

Neoplasms in Fish (Review)

Mona S. Zaki¹, Hammam A. M.², Olfat Fawzy³ and Suzan M. Omar³

¹Hydrobiology Department, National Research Center, Cairo, Egypt

²Reproduction Department, National Research Center, Cairo, Egypt

³Biochemistry Department, National Research Center, Cairo, Egypt

dr_mona_zaki@yahoo.co.uk

Abstract: As more data regarding fish tumors becomes available, regulatory agencies will then be able to determine the magnitude of a particular epizootic. To deal with these issues it is important to know not only which species exhibit neoplasms but whether the prevalence is increasing or decreasing. The most obvious question to answer is whether there is a relationship between tumor formation and chemical exposure. Some field studies have already demonstrated a relationship between certain types of pollutants and the presence of certain kinds of neoplasia in fish, especially liver neoplasia, but in other types of neoplasia, very little information is currently available. Other questions, not without significance, deal with the effects of the tumor on the health of the fish, whether seasonal patterns of tumor occurrence exist, and the relationship between tumor frequency and age of the fish.

[Mona S. Zaki, Hammam A. M, Olfat Fawzy and Suzan M. Omar. **Neoplasms in Fish (Review)**. *Nat Sci* 2014;12(8):134-145]. (ISSN: 1545-0740). <http://www.sciencepub.net/nature>. 19

Keyword: Neoplasms, Fish, Pollution

Introduction

Chemical induction of cancer was first suspected in 1775 by Dr. Percival Pott, an English physician, who documented the occurrence of scrotal cancers in chimney sweeps exposed to soot ^[1]. One-hundred and forty years later, Yamagiwa and Ichikawa ^[2] demonstrated the first chemically induced tumors in rodents. Although neoplasms in fish were reported in the scientific literature before 1915, the concept of chemical induction of cancer in wild fish populations was slow to develop. It is interesting that the high prevalence of liver neoplasia found in brown bullheads and white suckers from polluted sites was not reported in the literature before 1960.

Fish have already served mankind as indicators of environmental carcinogens. The discovery of the extremely potent carcinogenic action of aflatoxin B1, a common mould metabolite, resulted when a nearly world-wide epizootic (epidemic) of liver cancer developed in hatchery-raised rainbow trout (*Oncorhynchus mykiss*) ^[3]. The liver cancers were ultimately traced to trout food pellets containing mould-contaminated cottonseed meal. Due to this largely accidental discovery, peanuts and other foods which the mould can easily infect are now stored under conditions which inhibit mould growth. In addition, the U.S. Food and Drug Administration routinely monitors some foods such as peanut butter for the presence of the mould metabolites.

Grossly, cholangiomas may appear as white or cream-colored foci to larger white or cream-colored nodules that may exceed several centimetres in diameter. They may or may not bulge slightly above the liver capsule and are difficult to detect from

external examination when they are embedded within the liver. Early stage neoplasms of hepatocellular origin may be similar to the bile duct tumors in gross appearance, i.e., as white or cream-colored foci, or they may appear as pale foci just beneath the liver capsule. More advanced tumors may appear as white, gray, cream-colored, or reddish-tan colored masses bulging from, or as nodules within, the liver tissue. On occasion they may be visible only by examination of the cut surface. Any liver that is enlarged, hemorrhagic, bile-stained, or in which a smooth capsular surface is absent, is suspicious.

Etiology

1-Chemical causes:

A variety of chemical etiological causes have been attributed to piscine carcinogenesis in the veterinary literature, including methylazoxymethanol acetate (MAM), N-methyl-N0-nitro-Nnitrosoguanidine (MNNG), dihydroepiandrosterone (DHEA), multiple aflatoxins, nitrosamines, and polynuclear aromatic hydrocarbon (PAH), and while these compounds have been primarily reported to induce hepatic tumors, there are several reports of nephroblastomas in association with a confirmed carcinogen. ^[4]

Other environmental studies examining epizootics of hepatocellular and biliary carcinomas in Brown bullhead catfish (*Ameiurus nebulosus*), ^[5-7] lake whitefish (*Coregonus clupeaformis*), ^[8] and English sole (*Pleuronectes vetulus*) ^[9,10] and exocrine pancreatic tumors in mummichog (*Fundulus heteroclitus*) ^[11] have also shown a direct correlation between water contaminants and neoplastic transformation in various target tissues.

Chemical carcinogens are suspected in the etiology of brown bullhead liver neoplasms^[12]. Tumor prevalence may exceed 25 percent in older fish living in chemically contaminated environments^[13]. There is strong circumstantial evidence linking the presence of liver neoplasms with exposure to polynuclear aromatic hydrocarbons^[12].

Chromatophoromas and related dermal neoplasms have been reported as epizootic in wild populations of several different species of fish. Freshwater drum (*Aplodinotus grunniens* Raf.) from five contaminated locations in eastern Lake Erie and the Niagara River had a significantly higher frequency of such tumors than did drum from reference areas^[12]. However, tumor frequency varied greatly among the five polluted sites, weakening the evidence for a chemical etiology. Elevated chromatophoroma frequencies also occurred in two oceanic drum, nibe (*Nibea rnitsukurii* (J. & S.) and koichi (*Nibea albiflora* (Rich.) collected from polluted coastal waters of Japan^[14]. Furthermore, Kimura *et al.*^[14] induced chromatophoromas in drum with both N-methyl-N-nitro-N-nitrosoguanidine (MNNG, in the diet) and 7,12-139 dimethylbenz (a) anthracene (DMBA) (injection). Chromatophoromas have also been reported in certain populations of Hawaiian butterfly fish (*Chaetodon multicinctus* Garrett and *Chaetodon miliaris* (Q. & G.)) at frequencies up to 50 percent and 5 percent respectively^[15]. The author speculated that chemical runoff from agricultural acreage could have been a causal factor. Liver neoplasms have been more strongly associated with environmental carcinogens than any other group of lesions. Thirteen different species, all bottom feeders, have been reported to exhibit epizootics of liver tumors in association with sediment contamination in North America^[16]. One long term series of studies has focused on liver neoplasia in English sole (*Pleuronectes vetulus* (Gir.)) from different regions within Puget Sound, WA^[17]. Concentrations of both organic and inorganic contaminants in sediment and associated liver tumor frequencies in English sole were determined from 43 sites which were combined into 19 geographic sub-areas based upon analysis^[18]. English sole with the highest frequencies of liver neoplasms were taken from the Duwamish Waterway (16%, N = 136) and Everett Harbor (12%, N --- 66); frequencies of hepatic neoplasia in sole from other areas ranged from 0 to 5.5 percent. Only sediment concentrations of PAH were significantly correlated with the frequency of liver neoplasms in English sole. Concentrations of metals, as a group, significantly correlated with total (including non-neoplastic) hepatic lesions^[18]. Chlorinated hydrocarbon concentrations were not correlated with frequencies of either neoplasms or total hepatic lesions. Later studies

at two other Puget Sound locations heavily contaminated with PAH found English sole at these sites also had an elevated incidence of liver neoplasms. English sole from Mukilteo had a 7.5 percent incidence of hepatic neoplasms and a 16.7 percent incidence of areas of cellular alteration^[19], while those from Eagle Harbor had an incidence of 27 percent and 44 percent respectively, for these same lesions^[20]. Brown bullhead from eight different areas in North America have been reported as having epizootics of liver tumors^[16]; most of these locations are known to feature carcinogens in the sediments. One of the most studied locations is the Black River, Ohio which features high concentrations of PAH in sediment^[21] and fish^[13]. During a three year study (1980-- 1982) grossly visible liver tumors occurred in less than 2 percent of age 2 fish, 11 percent to 16 percent of age 3 fish, and 28 percent to 44 percent of age 4 fish^[15]. Histopathology of a randomly collected sample of these fish in 1982 (N = 125) found liver neoplasm frequencies (biliary and hepatic combined) of 56 percent for age 3 fish and 62 percent for age 4 fish^[22]. Furthermore, an additional 23 percent of the age 3 fish and 19 percent of the age 4 fish had livers with areas of hepatocellular alteration. Bullheads of ages 4 and 5 combined had a significantly greater incidence of biliary carcinomas than those of ages 2 and 3 combined^{[11][22]}. No grossly visible liver tumors were found in bullhead from two reference locations, Buckeye Lake (N -- 80) and Old Woman Creek (N = 144). Similarly, brown bullhead from Lake-of-the-Woods, Ontario (N -- 101) had less than a 2 percent liver tumor incidence^[23]. The correlation between sediment PAH and liver cancer in brown bullhead (Black River) and English sole (Puget Sound) seems indicative of a cause and effect relationship^[17,22]. Other fish species in which liver epizootics have been documented from a number of different locations include the white sucker and the winter flounder (*Pleuronectes americanus* Walb.)^[16]. As was true for brown bullhead, most of these epizootics were reported from polluted locations, although evidence for the role of PAH is less compelling. For instance white suckers collected from Lake Ontario had, in general, higher frequencies of liver neoplasia near urban industrialized areas than from rural reference locations with the highest incidence (7.4%) occurring in Sixteen Mile Creek near the industrialized Burlington-Oakville area of Ontario (V.W. Cairns, Department of Fisheries and Oceans, Burlington, Ontario, personal communication).

Similarly, winter flounder from Boston Harbor (N = 200) has a 10 percent incidence of preneoplastic and neoplastic hepatic lesions whereas no such lesions were found in 93 winter flounder from unpolluted locations along the coast of North America and

offshore on Georges Bank ^[24]. A cause and effect relation between carcinogenic contaminants and liver neoplasia in wild populations of fish has been bolstered by the experimental induction of liver tumors in fish using a variety of known carcinogens including two PAHs, DMBA and B(a)P ^[25,26]. DMBA was shown to induce liver tumors in *Poeciliopsis lucida* Miller and *P. monacha* Miller ^[27] and in the guppy (*Poecilia reticulata* Peters) by Hawkins *et al.* ^[28]. B(a)P was shown to induce liver tumors in both the guppy and the Japanese medaka (*Oryzias latipes* (T. & S.)) through waterborne exposure ^[29] and in the rainbow trout (*Oncorhynchus mykiss* (Walb.)) following dietary exposure and intraperitoneal injections ^[30]. Also Metcalfe *et al.* ^{[120]31} succeeded in including liver tumors in rainbow trout by injecting sac fry with extracts of contaminated sediment from Hamilton Harbour, Ontario. Similarly Black *et al.* ^[26] induced both hepatic and biliary neoplasms in brown bullhead fed commercial trout food to which sediment extracts from the PAH-contaminated Buffalo River, New York had been added. That hepatic neoplasms indistinguishable from those found in wild fish exposed to PAH contaminated sediment could be induced in a laboratory setting provides strong support for the usefulness of liver cancer as an indicator of ecosystem health.

2. Viral and multifactorial

OllcorhYllchus mlISOU virus (OMV) is a fish herpesvirus isolated from the ovarian fluid of landlocked masu salmon ^[31] and has a pathogenicity against the fry of masu salmon and several salmonid fish. In particular, masu, chum (*O. keta*) and kokanee salmon (*O. nerka*) usually exhibited high susceptibility with more than 80% of the fry dying within 4 months after infection ^[32]. Affected fish became dark and occasionally had severe exophthalmia and hemorrhage under the jaw before death, the kidney was pale and multiple white spots were observed on the liver^[31].

The oncogenic nature of OMV was first noticed in tumors of chum salmon which survived OMV infection at 130 days after infection, and the rate of tumor induction reached about 60% at 250 days post-infection. The most frequent site for tumor formation was above the mouth and, in decreasing frequency, the caudal fin, opercula and corneas of the eyes and one of the 52 fish was found to have had a renal tumor at 10.5 months after infection ^[33].

Some tumor epizootics are known to have a viral etiology, including lymphoma in northern pike (*Esox lucius* L.) and muskellunge (*Esox nrasquinongy* Mitch.). Lymphoma affect both of these species in pristine environments in North America and (in the case of the northern pike) in Europe ^[34-38]. The transmission of lymphoma with cell-free extract ^[36, 39,40] and the occurrence of reverse transcriptase ^[41,42]

strongly support a viral etiology for this condition in esocids. Herpesvirus have been implicated as the cause of some papillomas in carp^[43] and Yamame salmon (*Oncorhynchus masou* Brev.) ^[44], because of successful infection and papilloma induction by cell-free extract. Dermal sarcomas (fibroma/ fibrosarcoma) of walleye (*Stizostedion vitreum* (Mitch.)), had been found to contain retrovirus-like type-C particles ^[45], and occur in fish collected from a variety of pristine habitats, thus suggesting a purely viral origin. Recently this neoplasm was successfully transmitted by inoculating fingerling walleye with cell-free filtrates of sonicated tumor cells ^[46]. In two of the seven fingerlings successfully inoculated, C-type virus particles were identified budding from tumor cells. This evidence strongly supports a retroviral etiology for these neoplasms. Viruses have also been isolated from European eels (*Anguilla anguilla* (L.)) with oral epidermal papillomas ^[47,48]. However, no one has successfully transplanted either of these skin lesions, or induced them by injections of tumor homogenates or ultrafiltrates ^[49]. Thus viruses have not been demonstrated as the sole causative agent for oral papillomas in European eels ^[16], and a multifactorial origin for the lesions have been suggested ^[49]. Virus particles have also been associated with other lesions in fish, although their role, if any, in the etiology of those lesions is unknown. Viruslike particles had also been reported in the papil-137 lomas of white suckers (*Catostomus commersoni* (Lacép.))^[50]. However, the electron photomicrograph used in that paper was apparently mislabeled, since it was later republished ^[36] as depicting virus-like particles in a northern pike epidermal hyperplastic plaque ^[16]. Subsequent research failed to identify viruses in white sucker papillomas ^[51]. However, white suckers kept in presumably unpolluted well-water developed epidermal papillomas, and some papillomas and plaques in this species have the capability to regress ^[52]. Surveys of white sucker in Canadian nearshore waters have noted a correlation between pollution and papilloma incidence. One series of surveys encompassing 13 locations in Lake Ontario and 7 locations in Lake Huron revealed the highest papilloma frequencies in white sucker from Toronto, Hamilton Harbour, and other contaminated locations, while a population located in northern Lake Huron had less than a one percent incidence of such lesions (V.W. Cairns, Department of Fisheries and Oceans, Burlington, Ontario, personal communication). Another series of surveys also revealed a greater frequency of external lesions in white sucker from polluted versus reference locations ^{[96]53}. In these fish gross lesions defined as both plaques and papillomas displayed a continuum from mild hyperplasia to carcinoma. However, frequencies of papillomas even

in supposed reference locations were sometimes high in both surveys. This might reduce the usefulness of such tumors as a marker of contaminants, or at least suggests that a multifactorial etiology, involving both chemical pollutants and viruses, best explains the available data^[53].

Elevated frequencies of epidermal papillomas in brown bullhead (*Ameiurus nebulosus* (Lesueur)) were first reported in the early 1940's^[54]. The several hundred normal bullhead and 166 tumor-bearing fish examined were all collected from streams near Philadelphia^[55] and most were taken from the Delaware and Schuylkill Rivers^[54]. Tumors were diagnosed as epidermoid carcinomas because in the author's opinions the smaller, less invasive tumors were 'early stages of a neoplastic process which later assumes a more malignant character'^[55]. Both the Schuylkill and Delaware Rivers near Philadelphia would be expected to have polluted areas in the 1930's and 1940's as well as today, and epidermal papillomas were still found on bullhead from these locations in the 1980's^[56], suggesting a role for chemicals in the etiology of brown bullhead papillomas. A role for chemicals in the development of papillomas in black bullhead (*Ameiurus melas* Raf.) has also been suggested. Grizzle *et al.*^[57] reported that black bullhead from a 2-acre final sewage oxidation pond in Alabama had a 73 percent incidence of oral papillomas, much higher than in reference populations. Healthy black bullhead placed in cages in the pond also developed oral papillomas^[58]. No viruslike structures were found in papillomas examined with TEM, and an injection of cell-free tumor homogenate failed to transmit papillomas into healthy black bullhead^[59]. However, the frequency of papillomas in wild pond bullhead decreased from 73 percent in 1979--1980 to 23 percent in March of 1983; this was associated with an approximately 1/3 reduction in chlorination in November, 1979. Linear regression analysis of tumor prevalence by sample date indicated a significant decline ($P < 0.01$) in papillomas after the decrease in chlorine. The authors state that their data indicate 'a reduction in the carcinogenicity of the pond environment' following the reduction in chlorine^[58]. More recently brown bullhead from several polluted locations have also been reported with lip and skin neoplasms. The incidence of such neoplasms varied among years in fish from the Black and Buffalo Rivers. Some of the external tumors in bullhead from both Hamilton Harbour^[53] and the Black River^[13] were diagnosed as carcinomas, although papillomas dominate and many of these may not progress into neoplasms. To my knowledge no attempt has been made to demonstrate a viral etiology for bullhead papillomas, although one of the reference locations, Long Point Bay, also had

bullhead with an elevated rate of external neoplasms^[53] suggesting a possible role for virus as well as pollution. Black^[25] painted the skin of brown bullhead with an extract of Buffalo River sediment, which contained elevated concentrations of polynuclear aromatic hydrocarbons (PAH). Papillomas developed in 8 of 22 surviving fish after two years, while fish painted only with solvent remained essentially normal. In a related experiment mice were painted with extracts of sediments from the Buffalo and Black Rivers^[26]. The percentage of mice developing tumors was 30 when treated with 2 percent Buffalo River sediment extract, and 80 when treated with a 2 percent Black River sediment extract; none of the solvent (Acetone) control group developed tumors, while treatment with a 200 #g ml⁻¹ benzo (a) pyrene (B(a)P) positive control yielded a 64 percent tumor rate. These experiments strongly support a role for sediment carcinogens in the development of epidermal neoplasms in fish.

3. Genetic susceptibility

Some fish species and hybrids appear to be genetically susceptible to neoplasms. Platyfish x swordtail (*Xiphorus*) hybrids are predisposed to melanoma formation^[60].

Gonadal tumors reported in common carp x goldfish (*Cyprinus carpio* L. x *Carassius auratus* (L.)) hybrids from the Great Lakes^[61,62] might also have a genetic basis^[16,63]. Additional support for the genetic hypothesis in cyprinid gonadal tumors is the high frequency of ovarian tumor reported in ornamental carp, which are a product of repeated inbreeding in Japan^[64]. Carcinogens were not believed to be part of the etiology for these tumors because the fish were raised in water from mountain wells or springs^[65]. Similar tumors have also been reported in common carp x Crucian carp (*Carassius carassius* (L.)) hybrids collected from the Arrbcampo, a reservoir used to cool the Almaraz Nuclear Power Station in Spain^[66]. The unique genetic status of hybrids generally makes them unsuitable for monitoring ecosystem health. Epizootics of cancer in non-hybrid wild fish populations are less likely to have a purely genetic basis. The 13 benthic species which were listed by

Harshbarger & Clark^[16] as having had liver tumor epizootics have all had populations from unpolluted areas documented with tumor frequencies below 1 percent. This low tumor rate suggests that a purely genetic origin for more elevated tumor frequencies in these wild populations of non-hybrid fish is unlikely.

Epizootics have been recorded from relatively unpolluted locations, however, and for some of these a potential causative agent has not been identified. These examples, such as the liver, skin, and neural tumors in brown bullhead from Silver Stream

Reservoir, N.Y. [16], might seem to fit a genetic origin hypothesis, particularly if subpopulation inbreeding or hybridization are invoked. However, brown bullhead from Silver Stream have been diagnosed with at least four neoplasms from different cell types: hepatocarcinoma, cholangiocarcinoma, schwannoma, and squamous carcinoma. Such a diversity of tumors is not consistent with the genetic model, in which a single type of tumor should result [67]. Thus an external agent responsible for initiating tumors in brown bullhead from Silver Stream and similar locations is probably non-detected rather than non-existent.

Types of tumors in Fish

Neoplasms of the Urinary Tract in Fish

The veterinary literature contains scattered reports of primary tumors of the urinary tract of fish dating back to 1906. Many of the recent reports have been described in association with the RTLA, and the vast majority of the spontaneous neoplasms of the kidney and urinary bladder are single case reports. In rare instances, such as described in nephroblastomas of Japanese eels (*Anguilla japonica*) and tubular adenomas/adenocarcinomas of Oscars (*Astronotus ocellatus*), there is suggestion of a genetic predisposition of certain populations to specific renal neoplasms, environmental carcinogenesis, or potentially an unknown infectious etiology acting as a promoter.

Primary renal neoplasia in higher vertebrates and fish is predominantly classified into two forms, nephroblastomas and some variant of adenocarcinomas.

Japanese eels and, to a lesser extent, rainbow trout (*Oncorhynchus mykiss*) represent greater than 50% of all individual cases, but 16 distinct species of fish have been reported with nephroblastomas. The second largest group of spontaneous renal neoplasms consists of the epithelial tumors comprising various subtypes of benign adenomas and approximately equal numbers of adenocarcinomas. All told, these have been described in 17 diverse species and are typically believed to arise from terminally differentiated tubular epithelium.

Retroviruses have been associated with tumor formation in an ever expanding cohort of species, as have reports of DNA viruses such as herpesvirus, papovavirus, and adenovirus. [68-71]. One of the most comprehensively researched species-specific epizootics of piscine tumors are the damselfish neurofibromatosis and chromatophoromatosis, which have been associated with retroviruses [72,4]. Examples of similar outbreaks associated with retroviral etiologies include lymphomas in muskellunge (*Esox masquinongy*) [73], northern pike (*Esox lucius*) [74], and madai (*Pagrus major*), as well as epidermal tumors in

white sucker (*Catostomus commersoni*) [75], walleye (*Sander vitreus*) [76] and smelt (*Osmerus mordax*) [68]. While none of these are associated with renal-specific targeting for carcinogenesis, there have been several reports of primary renal and metastatic lymphomas associated with retroviral neoplastic transformation.

Salmonid herpesvirus type 2, colloquially known under a variety of names, such as Yamame tumor virus, Coho salmon herpesvirus, rainbow trout kidney virus, and Nerka tumor virus, among others, has been reported to form renal epithelial tumors in masu salmon (*Oncorhynchus masou*), sockeye salmon (*Oncorhynchus nerka*), chum salmon (*Oncorhynchus keta*), Coho salmon (*Oncorhynchus kisutch*), and rainbow trout, but the primary tumors are typically found within cutaneous tissues [70]. The virus causes age- and isolate correlated high rates of mortality, with experimentally infected rainbow trout having rates ranging from 34% to 77% mortality.

In surviving salmonids, tumors may develop in up to 100% of infected fish within a population [77]. Additional tumor associated herpesviruses that result in systemic disease include Herpesvirus cyprini, herpesvirus of Japanese flounder, and epizootic epitheliotropic disease virus of lake trout (*Salvelinus namaycush*). [78]

With the exception of lymphoma, nephroblastomas represent the most common primary renal neoplasm in fish, having been reported in both spontaneous and carcinogen-induced instances and affecting a wide variety of fish species.

Epizootics of spontaneous nephroblastoma have been reported in over 60 Japanese eels [79,80], while individual cases have been reported in European eels (*Anguilla argentina*), striped bass (*Morone saxatilis*), [81] koi (*Cyprinus carpio*) [82], Crucian carp (*Carassius carassius*), [83] Japanese dace (*Tribolodon hakonensis*), [84] smelt [85], Siamese fighting fish (*Betta splendens*) [86], sockeye salmon (RTLA), rose bitterling (*Rhodeus ocellatus*), [87] banded cichlid (*Heros severus*) [88], and rainbow trout [89-92]. While a definitive correlation to a specific etiology resulting in the high incidence of nephroblastomas in the Japanese eel has not been proven, one unpublished report suggested the presence of virions in correlation with an eel affected with a concurrent nephroblastoma [93].

The carcinogen theory is consistent with extensive research conducted in rainbow trout, which have been demonstrated to undergo neoplastic transformation to nephroblastoma when experimentally exposed to both dimethyl nitrosamine (DMN) and N-methyl-N0-nitro-N-nitroguanidine (MNNG) [94]. Furthermore, studies examining the environmental impact of MAM have produced neoplastic transformation in several visceral organs in a variety of species, including guppies (*Poecilia*

reticulata), zebrafish (*Danio rerio*), and medaka (*Oryzias latipes*).

The predominant populations of neoplasms were concentrated within the liver of each individual species, but medaka produced rare nephroblastomas when exposed to the carcinogen^[95]. While the clinical presentation in reported cases varies, several examples in the literature displayed some form of vertebral pathology, such as lordosis, combined with coelomic enlargement. The gross presentation also typically includes organ displacement and the presence of a large, firm, pale, frequently unencapsulated mass. Nephroblastomas vary in size from small protuberances within the kidney tissue of less than half a centimeter in diameter to large growths, attached to the dorsal body wall, displacing the abdominal viscera. The biggest nephroblastoma in the RTLA collection occurred in a 32-cm long rainbow trout and measured 7 _ 8.5 cm. Most descriptions indicate the surface of trout nephroblastoma to be smooth, sometimes lobulated, and grayish to darkly pigmented. On cut section, the neoplasms are frequently white to pale beige and either firm and often granular or cystic in texture. Tissue of origin also varies between species, with all incidents in Japanese eels arising exclusively from the posterior aspect of the kidney.

Considering the variety in anatomic structure of fish kidneys, the nephroblastomas are strictly limited to the genesis within the posterior kidney in all fish, but it stands to reason that those species with an anterior kidney predominantly composed of hematopoietic and endocrine tissues are overwhelmingly reported to have nephroblastomas developing in the posterior kidney. Predominantly, nephroblastomas in fish appear to be locally aggressive, expansile, and frequently cystic but rarely metastasize to distant sites. However, the reports in Crucian carp, Japanese dace, rainbow trout, and Japanese eels have described metastases to distant organs within affected animals^[96].

Nephroblastomas have been experimentally induced through administration of 2 different nitroso compounds. In the first of these experiments, rainbow trout were fed doses of dimethylnitrosamine ranging from 7 to 1920 mg/100-g dry diet in their daily ration for 12 to 20 months^[97]. These various exposures to dimethylnitrosamine resulted in a 1% incidence of nephroblastoma in the survivors. Another study found that juvenile rainbow trout injected with either single or repeated intraperitoneal doses of 100 mCi of Iodine 131 had an increased incidence of nephroblastoma formation^[97,98].

MNNG-induced nephroblastomas have been experimentally associated through treating both embryonic and near-adult stages of rainbow trout. In 1

study, MNNG was administered by stomach tube to 12- to 15-month-old fish, and nephroblastomas of macroscopic size were observed within 12 months^[99]. In another study, rainbow trout embryos were incubated in water containing 10 ppm MNNG for 24 hours at 10_C. In this instance, a nephroblastoma measuring approximately 4.5 cm was observed at 9 months following carcinogen exposure. The cumulative frequency of nephroblastoma in an effective group of 122 survivors was 7.5% with the peak of tumor incidence occurring at 15 months postexposure.⁴⁵ Further investigations have induced nephroblastomas in embryos after a single hour of MNNG exposure^[100].

Epithelial Tumors in Fish

There are only rare reports of spontaneous renal tubular cell tumors in the literature occurring in fish, and many of those that do appear range from a century ago. In 1911 and again in 1924, cystic adenocarcinomas were described in silver eels^[101,102]. Other early reports include a benign renal tumor in a catfish composed of neoplastic cells forming acini and papilliferous projections into cystic spaces, suggestive of a renal papillary cystadenoma^[103] and a similar spontaneous tumor that was described in the mesonephric duct epithelium of a Chinook salmon^[96].

Single case reports can also be found in goldfish, catfish^[103], Mozambique tilapia (*Oreochromis mossambicus*)^[88], and yellow or spotted seahorses (*Hippocampus kuda*)^[104]. Furthermore, a review of the RTLA archives revealed submission of a renal papillary cystadenoma in a winter flounder (*Pleuronectes americanus*), as well as references to similar tumors in a Tiger barb (*Barbus tetrazona*) and in a penguin tetra (*Thayeria obliqua*)^[105].

Renal Cystadenoma/Renal Tubular Adenoma.

Oscars appear to have a predisposition for some variant of renal adenomas, which have recently been determined to be of proximal tubular origin. There has been some debate on the cell of origin of these neoplasms, with the first having been described in 1996 but without proffering a definitive diagnosis at the time^[106]. In that case, the mass, which was composed of mildly pleomorphic epithelial cells forming papillary projections into cystic regions, significantly effaced the renal parenchyma. While determined to be locally expansile and potentially regionally aggressive, there was no evidence of malignancy, and the authors proffered a more benign categorization of the mass, with a favored diagnosis of an epithelial papilloma of mesonephric duct origin^[106].

There are individual case reports of renal adenomas scattered in the literature, including examples in a tilapia (*Sarotherodon spilurus*)^[107], Chinook salmon,^[96,108] brown bullhead^[103], rainbow trout, 50 and northern pike^[109] with experimentally

induced adenomas in zebrafish and medaka. For the most part, these are described as renal cystadenomas or papillary cystadenomas; however, the RTLA archives include examples of diagnoses of papillomas in various levels of the urinary tract.

A population of Crucian carp was affected by an epizootic of renomegaly. Upon necropsy, several of the animals were found to have renal adenomas as well as a high percentage of polycystic kidneys.^[110]

Lymphoma/Leukemia

Hematopoietic tumors of the kidneys of fish are described with some frequency in comparison with other types of neoplasm, and as opposed to mammals and birds, there is an anatomical basis for a lymphoma to be primary to the kidney. Lymphomas have been described in up to 22 species of fish, with the thymus and kidney being statistically the most common primary sites for neoplastic transformation^[111,112,113,114]. Historically, the species variation and histological anatomy of the fish kidney may have resulted in inaccurate diagnoses of lymphoma in the kidney. The normal presence of hematopoietic tissue within the anterior kidney of many fish species may have resulted in exaggerated descriptions of both mononuclear cell nephritis and lymphoma being maintained within the earlier published literature.

Typically, the histopathological descriptions of lymphoma in the fish kidney are similar to those in higher vertebrates. Reports consist of highly invasive round cell neoplasms that infiltrate, replace, and efface the renal architecture, forming sheets of distinct lymphoblastic cells separated by preexisting tissue. These cells often have a high nuclear to cytoplasmic ratio and a moderately high mitotic index with mild anisocytosis and anisokaryosis. Frequently, these tumors are noted to have metastasized widely throughout the viscera^[115,116]

Lymphoreticular tumors in northern pike from Ireland and in muskellunge from Canada have been shown to have a retroviral etiology, and unlike other forms of spontaneous lymphoma, both of these species-specific tumor types have a seasonal incidence and have been described as beginning within the cutaneous tissues and metastasizing to the viscera, including the kidney.

An epizootic in pen-raised Chinook salmon resulted in significant mortality in multiple production sites in British Columbia in the late 1980s and 1990s. The disease was colloquially known as marine anemia and was characterized by antemortem gill pallor and bilateral exophthalmos. Necropsy of selected animals revealed renal and splenic enlargement with the kidneys being uniformly enlarged and pale. Histopathologically, the affected tissues were severely infiltrated by innumerable neoplastic cells described by the authors as plasmablasts. The renal interstitium

was markedly expanded by the neoplasm, and frequently there was evidence of a glomerulopathy consisting of expansion of the glomeruli by leukocytes with concurrent thickened basement membranes and hyperplasia of the Bowman's capsule parietal cells. In one epizootic, the renal lesions in 50% of the fish were complicated by the presence of granulomatous inflammation with intracytoplasmic bacilli suggestive of *Renibacterium salmoninarum*. The same neoplastic cells were noted within the splenic vasculature, the heart, the intestinal tract, hepatic sinusoids, and the choroid gland. The neoplastic cells were characterized histopathologically and ultrastructurally as round cells with a large, clefted nucleus and with distinct nucleoli. Electron microscopy noted an abundant, regimented rough endoplasmic reticulum with occasionally dilated cisternae suggestive of Russel bodies. On the basis of these findings, the authors proffered a diagnosis of plasmacytoid leukemia. Plasmacytomas have been described in several fish species, and a single case of plasma cell leukemia has been described in a brown bullhead catfish. The reports in Chinook salmon proved critical as the tumors were found to be experimentally transmissible with cell-free filtrates, and reverse transcriptase activity was noted, suggesting a retroviral etiology.^[117]

References

1. Pott P., 1963. Chirurgical observations. Vol 3. London: L Hawes, W Clark, and R Collins, 1775:177-83.
2. Black, J. J., 1984. Aquatic animal neoplasia as an indicator for carcinogenic hazards to man. Hazard Assessment of Chemicals: Current Developments 3: 182--232.
3. Sinnhuber R.O., 1967. Aflatoxin in cottonseed meal and liver cancer in rainbow trout. In: Halver, J.E. and Mitchell, I.A.(eds.). Hepatoma Research Conference Papers. Research Report 70, Bureau of Sport Fisheries and Wildlife, Washington, DC, PP 48-55.
4. Campbell CE, Gibbs PDL, Schmale MC. Progression of infection and tumor development in damselfish. Marine Biotechnol. 2001; 3(suppl 1):S107-S114.
5. Baumann PC, Harshbarger JC. Decline in liver neoplasms in wild brown bullhead catfish after coking plant closes and environmental PAHs plummet. Environ Hlth Perspect. 1995; 103(2):168-170.
6. Baumann PC, Okihiro MS. Cancer. In: Ostrander GK, ed. The Laboratory Fish. San Diego, CA: Academic Press; 2000:591-616.
7. Pinkney AE, Harshbarger JC, Karouna-Renier NK, et al. Tumor prevalence and biomarkers of genotoxicity in brown bullhead (*Ameiurus*

- nebulosus) in Chesapeake Bay tributaries. *Sci Total Environ.* 2011;410–411:248–257.
8. Mikaelian I, de Lafontaine Y, Menard C, et al. Neoplastic and nonneoplastic hepatic changes in lake whitefish (*Coregonus clupeaformis*) from the St. Lawrence River, Quebec, Canada. *Environ Health Perspect.* 1998;106:179–183.
 9. Malins DC, Krahn MM, Myers MS, et al. Toxic chemicals in sediments and biota from a creosote-polluted harbor: relationships with hepatic neoplasms and other hepatic lesions in English sole (*Parophrys vetulus*). *Carcinogenesis.* 1985;6: 1463–1469.
 10. Masahito P, Ishikawa T, Sugano H. Fish tumors and their importance in cancer research. *J Cancer Res.* 1988;79:545–555.
 11. Fournie JW, Vogelbein WK. Exocrine pancreatic neoplasms in the mummichog (*Fundulus heteroclitus*) from a creosotecontaminated site. *Toxicol Pathol.* 1994;22:237–247.
 12. Black, J. J., 1983a. Field and laboratory studies of environmental carcinogenesis in Niagara River fish. *J. Great Lakes Res.* 9: 326–334.
 13. Baumann, P.C., W.D. Smith, and W.K. Parland. 1987. Contaminants concentrations and tumor frequencies in brown bullhead from an industrialized river and a recreational lake. *Trans. Amer. Fish. Soc.* 116:79–86.
 14. Kiumura, I., N. Taniguchi, H. Kumar, I. Tomita, N. Kinae, K. Yoshizaki, M. Ito & T. Ishikawa, 1984. Correlation of epizootiological observations with experimental data: Chemical induction of chromatophoromas in the croaker, *Nibea mitsukurii*. *Nat. Cancer Inst. Monogr.* 65: 139–154.
 15. Okihiro, M. S., 1988. Chromatophoromas in two species of Hawaiian butterflyfish, *Chaetodon muhicinctus* and *C. miliaris*. *Vet. Pathol.* 25: 422–431.
 16. Harshbarger, J. C. & J. B. Clark, 1990. Epizootiology of neoplasms in bony fish of North America. *Sci. Total Environ.* 94: 1–32.
 17. Myers, M. S., J. T. Landahl, M. M. Krahn, L. L. Johnson & B. B. McCain, 1990. Overview of studies on liver carcinogenesis in English sole from Puget Sound; evidence for a xenobiotic chemical etiology I: Pathology and epizootiology. *Sci. Total Environ.* 94: 33–50.
 18. Malins, D. C., B. B. McCain, D. W. Brown, S. Chan, M. S. Myers, J. T. Landahl, P. G. Prohaska, A. J. Friedman, L. D. Rhodes, D. G. Burrows, W. D. Gronlund & H. O. Hodgins, 1984. Chemical pollutants in sediments and diseases of bottom-dwelling fish in Puget Sound, Washington. *Environ. Sci. Technol.* 18(9): 75.
 19. Malins, D. C., M. M. Krahn, D. W. Brown, L. D. Rhodes, M. S. Myers, B. B. McCain & S. Chan, 1985a. Toxic chemicals in marine sediment and biota from Mukilteo, Washington: Relationships with hepatic neoplasms and other hepatic lesions in English sole (*Parophrys vetulus*). *J. Nat. Cancer Inst.* 74(2): 487.
 20. Malins, D. C., M. M. Krahn, M. S. Myers, L. D. Rhodes, D. W. Brown, C. A. Krone, B. B. McCain & S. Chan, 1985b. Toxic chemicals in sediments and biota from a creosotepolluted harbor: Relationships with hepatic neoplasms and other hepatic lesions in English sole (*Parophrys vetulus*). *Carcinogenesis* 6(10): 1463.
 21. Baumann, P. C., W. D. Smith & M. Ribick, 1982. Hepatic tumor rates and polynuclear aromatic hydrocarbon levels in two populations of brown bullheads (*Ictalurus nebulosus*). In: M. W. Cooke, A. J. Dennis & G. L. Fisher (eds), *Polynuclear Aromatic Hydrocarbons: Sixth International Symposium on Physical and Biological Chemistry*, pp. 93-- 102. Battelle Press, Columbus, Ohio. Baumann, P. C., W. D. Smith & W. K. Parland, 1987. Tumor frequencies and contaminant concentrations in brown bullheads from an industrialized river and a recreational lake. *Trans. Amer. Fish. Soc.* 116: 79--86.
 22. Baumann, P.C., J.C. Harshbarger, and K.J. Hartman. 1990. Relations of liver tumors to age structure of brown bullhead populations from two Lake Erie tributaries. *Science of the Total Environment.* 94:71-88.
 23. Brown, E. R., J. J. Hazdra, L. Keith, I. Greenspan & J. B. G. Kwapinski, 1973. Frequency of fish tumors found in a polluted watershed as compared to nonpolluted Canadian waters. *Cancer Res.* 33(2): 189–198.
 24. Murchelano, R. A. & R. E. Wolke, 1985. Epizootic carcinoma in the winter flounder. *Pseudopleuronectes americanus*. *Science* 228: 587--589.
 25. Black, J. J., 1983b. Epidermal hyperplasia and neoplasia in brown bullheads (*Ictalurus nebulosus*) in response to repeated applications of a PAH containing extract of polluted River sediment. In: M.W. Cooke&A.J. Dennis(eds)
 26. Black, J. J., H. Fox, P. Black & F. Bock, 1985. Carcinogenic effects of river sediment extracts in fish and mice. In: R. L. Bolley, R. J. Bull, W. P. Davis, S. Katz, M. H. Roberts, Jr. & V. A. Jacobs (eds), *Water Chlorination Chemistry: Environmental Impact and Health Effects*, pp. 415--427. Lewis Publishers, Chelsea, Michigan.
 27. Schultz, M. E. & R. J. Schultz, 1982. Diethylnitrosamineinduced hepatic tumors in

- wild versus inbred strains of a viviparous fish. *J. Heredity* 73: 43--48.
28. Hawkins, W. E., W. W. Walker, J. S. Lytle, T. F. Lytle & R. M. Overstreet, 1989. Carcinogenic effects of 7,12-dimethylbenz[a]anthracene on the guppy (*Poecilia reticulata*). *Aquat. Toxicol.* 15: 63--82.
 29. Hawkins, W. E., W. W. Walker, R. M. Overstreet, T. F. Lytle & J. S. Lytle, 1988a. Dose-related carcinogenic effects of water-borne benzo(a)pyrene on livers of two small fish species. *Ecotoxicol. Environ. Safety* 16: 219--231.
 30. Hendricks, J. D., T. R. Meyers, D. W. Shelton, J. L. Casteel & G. S. Bailey, 1985. The hepatocarcinogenesis of benzo-(a)pyrene to rainbow trout by dietary exposure and intraperitoneal injection. *J. Nat. Cancer Inst.* 74:839--851.
 31. Metcalfe, C. D., V. W. Cairns & J. D. Fitzsimons, 1988. Experimental induction of liver tumors in rainbow trout (*Salmo gairdneri*) by contaminated sediment from Hamilton Harbour, Ontario. *Can. J. Fish. Aquat. Sci.* 45: 2161--2167.
 32. KIMURA, T., M. YOSHIMIZU and M. T ANAKA (1981a); Studies on a new vi rus (OMV) from *Oncorhynchus maroulinus*. I. Characteris tics and pathogenicity. *Fish Pathology*, 15: 143-147.
 33. KIMURA, T., M. YOSHIMIZU and M. TANAKA (1981b); Studies on a new virus (OMV) from *Oncorhynchus masou*. II. Oncogenic nature. *Fish Pathology*, 15: 149- 153.
 34. Mulcahy, M. F., 1963. Lymphosarcoma in the pike, *Esox lucius* L., (Pisces; Esocidae) in Ireland. *Proc. Roy. Irish Acad.* 63 (Section B, No. 7): 103--129 + 2 plates. Hodges, Figgis, & Co., Ltd., Dublin.
 35. Sonstegard, R. A., 1975. Lymphosarcoma in muskellunge (*Esox masquinongy*). In: W. E. Ribelin & G. Migaki (eds), *The Pathology of Fishes*, pp. 907--924. Univ. Wisconsin Press, Madison.
 36. Sonstegard, R. A., 1976. Studies of the etiology and epizootiology of lymphosarcoma in *Esox lucius* L. and *Esox masquinongy*. In: F. Homburger (series ed.), *Progress in Experimental Tumor Research*, Volume 20. C. J. Dawe, D. G. Scarpelli & S. R. Wellings (volume eds), *Tumors in Aquatic Animals*, pp. 141--155. S. Karger, Basel.
 37. Ljungberg, O., 1976. Epizootiological and experimental studies of skin tumors in northern pike (*Esox lucius* L.) in the Baltic Sea. *Prog. Exper. Tumor Res.* 20: 156--165.
 38. Thompson, J. S., 1982. An epizootic of lymphoma in northern pike, *Esox lucius* L., from the Aland Islands of Finland. *J. Fish Diseases* 11: 359--364.
 39. Mulcahy, M. F. & A. O'Leary, 1970. Cell-free transmission of lymphosarcoma in the northern pike *Esox lucius* L. (Pisces; Esocidae). *Experientia* 26:891.
 40. Brown, E. R., L. Keith, J. J. Hazdra, P. Beamer, O. Callaghan & V. Nair, 1979. Water pollution and its relationship to lymphomas in poikilotherms. In: D. Yohn, B. Lapin & J. Blakeslee (eds), *Advances in Comparative Leukemia Research 1979*, pp. 209--210. Elsevier-North Holland, New York.
 41. Papas, T. S., J. E. Dahlberg & R. A. Sonstegard, 1976. Type C virus in lymphosarcoma in northern pike (*Esox lucius*). *Nature* 261: 506--508.
 42. Papas, T. S., T. W. Pry, M. P. Schafer & R. A. Sonstegard, 1977. Presence of DNA polymerase in lymphosarcoma in northern pike (*Esox lucius*). *Cancer Res.* 37:3214--3217.
 43. Sano, T., H. Fukuda, M. Furukawa, H. Hosoya & Y. Moriya, 1985. A herpesvirus isolated from carp papilloma in Japan. In: A. E. Ellis (ed.), *Fish and Shellfish Pathology: First International Conference of the European Association of Fish Pathologists*, pp. 307--312. Academic Press, Orlando, Florida.
 44. Sano, T., H. Fukuda, N. Okamoto & F. Kaneko, 1983. Yamame tumor virus: Lethality and oncogenicity. *Bull. Japan. Soc. Sci. Fish.* 49:1159--1163.
 45. Yamamoto, T., R. K. Kelly & O. Nielson, 1985. Epidermal hyperplasia of walleye, *Stizostedion vitreum* (Mitchill), associated with retrovirus-like type-C particles: Prevalence, histologic and electron microscopic observations. *J. Fish Diseases* 8: 425--436.
 46. Martineau, D., P. R. Bowser, G. A. Wooster & L. D. Armstrong, 1990. Experimental transmission of a dermal sarcoma in fingerling walleyes (*Stizostedion vitreum vitreum*). *Vet. Pathol.* 27: 230--234.
 47. Christiansen, M. & A. J. C. Jensen, 1950 (1947). On a recent and frequently occurring tumor disease in eel. I. Occurrence of the disease in the various years and its distribution. II. Investigations of the tumors. In: H. Blevad (ed.), *Rep. Danish Biol. Stat. Min. Agric. Fish.* 20: 31--44.
 48. Schwanz-Pfützner, I., 1976. Further studies of eel virus (Berlin) isolated from the blood of eels (*Anguilla anguilla*) with skin papilloma. *Prog. Exper. Tumor Res.* 20: 101-107.

49. Peters, G. & N. Peters, 1977. Temperature-dependent growth and regression of epidermal tumors in the European eel (*Anguilla anguilla* L.). Ann. N.Y. Acad. Sci. 298: 245--260.
50. Sonstegard, R. A., 1973. Relationship between environmental factors and viruses in the induction of tumors in fish. In: M. S. Mahdy & B. J. Dutka (eds), Proceedings of Symposium: Viruses in the Environment and Their Potential Hazards, pp. 119--129. Environ. Can., Can. Centre Int. Wat., Burlington, Ontario.
51. Smith, I. R., K. W. Baker, M. A. Hayes & H. W. Ferguson, 1989a. Ultrastructure of malpighian and inflammatory cells in epidermal papillomas of white sucker *Catostomus commersoni*. Diseases Aquat. Organ. 6:17--26.
52. Smith, I. R. & B. A. Zajdlik, 1987. Regression and development of epidermal papillomas affecting white suckers. *Catostomus commersoni* (Lacepede), from Lake Ontario, Canada. J. Fish Diseases 10: 487--494.
53. Smith, I. R., H. W. Ferguson & M. A. Hayes, 1989b. Histopathology and prevalence of epidermal papillomas epidemic in brown bullhead, *Ictalurus nebulosus* (Lesueur), and white sucker, *Catostomus commersoni* (Lacépède), population from Ontario, Canada. J. Fish Diseases 12: 373--388.
54. Lucke, B. & H. G. Schlumberger, 1941. Transplantable epithelioma of the lip and mouth of catfish. I. Pathology. Transplantation of anterior chamber of eye and into cornea. J. Exper. Med. 74: 397--408.
55. Schlumberger, H. & B. Lucke, 1948. Tumors of fishes, amphibians, and reptiles. Cancer Res. 8:657--753.
56. Anon, 1988. Fish health and contamination study. Delaware Estuary Use Attainability Project, Delaware River Basin Commission, W. Trenton, New Jersey, 120 pp.
57. Grizzle, J. M., T. E. Schweldler & A. L. Scott, 1981. Papillomas of black bullheads, *Ictalurus melas* (Rafinesque), living in a chlorinated sewage pond. J. Fish Diseases 4:345--351.
58. Grizzle, J. M., P. Melius & D. R. Strength, 1984. Papillomas on fish exposed to chlorinated wastewater effluent. J. Nat. Cancer Inst. 73:1133--1142.
59. Grizzle, J. M. & P. Melius, 1983. Causes of papillomas on fish living in chlorinated sewage effluent. US EPA, EPA-600153-82-07, Guff Breeze, FL, NTIS, Washington D.C. 27 pp.
60. Anders F (1967) Tumour formation in platyfishswordtail hybrids as a problem of gene regulation. *Experientia* 23, 1-100.
61. Sonstegard, R. A., 1977. Environmental carcinogenesis studies in fishes of the Great Lakes of North America. Ann. N.Y. Acad. Sci. 298: 261--269.
62. Down, N. E., R. E. Peter & J. F. Leatherland, 1988. Gonadotropin content of the pituitary gland of gonadal tumorbearing common carp x goldfish hybrids from the Great Lakes, as assessed by bioassay and radioimmunoassay. Gen. Comp. Endocrinol. 69: 288--300.
63. Mix, M. C., 1986. Cancerous Diseases in Aquatic Animals and their Association with Environmental Pollutants: A Critical Literature Review. In: G. W. Heath (ed.), *Marine Environmental Research*. Elsevier Appl. Sci. Spec. Issue. 20(1 & 2). 141 pp.
64. Ishikawa, T. & S. Takayama, 1977. Ovarian neoplasia in ornamental hybrid carp (nishikogoi) in Japan. Ann. N.Y. Acad. Sci. 298: 330--341.
65. Ishikawa, T., N. Kuwabara & S. Takayama, 1976. Spontaneous ovarian tumors in domestic carp (*Cyprinus carpio*): Light and electron microscopy. J. Nat. Cancer Inst. 57: 579--584.
66. Granado-Lorencio, C., F. Garcia-Novo & J. Lopez-Campos, 1987. Testicular tumors in carp-funa hybrid: Annual cycle and effect on a wild population. J. Wildl. Diseases 23:422--427.
67. Vielkind, J. R. & E. Dippel, 1984. Oncogene-related sequences in xiphophorus fish prone to hereditary melanoma formation. Can. J. Genet. Cytol. 26: 607--614.
68. Anders K, Hilger I, Moller H. Lentivirus-like particles in connective tissue tumours of fish from German coastal waters. *Dis Aquat Org.* 1991;11:151--154.
69. Calle PP, McNamara T, Kress Y. Herpesvirus-associated papillomas in koi carp (*Cyprinus carpio*). *J Zoo Wildl Med.* 1999;30:165--169.
70. Kimura T, Yoshimizu M, Tanaka M. Studies on a new virus (OMV) from *Oncorhynchus masou*. 11. Oncogenic nature. *Fish Pathol.* 1981;15:149--153.
71. Kollinger G, Schwab M, Anders F. Virus-like particles induced by bromodeoxyuridine in melanoma and neuroblastoma of xiphophorus. *J Cancer Res Clin Oncol.* 1979;95: 239--246.
72. Schmale MC, Aman MR, Gill KA. A retrovirus isolated from cell lines derived from neurofibromas in bicolor damselfish (*Pomacentrus partitus*). *J Gen Virol.* 1996;77:1181--1187.
73. Sonstegard R. Lymphosarcoma in muskellunge (*Esox masquinongy*). In: Ribelin WE, Migaki G, eds. *The Pathology of Fishes*. Madison: University of Wisconsin Press; 1975: 907--924.

74. Thompson JS. An epizootic of lymphoma in northern pike, *Esox lucius* L., from the Åland Islands of Finland. *J Fish Dis.* 1982;5(1): 1–11.
75. Sonstegard RA. Environmental carcinogenesis studies in fishes of the Great Lakes of North America. *Ann N Y Acad Sci.* 1977;298: 261–269.
76. Walker R. Virus associated with epidermal hyperplasia in fish. *Natl Cancer Inst Monogr.* 1969;31:195–207.
77. Furihata M, Suzuki K, Hosoe A, et al. Histopathological study on Oncorhynchus masou virus disease (OMVD) of cultured rainbow trout in natural outbreaks and artificial infection. *Fish Pathol.* 2005;40:161–168.
78. Anders K, Yoshimizu M. Role of viruses in the induction of skin tumors and tumor-like proliferations of fish. *Dis Aquat Org.* 1994; 19:215–232.
79. Masahito P, Ishikawa T, Okamoto N, et al. Nephroblastomas in the Japanese eel, *Anguilla japonica* Temminck et Schlegel. *Cancer Res.* 1992;52:2575–2579.
80. Nakatsuru Y, Minami K, Yoshikawa A, et al. Eel WT1 sequence and expression in spontaneous nephroblastomas in Japanese eel. *Gene.* 2000;245:245–251.
81. Helmboldt CF, Wyand DC. Nephroblastoma in a striped bass. *J Wildl Dis.* 1971;7:162–165.
82. Stegeman N, Heatley JJ, Rodrigues A, et al. Nephroblastoma in a koi (*Cyprinus carpio*). *J Exotic Pet Med.* 2010;19:298–303.
83. Bucke D, Feist SW. Histopathology of some fish tumours from British waters, including an olfactory glioma in coalfish, *Pottachius virens* L. *J Fish Biol.* 1985;27:293–305.
84. Masahito P, Ishikawa T, Takayama S, et al. Gonadal neoplasms in largemouth bass, *Micropterus salmoides* and Japanese dace (ugui), *Tribolodon hakonensis*. *Gann.* 1984;75:776–783.
85. Huizinga HW, Budd J. Nephroblastoma in the smelt, *Osmerus mordax* (Mitchell). *J Fish Dis.* 1983;6:389–391.
86. Lombardini ED, Law M, Lewis BS. Nephroblastoma in two Siamese fighting fish (*Betta splendens*). *Fish Pathol.* 2010;45: 137–139.
87. Harshbarger JC. Role of the Registry of Tumors in Lower Animals in the study of environmental carcinogenesis in aquatic animals. *Ann N Y Acad Sci.* 1978;29:280–289.
88. Grizzle JM, Buckley-Williams L, Harshbarger JC. Renal adenocarcinoma in Mozambique tilapia, neurofibroma in goldfish and osteosarcoma from channel catfish from a Puerto Rico hatchery. *J Aquat Anim Health.* 1995;7:178–183.
89. Ghittino P, Dalforno S, Bignami S, et al. Caso di nefroblastoma in *Anguilla argentina* di lagunicoltura. *Riv Ital Piscic Ittiopatol.* 1985;20:150–153.
90. Groff J. Neoplasia in fishes. *Vet Clin North Am Exot Anim Pract.* 2004;7:705–756.
91. Odense PH, Logan VH, Baker SR. Spontaneous nephroblastoma in a rainbow trout. *Can J Fish Aquat Sci.* 1973;30(4):549–551.
92. Rehulka J. Spontaneous nephroblastoma in a hatchery rainbow trout (*Oncorhynchus mykiss*). *Dis Aquat Org.* 1992;14:75–79.
93. Miyazaki T, Hyakkoku N. A histopathological study on nephroblastoma of the Japanese eel. *Bull Fac Fish Mie Univ.* 1987;14:21–32.
94. Bailey GS, Williams DE, Hendricks JD. Fish models for environmental carcinogenesis: the rainbow trout. *Environ Health Perspect.* 1996;104(suppl 1):5–21.
95. Grizzle JM, Goodwin AE. Neoplasms and related disorders. In: Leatherland JF, Woo PTK, eds. *Fish Diseases and Disorders.* 2nd ed. Cambridge, MA: CABI; 2010:19–84.
96. Lee BC, Hendricks JD, Bailey GS. Rare renal neoplasms in *Salmo gairdneri* exposed to MNNG (N-methyl-N0-nitro-N-nitrosoguanidine). *Dis Aquat Org.* 1989;6:105–111.
97. Ashley LM. Renal neoplasms of rainbow trout. *Bull Wildlife Dis Assoc.* 1967;3:86.
98. Ashley LM. Pathology of fish fed aflatoxins and other antimetabolites. In: Snieszko SF, ed. *A Symposium on Diseases of Fishes and Shellfishes.* American Fisheries Society Pub. No. 5. Washington, DC: American Fisheries Society; 1970:366–379.
99. Kimura I, Kitaori H, Yoshizaki K, et al. Development of tumors in rainbow trout following embryonic exposure to N nitroso compounds. In: Dawe CJ, Harshbarger JC, Kondo S, Sugimura T, et al., eds. *Phyletic Approaches to Cancer.* Tokyo: Japan Scientific Societies Press; 1981:241–252.
100. Hendricks JD, Scanlan RA, Williams JL, et al. Carcinogenicity of N methyl N0 nitro N nitrosoguanidine to the livers and kidneys of rainbow trout (*Salmo gairdneri*) exposed as embryos. *J Natl Cancer Inst.* 1980;64:1511–1519.
101. Plehn M. *Praktikum der Fischkrankheiten.* Stuttgart, Germany: E. Schweizerbart'sche; 1924:424–425.
102. Schmey M. *Über Neubildungen bei Fischen.* Frankf Z Pathol. 1911;6:230–252.

103. Schlumberger HC, Lucke' B. Tumors of fishes, amphibians and reptiles. *Cancer Res.* 1948;8:657-754.
104. LePage V, Dutton CJ, Kummrow M, et al. Neoplasia of captive yellow sea horses (*Hippocampus kuda*) and weedy sea dragons (*Phyllopteryx taeniolatus*). *J Zoo Wildl Med.* 2012;43:50-58.
105. Khudolei VV. Spontaneous and induced neoplasm in aquarium fishes. *Izdatelstvo Nauka Moskva.* 1972;74(3):473-481.
106. Oguri M, Sokabe H. Juxtaglomerular cells in the teleost kidneys. *Bull Jpn Soc Sci Fish.* 1968;34:882-888.
107. Haller RD, Roberts RJ. Dual neoplasia in a specimen of *Sarotherodon spilurus spilurus* (Günther) (¼*Tilapia spilurus*). *J Fish Dis.* 1980;3:63-66.
108. Lumsden JS, Marshall S. Sporadic neoplasms of farmed Chinook salmon, *Oncorhynchus tshawytscha* (Walbaum) from New Zealand. *J Fish Dis.* 2003;26:393-399.
109. Nigrelli RF. Tumors and other atypical cell growths in temperate freshwater fishes of North America: Transactions of the American Fisheries Society. Ann Arbor, MI: American Fisheries Society; 1954:262-289.
110. Hoole D, Bucke D, Burgess P, et al. Noninfectious diseases. In: Diseases of Carp and other Cyprinid Fishes. Ames: Iowa State University Press; 2001:140-143.
111. Blazer VS, Schrank CS. Malignant lymphoma in black bullhead from Allouez Bay, Superior, Wisconsin, USA. *Dis Aquat Organ.* 1995;23:229-234.
112. Bowser PR, McCoy CP, MacMillan JR. A lymphoproliferative disorder in a channel catfish, *Ictalurus punctatus* (Rafinesque). *J Fish Dis.* 1985;8:465-469.
113. Ehlinger NF. Kidney disease in lake trout complicated by lymphosarcoma. *Prog Fish Cult.* 1963;25:3-7.
114. Okihiro MS, Hinton DE. Lymphoma in the Japanese Medaka *Oryzias latipes*. *Dis Aquat Org.* 1989;7:79-87.
115. Haddow A, Blake I. Neoplasms in fish: a report of six cases with a summary of the literature. *J Pathol Bacteriol.* 1933; 36:41-47.
116. Hayashi S, Furukawa S, Abe M, et al. Lymphoma in a Japanese Killifish. *J Toxicol Pathol.* 2008;21:115-117.
117. Kent ML, Dawe SC. Experimental transmission of a plasmacytoid leukemia of Chinook salmon, *Oncorhynchus tshawytscha*. *Cancer Res.* 1990;50(17)(suppl):5679S-5681S.

8/3/2014