also noted that one preparation tested, crude liver oil of Greenland shark (*Somniosus microcephalus*), must have contained some components that had an irritating effect on the gastrointestinal tract of the mice and caused the death of some of the animals. Work by Kaneda and Ishii (1952), Kaneda *et al.* (1955), Brohult (1963), Peifer *et al.* (1965),

and Carlson (1966), as well as more recent experiments (Snyder *et al.*, 1971; Bandi *et al.*, 1971a), show that alkylglycerols and their esters, when given orally, are also relatively nontoxic to rats. Carlson (1966) found that dogs, as well as rats, fed chimyl, batyl, or selachyl alcohols at a level of 2.4 g per kg of body weight per day, did not manifest any ill effects.

When batyl alcohol was administered subcutaneously to mice (Berger, 1948; Penny *et al.*, 1964), the LD_{50} dose was found to be greater than 3 g per kg of animal weight (Berger, 1948). Arturson and Lindbäck (1951) found that intraperitoneal injections of batyl alcohol led to an increase of reticulocytes in mice. Evenstein *et al.* (1958) subcutaneously injected increasing amounts of batyl alcohol in rats over a period of 41 days; they did not observe any pathological changes in the animals. Hietbrink *et al.* (1962), also working with rats, found that intraperitoneal injections of batyl alcohol, at a level of 5 to 10 mg per kg of body weight per day, caused an increase in the weight of the spleen, but did not affect the activity of adenosine triphosphatase in this tissue or in the thymus gland of the animals. I. A. Evans *et al.* (1953; W. C. Evans *et al.*, 1957) administered batyl alcohol to cattle, both by intramuscular and intraperitoneal injections, and found that 1 g of this compound could be given intramuscularly over a period of 4 to 5 days without ill effects. Many other investigators administered rather small doses of alkylglycerols to experimental animals exposed to X-rays.

2. *Toxicity in Humans*

Sandler (1949) reported that he had given healthy adult men 45 mg of batyl alcohol per day for 10 days with no sign of ill effects. Several investigators administered rather small oral or intramuscular doses of alkylglycerols to patients suffering from radiation leukopenia or cancer. Brohult (1963) mentioned that amounts of alkoxylipids corresponding to 10–100 mg batyl alcohol per day are consumed in food by the average human being. There is no doubt that occasionally much larger amounts of alkyldiacylglycerols are ingested, at least by people eating shark products. Not only is the liver of Atlantic and Pacific dogfish (*Squalus acanthias* and *Squalus suckleyi*) a rich source of alkyldiacylglycerols (Mangold, 1961), but the rather oily flesh of these and other sharks also contains substantial amounts. For many decades, shark meat has been used for human consumption in Australia and New Zealand (*Callorhynchus milii*, *Galeorhinus australis*, and *Mustelus antarcticus*), in Germany and Great Britain (*Squalus acanthias*), in Japan, especially the northern islands (several species), and in the United States (*Lamna nasus*). In the West Indies the demand for shark meat is said to exceed the supply landed by local fishermen. To the best

of this author's knowledge, there are no reports of any ill effects from eating meat of the species mentioned, but meat of Greenland shark (*Somniosus microcephalus*) is allegedly unfit for human consumption because of its purgative effect.

A few isolated cases are known where the consumption of shark products has been harmful. Ill effects caused by eating shark livers and shark liver oils in New Zealand could be related to an overdose of fat-soluble vitamins and when, during the war, a restaurant in Japan used shark liver oil for frying sea food, thereby giving its patrons diarrhea, this was probably related to the oil's high squalene content.

B. 2-Alkylglycerols and 2-Alkyl-1,3-diacylglycerols

Symmetrical alkylglycerols and their acyl derivatives have not been found in nature. The behavior of synthetic 2-alkylglycerols in the gastrointestinal tract has been studied (see Section III, B), but attempts have not been made to assess the toxicity of these compounds and their acyl derivatives.

C. 1,2- and 1,3-Dialkylglycerols and Their Acyl Derivatives

It has been reported that phospholipids derived from 1,2-dialkylglycerols occur in the human heart (Popović, 1965). The behavior of synthetic 1,2- and 1,3-dialkylglycerols and of various 1,2-dialkyl phospholipids in the gastrointestinal tract has been studied (see Section III, C), and acyl derivatives of the dialkylglycerols have been used in biochemical investigations (see Section IV), but whether these compounds exhibit toxic effects has not been determined.

D. Trialkylglycerols

These compounds have not been found in nature. However, synthetic trialkylglycerols (Baumann and Mangold, 1966) have recently attracted considerable interest. Because they are not hydrolyzed or otherwise changed in the gastrointestinal tract, they may become useful as nonabsorbable substitutes for dietary fats, and in fat absorption studies the trialkylglycerols may become useful as reference markers for dietary lipids.

Studies on rats eating a labeled trialkylglycerol, (9,10-^{3}H)-hexadecyldidodecylglycerol, in cumulative amounts of more than 200 mg over 28 days, showed no evidence of toxicity at autopsy (Hofmann, 1969). On histological examination all of the following tissues appeared normal: brain, heart, liver, spleen, kidney, adrenal gland, pancreas, lung, intestine, bone marrow, and adipose tissue (Karlson, 1969).

E. Steryl Ethers

Very small amounts of cholesteryl alkyl ethers (Funasaki and Gilbertson, 1968) and cholesteryl alk-1-enyl ethers (Gilbertson *et al.*, 1970) were recently detected in bovine cardiac muscle; toxicological studies were not reported. Kaufmann *et al.* (1970) found disteryl ethers such as dicholesteryl, disitosteryl, distigmasteryl, and dibrassicasteryl ethers in refined vegetable oils. They showed that the disteryl ethers are formed during bleaching of the crude oils with mineral clay. Dicholesteryl ether was found to be noncarcinogenic, at least in rats.

III. Absorption of Alkoxylipids and Use of Alkoxylipids in "Fat" Absorption Studies

A. 1-Alkylglycerols and 1-Alkyl-2,3-diacylglycerols

With the aid of ^{14}C-labeled compounds it was established that dietary 1-alkylglycerols are almost completely absorbed by rats (Bergström and Blomstrand, 1956; Blomstrand, 1959; Swell *et al.*, 1965) as well as humans (Blomstrand and Ahrens, 1959). Some of the dietary 1-alkylglycerol is absorbed intact and acylated in the intestinal mucosa (Blomstrand, 1959; Bandi *et al.*, 1971b), but the major portion is cleaved at the ether linkage, and the long-chain alkyl moiety is converted to a fatty acid (Blomstrand and Ahrens, 1959). The same reactions occurred when a 1-alkyl-2,3-diacylglycerol was fed (Blomstrand, 1959). The alkyl moieties in naturally occurring alkoxylipids are almost exclusively saturated and monounsaturated. Bandi *et al.* (1971a) fed rats a synthetic polyunsaturated 1-alkylglycerol, *cis*,*cis*-9,12-octadecadienylglycerol (α-linoleylglycerol) and demonstrated that it underwent the same reactions as the labeled saturated 1-alkylglycerols.

The results of *in vitro* studies by Sherr *et al.* (1963), Sherr and Treadwell (1965), and Gallo *et al.* (1968) confirmed that, in the intestinal mucosa of the rat, 1-alkylglycerols can be acylated to form 1-alkyl-2,3-diacylglycerols, even though to a very limited extend. These authors showed, too, that 2-alkylglycerols can also be acylated. Kern and Borgström (1965) demonstrated the acylation of 1-alkylglycerols and 2-alkylglycerols in hamster intestinal rings. Snyder *et al.* (1970) found that cellfree homogenates from fat liver contain enzymes that catalyze the acylation of alkylglycerols. Accordinging to these authors, acylation of racemic 1-alkylglycerols produces only 1-alkyl-3-acylglycerols, whereas the acylation of 2-alkylglycerols leads to 2-alkyl-1,3-diacylglycerols. Of great interest, in this context, is a publication by Lewis (1966), who reported the occurrence of

large proportions of 1-alkyl-2,3-diacylglycerols in the stomach oil of a marine bird, the Leach's petrel (*Oceanodroma leucorhoa*). The origin and function of these acylated alkylglycerols is unknown.

Whereas both enantiomeric 1-acylglycerols are acylated in the intestinal mucosa, acylation of the 1-alkylglycerols proceeds in a strictly stereospecific manner in that only the naturally occurring enantiomers serve as substrates *in vivo* and *in vitro* (Paltauf, 1971).

B. 2-Alkylglycerols and 2-Alkyl-1,3-diacylglycerols

Because of their stability against lipases, and because of the fact that they do not undergo isomerization, the 1-alkyl- and 2-alkylglycerols were used as model substances in studies aimed at elucidating the reactions that lead to the resynthesis of triacylglycerols in the intestinal mucosa. As mentioned in the preceding section, several authors found that both the 1-alkylglycerols and 2-alkylglycerols are acylated to the respective alkylacylglycerols and alkyldiacylglycerols almost as readily as the acylglycerols are further acylated. Using the isomeric octadecylglycerols as model substances, Gallo *et al.* (1968) tried to establish which of the isomeric acylglycerols, and which diacylglycerol, are preferred for the resynthesis of triacylglycerols. The authors concluded that the mucosa of the rat intestine utilizes 2-acylglycerols for the formation of triacylglycerols, which means that the intermediates are 1,2-diacylglycerols and that utilization of 1,3-diacylglycerols probably requires their isomerization to the 1,2-isomer.

C. 1,2- and 1,3-Dialkylglycerols and Their Acyl Derivatives

Only one investigator, Paltauf (1969) has studied the intestinal absorption of the isomeric dialkylglycerols. He fed various ^{14}C-labeled 1,2-dialkylglycerols and 1,3-dialkylglycerols to rats and found that isomeric compounds having the same chain lengths were absorbed at equal rates, but that the chain lengths of the alkyl moieties had a pronounced effect on the extent these compounds were absorbed. Thus, less than 10% of the dioctadecylglycerols were absorbed, but over 50% of the dioctylglycerols. The rate of acylation during passage through the gut was found to be quite different for isomeric compounds, the 1,2-dialkylglycerol being the favored substrate. This finding certainly supports the conclusions that Gallo *et al.* (1968) had drawn when interpreting their results (see Section III, B).

Paltauf (1969) also studied the absorption of 1,2-dialkyl analogs of phosphatidic acid as well as those of choline phospholipids and ethanolamine phospholipids. He found that these compounds were rather poorly absorbed. After feeding the ionic compounds to rats, he could detect only traces of alkoxylipids in their lymph.

D. Trialkylglycerols

Long-chain trialkylglycerols are isosteric to triacylglycerols, the "fats," but they are neither hydrolyzed nor absorbed in the alimentary canal. These facts were demonstrated first by Spener *et al.* (1968), and their findings have been confirmed since (Carlson and Bayley, 1970; Morgan and Hofmann, 1970b).

Spener *et al.* (1968) used a ^{14}C-labeled trialkylglycerol to assess the amount of "fat" a rat can absorb, possibly through pinocytosis, without prior hydrolysis of the triacylglycerols. They administered tri-(1-^{14}C)-*cis*-9-octadecenylglycerol (trioleylglycerol) to normal rats and to rats provided with a thoracic duct fistula. Spener *et al.* measured the radioactivity of the lipids in the lymph during the first 24 hours after feeding. In addition they determined the radioactivity in various organs, and in the remaining carcass. Spener *et al.* found that only 0.14% of the trialkylglycerol fed had been absorbed (most of the adsorbed material was detected in the liver) and they concluded that intact long-chain triacylglycerols are probably absorbed at about the same rate. Simple pinocytosis of lipid droplets can therefore be ruled out as a quantitatively significant process of fat absorption.

In acute feeding experiments, Morgan and Hofmann (1970a) found that rats absorbed less than 0.2% of an ^{3}H-labeled trialkylglycerol, (9,10-^{3}H)-hexadecyldidodecylglycerol. The trialkylglycerol was found unchanged in the feces, indicating that it had not been degraded by digestive or bacterial enzymes. Chronic feeding experiments in rats confirmed that hexadecyldidodecylglycerol is absorbed no more than a fraction of 1%, that it is nontoxic, and that it does not influence the absorption of dietary triacylglycerols. Almost all of the trialkylglycerol absorbed was found in the liver, spleen, and adipose tissue of the animals.

Carlson and Bayley (1970) showed that tridodecylglycerol passes through the rat's digestive tract in association with other lipids, but remains unabsorbed; these authors were able to recover about 97% of the fed trialkylglycerol from the feces. This agrees substantially with the findings of Spener *et al.* (1968) and Morgan and Hofmann (1970a).

In a recent publication, Morgan and Hofmann (1970b) proposed (9,10-^{3}H)-hexadecyldidodecylglycerol as a marker for the quantitative evaluation of fat malabsorption. They fed this compound, together with a ^{14}C-labeled triacylglycerol, to normal rats and to rats with cholestyramine-induced steatorrhea. Fat absorption was estimated both from the ratio of $^{3}H/^{14}C$ in the meal and in the feces, and from the total fecal excretion of ^{14}C-labeled material. The values for fat absorption obtained by the two methods agreed within a range of 50–100%. Reference is made to a recent

and more extensive review on the chemistry and biochemistry of trialkylglycerols (Mangold *et al.*, 1972).

E. Steryl Ethers

It is not known if, and to what extent, cholesteryl esters are absorbed intact by the intestinal mucosa, or whether only cholesterol and fatty acids can be absorbed after hydrolytic cleavage of the esters. In order to get some idea of the magnitude of the absorption of intact cholesteryl esters, Borgström (1968) studied the behavior of the corresponding ethers, as these can be expected to be more resistant to the enzymes present in the digestive tract. He found that ingested cholesteryl alkyl ethers with alkyl chains up to ten carbon atoms long are absorbed by the intestinal musosa and transported in the thoracic lymph duct of rats. The recovery of the cholesteryl alkyl ethers from the lymph decreased with increasing chain length of the alkyl moiety. About 4% of the cholesteryl decyl ether could be recovered. It can be assumed that ethers having chain lengths similar to those of the naturally occurring cholesteryl esters, namely, C_{16}, C_{18}, and C_{20}, are absorbed to an extent considerably less than 1%. The synthesis of such cholesteryl alkyl ethers was reported (Paltauf, 1968); however, the absorption of these substances has not been studied. The fate of disteryl ethers (Kaufmann *et al.*, 1970) in the alimentary tract is unknown.

IV. Alkoxylipids as Substrates for Acyl Hydrolases

Pure synthetic alkoxylipids have been successfully used in studies of the physicochemical state of lipids in intestinal content during digestion and absorption. Hofmann (1963) determined the solubilization of monosubstituted glycerols, including 1-alkylglycerols, under *in vitro* conditions simulating the conditions prevailing in the human small intestine. As an extension of this work, Hofmann and Borgström (1963) presented observations on the action of pancreatic lipase on mixed bile salt/lipid micelles. More recently, Paltauf (1969) showed a good correlation between micellar solubility and rate of absorption of alkylglycerols, dialkylglycerols, and trialkylglycerols. Borgström (1965) used gel filtration to determine the dimensions of the micelles formed between bile salts and a series of lipids that included 1-alkylglycerols.

Several authors used alkoxylipids as substrates in studies of the specificities of enzyme preparations. Thus, Greten *et al.* (1970) studied the positional specificity of lipases with two isomeric dialkylacylglycerols as substrates. And Slotboom *et al.* (1970) investigated the action of purified

lipase preparations from porcine pancreas and from the mold *Rhizopus arrhizus* on synthetic 1,2-diacyl-, 1-alkyl-2-acyl-, and 1-alk-1′-enyl-2-acyl-choline phosphoglycerides. They found that the enzyme(s) from the two sources hydrolyze only the 1-acyl ester bond of choline phosphoglycerides, which means that phospholipase A_1 may actually be identical to lipase.

Anatol *et al.* (1964) mentioned that they were preparing a peralkylated analog of cardiolipin for use in the Wassermann test.

V. Applications of Alkoxylipids in Therapy

A. Bacteriostatic Properties

In 1952, Emmerie *et al.* used the nonsaponifiable matter of cod liver oil to isolate a fraction of 1-alkylglycerols that had strong inhibitory action *in vitro* upon the growth of human tubercle bacillus (*Mycobacterium tuberculosis*). The material was toxic to guinea pigs, and therefore its effectiveness in experimental tuberculosis could not be studied in these animals. Emmerie *et al.* ascribed the bacteriostatic properties of the fraction they had isolated to the presence of unsaturated 1-alkylglycerols, although pure natural selachyl alcohol was less active than their mixture of compounds. Ten years after the above-mentioned publication, Emmerie and Engel (1962) provided evidence for the occurrence of polyunsaturated 1-alkylglycerols in the nonsaponifiable matter of cod liver oil. They claimed that these compounds were in fact responsible for the bacteriostatic properties they had found in 1952. The interesting experiments of Emmerie and his associates certainly ought to be repeated with pure synthetic compounds, keeping in mind that tuberculostatic properties have also been attributed to diaryl ethers (Barry *et al.*, 1947).

B. Hemopoietic Effects

More than 40 years ago, bone marrow was successfully used for the treatment of secondary anemia (Giffin and Watkins, 1930). A few years later, Marberg and Wiles (1938) demonstrated that the material stimulating the formation of erythrocytes was present in the nonsaponifiable matter of yellow bone marrow. After Holmes *et al.* (1941) had found batyl alcohol in the nonsaponifiable fraction of bovine yellow bone marrow, several investigators studied the hemopoietic effects of the common 1-alkylglycerols. Sandler (1949) reported that not only the "nonsaponifiables" of bone marrow, but also batyl alcohol had a beneficial effect on the erythrocyte count of both normal rats and those poisoned with benzene. Moreover, Sandler found that subcutaneous injections of pure, synthetic, optically

inactive, 1-octadecylglycerol produced an increase in the circulating reticulocytes in human subjects. The erythropoietic, thrombopoietic, and granulopoietic stimulatory activities of both optically active and racemic 1-octadecylglycerol were later confirmed by several investigators (Arturson and Lindbäck, 1951; Brohult and Holmberg, 1954; Brohult, 1957; Hasegawa *et al.*, 1961; Linman, 1958, 1960; Linman *et al.*, 1958, 1959a; De Gaetani and Baiotti, 1959; Suki and Grollman, 1960; Osmond *et al.*, 1963). Brohult (1957) noted that there is an optimum dose which should not be exceeded, and Linman and Bethell (1956, 1961) pointed out that 1-octadecylglycerol possesses the same properties as the plasma fraction that stimulates erythropoiesis. However, batyl alcohol had no effect on the uptake of ^{59}Fe by hemoglobin *in vitro* and *in vivo* (Linman *et al.*, 1959a,b).

Suki and Grollman (1960) found that chimyl alcohol is also able to stimulate hemopoiesis, whereas selachyl alcohol is rather inactive. Linman (1960) and Osmond *et al.* (1963) found that both natural and synthetic *cis*-9-octadecenylglycerol are devoid of hemopoietic stimulatory activity in normal rats. Evenstein *et al.* (1958) questioned the erythropoietic effect of 1-octadecylglycerol in rats. And other investigators found this compound of little or no value in the treatment of leukopenia caused by irradiation (see Section V, C) or bracken poisoning in cattle (see Section V, D), conditions which also produce damage to the bone marrow.

In several laboratories the effects of "radiomimetic compounds," substances causing damage similar to that observed after irradiation, could be counteracted by intravenous injections of bone marrow (Talbot and Elson, 1958; Tran Ba Loc and Bernard, 1958). However, the aplastic anemia induced in cattle or calves by feeding trichloroethylene-extracted soybean meal could not be prevented by injecting synthetic 1-octadecylglycerol by various routes (Schultze *et al.*, 1958). A publication on the distribution and biosynthesis of alkylacyl phosphoglycerides in hematopoietic bone marrow certainly is of interest in this connection (Thompson and Hanahan, 1963).

Reference is made to a paper by Heller *et al.* (1963) on the presence of a lipophilic agent in shark liver that stimulates the reticuloendothelial system. This material was said to be rather unstable. Although it was not characterized further, it may well be an alkoxylipid, possibly identical or similar to the 1-alk-1′-enyl-2,3-diacylglycerols ("neutral plasmalogens") that are found in the liver of a species related to the sharks, the ratfish (*Hydrolagus collieï*), a chimaera (Schmid *et al.*, 1967).

A few years ago, the Astra Nutrition AB (1965) claimed a patent on the use of shark liver oil plus several vitamins in a "vitamin capsule." This preparation is meant to be used "to raise the percentage of glycerol ethers

in natural fats and foods." Supposedly, "the glycerol ethers stimulate the formation of white and red blood corpuscles and promote the growth of intestinal Lactobacilli." The latter claim is based on a publication by Brohult (1960).

C. Protection against Radiation Damages

Marberg and Wiles' (1938) report on the treatment of leukopenia with extracts of bone marrow, and Sandler's finding (1949) of the hemopoietic activity of "batyl alcohol," stimulated research on the effects of 1-alkylglycerols and their acyl derivatives on radiation injuries to erythropoietic tissues. Simultaneously, but independently, Brohult and Holmberg (1954) and Edlund (1954) published that they had been successful in protecting human subjects and mice, respectively, against radiation damage by giving them various alkoxylipids. Brohult and Holmberg (1954) administered concentrates of 1-alkylglycerols and their esters orally to patients suffering from radiation leukopenia, whereas Edlund (1954) gave subcutaneous injections of synthetic 1-octadecylglycerol dissolved in peanut oil to mice that had been given total body irradiation. Brohult (1957, 1958, 1962; Brohult *et al.*, 1970) extended these studies and, in 1963, presented a comprehensive review of her results.

In the course of the last 10 years the effects of 1-alkylglycerols in the treatment of radiation-induced leukopenia have been studied extensively. Some investigators confirmed the beneficial action of these compounds, especially of selachyl alcohol and its esters (Alexander *et al.*, 1959; Dudin, 1961; Mozharova *et al.*, 1961; Rusanov *et al.*, 1962; Sviridov *et al.*, 1964; Chebotarev, 1965). Others did not find the desired effects (Mizuno *et al.*, 1960; Ghys, 1962; Hietbrink *et al.*, 1962; Bassi and Dunjic, 1962; Prokhonchukov and Panikarovskii, 1963; Snyder *et al.*, 1971). Snyder *et al.* (1971) studied not only the 1-alkylglycerols and their acyl derivatives, but also 1-alk-1′-enyl-2,3-diacylglycerols, various diol lipids, long-chain alcohols, and other compounds. These substances were administered orally, intraperitoneally, and intramuscularly to rats that had been exposed to total body radiation. The number of circulating leukocytes was chosen as the criterion for effectiveness, and it was found that none of the various lipids investigated was able to alter the course of radiation-induced leukopenia.

It is interesting that 1-alkylglycerols occur in the nonsaponifiable matter from the bone marrow of rats even after exposure to total body irradiation (Snyder and Cress, 1963).

According to Maqsood and Ashikawa (1961; Ashikawa, 1961), intraperitoneal injection of olive oil and other vegetable oils increases survival

of mice after whole-body radiation. These oils are known to contain little alkoxylipids, if any. (See Chapter XVI.)

D. Treatment of Bracken Poisoning

After eating fern, cattle and calves develop severe leukopenia that is almost invariably fatal. W. C. Evans *et al.* (1957; I. A. Evans *et al.*, 1953) claimed that this "bracken poisoning" can be alleviated by subcutaneous injections of a solution of batyl alcohol in olive oil. However, neither Dalton (1964) nor Penny *et al.* (1964), who tested this therapy, found it effective.

E. Healing of Wounds

For generations various fats and oils, including fish oils, have been used as household medicine in the treatment of burns. Bodman and Maisin (1958) and Maisin *et al.* (1959) claimed that the alleged beneficial effects of certain fish oils are due to their alkoxylipid content. They reported striking results in the treatment of wounds by topical application of 1-alkylglycerols. Such therapy was reportedly beneficial in the treatment of nonhealing septic wounds in elderly patients, of nonhealing wounds associated with surgical treatment of fractures and malignant tumors, and of wounds and burns resulting from X-ray treatment. However, local application of 1-alkylglycerols was ineffective in the treatment of accidental burns in normal healthy human beings.

In a patent issued in 1966, Chalmers *et al.* claimed that 1-alkylglycerols dissolved in cottonseed oil are of value in the treatment of inflammatory diseases, chimyl alcohol supposedly being as efficacious as hydrocortisone.

Recently, the beneficial effects of the 1-alkylglycerols in wound healing have been questioned. Stansby *et al.* (1967) investigated the effects of various fats and oils in the treatment of wounds and burns of hairless mice. The authors found that the topical application of any oil had a slightly accelerating effect on the healing process when compared to no treatment at all. A fish liver oil having a high vitamin A content and a fish body oil to which 1-alkylglycerols had been added had the same effect as plain mineral oil. In the opinion of this author the alleged beneficial effects of 1-alkylglycerols in wound healing are not yet proven.

F. Inhibition of Neoplastic Growth

Abaturova and Shubina (1964) fed about 1 mg of batyl alcohol or selachyl alcohol per day for 3 months to rats bearing subcutaneous transplantable tumors. They claimed that both of these compounds slightly retarded growth of the tumors, selachyl alcohol being the more effective

of the two. In 1970, Brohult *et al.* reported the use of 1-alkylglycerols in cancer therapy in connection with radiation treatment of a large number of patients. 1-Alkylglycerols from the liver of Greenland shark (*Somniosus microcephalus*) were fed for several weeks, at a level of 0.6 g/day, to patients with cancer of the uterine cervix. One group of patients received these substances prophylactically 8 days before treatment with X-rays; another group received them only during the treatment. According to Brohult *et al.*, the 1-alkylglycerols given to the patients affected their tumors before as well as after radiation treatment, and reduced the mortality rates. The authors recommended that therapy should be started with 1-alkylglycerols before X-ray treatment. In experiments with rats, Delmon and Biraben (1966) did not observe any inhibitory effect of 1-octadecylglycerol on the development of carcinoma T 8; however, treatment with this compound appeared to lengthen the survival time of the animals.

It should be noted that most healthy human and animal tissues contain 1-alk-1′-enyl-2,3-diacylglycerols and 1-alkyl-2,3-diacylglycerols in small and roughly equal amounts (Tuna and Mangold, 1963; Schmid and Mangold, 1966). Recently, neutral and ionic lipids derived from 1-alkylglycerols were found to be present at a much higher level in transplantable rat and mouse tumors (Snyder and Wood, 1968) as well as in neoplastic human tissues (Snyder and Wood, 1969). The corresponding derivatives of 1-alk-1′-enylglycerols occur in rather small proportions in the neutral lipid fraction, but are at relatively high levels in the ionic lipids. (See Chapter X.) The role of alkoxylipids in tumors and the reported inhibition of neoplastic growth by 1-alkylglycerols remains a field wide open to further exploration.

G. Neuromuscular Activities

Several 1-alkylglycerols and 1-arylglycerols, when given subcutaneously or intraperitoneally, were found to produce transient muscular relaxation and paralysis in mice, probably due to a depressant action on their central nervous system (Berger and Bradley, 1946, 1948). Many of the compounds studied reduced blood pressure and heart rate and also caused vasodilatation (Berger, 1948). One aryl ether of glycerol, 1-guajacylglycerol, has become a widely used medicinal remedy and has been incorporated into several pharmacopoeas.

VI. Possible Functions of Naturally Occurring Alkoxylipids

In surveying the literature it becomes very evident that, although much work has been done on the alkylglycerols, the biological activities and

functions of their naturally occurring derivatives, namely the alkyldiacylglycerols and the various alkylacyl phospholipids, have hardly been studied. Malins and Barone (1970) as well as Lewis (1970) showed that 1-alkyl-2,3-diacylglycerols and triacylglycerols have different specific gravities. Malins and Barone (1970) suggested that a regulatory mechanism involving the selective metabolism of these two types of lipids is used by sharks in the maintenance of neutral buoyancy during vertical migration. This regulatory mechanism may serve as a substitute for the commonly found gas-filled swim bladder. (See Chapter XI.)

Little is known about the biological effects of neutral and ionic lipids containing alk-1-enyl moieties. Shah and Schulman (1965) demonstrated that the surface potential of alk-1-enylacylcholine phosphoglycerides is lower than that of diacylcholine phosphoglycerides. The authors attributed this to the presence of an additional induced dipole in the double bond of the alk-1-enyl moiety. Gottfried and Rapport (1963) compared the hemolytic activities of choline lysophosphoglycerides having an alkyl, alk-1-enyl, or acyl moiety. They did not find appreciable differences in the activities of these substances, but it should be noted that according to Safanda and Holocek (1965), chimyl alcohol markedly inhibits hemolysis by choline lysophosphoglycerides. Robertson and Lands (1962) injected emulsions of alk-1-enylacylcholine phosphoglycerides intravenously into rabbits and observed that 90% of this material disappeared from the bloodstream within 5 hours. Of great interest is a recent publication by Roots and Johnston (1968), who determined the plasmalogen content in the brain of goldfish maintained at different temperatures. These authors found a significant increase in the content of alk-1-enylacyl phosphoglycerides in goldfish brain with increasing environmental temperature. According to Roots and Johnston, this change is the most striking modification of brain lipids in response to changes in temperature so far recorded. Thiele *et al.* (1960) found that, in muscle, the concentration of plasmalogens decreased during exercise, despite an increase in the total phosphoglyceride content. Vogt (1949, 1957) reported the isolation of an acidic lipid fraction, from equine intestine, that acted as smooth muscle stimulant. Quite recently, Wiley *et al.* (1970) pointed out that this fraction was most likely a mixture of compounds derived from alk-1-enylacyl phospholipids by treatment with alkali. They thought that the major constituents of this mixture were acetals of long-chain aldehydes with glycerol phosphate.

Stowe (1960) reported that selachyl alcohol promotes the growth of pea stem sections. This finding is of particular interest as very little is known about the occurrence of alkoxylipids in plant tissues. (See Chapter XVI.)

In addition to the rather well known derivatives of the alkyl and

alk-1-enylglycerols occurring in nature, several "new" alkoxylipids have been found in recent years. The following paragraph lists some of these substances and the sources from which they were isolated. In a few instances the structures of the new compounds have not been fully elucidated.

Methoxy-substituted 1-alkylglycerols were isolated from shark livers (Hallgren and Ställberg, 1967), dialkylpentanediols from the jaw oil of a porpoise (*Phocoena phocoena*) (Varanasi and Malins, 1969), alkylacylglycerol galactosides from bovine brain (Norton and Brotz, 1963), and an alkoxy inositol phosphoglyceride (Klenk and Hendricks, 1961) from human brain. "New" lipids containing alk-1-enyl moieties include 1-alk-1′-enyl-2,3-diacylglycerols from human perinephric fat (Schmid and Mangold, 1966) and from the liver of the ratfish (*Hydrolagus colliei*) (Schmid *et al.*, 1967), alk-1-enylacyl ethanediols from rat liver, cod liver, mutton fat and other sources (Bergelson *et al.*, 1966), and "sphingoplasmalogens" from bovine brain (Kochetkov *et al.*, 1964). The function of these substances in living organisms and their effects on biological systems are totally unknown.

The alkyl and alk-1-enyl moieties in neutral and ionic alkoxylipids are, as a rule, exclusively saturated and monounsaturated, but polyunsaturated alk-1-enyl moieties were found in choline phospholipids of a human brain meningioma (Bell *et al.*, 1967). It is of interest, in this connection, that saturated and monounsaturated acids and alcohols are interconverted in the gastrointestinal tract (Stetten and Schoenheimer, 1940; Bandi and Mangold, 1971), whereas polyunsaturated acids are not readily reduced (Bandi and Mangold, 1971). Thus, it appears that polyunsaturated alkyl and alk-1-enyl moieties are not normally found in the alkoxylipids of human and animal organs because precursors, i.e., polyunsaturated alcohols, are not produced in these tissues (Bandi *et al.*, 1971b). Recently, it was shown that alkoxylipids containing polyunsaturated alkyl and alk-1-enyl moieties can be synthesized, at least in the rat, from dietary polyunsaturated alcohols (Bandi *et al.*, 1971a,b).

Recently, alkoxylipids have been identified in membranes, such as the synaptic plasma membranes from rat brain (Cotman *et al.*, 1969). It would be most interesting to learn how the changes in composition reported by Bandi *et al.* (1971a,b) affect the functions of membranes in various tissues.

VII. Conclusions

It can be seen from the foregoing discussion that knowledge of the biological effects of the various alkoxylipids is slim. This is in large measure due to the fact that such compounds had not been available in pure form. There is little doubt that in the future the functions and the biological

effects of derivatives of the alkyl- and alk-1-enylglycerols will be studied extensively, as pure substances are now available. Obviously, particular attention will be given to the exploration of the role the alkoxylipids may play in central and peripheral nerve tissues.

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