ROLE OF THE REGISTRY OF TUMORS IN LOWER ANIMALS IN THE STUDY OF ENVIRONMENTAL CARCINOGENESIS IN AQUATIC ANIMALS

1977

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This year the Registry of Tumors in Lower Animals is observing one decade as a diagnostic center, a literature center, a specimen depository, a research group, and a general clearinghouse for information on neoplasia and related disorders in invertebrate and cold-blooded vertebrate animals. Its founding in 1966[1] (initially approved in 1965) was made possible by funds provided by the National Cancer Institute, due largely to the efforts of Drs. Clyde J. Dawe, Harold L. Stewart, Thelma B. Dunn, and Mearl F. Stanton, and by space provided at the Smithsonian Institution, due largely to the efforts of Dr. Donald F. Squires.

During this 10 years, approximately 10,000 specimens (divided among nearly 1500 accessions) with cryptogenic or induced lesions have been received from natural habitats, zoological parks, aquaria, and laboratory experiments. A surprisingly large minority of these contributions were from laymen, reflecting, as some have acknowledged, their concern with the effects of pollution on the environment, especially its potential to cause cancer, and their desire to aid and abet the government's effort to reduce environmental contamination. Most contributions, however, have been from scientists who were either studying lower animal tumors or who discovered tumors fortuitously. One continuing source of material is the Committee on Comparative Oncology of the International Union Against Cancer,[2] which uses the registry as a diagnostic center for its worldwide survey of neoplasms in aquatic animals. The registry also acquires material by survey of a specific population either alone or, more likely, at the invitation of state and/or federal agencies on a routine survey of a river or lake. This fall, for example, the registry participated in the Ohio River Valley Water Sanitation Commission's survey of the entire Ohio River. Upon receipt, specimens are registered, photographically and histologically processed as required, studied microscopically, and a diagnosis is sent to the contributor. When unique lesions or populations with a significant incidence of neoplasms are identified, further studies may be recommended to the contributor or undertaken by the registry with the contributor's cooperation and/or permission. Activities Reports,[3–5] including a complete indexed list of accessions, are available on request.

TABLE 1 shows the distribution of neoplastic and nonneoplastic lesions among the different classes of specimens received. Neoplastic lesions have been received from all five classes of cold-blooded vertebrates and from two phyla of invertebrates: the mollusks and the arthropods. Slightly more than half of all of the lesions received are neoplastic. The nonneoplastic lesions include infections by all types of microorganisms and parasitic metazoa, metabolic disorders, toxicosis, developmental anomalies, and traumatic injuries.

TABLE 2 shows the system of origin represented by neoplasms in the collection for the different classes of animals. A few systems not yet represented in the registry but reported in the literature are also indicated. This Table shows that cell types from

TABLE 1

DISTRIBUTION OF LESIONS AMONG SPECIMENS RECEIVED

Phylogenetic Group	Type of Disease: Neoplastic	Non-neoplastic	Not Diagnosed	Total
Reptiles	54	93	2	149 (10%)
Amphibians	91	51	3	145 (10%)
Bony fish	386	238	37	661 (45%)
Sharks	5	8	0	13 (1%)
Lampreys and hagfish	37	16	0	53 (4%)
Tunicates	0	11	0	11 (1%)
Mollusks	191	97	3	291 (20%)
Arthropods	7	78	0	85 (6%)
Annelids	0	24	0	24 (2%)
Other (echinoderms, nematodes, protozoa, fungi, acanthocephala, platyhelminths, coelenterates, porifera)	0	29	7	36 (2%)
Totals	771 (53%)	645 (44%)	52 (4%)	1468 (100%)
Percentage of those diagnosed	(54)	(46)		

nearly every determined system in reptiles, amphibians, and fish are known to be capable of neoplastic transformation. Transformed cell types are known from eight of the 12 systems in sharks, three of 12 in agnathans, seven of 12 in mollusks, and four in arthropods. Because almost two-thirds of these cell types have been uncovered

TABLE 2

ANIMAL GROUP AND TISSUE SYSTEM OF ORIGIN OF NEOPLASMS

Tissue System of Origin	Animal Group: Reptiles	Amphibians	Bony Fish	Sharks	Agnathans	Mollusks	Arthropods
Integumentary	R*	R	R			R	R
Skeletal	R	L†	R	L			
Muscular	R	L	R			R	
Endocrine	R	L	R	L	R		
Digestive	R	R	R	L	R		
Reproductive	R	R	R	R		R	R
Hematopoietic	R	R	R	R		R	R
Circulatory	R	R	R	L			
Mesenchymal	R	R	R	R		R	
Nervous		R	R	R		R	R
Pigment cell	R	R	R	L	R		
Excretory	R	R	R				
Respiratory	L		L			R	

*R, Examples in the Registry of Tumors in Lower Animals.

†L, Not in the Registry of Tumors in Lower Animals but reported in the literature (see Wellings[77] for fish references, Balls and Clothier[78] for amphibian references, and Billups and Harshbarger[1] for reptile references).

TABLE 3

AQUATIC ANIMAL POPULATIONS FROM WHICH NEOPLASMS HAVE BEEN REPEATEDLY FOUND SINCE 1966

Animal and References	Type of Lesion	Source
Green turtle[5,7]	cutaneous fibroepithelioma	Hawaii and Caribbean
Tiger salamander[8,9]	fibroma, fibrosarcoma, melanocytoma, and epidermal papilloma	sewage pond in Texas
Leopard frog[10–12]	renal adenocarcinoma	northeastern and north central United States and adjacent Canada
Cunner[13]	variably differentiating lip and dental neoplasms	estuary in Rhode Island
White croaker[14,15]	oral epidermal papilloma	sewage outfalls off United States West Coast
Bullhead[16–18]	epidermal papilloma/carcinoma	central Florida, eastern Pennsylvania, and North American Great Lakes
Atlantic eel[19–22]	oral epidermal papilloma	North Sea and European spawning streams
Various flatfish[23–25]	epidermal papilloma	Pacific coast of North America from northwestern Mexico to Alaska, Japan, and Ireland
White sucker[26]	epidermal papilloma	North American Great Lakes
Yellowfin goby[27]	epidermal papilloma	Japan and Korea
Pacific and Atlantic cod[28,29]	parabranchial body adenoma	northeastern Pacific and northwestern Atlantic
Coho salmon[30,31]	thyroid goiter	North American Great Lakes
White sucker[32]	hepatoma and cholangioma	lakes in western Maryland
Rainbow trout[33]	hepatocellular carcinoma	hatchery ponds and aquaria
Northern pike[34]	lymphosarcoma	Ireland, Scandinavia, Canada, and northern United States
Muskellunge[35]	lymphosarcoma	ponds and lakes in United States and Canada
Goldfish[36,37]	neurilemmoma	ponds and lakes in United States
Gray and dog snappers and schoolmaster[38]	neurilemmoma	Florida Keys
Sauger[39]	ossifying dermal fibroma	Torch Lake, Michigan
Walleye[40]	dermal fibroma and fibrosarcoma	Various United States lakes
Striped mullet[41,42]	dermal fibroma and fibrosarcoma	Gulf of Mexico
Yellowtail, eel, seabream and various salmon and trout[43]	gastric polypoid adenoma	hatchery ponds in Japan
"Fancy carp"[44]	ovarian teratoma	aquaria and breeding ponds in Japan
Goldfish, carp, and their hybrids[38]	Sertoli cell tumor	North American Great Lakes
Yellow perch[45]	gonadal tumors	Lake Huron
Agevrusomus argentata[46]	melanoma	estuaries in Japan
Xiphophorus sp.[47–49]	melanoma	laboratory aquaria
Hagfish[50,51]	hepatoma	Gulmar Fjord on Atlantic coast of Sweden
Rock oyster[52,53]	epithelioma of the mantle	several estuaries in southeastern Australia
American oyster[54,55]	hematopoietic neoplasm of hyaline hemocyte origin	Chesapeake Bay and vicinity
Macoma balthica[56]	carcinoma of gill epithelium	Chesapeake Bay
Soft-shell clam[57,58]	germinoma	Searsport, Maine
Soft-shell clam[57,58]	hematopoietic neoplasm	northeastern United States
Blue mussel and Olympia oyster[59,60]	mesenchymal neoplasm	Yaquina Bay, Oregon

TABLE 4
SOME CARCINOGENS THAT HAVE BEEN REPORTED TO INDUCE NEOPLASMS AND HYPERPLASIA IN LOWER ANIMALS EXPERIMENTALLY

Carcinogen	Animal and References	Lesion
Acetoaminofluorene	guppy[41,60]	hepatocarcinoma and cholangiocarcinoma
	rainbow trout[43]	hepatocarcinoma
	house fly[69]	hyperplasia of regenerative nidi
Aflatoxins	rainbow trout[23]	hepatoma
	guppy[64]	nodular hepatic neoplasms
	sockeye salmon[73]	hepatoma
	brook trout[62]	hepatoma
Aminoazotoluene	guppy[64]	cholangiocarcinoma and hepatocarcinoma
	rainbow trout[43]	hepatocarcinoma
Benzpyrene	carp, threespine stickleback, and bitterling[61]	epithelioma
	apple snail[72]	adenomatous tumors
	guppy[65]	intestinal hyperplasia
Bracken	zebrafish[66]	hepatic neoplasms
Cycad nut meal	rainbow trout[43]	hepatocarcinoma
DDT	guppy[64]	hepatocarcinoma and cholangiocarcinoma
Diethylnitrosamine	zebrafish[67]	hepatocarcinoma
	medaka[74]	hepatocarcinoma
Dimethylaminoazobenzene	guppy[64]	hepatocarcinoma
	rainbow trout[43]	hepatocarcinoma
Dimethylnitrosamine	guppy[43,64]	hepatocarcinoma and cholangiocarcinoma
	rainbow trout[43]	hepatocarcinoma and nephroblastoma
	crayfish[70]	hyperplasia of hepatopancreas
Methylcholanthrene	threespine stickleback and bitterling[61]	epithelioma
	apple snail[71]	adenomatous tumors
Nitrosomorpholine	guppy and zebrafish[64]	hepatocarcinoma, cholangiocarcinoma, and intestinal adenocarcinoma
Urethane	rainbow trout[63]	hepatocarcinoma

during the increased and improved surveillance of the last decade, it seems safe to conjecture that more transformable cell types will be discovered in these animals and probably in other invertebrate phyla as well.

TABLE 3 shows aquatic species from which neoplasms have been repeatedly found since 1966 in specific habitats. From this Table, it is clear that neoplasms occur in both fresh- and saltwater species. It also illustrates a point previously made, that the preponderance of involved field species are bottom feeders, such as filtering and detritis-grazing mollusks and scavenging fish. Presumably, carcinogenic chemicals absorb to particulates, which ultimately settle to the bottom, increasing the exposure of bottom feeders. Fish and shellfish are susceptible to many of the same chemical carcinogens as are mammals (TABLE 4) and metabolize them in a similar manner.[75]

Complementary to the specimen collection, a virtually complete library of relevant literature that contains more than 3000 references has been assembled and computerized by the same key word abstract being used for the specimen collection, namely, the source and taxonomy of the host; location, diagnosis, and behavior of the lesions; and evidence for etiologic factors. This literature bank shows that nearly every type of fish neoplasm being found today was known prior to 1940. Thus, there are no likely types of fish tumors that are specifically caused by the synthetic organic insecticides that largely became marketable after 1940. However, most early reports were of isolated cases rather than epizootics, suggesting that the frequency of fish neoplasms has increased substantially. The possibility that this increased incidence is due in part to synergism of existing carcinogens by organic pesticides cannot be ruled out. In contrast to fish, almost all neoplasms in bivalve mollusks were discovered after 1960. This point is mostly explained by the greatly increased opportunities for discovery that have resulted from large histologic surveys initiated in numerous estuaries following outbreaks of several infectious diseases.

With support from the United States Food and Drug Administration, the registry is electron microscopically examining molluscan neoplasms for possible oncogenic viruses and for characterization of tumor fine structure. The examination of inclusions seen in some animals that did not have neoplasms has resulted in the first discovery of several groups of zoonotic pathogens in bivalves, including chlamydiae in *Mercenaria mercenaria,* mycoplasmas in *Crassostrea virginica,* and rickettsiae in *Mya arenaria.* The first chlamydiophage was also found.[76] Because these mollusks are commercial species often consumed raw, this finding may have considerable economic and public health significance.

In conclusion, the registry is mainly involved in specimen storage, diagnostics, information retrieval, and other service activities. In addition, however, the registry participates in surveys, identifies unique lesions or tumorous populations, and takes a supportive or dominant role in pertinent research projects. It is hoped that these efforts will benefit the fight against cancer by contributing further to the discovery of new carcinogens, indicators of environmental carcinogens, animal models for cancer studies, efficacious methods for screening carcinogens, and of reservoirs of carcinogens in food sources and by helping to provide an overall understanding of the neoplastic process.

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AQUATIC POLLUTANTS AND BIOLOGIC EFFECTS WITH EMPHASIS ON NEOPLASIA

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