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# An epizootic of an epitheliotropic lymphoblastic lymphoma in coho salmon *Oncorhynchus kisutch*

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ABSTRACT: Juvenile coho salmon *Oncorhynchus kisutch* reared at a freshwater hatchery on Vancouver Island, Canada, exhibited high, chronic losses associated with an epitheliotropic lymphoblastic lymphoma of thymic origin. Cumulative mortality of 45% occurred over an 8 mo period in one year class. The disease was observed in the fish until release from the hatchery for seawater migration. Saltwater challenge tests indicated that the affected fish had impaired osmoregulation and thus poor seawater survival was expected. Histological examination of the moribund fish revealed a marked proliferation of neoplastic lymphoid cells in the thymus. The cells infiltrated the gills, the integument of the opercular cavity, and the skin around the nares and eyes. The neoplastic cells were oval with a moderate amount of finely granular eosinophilic cytoplasm, and had a centrally located nucleus. The cell population was morphologically heterogeneous and was composed of large blastoid cells and apparently more mature lymphoid cells with hyperchromic nuclei and inapparent nucleoli. Cells with cleft nuclei and multinucleated cells were observed. Ultrastructural examination of the neoplastic cells revealed abundant rough endoplasmic reticula with no evidence of desmosomes. No particles suggestive of viruses were detected in or around the neoplastic cells. The disease was judged to be a neoplasia, rather than a reactive lymphoblastosis, because the proliferative cells were morphologically immature, there was little other inflammatory involvement or necrosis, and the lesions were invasive and persistent. The fish continued to die until release from the hatchery.

## INTRODUCTION

An unusual, epitheliotrophic lymphoblastic lymphoma of thymic origin was associated with high mortality in coho salmon *Oncorhynchus kisutch*, reared at the Big Qualicum Hatchery, Vancouver Island, British Columbia, Canada. The Salmon Enhancement Program (SEP) of the Department of Fisheries and Oceans of Canada rears Pacific salmon from eggs through their freshwater phase of development at hatcheries throughout British Columbia. The Big Qualicum Hatchery is an important supplier of coho and chinook *O. tshawytscha* for SEP From egg to release, coho spend ca 18 mo in the hatchery.

Hemic neoplasms have been reported in many wild or cultured fishes, including salmonids (Fredrickson et al. 1991). Most reports are from only one or a few specimens, but a few epizootics of hemic neoplasia have occurred, particularly in the order Salmoniformes. A plasmacytoid leukaemia was reported in hatchery-reared and pen-reared chinook salmon (Harshbarger 1984, Kent et al. 1990), and a high prevalence of lymphoma has occurred in wild northern pike *Esox lucius* in North America (Sonstegard 1976) and Europe (Mulcahy 1976, Thompson 1982). Described here are the mortality patterns, clinical effects, and gross and microscopic changes associated with an epizootic of an unusual lymphoma in coho salmon.

## MATERIALS AND METHODS

**Diagnostic evaluation.** This study represents the sequential diagnostic evaluation of affected fish that was requested by hatchery personnel at the Big Qualicum Hatchery. Initial samples from the 1985 brood year were taken in January 1986 because of an increase in mortalities. More frequent sampling commenced in July 1987 on the 1986 brood year. Because of the diagnostic nature of the evaluation, intervals between samples, number of fish examined per case, and sampling techniques varied.



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At sampling, fish were examined externally and internally for gross abnormalities. Wet mount preparations of gills and skin scrapings were also examined. Kidney tissue was cultured on tryptic soy agar and kidney imprints were evaluated by Gram stain for the detection of bacterial pathogens. For most samples, a minimum of 6 fish was examined. When haematological evaluations were done, haematocrit readings and blood smears were taken from a minimum of 20 fish.

Dates and numbers of fish sampled for histological evaluation were as follows: 8 July 1987 (4 fish), 15 October 1987 (6 fish), 27 October 1987 (16 fish), 10 November 1987 (16 fish), 22 December 1987 (14 fish), 8 February 1988 (8 fish), 18 February 1988 (9 fish), 15 April 1988 (4 fish). and 19 May 1988 (6 fish).

**Light and electron microscopy.** Tissues were preserved in Bouin's fixative, processed for histological examination, and stained with haematoxylin and eosin. Tissue sections were made from sagittal sections of the head that included the gills and thymus. Visceral organs were examined in cross section.

Material for electron microscopy was prepared from gill tissue of 4 fish collected on 15 April 1988. The tissue was fixed in 4 % glutaraldehyde in Milloning's phosphate buffer, post-fixed in 1 % $OsO_4$, embedded in Epon plastic, sectioned, stained with lead citrate and uranyl acetate, and examined with a transmission electron microscope.

**Record keeping.** Hatchery staff collected dead fish at the downstream end of the rearing channel on a daily basis and kept all mortality records. These data were used for calculations of cumulative mortality.

**Seawater challenge.** Seawater challenge tests were carried out according to the method described by Blackburn & Clarke (1987).

## RESULTS

### Disease history

For 2 consecutive brood years (1985 and 1986), under-yearling coho at the Big Qualicum Hatchery showed unusually high losses associated with proliferative, chronic gill problems. The disease history given here is based on the 1986 brood year which suffered high losses in the fall/spring of 1987/1988.

Earliest indications of the problem were noticed in September with a change in behaviour Many fish began to inhabit the slow-flowing areas of the channels, but at the same time they showed bursts of hyperactivity. At this stage, there were no increases in mortality rates and the losses were still less than 1 % per month (Fig. 1). By October, a general weakness of the fish was obvious, although most fish showed no obvious external or internal disease signs. All moribund fish exhibited pale gills, suggestive of anaemia. However, haematocrit values in the sampled fish were normal at 35 to 45 %. In general, blood smears were also normal, and leucocyte proliferative changes suggestive of leukaemia were absent.

Although cellular infiltration of the buccal cavity and lower gill areas was noticed as early as July, a nodular hyperplasia in the branchial area was observed for the first time in October. During November, 3.6 % of the 1.12 million fish in the channel died.

Because moribund fish exhibited proliferative gill lesions that persisted from October through December, the water quality of this channel was considered to be a potential problem In an attempt to improve the situation, all fish were moved out of the rearing channel in December to other rearing areas upstream on river water. However, after a short apparent improvement, fish health continued to deteriorate. Losses in February were 8.4 %. Fish were released towards the end of May with a monthly loss of 13.7 % and a cumulative mortality of 45 % from September through May (Fig. 1).

Although all moribund fish exhibited gill lesions, many fish had one or more secondary infections. Mixed bacterial gill disease, as well as infections with one or more of the following pathogens were found: *Aeromonas salmonicida, Renibacterium salmoninarum, Costia* sp., *Trichodina* sp., *Epistylis* sp., *Loma salmonae, Cryptobia* sp., *Scyphidium* sp., *Tetracotyle* sp., and a *Saprolegnia*-like fungus. To combat these secondary infections, fish were given oral treatments with oxy-

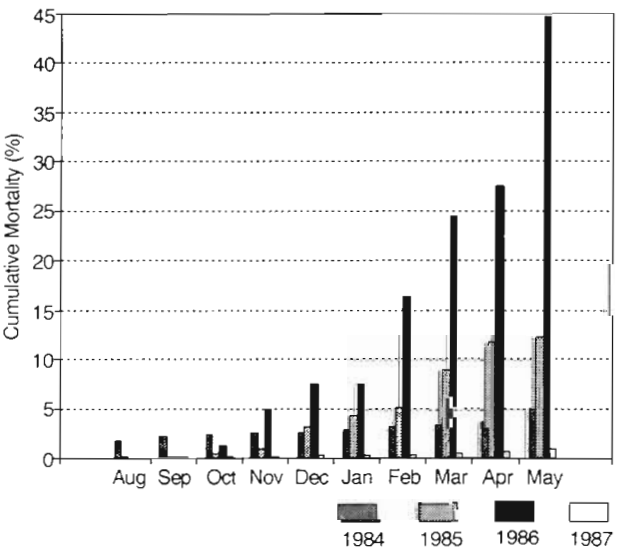


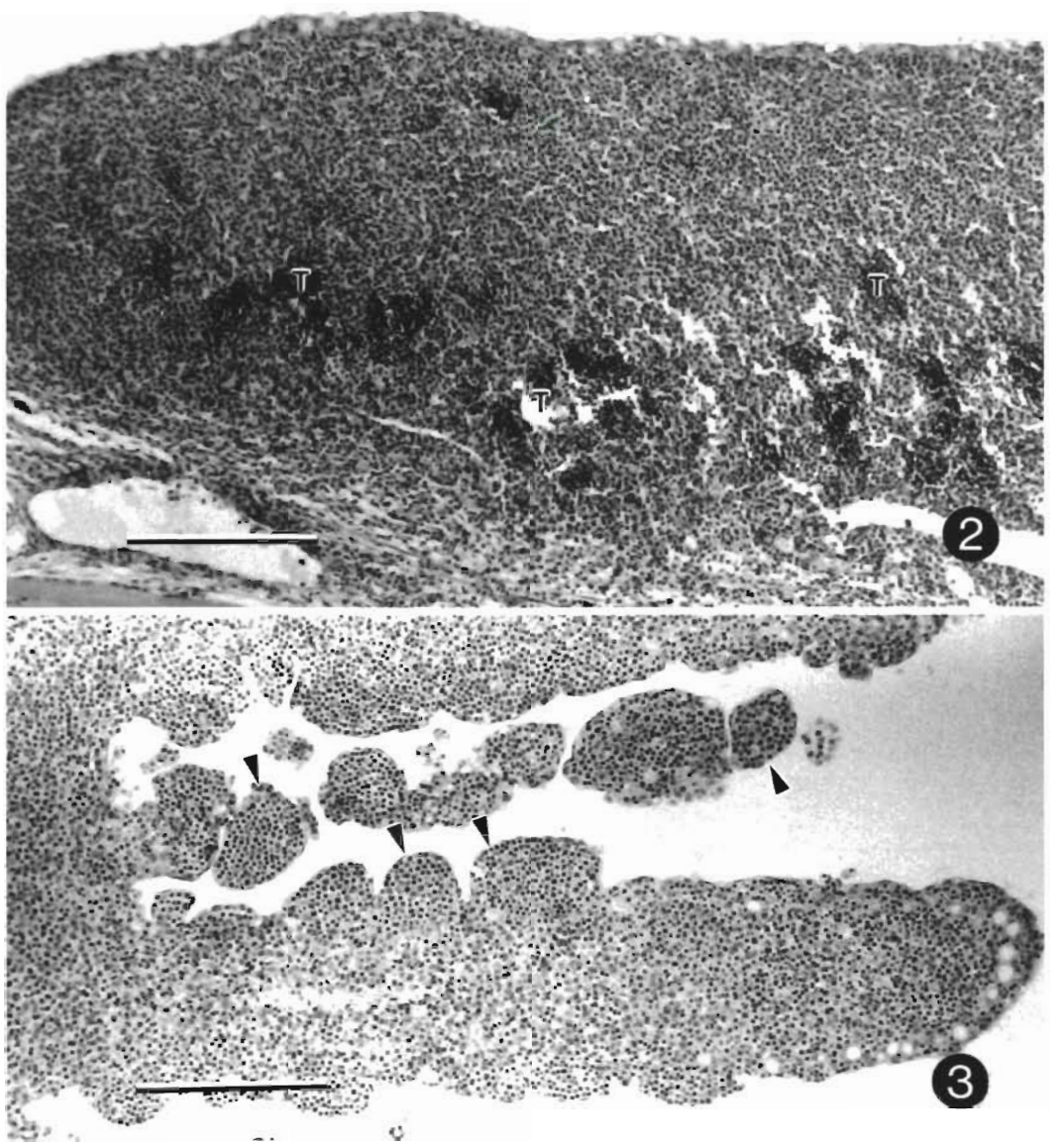

Fig. 1. *Oncorhynchus kisutch*. Comparison of monthly mortalities in cumulative percent for coho salmon from each brood year between 1984 and 1987 at the Big Qualicum Hatchery, B.C., Canada. Brood years 1985 and 1986 exhibited a lymphoblastic lymphoma; brood years 1984 and 1987 were unaffected

tetracycline and bath treatments of malachite green and formalin as required. Despite the treatments, the parasite load increased and the bacterial gill disease became more severe even after a Chloramine T bath.

### Light and electron microscopy

Histological examination of moribund fish revealed a marked increase in cellularity in the thymus, the integument of the opercular cavity, and the skin around the eyes and nares due to proliferation of apparently neoplastic lymphoid cells. The thymus, followed by the gills, was the principal organ affected. The thymus was affected in all fish examined, whereas the gills were affected in 76.6% (38/44) of the fish. The thymus was enlarged, the enlargement being correlated with the severity of proliferation of the neoplastic cells. In severely affected thymuses, only small islands of more typical, basophilic lymphocytes remained (Fig. 2).

The primary and secondary gill lamellae were distended due to invasion by, and proliferation of, the neoplastic cells (Fig. 3). Primary lamellae were often obscured, and there was diffuse infiltration of the cells




Figs. 2 and 3. *Oncorhynchus kisutch*. Thymus and gill of coho salmon with lymphoblastic lymphoma. H & E, bar = 200 µm. Fig. 2. Enlarged thymus with massive proliferation of neoplastic cells. Note nest of normal thymocytes (T). Fig. 3. Gill with massive proliferation and invasion of neoplastic cells. Note complete obliteration of lamellar spaces and discrete nests of cells (arrowheads)

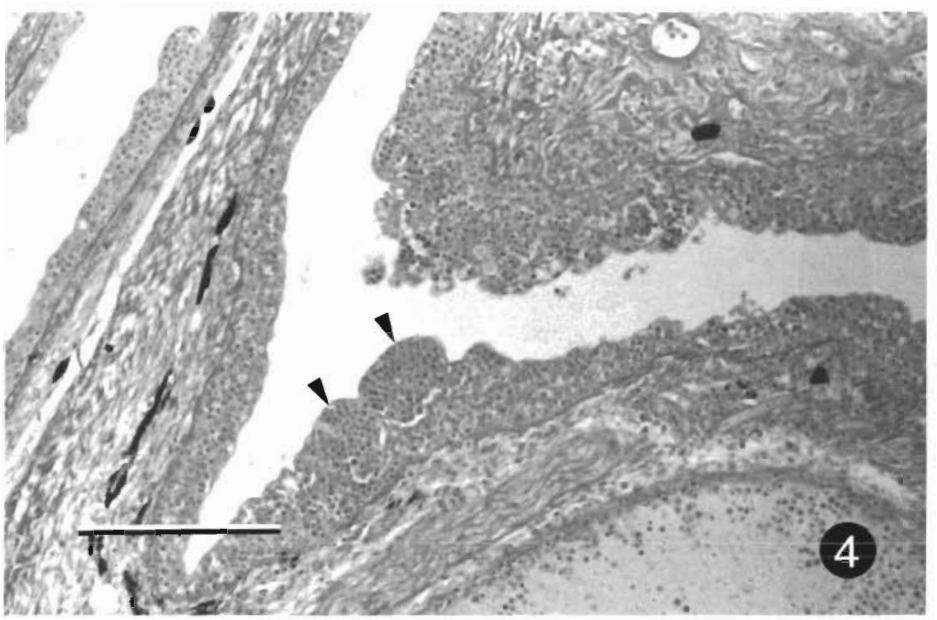



Fig. 4. *Oncorhynchus kisutch*. Skin surrounding conjunctiva from a coho salmon with lymphoblastoma. The neoplastic cells have diffusely invaded the epithelium and also occur in discrete nests (arrowheads). H & E, bar = 200 µm

into the epithelium of the secondary lamellae, causing occlusion of the lamellar spaces. In addition, the neoplastic cells also occurred in distinct, focal aggregates that were delineated by distended epithelial cells.

The pseudobranch, the adjacent muscle, and connective tissue were rarely invaded. The integument of the opercular cavity and the skin around the nares and eyes showed a similar pattern to that of the gills: diffuse infiltration of the epithelium and formation of distinct nests of neoplastic cells that were delineated by epithelial cells (Fig. 4).

The neoplastic cells were usually oval and had a moderate amount of finely granular eosinophilic cytoplasm with centrally located nuclei (Fig. 5). The cells were pleomorphic and ranged in morphology from large blastoid cells with distinct nucleoli to smaller, apparently more mature, lymphoid cells with deep staining nuclei and inconspicuous nucleoli. The nuclei, particularly in larger cells, were occasionally cleft. Some larger cells were also multinucleated.

Ultrastructural examination of gill tissue supported the light microscopic observations (Figs. 6 & 7). Aggregates of the lymphoid cells infiltrated the epithelium of the secondary lamellae. The cellular aggregates were delineated by the overlying epithelium and by the basal lamina of the capillaries. There was apparently no invasion into the capillaries. No cellular junctions (desmosomes) were observed in the lymphoid cells. The cytoplasm of these cells contained sparse mitochondria and abundant rough endo-

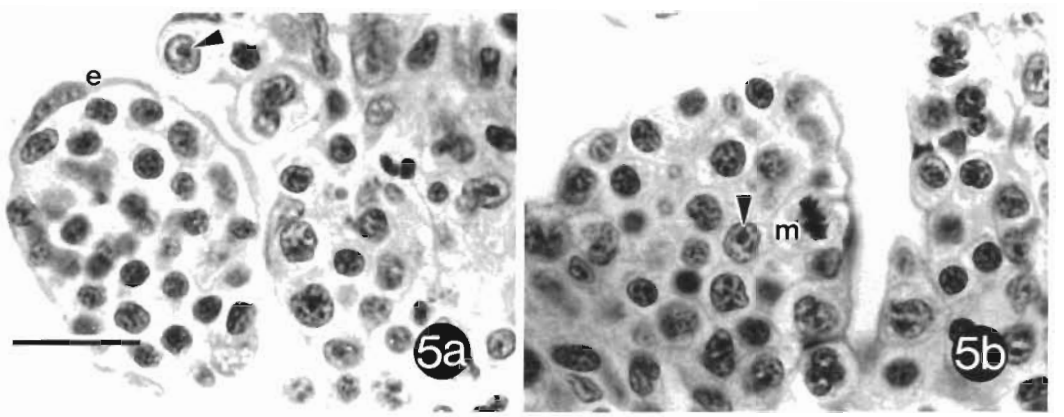
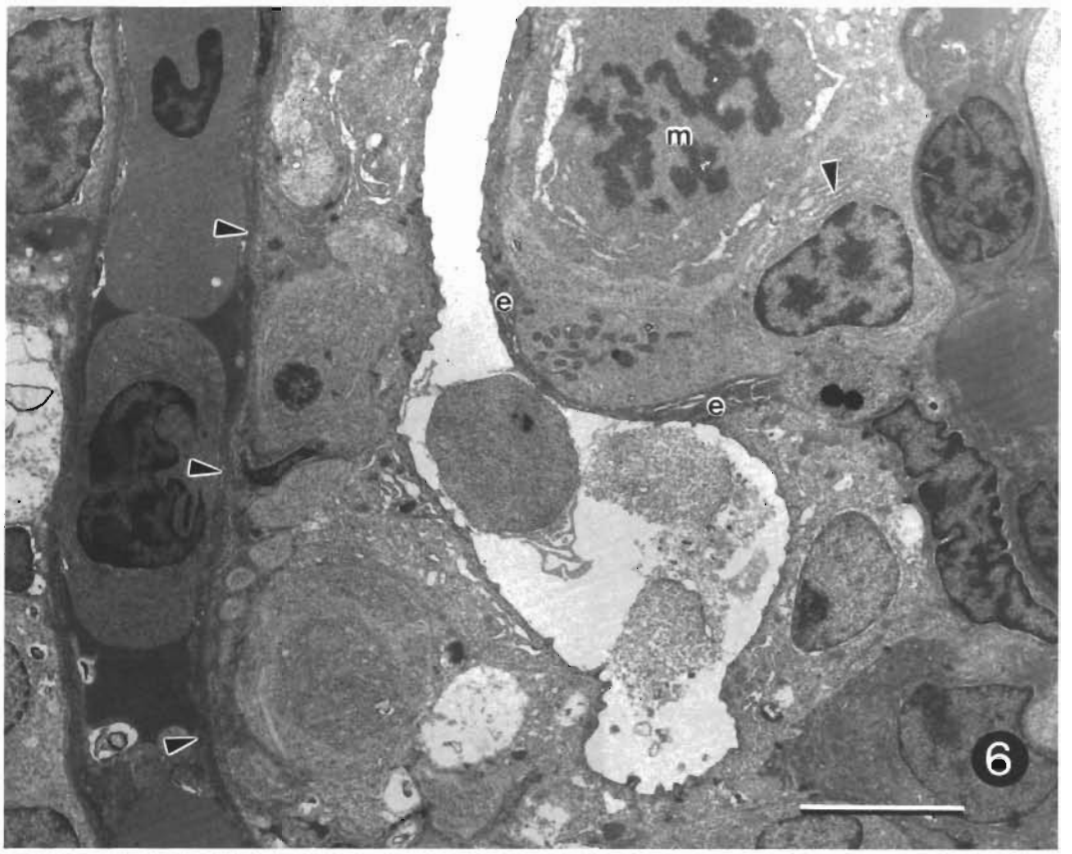
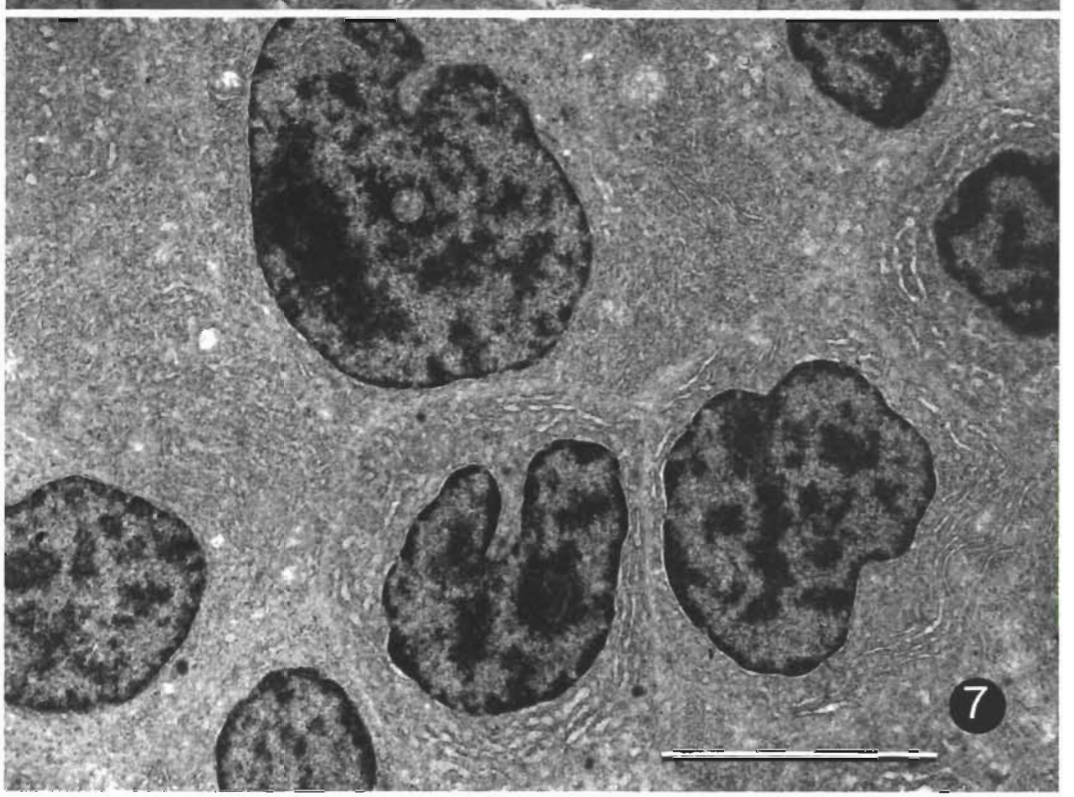



Fig. 5. *Oncorhynchus kisutch*. Neoplastic lymphocytes in the gill epithelium. Cells have moderate to abundant cytoplasm, central nuclei, and occasionally contain nucleoli (arrowheads). H & E, bar = 20 µm. (a) Nodule of neoplastic cells delineated by the gill epithelium. e: gill epithelial cell. (b) m: neoplastic cell in mitosis




Figs. 6. and 7. *Oncorhynchus kisutch*. Electron micrographs of gill from a coho salmon with lymphoblastic lymphoma. Bar = 5 µm. Fig. 6. Lymphocytes are proliferating between surface epithelial cells (e) and basal lamina of the gill capillary (arrowheads). m: neoplastic cell in mitosis. Fig. 7. Neoplastic cells in the gill epithelium. Note abundant rough endoplasmic reticulum, and central, cleft nuclei

plasmic reticulum (RER) that was often arranged in parallel arrays with mild to moderate distention of the cisternae. Golgi zones were not apparent. As observed by light microscopy, the nuclei were centrally located and were oval or cleft, the nucleoli were seldom evident, and the chromatin was distributed in a pachychromatic pattern. No particles suggestive of viruses were detected in or around the neoplastic cells.

### Seawater challenge

Prior to release, groups of fish were tested for their ability to osmoregulate in salt water. Table 1 shows a comparison of the smolts of an affected brood year with those of the normal brood year. Upon seawater challenge the affected fish had considerably higher losses than smolts from an unaffected brood year. In addition, mean plasma sodium in the affected fish was higher than in the smolts from an unaffected brood year in which values considered normal for coho smolts were observed (Clarke & Blackburn 1978).

## DISCUSSION

The impact of the disease on the Big Qualicum coho stocks prior to release from the hatchery during the 2 years in which losses occurred was severe. Losses in the affected brood years (1985 and 1986) totalled 12% and 45%, respectively. These pre-release losses must be compared to the 5% and 2% losses experienced with the brood years 1984 and 1987, respectively (Fig. 1). High mortality upon seawater challenge (Table 1) indicated that the 1986 year class fish had impaired osmoregulatory capabilities (Wedemeyer et al. 1980). Clarke & Blackburn (1978) compared blood sodium levels after seawater challenge for coho salmon from a number of hatcheries and streams. They concluded that hatchery-reared coho can adapt well to seawater if their blood sodium concentrations at testing are below 170 mmol $l^{-1}$. The levels observed in the affected fish, therefore, indicate that the osmoregulatory capabilities of these fish were compromised. It is likely that the 1986 brood year experienced considerable additional losses after their release to seawater.

The consistent occurrence and severity of the thymic and gill lesions, and the lack of other pathological changes or infectious agents, strongly indicates that the lesions were the primary cause of the morbidity observed in the coho salmon. The disease was diagnosed as lymphoblastic lymphoma of thymic origin. Some proliferating cells exhibited characteristics of lymphoblasts that appeared to originate in the thymus. The disease was judged to be a neoplasia, in contrast to a reactive lymphoblastosis, because the cells were morphologically immature, there was little other inflammatory involvement or necrosis, and the lesions were invasive and persistent. Furthermore, the fish continued to die until release from the hatchery, suggesting that the condition was progressive and irreversible.

Numerous thymic lymphomas have been described from fishes (Okihiro & Hinton 1989, Battalora et al. 1990, Harada et al. 1990, Fredrickson et al. 1991), including salmonids (Dunbar 1969, Meyers & Hendricks 1983, Bernstein 1984, Warr et al. 1984). These lymphomas differ from the neoplasm described here in several respects. The previously described thymic lymphomas were generally characterized by large, macroscopically visible masses that occasionally invaded the anterior kidney and other adjacent organs. In contrast, the lymphoma described here did not form distinct macroscopically visible masses but exhibited instead a distinct epithelial tropism without involvement of the visceral organs. In addition, in contrast to the neoplastic cells observed in the coho salmon, previously described thymic lymphomas were comprised of monomorphic lymphocytes. The abundant RER in the neoplastic cells described in the present report is also unique for thymic lymphomas in fishes and suggests affinities of the cells

Table 1. *Oncorhynchus kisutch*. Seawater challenge results comparing the 1986 and 1987 brood years. The lymphoma condition occurred in the 1986 brood and was absent in the 1987 brood

| Brood year<br>Sea water challenge: | 1986<br>May 1988 | 1987<br>May 1989 |
|---|---|---|
| Number challenged | 329 | 252 |
| Mortality during test | 64 (19.5 %) | 3 (1.2 %) |
| Mean plasma sodium of survivors (mmol $l^{-1}$)[a] | 182.1 | 165.6 |
| Fish with plasma Na below 170 mmol $l^{-1}$ | 28 % | 70 % |
| Mean fish weight (g) | 21.4 | 21.1 |

[a] Blood sodium levels of 170 mmol $l^{-1}$ or less are considered normal for well-smolted, hatchery-reared coho (Clarke & Blackburn 1978)

to plasma cells. Plasma cells have been reported in the thymus of many vertebrates, including fishes (Zapata 1981), and plasmacytoid cells have been identified in the T zones of human lymphoid tissue in both reactive and neoplastic conditions (Bieske et al. 1987). A plasmacytoid leukaemia has also been reported in chinook salmon in British Columbia (Kent & Dawe 1990, Kent et al. 1990). However, in the chinook disease, essentially all the visceral tissues were invaded by the proliferating cells and the thymus was unaffected. The lymphomas of pike were epitheliotropic (Mulcahy 1976, Sonstegard 1976, Thompson 1982). However, unlike the coho lymphoma, these neoplasms were characterized by macroscopically visible, raised, reddened dermal masses (Fredrickson et al. 1991).

In comparison to lymphomas of higher vertebrates, the coho lymphoma was most similar to mycosis fungoides of man and dogs (Greaves et al. 1988). Both diseases are markedly epitheliotropic, the neoplastic lymphocytes often being encapsulated in discrete nests by epithelial cells with little, if any, invasion into the circulatory system. Furthermore, both diseases may be of T-cell origin. The neoplastic cells are similar in morphology in that they have abundant, eosinophilic cytoplasm and occasionally indented nuclei. However, abundant RER is not characteristic in the neoplastic cells of mycosis fungoides.

The cause of the coho lymphoma was not determined, but the high prevalence of the disease may suggest an infectious etiology. Infectious agents have been indicated as the causes of several hemic neoplasms in fishes (Mulcahy & O'Leary 1970, Papas et al. 1976, Sonstegard 1976, 1979, Gross 1983, Harada et al. 1990, Kent & Dawe 1990), and they are well recognized as the causes of hemic neoplasms in higher animals. However, no infectious agent was consistently associated with the coho disease, and the bacteria, fungi, and protozoan parasites observed on some of the affected coho were probably secondary, opportunistic pathogens.

Hemic neoplasms may also be induced by chemical carcinogens, and lymphosarcoma was observed in channel catfish, *Ictalurus punctactus*, exposed to N-methyl-N'-nitro-N-nitroguanidine (Chen et al. 1985).

The only known anthropogenic contaminant that could have been associated with the coho disease was Tebuthiuron. This herbicide was sprayed in 1985 and 1986 in an area uphill from the affected channel. Circumstantial evidence suggests that use of the herbicide is followed by the disease, and when spraying of Tebuthiuron was discontinued the disease apparently disappeared. However, mass spectrometric tests done by a contract laboratory did not detect the chemical in the water during the occurrence of problem (unpubl.). Also this compound has not been recorded as inducing neoplasms in fish (NIOSH 1990).

In an attempt to study the progression of the disease within the stock, samples for histological evaluation were taken from the next year class (1987 brood year) on a monthly basis between July 1988 and January 1989 and then every second month until release time (unpubl.). However, no evidence of the proliferative disorder was seen in that year class and cumulative percent losses for that brood year totalled less than 2 % between August 1988 and the following May (Fig. 1). This again indicates that the disease was the major contributor to the high losses experienced in the 1985 and 1986 brood group.

While the coho were experiencing losses due to the lymphoma epizootic in the 2 year classes, chinook were also being reared at the Big Qualicum Hatchery. Chinook are reared for 90 d after hatching in contrast to the 18 mo rearing period for coho. During the period discussed above, histological evaluations of the chinook did not reveal any tissue changes suggestive of the disease.

If the disease recurs, we plan to conduct further studies, including transmission experiments, to determine whether the disease is caused by an infectious or chemical agent.

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