

## Immunoblastic lymphomas in Sprague-Dawley rats following exposure to the gasoline oxygenated additives methyl-tertiary-butyl ether (MTBE) and ethyl-tertiary-butyl ether (ETBE): early observations on their natural history

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F. Belpoggi, M. Soffritti e C. Maltoni: Linfomi immunoblastici in ratti Sprague-Dawley in seguito ad esposizione agli additivi ossigenati della benzina, metil-ter-butil etere (MTBE) ed etil-ter-butil etere (ETBE): prime osservazioni sulla loro storia naturale. Eur. J. Oncol., 4 (5), 563-572, 1999

### Summary

Methyl-tertiary-butyl ether (MTBE) and ethyl-tertiary-butyl ether (ETBE) cause an increase in dysplasias and immunoblastic lymphomas among Sprague-Dawley rats (respectively female, and male and female). The morphological characteristics are here described, together with the possible sequence of histopathological pictures which occur in the histogenesis of such lymphomas. The following sequence has been envisaged: reactive hyperplasia (aspecific phase), immunoblastic dysplasia, immunoblastic lymphoma with various stages of extension and grading and various degrees of malignancy (as a progression). In the genesis of this kind of lymphoma, which holds a growing interest for human pathology, it is suggested that there may be synergy between direct carcinogenic effects and proliferative stimulation effects caused by immune mechanism.

**Key words:** MTBE, ETBE, rat, immunoblastic lymphoma

### Riassunto

Il metil-ter-butil etere (MTBE) e l'etil-ter-butil etere (ETBE) causano in ratti Sprague-Dawley, rispettivamente femmine, e maschi e femmine, un aumento di displasie e linfomi immunoblastici. In questo resoconto vengono riferite le caratteristiche morfologiche e la possibile sequenza dei quadri istopatologici che si manifestano nell'istogenesi di tali linfomi. È stata prospettata la seguente sequenza: iperplasie reattive (fase aspecifica), displasie immunoblastiche, linfomi immunoblastici con vari stadi di estensione e grading e vari gradi di malignità (in progressione). Nella genesi di questo tipo di linfoma, che riveste crescente interesse in patologia umana, è stata infine formulata l'ipotesi di una sinergia fra effetti cancerogeni diretti ed effetti della stimolazione proliferativa indotta dai meccanismi immunitari.

**Parole chiave:** MTBE, ETBE, ratto, linfomi immunoblastici

### Introduction

In the course of the experimental study project on the carcinogenicity of gasoline oxygenate additives, conducted at the Cancer Research Centre (CRC) of the European Ramazzini Foundation

of Oncology and Environmental Sciences (RF), it was observed that methyl-tertiary-butyl ether (MTBE) and ethyl-tertiary-butyl ether (ETBE) cause an increase in leukaemias and lymphomas among Sprague-Dawley rats, and that the increase is largely due to lymphoimmunoblastic lymphomas (Maltoni and Soffritti, 1995; Belpoggi, Soffritti and Maltoni, 1995; Belpoggi *et al.*, 1997; Belpoggi, Soffritti and Maltoni, 1998; Maltoni *et al.*, in this issue). In the case of MTBE the increase was only observed in females; with ETBE, though to a lesser extent, in both males and females. The compound MTBE has also been reported to cause an

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increase in haemolymphoreticular dysplasias (Belpoggi *et al.*, 1995, 1997, 1998).

Such data clearly hold a specific interest for public health and the risks attaching to the use and diffusion of MTBE and ETBE, together with a more general interest linked to the specific histocytopathological typing of the lymphomas produced, i.e. the immunoblastic kind, where the increased incidence is more strictly correlated with MTBE and ETBE exposure.

In human pathology, these lymphomas have been related to situations of immunological imbalance (Knowles *et al.*, 1995; Kinlen, 1996). It may thus be presumed that the immunoblastic lymphomas caused by MTBE and ETBE in Sprague-Dawley rats are due not only to specific genotoxic effects of such compounds, or the specific proneness by the rat colony used at the CRC/RF to develop this neoplastic form (which is indeed a frequent spontaneous occurrence among such animals), but also to alteration of the immune function. An interesting tie-up, here, is the observation of immunopathological effect (allergy) in people exposed to MTBE (Vojdani, Namatalla and Brautbar, 1997; Vojdani and Brautbar, 1998).

We thus feel that the immunoblastic lymphomas we observed comprise a suitable model for studying the role of immunological mechanisms in the genesis and natural history of certain neoplasias originating from immunocompetent cells, as well as the possible interaction between immunotoxicity due to environmental (and specifically industrial) agents and carcinogens.

The CRC/RF accordingly set up a research project to study the natural history and pathogenetic mechanisms of immunoblastic lymphomas and the connected lymphoreticular neoplasias.

What follows is an account of preliminary observations on the features and possible sequence of histocytopathological pictures (histogenesis) we have found, and the guide they offer in reconstructing the natural history of MTBE- and ETBE-related immunoblastic lymphomas in the rat strains studied.

**Materials and methods**

We systematically re-examined all the tissues and organs of the experimental animals used in the project on gasoline oxygenated additives relating to MTBE and ETBE, wherever haemolymphoreticular pathology was found and whatever its type (reactive hyperplasia, dysplasia, neoplasia).

Data on the incidence of these pictures, some of them already published (Belpoggi *et al.*, 1995, 1997, 1998; Maltoni *et al.*, in this issue) are reported in Tables 1-5 regarding females exposed

to MTBE and Tables 6-11 regarding males and females exposed to ETBE. The slides we examined were coloured with haematoxylin and eosin and, in the most illustrative cases, with methyl green-pyronin, according to the Brachet method, as well as by silver-chromic impregnation to highlight the reticulum.

The histocytological features and possible sequences of the histopathology pictures in question were especially assessed in the lungs (peribronchial lymphoid tissue), surface lymph nodes (armpits and groin) and deep-lying lymph nodes (mediastinum and abdomen). These are the commonest targets, with the greatest number of alterations, and hence afford the best opportunity for reconstructing the natural history by the route of pathology.

**Results**

*Lung pathology*

The most frequent alteration is a reactive hyperplasia of the peribronchial lymphoplasmacellular tissue. Such reactive-hyperplastic tissue is formed of: 1) small and medium-sized lymphocytes; 2) plasmacells in various degrees of differentiation, above all mature; and 3) distinct anlagen of lymphocyte follicles formed of cell elements with no signs of atypia. The elements in the plasmacell series show pyroninophile cytoplasm directly proportionate in its intensity to the degree of cell maturation.

**Table 1** - CRC/RF project: long-term carcinogenicity bioassays on methyl-tertiary-butyl ether (MTBE), administered by stomach tube to male (M) and female (F) Sprague-Dawley rats (Experiment BT 958). Plan of the experiment

Group	Dose (mg/kg b.w. in olive oil)	Age at start (weeks)	Animals	
			Sex	No.
I	1000	8	M	60
			F	60
			M+F	120
II	250	8	M	60
			F	60
			M+F	120
III	0 <sup>(a)</sup>	8	M	60
			F	60
			M+F	120

<sup>(a)</sup> Olive oil alone

**Table 2** - CRC/RF project: long-term carcinogenicity bioassays on methyl-tertiary-butyl ether (MTBE), administered by stomach tube to male (M) and female (F) Sprague-Dawley rats (Experiment BT 958). Peribronchial lymphoplasmacellular hyperplasia and chronic reactive lymphadenitis among female rats

Group no.	Dose (mg/kg b.w. in olive oil)	Animals		Animals bearing peribronchial lymphoplasmacellular hyperplasia		Animals bearing chronic reactive lymphadenitis <sup>(a)</sup>	
		Sex	No.	No.	%	No.	%
I	1000	F	60	10	16.7	57	95.0
II	250	F	60	14	23.3	60	100.0
III	0 <sup>(b)</sup>	F	60	11	18.3	59	98.3

<sup>(a)</sup> In one or more lymph nodes

<sup>(b)</sup> Olive oil alone

Within the picture of reactive hyperplasia described, dysplastic pictures appear. They take the form of dystypical immunoblasts. They are sharp-edged, medium- or large-sized cells of a rounded, ovalar and more often polygonal shape, with a distinctly

eosinophile and pyroninophile cytoplasm, voluminous vesicular nuclei (the nucleolemma is particularly marked) and prominent intensely eosinophile and pyroninophile nucleoles. These dystypical immunoblasts are seen in the vicinity of a diffuse lymphoplasmacellular hyperplasia or in the germinative centres of follicle structures. They may be numerous and diffuse (fig. 1), or else gathered in clusters formed of cell groups varying in number.

In association with reactive hyperplasia and dysplasia one finds broad clusters of clearly atypical plasmoblasts, varying in size and shape, with more pronounced morphological features than the dysplastic pictures and again with accentuated eosinophilia and pyroninophilia, though less intense in the cells with a higher degree of atypia. This picture should be seen as an early immunoblastic lymphoma (fig. 2).

Along with pictures of dysplasia and early immunoblastic lymphoma, one observes formations of extensive immunoblastic lymphoma (figs. 3-5). They vary in the degree of neoplastic deviation, and at the times there are "monstrous" cells present. Such lymphomas of the peribronchial lymphoid tissue may spread to most of the lung lobe in massive quantity (fig. 6), and be found in a number of lobes. Often one notes a characteristic perivascular

**Table 3** - CRC/RF project: long-term carcinogenicity bioassays on methyl-tertiary-butyl ether (MTBE), administered by stomach tube to male (M) and female (F) Sprague-Dawley rats (Experiment BT 958). Results: lymphoimmunoblastic dysplasias among female rats

Group No.	Dose (mg/kg b.w. in olive oil)	Animals		Animals bearing haemolymphoreticular dysplasias <sup>(a)</sup>	
		Sex	No.	No.	%
I	1000	F	60	12	20.0
II	250	F	60	16	26.7
III	0 <sup>(b)</sup>	F	60	3	5.0

<sup>(a)</sup> Dysplasias observed in animals bearing lymphomas and leukaemias are not included

<sup>(b)</sup> Olive oil alone

**Table 4** - CRC/RF project: long-term carcinogenicity bioassays on methyl-tertiary-butyl ether (MTBE), administered by stomach tube to male (M) and female (F) Sprague-Dawley rats (Experiment BT 958). Results: haemolymphoreticular neoplasias among female rats and their distribution by histocytotype

Group No.	Dose (mg/kg b.w. in olive oil)	Animals		Animals bearing haemolymphoreticular neoplasias							
		Sex	No.	Total <sup>(a)</sup>		Lymphoblastic lymphoma <sup>(b)</sup>		Lymphoblastic leukaemia <sup>(b)</sup>		Immunoblastic lymphoma <sup>(b)</sup>	
				No.	%	No.	%	No.	%	No.	%
I	1000	F	60	12	20.0	3	25.0	1	8.3	8	66.7
II	250	F	60	7	11.7	0	–	1	14.3	6	85.7
III	0 <sup>(c)</sup>	F	60	2	3.3	1	50.0	0	–	1	50.0

<sup>(a)</sup> Percentages refer to the number of animals at start

<sup>(b)</sup> Percentages refer to the total number of animals bearing haemolymphoreticular neoplasias

<sup>(c)</sup> Olive oil alone

**Table 5** - CRC/RF project: long-term carcinogenicity bioassays on methyl-tertiary-butyl ether (MTBE), administered by stomach tube to male (M) and female (F) Sprague-Dawley rats (Experiment BT 958). Results: distribution of haemolymphoreticular neoplasias (HLRN) in female rats by site

Group No.	Dose (mg/kg b.w. in olive oil)	Animals		No. of HLRN	Distribution of haemolymphoreticular neoplasias by site <sup>(a)</sup>				
		Sex	No.		Sites involved	Total	Lymphoblastic lymphoma	Lymphocytic leukaemia	Immunoblastic lymphoma
						No.	No.	No.	No.
I	1000	F	60	12	Nodes	9	4	1	4
					Spleen	4	2	1	1
					Liver	5	2	2	1
					<b>Lung</b>	11	3	1	7
					Other	3	2	1	0
II	250	F	60	7	Nodes	1	0	0	1
					Spleen	2	0	1	1
					Liver	1	0	1	0
					<b>Lung</b>	5	0	0	5
					Other	0	0	0	0
III	0 <sup>(b)</sup>	F	60	2	Nodes	2	1	0	1
					Spleen	2	1	0	1
					Liver	1	1	0	0
					Lung	0	0	0	0
					Other	1	0	0	1

<sup>(a)</sup> The haemolymphoreticular neoplasias may affect many different anatomical sites; in this table all localizations have been taken into account

<sup>(b)</sup> Olive oil alone

**Table 6** - CRC/RF project: long-term carcinogenicity bioassays on ethyl-tertiary-butyl ether (ETBE), administered by stomach tube to male (M) and female (F) Sprague-Dawley rats (Experiment BT 959). Plan of the experiment

Group	Dose (mg/kg b.w. in olive oil)	Age at start (weeks)	Animals	
			Sex	No.
I	1000	8	M	60
			F	60
			M+F	120
II	250	8	M	60
			F	60
			M+F	120
III	0 <sup>(a)</sup>	8	M	60
			F	60
			M+F	120

<sup>(a)</sup> Olive oil alone

**Table 8** - CRC/RF project: long-term carcinogenicity bioassays on ethyl-tertiary-butyl ether (ETBE), administered by stomach tube to male (M) and female (F) Sprague-Dawley rats (Experiment BT 959). Results: lymphoimmunoblastic dysplasias

Group No.	Dose (mg/kg b.w. in olive oil)	Animals		Animals bearing lymphoimmunoblastic dysplasias <sup>(a)</sup>	
		Sex	No.	No.	%
I	1000	M	60	11 <sup>(b)</sup>	18.3
		F	60	11	18.3
		M+F	120	22	18.3
II	250	M	60	9	15.0
		F	60	11 <sup>(b)</sup>	18.3
		M+F	120	20	16.7
III	0 <sup>(c)</sup>	M	60	9	15.0
		F	60	6	10.0
		M+F	120	15	12.5

<sup>(a)</sup> Dysplasias observed in animals bearing haemolymphoreticular neoplasias are not included

<sup>(b)</sup> 2 borderline with an immunoblastic lymphoma

<sup>(c)</sup> Olive oil alone

**Table 7** - CRC/RF project: long-term carcinogenicity bioassays on ethyl-tertiary-butyl ether (ETBE), administered by stomach tube to male (M) and female (F) Sprague-Dawley rats (Experiment BT 959). Peribronchial lymphoplasmacellular hyperplasia and chronic reactive lymphadenitis among male and female rats

Group no.	Dose (mg/kg b.w. in olive oil)	Animals		Animals bearing peribronchial lymphoplasmacellular hyperplasia		Animals bearing chronic reactive lymphadenitis (a)	
		Sex	No.	No.	%	No.	%
I	1000	M	60	12	20.0	59	98.3
		F	60	12	20.0	60	100.0
		M+F	120	24	20.0	119	99.2
II	250	M	60	10	16.7	58	96.7
		F	60	13	21.7	60	100.0
		M+F	120	23	19.2	118	98.3
III	0 <sup>(b)</sup>	M	60	12	20.0	60	100.0
		F	60	9	15.0	60	100.0
		M+F	120	21	17.5	120	100.0

<sup>(a)</sup> In one or more lymph nodes

<sup>(b)</sup> Olive oil alone

**Table 9** - CRC/RF project: long-term carcinogenicity bioassays on ethyl-tertiary-butyl ether (ETBE), administered by stomach tube to male (M) and female (F) Sprague-Dawley rats (Experiment BT 959). Haemolymphoreticular neoplasias and their distribution by histocytotype

Group No.	Dose (mg/kg b.w. in olive oil)	Animals		Animals bearing haemolymphoreticular neoplasias											
		Sex	No.	Total <sup>(a)</sup>		Lymphoblastic lymphoma <sup>(b)</sup>		Lymphocytic lymphoma <sup>(b)</sup>		Immunoblastic-lymphoma <sup>(b)</sup>		Histiocytic sarcoma <sup>(b)</sup>		Myeloid leukaemia <sup>(b)</sup>	
				No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
I	1000	M	60	6	10.0	0	–	0	–	5	83.3	1	16.7	0	–
		F	60	5	8.3	0	–	1	20.0	2	40.0	2	40.0	0	–
		M+F	120	11	9.2	0	–	1	9.1	7	63.6	3	27.3	0	–
II	250	M	60	8	13.3	1	12.5	0	–	4	50.0	1	12.5	2	33.3
		F	60	6	10.0	1	16.7	1	16.7	3	50.0	0	–	1	16.7
		M+F	120	14	11.6	2	14.3	1	7.1	7	50.0	1	7.1	3	21.4
III	0 <sup>(c)</sup>	M	60	3	5.0	0	–	0	–	2	66.7	1	33.3	0	–
		F	60	3	5.0	0	–	0	–	1	33.3	2	66.7	0	–
		M+F	120	6	5.0	0	–	0	–	3	50.0	3	50.0	0	–

<sup>(a)</sup> Percentages refer to the number of animals at start

<sup>(b)</sup> Percentages refer to the total number of animals bearing haemolymphoreticular neoplasias

<sup>(c)</sup> Olive oil alone

**Table 10** - CRC/RF project: long-term carcinogenicity bioassays on ethyl-tertiary-butyl ether (ETBE), administered by stomach tube to male (M) and female (F) Sprague-Dawley rats (Experiment BT 959). Distribution of haemolymphoreticular neoplasias (HLRN) in male rats by site

Group No.	Dose (mg/kg b.w. in olive oil)	Animals		No. of HLRN	Sites involved	Distribution of haemolymphoreticular neoplasias by site <sup>(a)</sup>					
		Sex	No.			Total	Lymphoblastic lymphoma	Lymphocytic lymphoma	Lymphoimmunoblastic lymphoma	Histiocytic sarcoma	Myeloid leukaemia
I	1000	M	60	6	Nodes	2	0	0	1	1	0
					Spleen	1	0	0	0	1	0
					Liver	1	0	0	0	1	0
					<b>Lung</b>	6	0	0	5	1	0
					Other	2	0	0	1	1	0
II	250	M	60	8	Nodes	6	1	0	2	1	2
					Spleen	3	0	0	0	1	2
					Liver	3	0	0	0	1	2
					<b>Lung</b>	7	1	0	4	0	2
					Other	3	0	0	1	0	2
III	0 <sup>(b)</sup>	M	60	3	Nodes	2	0	0	1	1	0
					Spleen	0	0	0	0	0	0
					Liver	1	0	0	0	1	0
					<b>Lung</b>	1	0	0	1	0	0
					Other	1	0	0	1	0	0

<sup>(a)</sup> Haemolymphoreticular neoplasias may affect many different anatomical sites; in this table all localization have been taken into account

<sup>(b)</sup> Olive oil alone

**Table 11** - CRC/RF project: long-term carcinogenicity bioassays on ethyl-tertiary-butyl ether (ETBE), administered by stomach tube to male (M) and female (F) Sprague-Dawley rats (Experiment BT 959). Distribution of haemolymphoreticular neoplasias (HLRN) in female rats by site

Group No.	Dose (mg/kg b.w. in olive oil)	Animals		No. of HLRN	Sites involved	Distribution of haemolymphoreticular neoplasias by site <sup>(a)</sup>					
		Sex	No.			Total	Lymphoblastic lymphoma	Lymphocytic lymphoma	Lymphoimmunoblastic lymphoma	Histiocytic sarcoma	Myeloid leukaemia
I	1000	M	60	5	Nodes	4	0	1	2	1	0
					Spleen	2	0	0	0	2	0
					Liver	2	0	0	0	2	0
					<b>Lung</b>	2	0	0	1	1	0
					Other	2	0	1	0	1	0
II	250	M	60	6	Nodes	6	1	1	3	0	1
					Spleen	2	0	0	1	0	1
					Liver	2	0	0	1	0	1
					<b>Lung</b>	3	0	0	2	0	1
					Other	3	0	1	1	0	1
III	0 <sup>(b)</sup>	M	60	3	Nodes	1	0	0	0	1	0
					Spleen	1	0	0	0	1	0
					Liver	2	0	0	0	2	0
					<b>Lung</b>	2	0	0	1	1	0
					Other	1	0	0	0	1	0

<sup>(a)</sup> Haemolymphoreticular neoplasias may affect many different anatomical sites; in this table all localization have been taken into account

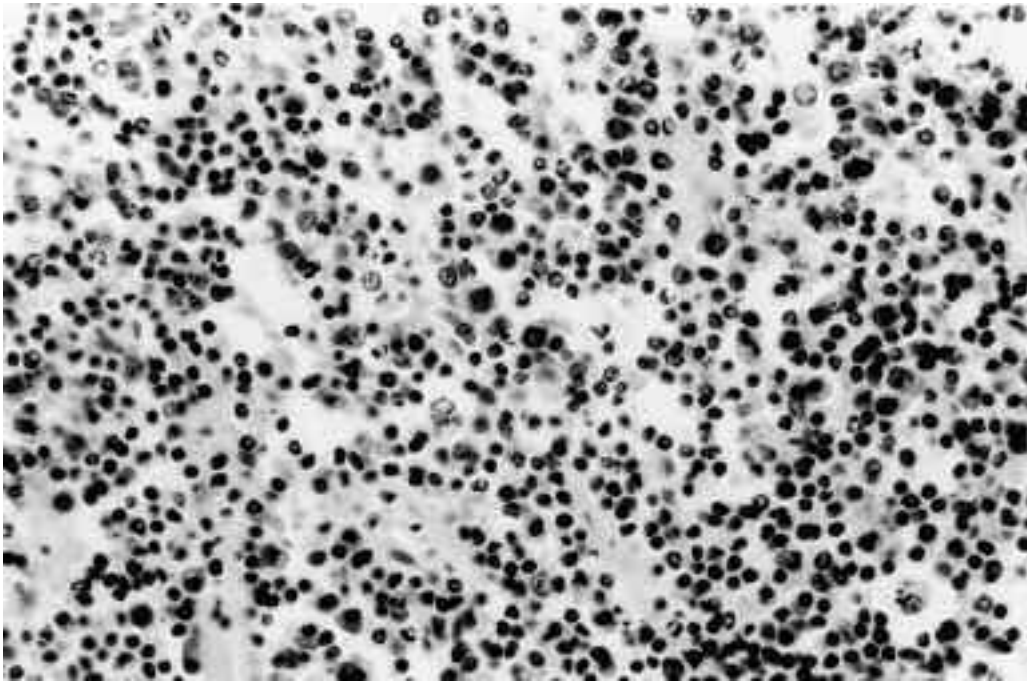
<sup>(b)</sup> Olive oil alone

arrangement (figs. 7, 8). The cells' degree of eosinophilia and pyroninophilia is inversely proportional to the extent of differentiation. At times the pyroninophile material takes on a clod-like arrangement. When the pulmonary involvement is massive, the lack of dysplastic pictures is almost certainly due to their being replaced by neoplastic tissue proper. A certain parallelism exists between the degree of neoplastic deviation and the extent of the lymphoma.

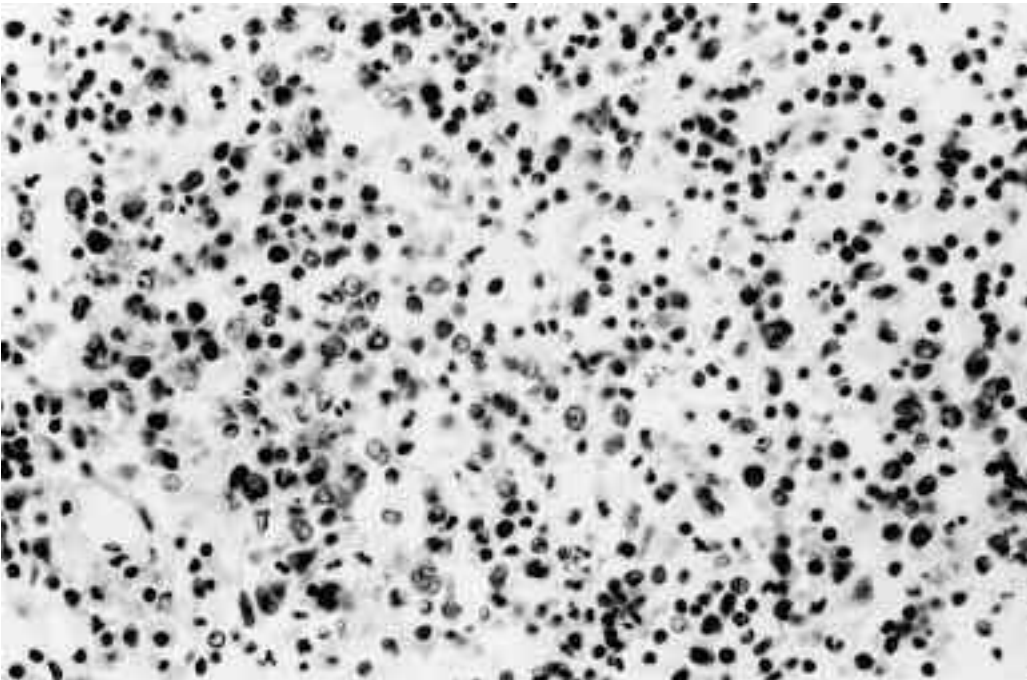
*Lymph node pathology*

One or more lymph nodes may be involved (neighbouring and/or distant lymph nodes).

The commonest alteration is chronic reactive lymphadenitis characterized by plasmacell hyperplasia in the medullary and cortical zones, hypertrophy of the follicles, an enlarging of the follicle centre area and the appearance in this area of cell elements show-



**Fig. 1** - Lung. Peribronchial immunoblastic dysplasia. E.-E. x 512.



**Fig. 2** - Lung. Early immunoblastic lymphoma. E.-E. x 512.

ing plasmacellular differentiation. There are points in common with the picture of peribronchial reactive hyperplasia described above. At times, though not frequently, lymph nodes with lymphadenitis are found to contain fairly clearly outlined areas of reticulolymphocytic hyperplasia.

Where there are zones of chronic reactive lymphadenitis, there appear dysplastic pictures consisting in the emergence of im-

munoblastic elements with the same features as observed in peribronchial tissue. Less commonly, dystypical immunoblasts in small numbers may be found in the vicinity of reticulolymphocytic hyperplasia. Nearly always associated to lymphadenitis or dysplasia, one finds immunoblastic lymphomas varying in extent and deviation, affecting a part or the whole of the lymph node, and one or more neighbouring and/or distant other lymph nodes.

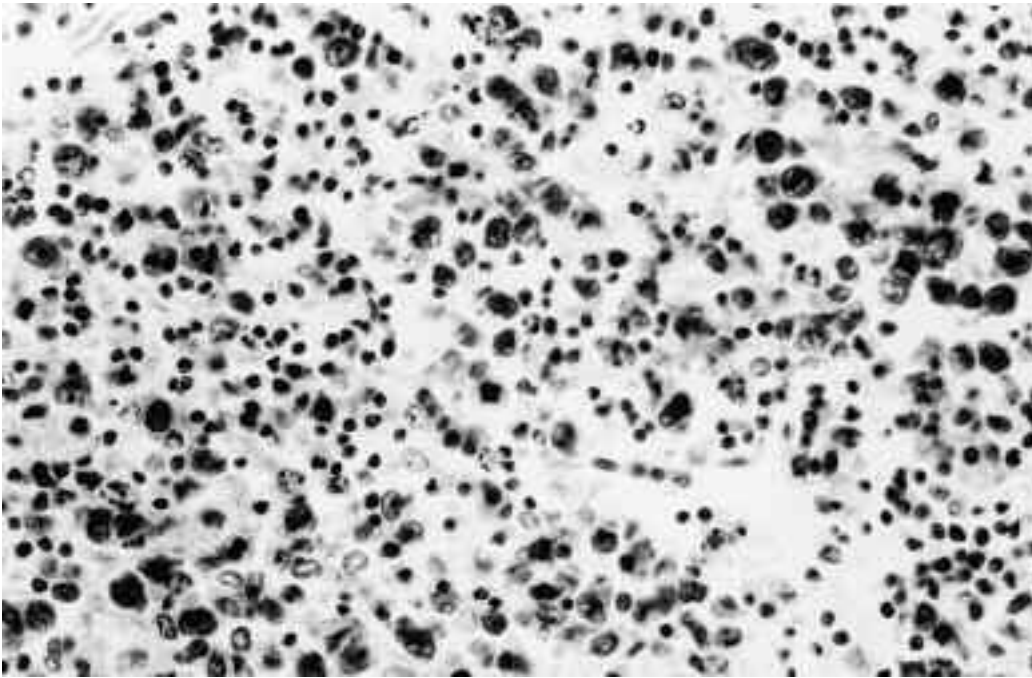


Fig. 3 - Lung. Immunoblastic lymphoma. E.-E. x 512.

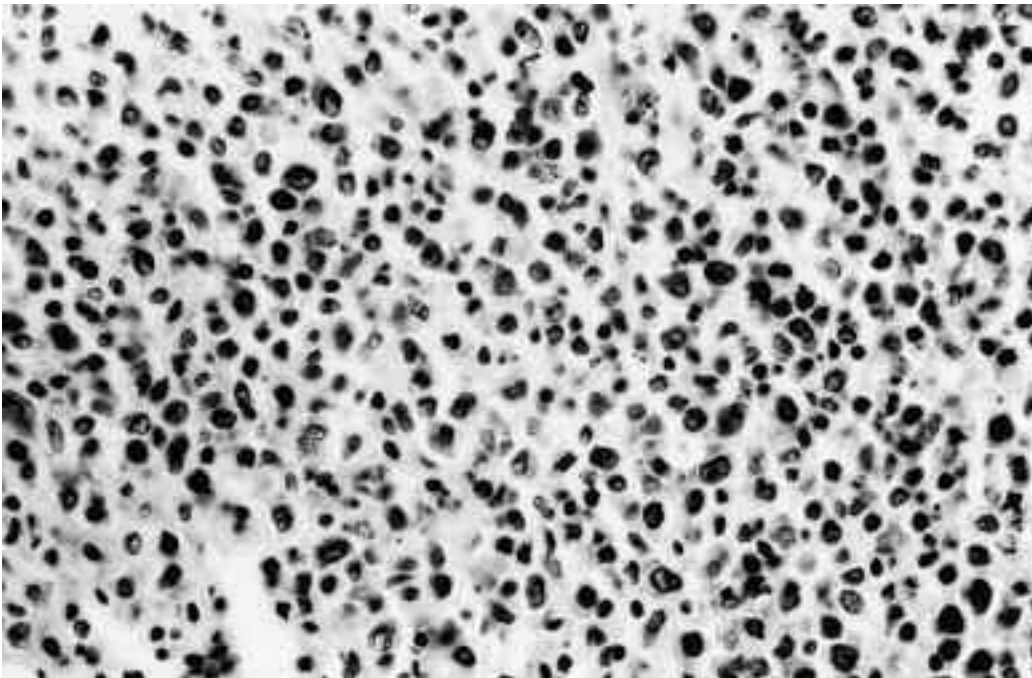
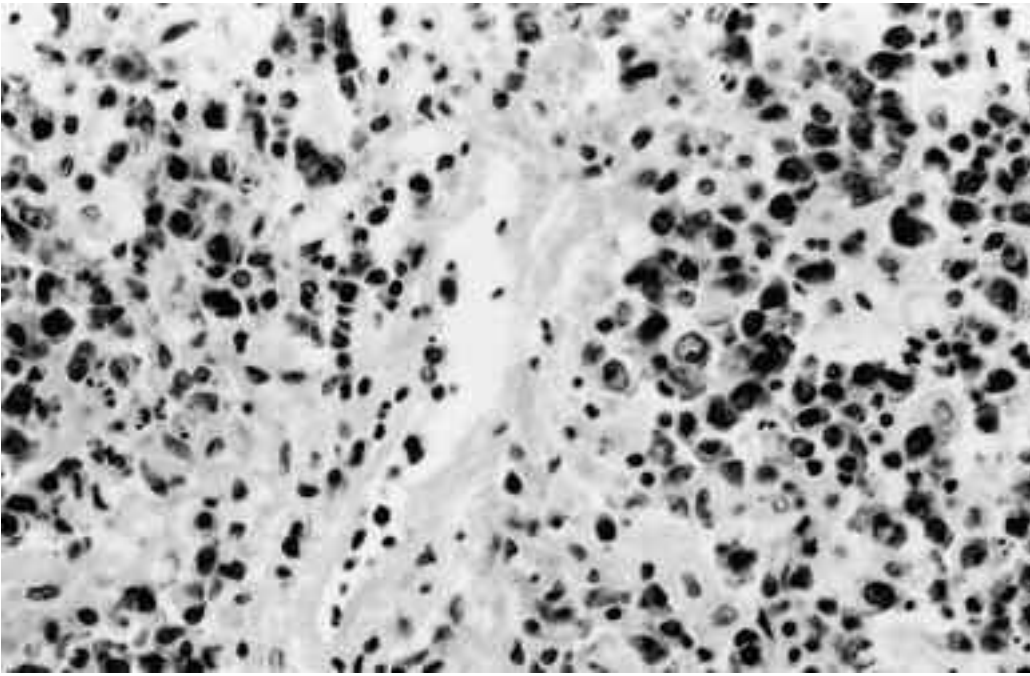


Fig. 4 - Lung. Immunoblastic lymphoma. E.-E. x 320.

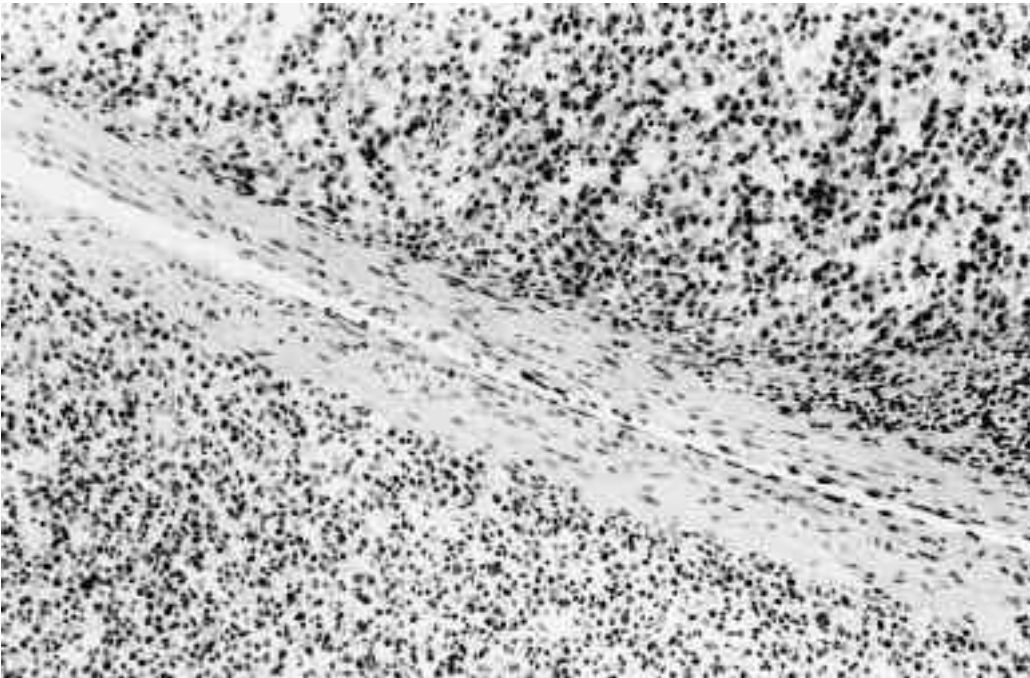
### Discussion and conclusions

The findings we report come from animals that died a spontaneous death. For a clearer definition of the histogenesis of immunoblastic lymphomas within the experimental study system, the study should involve periodic sacrifices of groups of animals. From what we have observed it nonetheless appears that:

- 1) peribronchial and lymph node reactive hyperplasia are not specific steps in the process. In their incidence they do not correlate with MTBE and ETBE treatment and thus with any increase in the incidence of dysplasias and immunoblastic lymphomas. Nonetheless they are the context in which dysplasias and immunoblastic lymphomas are found to arise;



**Fig. 5** - Lung. Immunoblastic lymphoma. E.-E. x 512.



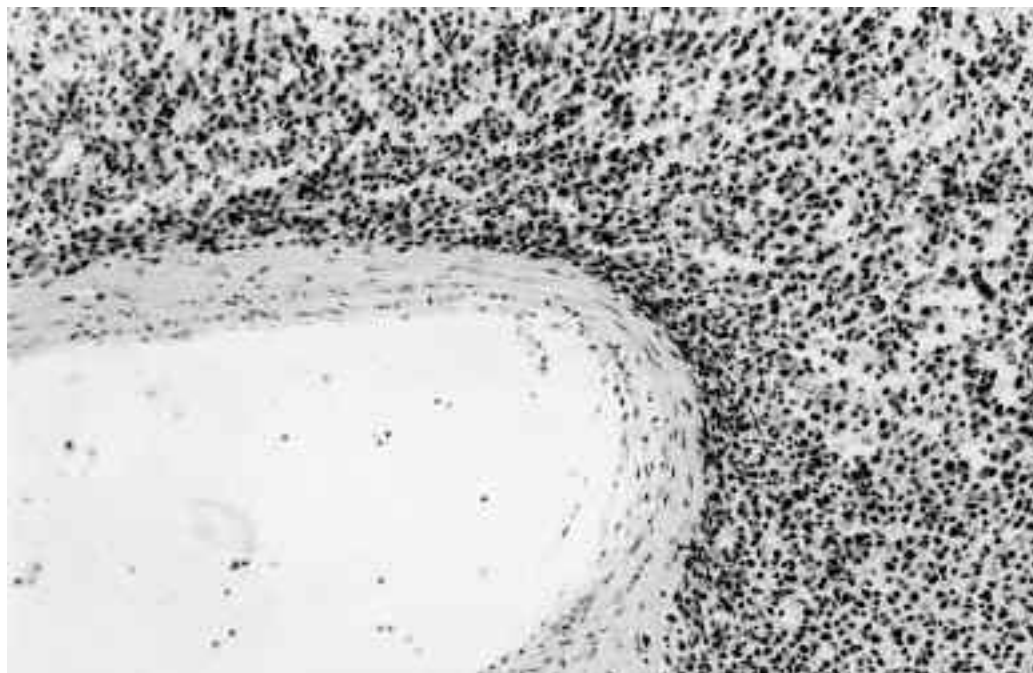
**Fig. 6** - Lung. Immunoblastic lymphoma: massive spreading. E.-E. x 200.

2) by contrast, dysplasias are a more specific precursor, given the similarity between the features of dysplastic and neoplastic formations, and the correlation of dysplasias with the treatment triggering a rise in the incidence of immunoblastic lymphomas; 3) in view of the similarity in cell morphology, initial immunoblastic lymphomas should be seen as the stage prior to extensive forms. Whether all initial forms evolve into extensive forms or not is a question our findings cannot answer;

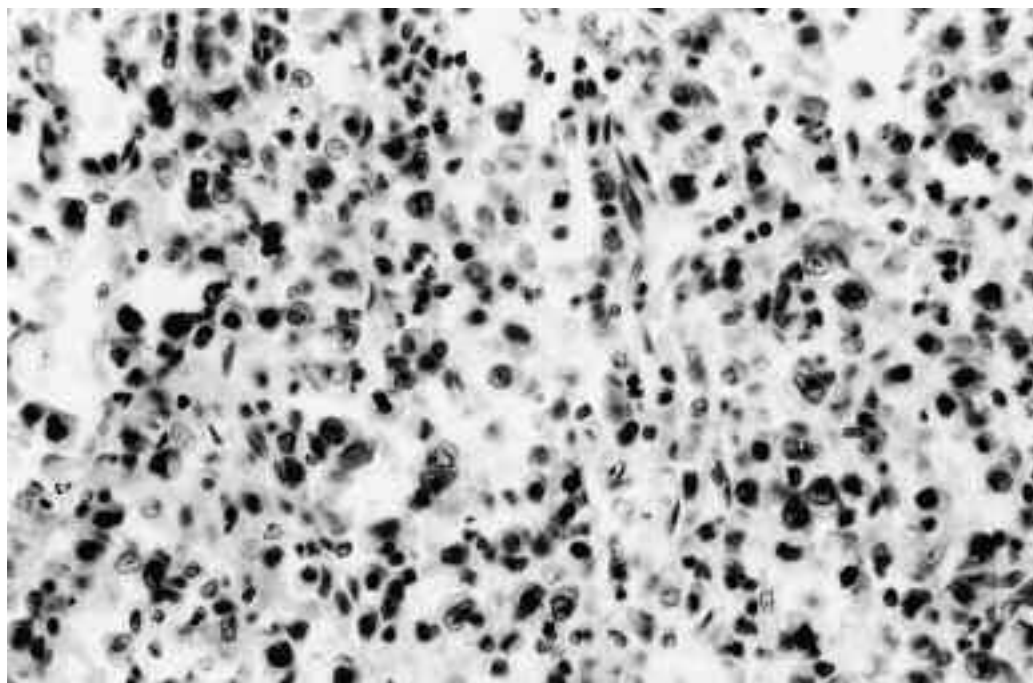
4) extensive lymphomas may evolve in more and more diffuse form with greater and greater malignancy.

The histogenetic sequence may thus be reconstructed: 1) reactive hyperplasia (non-specific but necessary); 2) dysplasia (specific); 3) initial neoplasia (preceding the full form); 4) outright neoplasia (progressing).

Immunoblastic lymphomas arise, then, in states of reactive hyperplasia characterized by immunocompetent cell proliferation.



**Fig. 7** - Lung. Immunoblastic lymphoma: characteristic perivascular arrangement. E.-E. x 200.



**Fig. 8** - Lung. The same immunoblastic lymphoma of fig. 7. E.-E. x 512.

Although not specific, this picture seems a necessary step in the histogenesis of neoplasia. Where exogenous agents give rise to such lymphomas, one should thus bear in mind the possibility of synergic immune mechanisms together with genotoxic action, if only, perhaps, as proliferative stimuli. It seems a by no means implausible hypothesis that MTBE and ETBE cause a rise in the onset of lymphoimmunoblastic, dysplastic and neoplastic pathology via a direct genotoxic action and via a proliferative stimulus due

to the formation (which remains to be proved) of derivatives of such compounds (or their transformation products) together with proteins acting as antigens.

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