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ALKOXYGLYCEROL-ESTERS IN IRRADIATION TREATMENT

ASTRID BROHULT
Radiumhemmet, Stockholm, Sweden

The effect of alkoxyglycerols and alkoxyglycerol-esters obtained from bone marrow and shark liver oil respectively has been studied in cases of leucopenia caused by irradiation. The preparation has also been tried in thrombocytopenia. Experiments with alkoxyglycerol-esters in leukæmia are in progress. A preliminary communication was published in *Nature* (Brohult and Holmberg, 1954). Simultaneously, but independently, Edlund (1954) obtained a beneficial protective effect on irradiation in mice using synthetic batyl alcohol.

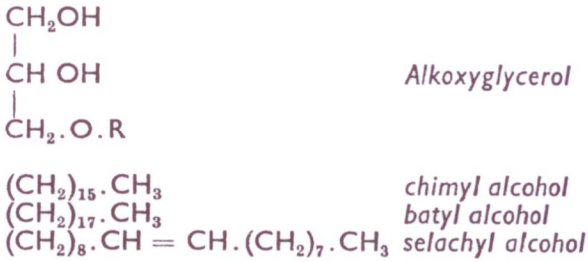
In 1952, experiments were started in cases of children's leukæmia in co-operation with Holmberg, using unsaponifiable fat from cattle bone marrow. Since there was reason to assume that the active component of this unsaponifiable fraction consisted of alkoxyglycerols, primarily of batyl alcohol, preparations containing both batyl alcohol and other alkoxyglycerols were then used instead for the treatments. On the basis of experience gained in this connection, the irradiation treatment experiments have been developed.

It is not a new idea to administer extracts from blood-forming tissue in blood disturbances. In 1930 Watkins (Watkins and Giffin, 1933) for the first time reported promising results from oral administration of cattle bone marrow in granylocytopenia. However, it proved that the medication was unsuitable since the marrow had to be taken in such large quantities that it caused digestive disturbances. Marberg and Wiles (1937 and 1938) showed that the same effect on the blood could be obtained by using solely the unsaponifiable fraction of the fat. This fraction constitutes only about 2% of the bone marrow. Holmes *et al.* (1941) found that batyl alcohol is a component of this fraction. Sandler (1949) published a paper on the stimulating effect on blood of both unsaponifiable bone marrow fat and of pure batyl alcohol.

In all natural sources the alkoxyglycerols are found esterified with fatty acids. In the bone marrow about 2% of the fat of the gelatinous tissue and about 0·6% of the spongy tissue consists of alkoxyglycerol-esters. The alkoxyglycerols have the following general formula:

$$R—OCH_2—CHOH—CH_2OH.$$

The alcohols commonly found are: batyl alcohol, chimyl alcohol and selachyl alcohol (Fig. 1). The main portion of the alkoxyglycerols of bone marrow consists of batyl alcohol (approximately 60%). Unpublished investigations by Holmberg prove that alkoxyglycerol-esters are present in many kinds of human and animal fats. Besides being in bone marrow, they are also found in, for example, the spleen, liver and the red cells.



	Alkoxyglycerols	
	in bone marrow	*in shark liver oil*
	0·2–0·7%	16–17%
(as diesters	0·6–2%	46–50%)
Distribution:		
chimyl alcohol	?	5
batyl alcohol	*approx.* 60	43
selachyl alcohol	?	52
polyunsaturated alcohols	?	<1

FIG. 1. Alkoxyglycerols and their distribution.

When it proved difficult to obtain sufficient quantities of a concentrated preparation from bone marrow two methods of progress were open: to try a synthetic preparation or to find another source of alkoxyglycerols. Large quantities of alkoxyglycerols are found in some sharks. For example, the liver oil of *Somniosus microcephalus*, Greenland shark, contains up to 50% of alkoxyglycerol-esters. The approximate proportions of the alkoxyglycerol components are: selachyl alcohol 52%, batyl alcohol 43% and chimyl alcohol 5%. The alkoxyglycerols are esterified mainly with polyunsaturated fatty acids. So far it is chiefly this type of 40-50% shark liver oil which has been used in the investigations. Lately it has been possible to achieve a concentrate yielding practically pure alkoxyglycerol-esters (95%). The preparation has been administered orally in the form of sugar-coated tablets, capsules or as an emulsion, the dosage being 1-2 g. of oil per day for adults.

Alkoxyglycerol-esters have been given to about a hundred patients suffering from irradiation leucopenia. Of these, 75% responded with an increased

leucocyte count in spite of continued irradiation treatment. In 15% of the cases the leucocyte level was stabilised and only 10% showed a further decrease.

Alkoxyglycerol-esters were given to a nurse who had been occupationally exposed to radium, and who for more than one year had a leucocyte count of approximately 2,000. After 3 days' treatment the count had risen to 3,600. This level has been maintained for more than one year by five treatments, the treatment periods being of 3-5 days' duration (Fig. 2).

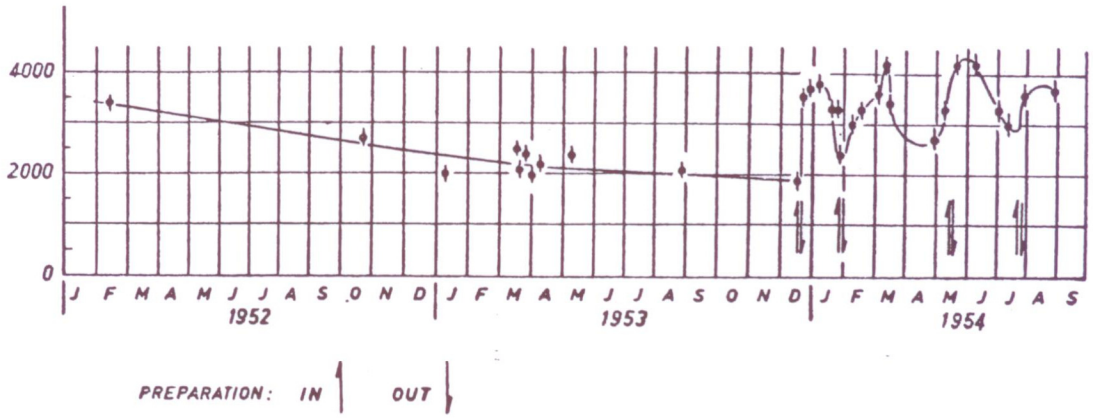


FIG. 2. The white cell count of a radium nurse before and after the administration of alkoxyglycerol-esters.

To obtain directly comparable results from treated and non-treated cases, alkoxyglycerol-esters were administered to patients suffering from cancer of the uterine cervix. These patients form the largest homogeneous group of irradiation treatment cases at Radiumhemmet. They are generally treated by two series of intracavitary radium applications in which radium cylinders are introduced into the corpus and packed against the cervix. The treatments are carried out with an interval of about three weeks. After 3 more weeks, X-ray treatment is given for 3–4 weeks. Alkoxyglycerol-esters have been administered to every second patient, each day during the treatment. Each alternate case has been used as a control and 125 cases of each kind have been studied and followed by blood examinations.

The results are summarised in Figure 3.

The initial leucocyte count for both groups lies at 6,000. The controls at the beginning of the X-ray treatments have a white cell count (V_F of 4,000, the corresponding value for the group which has received alkoxyglycerol-esters is 4,700. The white cell count at the end of the treatment (V_S) is 3,200 for the control group and 3,900 for the prophylactic or treated group. The mean value of the number of white cells during the X-ray treatment (V_M) is 3,450 for the control and 4,000 for the group which received alkoxyglycerol-esters. The difference between the two groups is highly significant. ($P = 0{\cdot}0001$.)

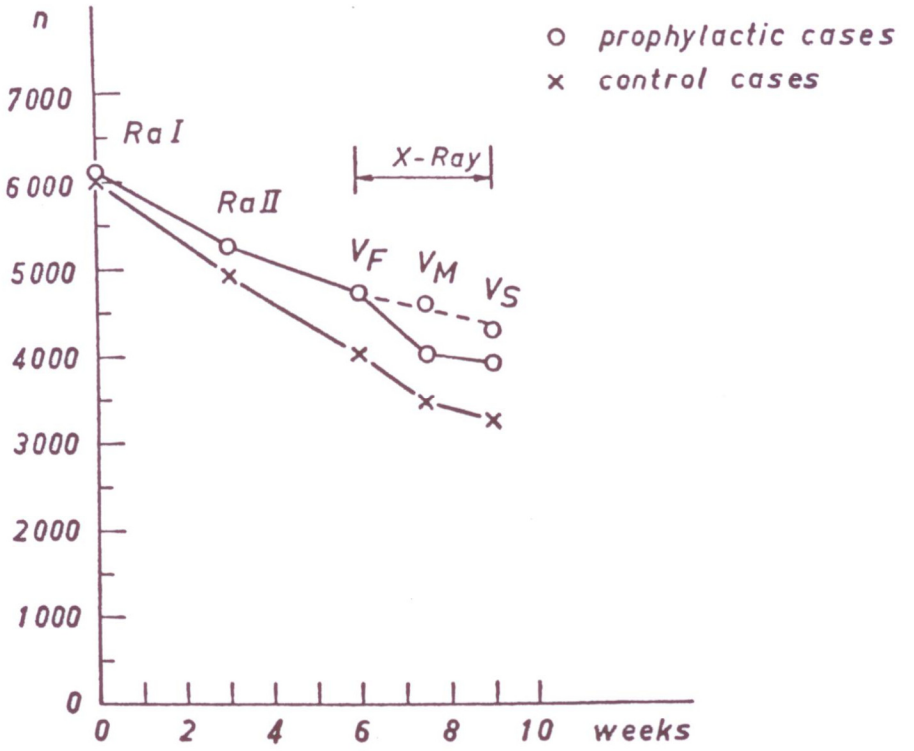


FIG. 3. Cancer of the uterine cervix: white cell count during the radiation treatment.

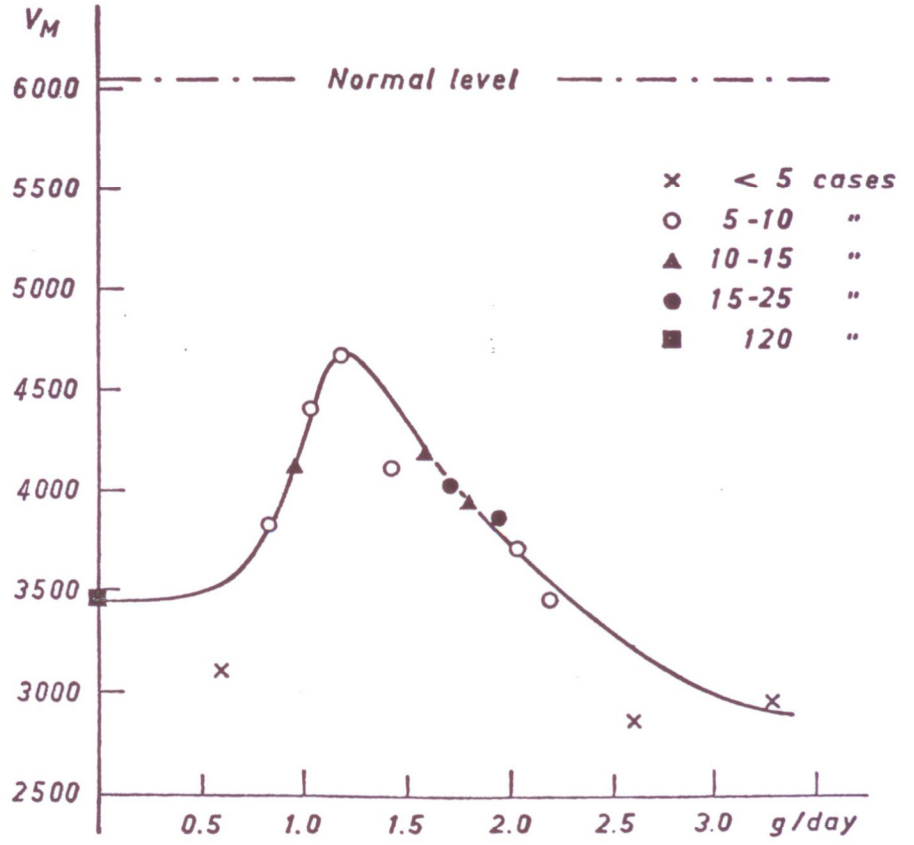


FIG. 4. White cell count (V_M) as a function of the amount of oil taken.
V_M: Mean value of the number of white cells during the whole X-ray treatment.

As already stated, these averages relate to all cases. If the 'prophylactic' group is subdivided according to the amounts of alkoxyglycerols administered, a correlation between effect and dose becomes apparent. This is shown by the dotted line. There seems to be an optimal dosage during the X-ray treatment period amounting to 1·2 g. of oil per day. With this dosage V_M is 4,650. Both larger and smaller doses give lower values. Doses higher than 2·5 g. seem to give lower counts than in the controls (Fig. 4).

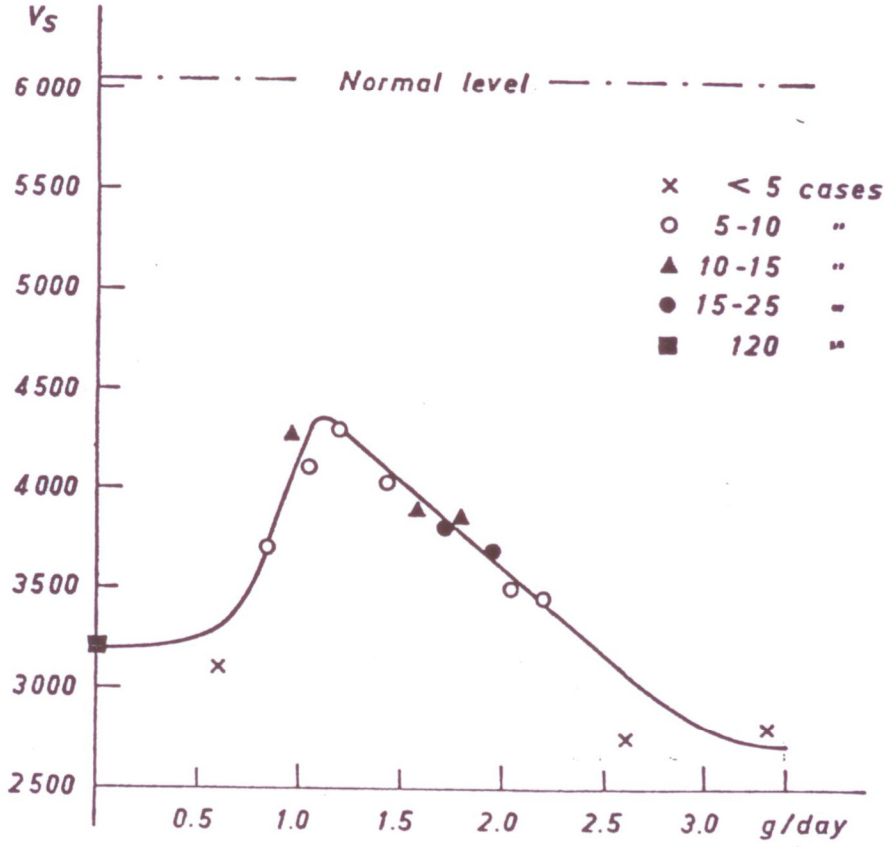


FIG. 5. White cell count (V_S) as a function of the amount of oil taken.
V_S: Mean value of the number of white cells at the end of the X-ray treatment.

Exactly the same relationship was also found if the blood count at the end of the course of X-ray treatment (V_S) is plotted against the amount of oil taken (Fig. 5).

As regards the average of the absolute number of lymphocytes during the irradiation treatment the optimal dose of oil seems to be the same.

The thrombocyte average count during the X-ray treatment at this optimal dosage is 190,000 and the corresponding figure for the controls is 155,000 (Fig. 6).

It has not been possible to demonstrate any definite effect on the erythrocytes.

The results have varied somewhat with different preparations of alkoxyglycerol-esters. The effect produced by the concentrated preparation is

lower than expected and it cannot at the present state of this investigation be decided if the activity is due to the whole complex of alkoxyglycerol-esters in the shark liver oil, or to some special alkoxyglycerol-esters or even to some other unknown component of the oil.

We hope that experiments in progress with pure alkoxyglycerols and alkoxyglycerol-esters will provide more information about the active principle.

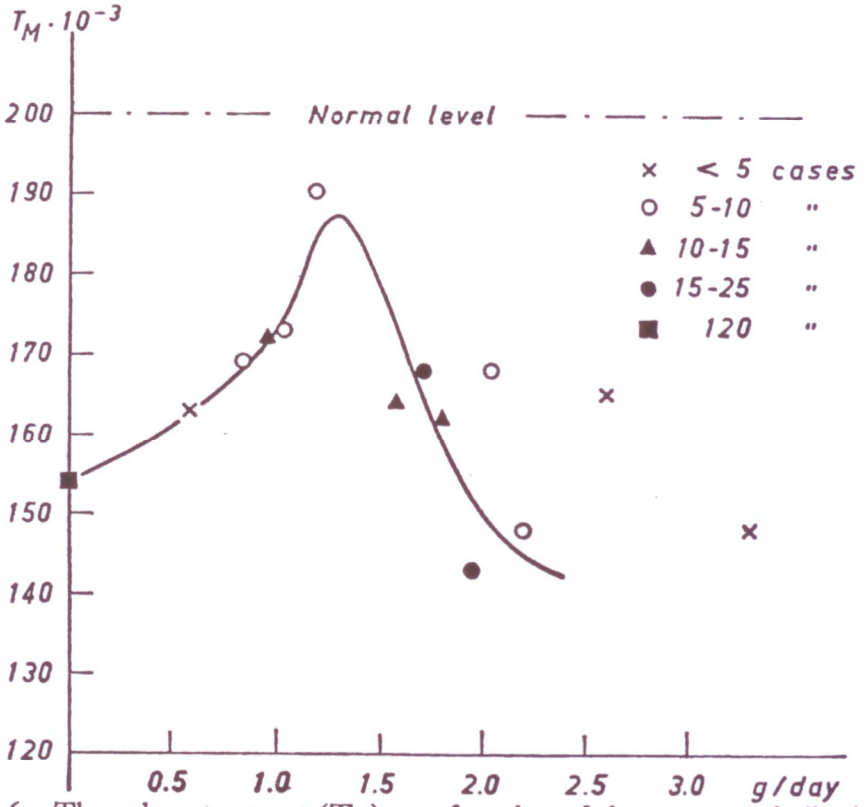


FIG. 6. Thrombocyte count (T_M) as a function of the amount of oil taken.
T_M: Mean value of the number of thrombocytes during the whole X-ray treatment.

Not enough time has passed to be certain whether the alkoxyglycerol-esters influence the effectiveness of the radiation therapy, but all the indications are that the effect on the tumours is in no way reduced. Moreover, in some cases it may be possible by giving the oil to continue radiation treatment of patients whose blood picture would otherwise have made it impossible to do so.

Acknowledgments

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