Cancer and Parasitic Infection

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Abstract: Cancer is the cells that grow out of control. Cancer cells can also invade other tissues. Growing out of control and invading other tissues are what makes a cell a cancer cell. Involved in more than 100 diseases, the cancer can cause serious illness and death. Normally, the cells become cancer cells because of DNA damage. This material is a literature collection of the researches on the cancer and parasitic infection.
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1. Introduction

Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries.

Literatures

Abol-Enein, H. (2008). "Infection: is it a cause of bladder cancer?" Scand J Urol Nephrol Suppl(218): 79-84.

This article reviews the literature regarding the possible correlation between infection and occurrence of bladder cancer. The PubMed literature database was searched from inception to January 2008. Keywords of bladder, cancer, parasitic, bacterial, viral and infection, were used. Forty studies were included in the review. Several investigators support the idea that schistosomiasis is aetiologically related to the development of bladder cancer in individuals infected with Schistosoma haematobium. Approximately 70% of those with chronic schistosomiasis who have bladder cancer develop squamous cell rather than transitional cell carcinoma. Several investigators suggest that bacteria may play a role in inducing bladder cancer. Clinically, researchers have linked the development of infection, urinary stones and indwelling catheters with bladder cancer. Nevertheless, to date, no prospective study has examined the association between urinary tract infection and bladder cancer risk. The possibility that infection by human papilloma virus (HPV) is a risk factor contributing to bladder cancer has been investigated but no definite conclusions have been drawn. Thus, the debate remains open as to whether there is any direct link between chronic HPV infection and bladder cancer. Only 15 cases of vesical carcinoma have been reported, to date, in the setting of human immunodeficiency virus (HIV). The rare occurrence of bladder cancer during HIV infection and the lack of correlation with the laboratory markers of HIV disease progression may suggest a trivial association between two unrelated disorders. BK virus is oncogenic in newborn hamsters and can transfer to mammalian cells in vitro, but there is little consistent evidence of a link with human bladder cancer. Studies showed no correlation between herpes simplex virus (HSV) and bladder cancer, but bladder cancer becomes infected with HSV much more easily than non-neoplastic urothelium. In conclusion, with the exception of chronic infection with S. haematobium, the association between the occurrence of bladder cancer and chronic bacterial or viral infections could not be confirmed. Prospective studies with large numbers of patients and controls are required to confirm this issue.

Akaogi, E., O. Ishibashi, et al. (1993). "Pulmonary dirofilariasis cytologically mimicking lung cancer. A case report." Acta Cytol **37**(4): 531-4.

A case report on a 64-year-old male with pulmonary dirofilariasis cytologically mimicking lung cancer is presented. By transbronchial brushing cytology, several suspect cells with a papillary arrangement showing a high nuclear/cytoplasmic ratio, irregularity of nuclear shape, nuclear enlargement and a macronucleolus were obtained. These cells seemed to originate in the reparative process of the bronchiolar epithelium around the infarcted lesion containing Dirofilaria immitis.

Anthony, P. P. (1976). "Precursor lesions for liver cancer in humans." Cancer Res **36**(7 PT 2): 2579-83.

Our knowledge of the cellular changes that lead to liver cell carcinoma in humans is limited by proper and necessary ethical restriction on clinical research. We know rather more about risk factors, the most important of which is cirrhosis, it seems that both the causative agent and the time of duration of the cirrhotic process are relevent to the magnitude of this risk. According to present knowledge, alpha1-antitrypsin deficiency, alcoholism, naturally occurring carcinogens, drugs, and the hepatitis B virus seem to carry the greatest risk of cancer developing in a cirrhotic patient. Cirrhosis, however, is not an essential prerequisite, and some or possibly all of these agents can also induce cancer without cirrhosis. Bile duct carcinoma commonly follows infestation with liver flukes. Cirrhosis is usually absent but duct epithelial hyperplasia is present prior to the development of cancer. Many cellular changes have been observed in patients and among populations considered to be at risk from liver cancer. Of these, liver cell dysplasia is the most striking and studies of its prevalence, natural history, and association with cirrhosis suggest that it is a precancerous change.

Aoki, K., T. Kuroishi, et al. (1979). "An epidemiologic approach to host factors in the etiology of cancer." Natl Cancer Inst Monogr(53): 17-23.

We examined the contribution of host factors in carcinogenesis by evaluating the frequency distributions and secular trends in available epidemiologic data of mortality and morbidity around the world. In most developed countries, the age-adjusted death rates of cancer of all sites have levelled off in recent years and the intercountry difference in mortality is small. Deaths from cancer account for approximately 20% of total deaths in these countries. It is believed that the difference in cancer mortality of all sites between the developed and developing countries can be explained by the different levels of mortality from infectious and parasitic diseases, including deaths from tuberculosis. A certain upper limit for the number of cancer deaths in each population is strongly suggested by the unaltered cumulative mortality rate from cancer and tuberculosis up to 85 years of age in a defined birth cohort in the developed countries. The apparent age dependency in cancer mortality as well as some other essential epidemiologic implications in carcinogenesis, the commonly observed proportion of cancer deaths of around 20% of total deaths, and the well-known etiologic importance of environmental factors which determines the site-specific cancer mortality and morbidity lead one to consider the definite existence of "susceptibles to cancer" in each population. However, the concept of susceptibles to cancer is different from the usual one of hereditary predisposition to so-called "intractable diseases," which have low incidence rates.

Badawi, A. F., M. H. Mostafa, et al. (1992). "Promutagenic methylation damage in bladder DNA from patients with bladder cancer associated with schistosomiasis and from normal individuals." Carcinogenesis **13**(5): 877-81.

Radioimmunoassays (RIAs) have been used to detect the promutagenic lesion O6-methyldeoxyguanosine (O6-MedG) in DNA isolated from the bladder tissues of Egyptian patients presenting with bladder carcinoma and concomitant schistosomiasis (bilharziasis), a parasitic disease known to be associated with the presence of N-nitrosamines in the urine. Alkylation damage was present in the DNA of the majority of the samples (44/46, 96%); 38 samples were of tumour tissue and 8 from uninvolved bladder mucosa. Levels of O6-MedG ranged from undetectable (ND; i.e. less than 0.01 mumol O6-MedG/mol dG) to 0.485 mumol/mol dG with an overall mean of 0.134 +/- 0.10 mumol/mol dG, including the two samples that were below the limit of detection. In contrast, methylation damage was detected in only 4/12 (33%) of the DNA samples from normal bladder tissue of European origin. In these samples levels of O6-MedG ranged from ND to 0.225 mumol/mol dG with an overall mean of 0.046 +/- 0.082 mumol O6-MedG/mol dG. These results confirm that alkylation events can be detected in the DNA of schistosome-infected human bladder tissue. The methylation of uninvolved and tumour tissue DNA to similar extents suggests that the alkylating intermediate may have been present in the urine. These results indicate the need for further investigation to determine whether relationships exist between levels of DNA damage and the prevalence of schistosome infection and/or the extent and type of bacterial infection that frequently accompanies this disease.

Bailey, W. S. (1963). "Parasites and Cancer: Sarcoma in Dogs Associated with Spirocerca Lupi." Ann N Y Acad Sci **108**: 890-923.

Barson, W. J. and M. T. Brady (1987). "Management of infections in children with cancer." Hematol Oncol Clin North Am **1**(4): 801-39.

Infectious complications remain a frequent cause of morbidity and mortality in children with cancer, especially in those who are granulocytopenic. Physicians caring for these children must approach each new febrile episode as if it were life threatening. Questions concerning the present illness must be comprehensive. The physical examination should be done in a compulsive manner because the more

obvious signs of inflammation are often absent because of granulocytopenia. Immediate initiation of broad-spectrum intravenous antibiotic coverage is required once the appropriate specimens for diagnostic microbiology studies have been obtained. Because these patients may exhibit either dramatic or, more often, only subtle clinical findings, they must be monitored closely and have a complete physical examination at least daily. The laboratory studies frequently determine the etiology of the fever. Therapy can then be modified, based upon the particular pathogen isolated or the type of infection identified. Because bacterial infections are responsible for most infectious febrile episodes in the granulocytopenic child with cancer, appropriate antibiotic therapy usually is curative. However, some patients remain febrile and granulocytopenic without explanation. These patients frequently have a fungal infection and respond to amphotericin B therapy. Our present armamentarium of antimicrobial agents against the common pathogens encountered in cancer patients, except for cytomegalovirus, is adequate. Future advances in therapy of infections in children with cancer will probably be in the area of immunotherapy. This would include both passive administration of products to strengthen a debilitated immune system, together with active immunization with the aim to prevent infectious complications. Prevention of infection in the cancer population may be one of the keys to producing longer remissions and prolonged overall survival, by enabling pediatric oncologists to administer more intensive induction chemotherapy.

Bartsch, H., H. Ohshima, et al. (1990). "Exposure of humans to endogenous N-nitroso compounds: implications in cancer etiology." Mutat Res **238**(3): 255-67.

Two sensitive procedures to quantitate human exposure to endogenous N-nitroso compounds (NOC) and/or methylating agents have been developed. One, the NPRO test, is based on the excretion of N-nitrosoproline (NPRO) and other N-nitrosoamino acids in the urine, that are measured as an index of endogenous nitrosation, following ingestion of precursors. The NPRO test has been applied to human subjects in clinical and epidemiological studies, and the kinetics and dietary modifiers of endogenous nitrosation have been investigated. Results obtained after application of the NPRO test to subjects at high risk for cancers of the stomach, esophagus, oral cavity and urinary bladder are summarized. In most instances, higher exposures to endogenous NOC were found in high-risk subjects, but individual exposure was greatly affected by dietary modifiers or disease state. Vitamin C efficiently lowered the body burden of intragastrically formed NOC. In experimental animals 3-methyladenine (3-MeAde) is excreted in urine following exposure to methylating NOC. Humans normally excrete 3-MeAde, the origin of which remains unknown. Recently developed analytical methodology permits large numbers of human urine samples to be analyzed and a wide variation is observed. Preliminary results suggest a weak correlation between basal NPRO excretion and background 3-MeAde excretion. Taken together, the results point to an etiological role of endogenously formed NOC in certain human cancers, and provide an interpretation of epidemiological findings that have shown protective effects of fruits and vegetables against several malignancies.

Bedwani, R., E. Renganathan, et al. (1998). "Schistosomiasis and the risk of bladder cancer in Alexandria, Egypt." Br J Cancer **77**(7): 1186-9.

The relationship between history of schistosomiasis and bladder cancer risk was investigated using data from a case-control study conducted between January 1994 and July 1996 in Alexandria, Egypt. Cases were 190 subjects with incident, histologically confirmed invasive cancer of the bladder, and controls were 187 subjects admitted to hospital for acute, non-neoplastic, non-urinary tract conditions. Eighty-six cases (45%) vs 69 controls (37%) reported a history of urinary schistosomiasis. The corresponding multivariate odds ratio (OR) of bladder cancer -- after allowance for age, sex, education, smoking, other urinary infections and high-risk occupations -- was 1.72 (95% confidence interval (CI) 1.0-2.9). The ORs were 0.22 (95% CI 0.1-0.4) for intestinal schistosomiasis and 0.32 (95% CI 0.1-1.9) for schistosomiasis of other types. The OR for urinary schistosomiasis was higher in subjects who were younger at first diagnosis (OR of 3.3 for <15 years) and in those with a long time since first diagnosis (OR of 3.0 for > or = 35 years). The ORs were 15.8 for male ever-smokers with a history of urinary schistosomiasis, compared with never-smokers without such a history, and 3.2 for men ever-infected with urinary Schistosoma haematobium and ever-employed in high-risk occupations, compared with those never-infected and with no high-risk occupational history. This study confirms that clinical history of urinary schistosomiasis is significantly, but modestly, associated with increased bladder cancer risk, explaining some 16% of bladder cancer cases in this Egyptian population.

Bhattachary-Chatterjee, M., R. Nath Baral, et al. (2000). "Counterpoint. Cancer vaccines: single-epitope anti-idiotype vaccine versus multiple-epitope

antigen vaccine." Cancer Immunol Immunother **49**(3): 133-41.

Anti-idiotype (Id) vaccine therapy has been tested and shown to be effective, in several animal models, for triggering the immune system to induce specific and protective immunity against bacterial, viral and parasitic infections. The administration of anti-Id antibodies as surrogate tumor-associated antigens (TAA) also represents another potential application of the concept of the Id network. Limited experience in human trials using anti-Id to stimulate immunity against tumors has shown promising results. In this "counter-point" article, we discuss our own findings showing the potential of anti-Id antibody vaccines to be novel therapeutic approaches to various human cancers and also discuss where anti-Id vaccines may perform better than traditional multiple-epitope antigen vaccines.

Blair, A., M. Dosemeci, et al. (1993). "Cancer and other causes of death among male and female farmers from twenty-three states." Am J Ind Med **23**(5): 729-42.

Occupation and industry codes on death certificates from 23 states for 1984-1988 were used to evaluate mortality risks among white and nonwhite, male and female farmers. Proportionate mortality and proportionate cancer mortality ratios were calculated using deaths among nonfarmers from the same states to generate expected numbers. Among farmers there were 119,648 deaths among white men, 2,400 among white women, 11,446 among nonwhite men, and 2,066 among nonwhite women. Deficits occurred in all race-sex groups for infective and parasitic diseases, all cancer combined, lung cancer, liver cancer, diseases of the nervous system, multiple sclerosis, hypertension, and emphysema. As reported in other studies, white male farmers had excesses of cancer of the lymphatic and hematopoietic system, lip, eye, brain, and prostate. Excesses of cancers of the pancreas, kidney, bone, and thyroid were new findings. Regional patterns were evident, particularly among white men. Significant excesses for accidents, vascular lesions of the central nervous system (CNS), and cancers of the prostate tended to occur in most geographic regions, while excesses for mechanical suffocation, non-Hodgkin's lymphoma, and cancers of the lip, brain, and the lymphatic and hematopoietic system were limited to the Central states. Increases among nonwhite men were similar to those in white men for some causes of death (vascular lesions of the CNS and cancers of the pancreas and prostate), but were absent for others (lymphatic and hematopoietic system, lip, eye, kidney, and brain). Women (white and nonwhite) had excesses for vascular lesions of the CNS, disease of the genitourinary system (white women only), and cancers of the stomach and cervix (nonwhite women only). Cancer of the buccal cavity and pharynx was slightly elevated among women, and white women had nonsignificant excesses of multiple myeloma and leukemia. Excesses for leukemia and non-Hodgkin's lymphoma occurred among white men and women, but not among nonwhites. Excesses for several types of accidental deaths were seen among all race-sex groups.

Bovio, S., F. Porpiglia, et al. (2007). "Adrenal pseudocyst mimicking cancer: a case report." J Endocrinol Invest **30**(3): 256-8.

Adrenal cysts are infrequently observed, since less than 500 cases have been reported in Western literature. Adrenal cysts are conventionally divided into four categories: epithelial, parasitic, endothelial, and hemorrhagic. They are characterized by different etiological and pathological features. Some authors suggest that endothelial and hemorrhagic cysts are related and may represent a spectrum of lesions. We report herein the case of an adrenal hemorrhagic pseudocyst that simulated adrenocortical cancer and argue on the clinical clues for a differential diagnosis with other adrenal tumors.

Brennan, M. J. (1976). "Murine and rat mammary tumors as models for the immunological study of human breast cancer." Cancer Res **36**(2 pt 2): 728-33.

The human breast cancer process and some aspects of experimental mammary cancer are compared in the light of Huxley's hypothesis that each neoplastic cell line may be viewed as a new obligate parasitic species derived from metazoan cells. Sufficient correlations are found to justify the hope that the viral-induced mouse mammary oncogenic process and the carcinogen-induced rat mammary system may serve as reasonable models of the human disease for immunological studies.

Brown, L. M., G. Gridley, et al. (1997). "Cancer risk and mortality patterns among silicotic men in Sweden and Denmark." J Occup Environ Med **39**(7): 633-8.

Data from nationwide registry-based cohorts of patients hospitalized for silicosis in Sweden from 1965 to 1983 and Denmark from 1977 to 1989 were linked to national cancer registries in both countries and to mortality data in Sweden to evaluate the risk of cancer and other disorders among hospitalized silicotic patients. The overall cancer standardized incidence ratio (SIR) was 1.5 (95% confidence interval [CI], 1.3 to 1.7) in Sweden and 1.7 (95% CI, 1.2 to 2.3) in Denmark, primarily because of elevations in primary lung cancer in both Sweden (SIR, 3.1; CI, 2.1 to 4.2) and Denmark (SIR, 2.9; CI, 1.5 to 5.2). For Sweden, the all-causes standardized

mortality ratio (SMR) was 2.0 (1.9 to 2.2). The SMR for all malignancies was 1.5 (1.2 to 1.7), primarily because of excesses of lung cancer (SMR, 2.9; CI, 2.1 to 3.9). The significant increase in mortality for all infectious and parasitic conditions (SMR, 11.2) was primarily due to tuberculosis (SMR, 21.8). Significant excesses in mortality from silicosis (SMR, 523), bronchitis (SMR, 2.6) and emphysema (SMR, 6.7) contributed to the elevation in nonmalignant respiratory deaths (SMR, 8.8), whereas excess mortality from musculoskeletal disorders (SMR, 5.9) was due to six deaths from autoimmune diseases. Despite limitations of the available data, our findings are consistent with previous reports indicating that silicotic patients are at elevated risk of lung cancer, nonmalignant respiratory diseases, tuberculosis, and certain autoimmune disorders.

Chandramathi, S., K. G. Suresh, et al. (2009). "Attenuation of hydrogen peroxide and ferric reducing/antioxidant power serum levels in colorectal cancer patients with intestinal parasitic infection." Malays J Med Sci **16**(2): 15-20.

BACKGROUND: This study assessed several common oxidative indices in subjects infected with intestinal parasites, as well as in colorectal cancer (CRC) patients both with and without intestinal parasites. METHOD: Serum levels of malondialdehyde (MDA), ferric reducing/antioxidant power (FRAP), and hydrogen peroxide (H(2)O(2)) were measured, as were plasma levels of advanced oxidation protein products (AOPP), all according to established methods. The presence of intestinal parasites was confirmed by stool examination. RESULTS: All intestinal parasiteinfected subjects and CRC patients showed the presence of oxidative stress. Thirtysix percent of the CRC patients had intestinal parasitic infections. The levels of H(2)O(2) and FRAP in parasite-infected subjects were significantly higher than in CRC patients, but these levels were significantly lower in the CRC patients with parasitic infections. CONCLUSION: Parasitic infection and CRC may contribute to oxidative stress independently, but when present together, the oxidative stress burden imposed by parasites may be attenuated.

Chanock, S. J. and P. A. Pizzo (1995). "Infection prevention strategies for children with cancer and AIDS: contrasting dilemmas." J Hosp Infect **30 Suppl**: 197-208.

Infectious complications represent significant challenges for children with cancer and those infected with HIV. Although both have similarities in the disease- and treatment-related alterations in host defences, there are significant differences that can have an impact on the approach to treatment and prevention of the dominant infectious complications. An important difference is that children with cancer readily recover from neutropenia. Thus, the immune deficits are interspersed with intervals of immunological recovery. On the other hand, children with HIV infection do not appreciably recover from the progressive, immunological changes associated with the underlying HIV infection. The loss of cellular and humoral immunity is generally not reversible, and thus the risk of infection only increases over time. Bacteria constitute the predominant pathogen for paediatric cancer patients but invasive mycoses, viruses and parasitic infections are emerging as important pathogens. In paediatric cancer patients, strategies have been directed at altering or suppressing the endogenous colonization patterns of pathogenic bacteria. The success of this approach has been limited and at the expense of selecting for antibiotic-resistant bacterial infections. Children with HIV infection are at risk of developing a wide spectrum of pathogens. Strategies for infection prevention in the HIV setting have been directed at specific organisms, generally using more specific antimicrobial agents and with greater success.

Chen, M. C., P. Y. Chang, et al. (1981). "Colorectal cancer and schistosomiasis." Lancet **1**(8227): 971-3.

The risk of colorectal cancer is known to be increased in patients with long-standing schistosomal colitis. A retrospective review of clinical data and surgical specimens from 60 patients with schistosomal granulomatous disease of the large intestine but without carcinoma demonstrated that 36 of them had mild to severe grades of colonic epithelial dysplasia. This was either focal or diffuse in distribution and occurred in flat mucosa, in pseudopolyps, or in regenerating epithelium at the edges of ulcers. These dysplastic changes are regarded as the pathological basis for the malignant potential of schistosomal colitis, and they resemble the changes found in long-standing chronic ulcerative colitis.

Chen, Y., M. Lopez-Sanchez, et al. (2008). "A series of potent and selective, triazolylphenyl-based histone deacetylases inhibitors with activity against pancreatic cancer cells and Plasmodium falciparum." J Med Chem **51**(12): 3437-48.

The discovery of the rules governing the inhibition of the various HDAC isoforms is likely to be key to identifying improved therapeutics that act as epigenetic modulators of gene transcription. Herein we present results on the modification of the CAP region of a set of triazolylphenyl-based HDACIs, and show that the nature of substitution on the phenyl ring plays a role in their selectivity for HDAC1 versus HDAC6, with low to moderate selectivity (2-51-fold)

being achieved. In light of the valuable selectivity and potency that were identified for the triazolylphenyl ligand 6b in the inhibition of HDAC6 (IC50 = 1.9 nM), this compound represents a valuable research tool and a candidate for further chemical modifications. Lastly, these new HDACIs were studied for both their anticancer and antimalarial activity, which serve to validate the superior activity of the HDACI 10c.

Chualain, C. N., M. Hayes, et al. (2009). "Hematodinium sp. in Irish Cancer pagurus fisheries: infection intensity as a potential fisheries management tool." Dis Aquat Organ **83**(1): 59-66.

Infection of Cancer pagurus by a parasitic dinoflagellate of the genus Hematodinium is described for the first time in Ireland. An industry-based monitoring programme was established to determine seasonality of infection intensity and prevalence in the country's 3 largest brown crab fisheries in the southwest, north and southeast. The parasite was present in all areas for the majority of sampling periods, with highest prevalences recorded in pre-recruit animals of both sexes. Microscopic examination of haemolymph revealed trophont, plasmodial and dinospore stages of the parasite. Overall prevalence in males (16%) was higher than in females (9%). Prevalence of Hematodinium sp. infection ranged from 0 to 51%, but a distinct seasonal trend was not apparent. Infection intensity was seasonal with significantly higher peaks occurring in late autumn/early winter months than in other quarters, corresponding to industry reports of moribund and dead pink-shelled crabs in commercial catches. We postulate that seawater temperature or a temperature-linked process is a key factor in triggering the final stages of infection, as significant autumn peaks were followed by a reduction in infection intensity as temperature decreased in the late winter/early spring months with no increase in intensity again until the following autumn. We propose that infection intensity, rather than prevalence, provides a more appropriate indication of the period when there is greatest potential for biological and economic impacts; the parameter's application as a fisheries management tool is discussed.

Collin, B. A. and R. Ramphal (1998). "Pneumonia in the compromised host including cancer patients and transplant patients." Infect Dis Clin North Am **12**(3): 781-805, xi.

Pneumonia remains a major cause of morbidity and mortality in the immunocompromised host. The type and timing of immunosuppression will predispose the patient to infections with certain pathogens. This article discusses the types of immunosuppression and their infectious and noninfectious implications. Key points of the most commonly involved pathogens are mentioned. Finally, an approach to diagnosis and empiric therapy is discussed.

Dorn, C. R. (1967). "The epidemiology of cancer in animals." Calif Med **107**(6): 481-9.

The principles of epidemiology are applicable to the study of the distribution and determinants of cancer in both human and animal populations. There are many examples of epidemiologic factors (host, environment, agent and time) related to cancer in animals. Certain host characteristics such as age, sex and breed are related to risk of developing cancer. Some environmental influences are illustrated by differences in the geographical distribution of certain types of animal cancer. Aggregations of cancer cases have been reported in herds, families and households. However, the usual distribution of cases in a population does not resemble epidemics typical of infectious diseases. Several factors (radiological, chemical, dietary, parasitic, mechanical, genetic and viral) have been identified as influences that affect the development of animal tumors. Animal species that have been domesticated live longer and consequently malignant disease develops in more of them. Cancer incidence rates now available from data compiled by an animal neoplasm registry in Alameda and Contra Costa counties, California, indicate that some of the frequent sites of cancer in man (skin, breast and the hemic and lymphatic systems) are among the most frequent sites in dogs and cats, man's closest animal associates.

Enwonwu, C. O. (1984). "The role of dietary aflatoxin in the genesis of hepatocellular cancer in developing countries." Lancet **2**(8409): 956-8.

Impaired activity of the liver microsomal mixed-function-oxidase (MFO) system is characteristic of protein malnutrition. It explains the accumulation of aflatoxin (AFB1) in livers of kwashiorkor victims, whose staple foods are usually heavily contaminated with this fungal toxin. Dietary rehabilitation of such children with high-protein foods not only increases the activity of the liver MFO system but also stimulates DNA replication and rapid regeneration of liver cells. Under such circumstances highly reactive metabolites of AFB1, such as the AFB1-epoxide, can produce malignant transformation of the cells by binding covalently with genetic macromolecules. Alternating cycles of food shortage and sufficiency, which usually characterise impoverished communities, and liver-cell hyperplasia stimulated by the non-genetic cytotoxic effects of

AFB1 or parasitic infestation promote rapid replication of the transformed cells.

Esteller, M. and J. G. Herman (2002). "Cancer as an epigenetic disease: DNA methylation and chromatin alterations in human tumours." J Pathol **196**(1): 1-7.

Cancer is an epigenetic disease at the same level that it can be considered a genetic disease. In fact, epigenetic changes, particularly DNA methylation, are susceptible to change and are excellent candidates to explain how certain environmental factors may increase the risk of cancer. The delicate organization of methylation and chromatin states that regulates the normal cellular homeostasis of gene expression patterns becomes unrecognizable in the cancer cell. The genome of the transformed cell undergoes simultaneously a global genomic hypomethylation and a dense hypermethylation of the CpG islands associated with gene regulatory regions. These dramatic changes may lead to chromosomal instability, activation of endogenous parasitic sequences, loss of imprinting, illegitimate expression, aneuploidy, and mutations, and may contribute to the transcriptional silencing of tumour suppressor genes. The hypermethylation-associated inactivation affects virtually all of the pathways in the cellular network, such as DNA repair (hMLH1, BRCA1, MGMT, em leader), the cell cycle (p16(INK4a), p14(ARF), p15(INK4b), ...), and apoptosis (DAPK, APAF-1, ...). The aberrant CpG island methylation can also be used as a biomarker of malignant cells and as a predictor of their behaviour, and may constitute a good target for future therapies.

Ewald, P. W. (2009). "An evolutionary perspective on parasitism as a cause of cancer." Adv Parasitol **68**: 21-43.

For the past half-century, the dominant paradigm of oncogenesis has been mutational changes that disregulate cellular control of proliferation. Parasitic causes of cancer were first incorporated into this paradigm by suggesting mechanisms through which parasitism might increase mutational damage, such as generation of mutagenic compounds during immunological activity. The growing recognition of the molecular mechanisms of pathogen-induced oncogenesis and the difficulty of generating oncogenic mutations without first having large populations of dysregulated cells, however, suggests that pathogens, particularly viruses, are major initiators of oncogenesis for many if not most cancers, and that the traditional mutation-driven process becomes the dominant process after this initiation. Molecular phylogenies of individual cancers should facilitate testing of this idea and the identification of causal pathogens.

Fernandes, H., C. R. D'Souza, et al. (2009). "Ameboma of the colon with amebic liver abscess mimicking metastatic colon cancer." Indian J Pathol Microbiol **52**(2): 228-30.

Amebic colitis is common in developing countries, with its variable and non-specific symptoms. Amebomas occur rarely, resulting from the formation of annular granulation tissue, usually in the cecum and in the ascending colon. This report describes the case of a 59-year-old male who presented with abdominal pain. Radiological examination depicted concentric thickening of the cecal wall with mass formation and a cystic lesion in the liver. The endoscopy performed showed a growth in the ascending colon. Biopsy revealed extensive necrosis and inflammatory cells. The patient was referred to this hospital for surgical treatment with a provisional diagnosis of carcinoma of the colon. Peroperatively, a cecal mass was identified. However, suspected secondaries were not seen on the surface of the liver. Histological examination of the right hemicolectomy specimen revealed cecal and ascending colon amebomas. Trophozoites of Entamoeba histolytica were better recognized after periodic acid-Schiff staining. Treatment with Metronidazole for 2 weeks followed by diloxanide furoate for an additional 2 weeks was administered. The liver lesion resolved completely after 8 weeks. Colonic ameboma accompanied by amebic liver abscess may be misdiagnosed as metastatic colon cancer. A high index of suspicion is essential for diagnosis when dealing with colonic masses and liver lesions, especially in the tropics.

Fu, S. L., J. Pierre, et al. (2008). "Immunoglobulin E antibodies from pancreatic cancer patients mediate antibody-dependent cell-mediated cytotoxicity against pancreatic cancer cells." Clin Exp Immunol **153**(3): 401-9.

In addition to allergy and parasitic infections, immunoglobulin E (IgE) has been shown recently to possess anti-viral and anti-cancer effects. We investigated serum levels of IgE, its low-affinity receptor, soluble CD23 (sCD23) in patients with pancreatic cancer and the effect of IgE against pancreatic cancer cells. Twelve patients were evaluated for pancreatic cancer by imaging and confirmed by biopsy. Fifteen healthy volunteers served as controls. Serum Igs (IgG, IgM, IgA, IgE) and sCD23 levels were determined (enzyme-linked immunosorbent assay, nephelometry) and the presence of cancer-specific IgE was assessed (fluorescence microscopy, Western blot). IgE anti-cancer activity was determined by antibody-dependent cell-mediated cytotoxicity (ADCC). Serum levels of IgE and sCD23

were elevated significantly in patients with pancreatic cancer versus controls, whereas no differences were observed in other Ig isotypes (IgG, IgM, IgA). Flow cytometry and immunofluorescence microscopy demonstrated similar presence of IgG and IgE pancreatic cancer Igs. However, Western blot analysis indicated differences in IgG and IgE antigen-specific antibodies; IgE antibody recognized a 50 kD protein. ADCC studies demonstrated that serum and purified IgE-mediated cytotoxicity against pancreatic cancer cells, effects which were reversed with anti-IgE neutralizing antibody and IgE depletion (immunoaffinity); greater cytotoxicity was observed in patient serum when compared with healthy controls. These data suggest that IgE and sCD23 may serve as useful biomarkers for patients with pancreatic cancer and may be important in the immune response to this disease in that IgE-directed therapy may help to direct treatment.

Grandics, P. (2006). "The cancer stem cell: evidence for its origin as an injured autoreactive T cell." Mol Cancer **5**: 6.

This review explores similarities between lymphocytes and cancer cells, and proposes a new model for the genesis of human cancer. We suggest that the development of cancer requires infection(s) during which antigenic determinants from pathogens mimicking self-antigens are co-presented to the immune system, leading to breaking T cell tolerance. Some level of autoimmunity is normal and necessary for effective pathogen eradication. However, autoreactive T cells must be eliminated by apoptosis when the immune response is terminated. Apoptosis can be deficient in the event of a weakened immune system, the causes of which are multifactorial. Some autoreactive T cells suffer genomic damage in this process, but manage to survive. The resulting cancer stem cell still retains some functions of an inflammatory T cell, so it seeks out sites of inflammation inside the body. Due to its defective constitutive production of inflammatory cytokines and other growth factors, a stroma is built at the site of inflammation similar to the temporary stroma built during wound healing. The cancer cells grow inside this stroma, forming a tumor that provides their vascular supply and protects them from cellular immune response. As cancer stem cells have plasticity comparable to normal stem cells, interactions with surrounding normal tissues cause them to give rise to all the various types of cancers, resembling differentiated tissue types. Metastases form at an advanced stage of the disease, with the proliferation of sites of inflammation inside the body following a similar mechanism. Immunosuppressive cancer therapies inadvertently re-invigorate pathogenic microorganisms and parasitic infections common to cancer, leading to a vicious circle of infection, autoimmunity and malignancy that ultimately dooms cancer patients. Based on this new understanding, we recommend a systemic approach to the development of cancer therapies that supports rather than antagonizes the immune system.

Guarner, J., T. Matilde-Nava, et al. (1997). "Frequency of intestinal parasites in adult cancer patients in Mexico." Arch Med Res **28**(2): 219-22.

Approximately 28% of the Mexican population has intestinal parasites. Oncologic patients receiving chemotherapy should have a coproparasitoscopic study to avoid disseminated parasitic infections. The frequency of intestinal parasites, including Cryptosporidium and Isospora, was evaluated in 100 diarrheic (DS) and 100 formed stools (FS) from adult patients recently diagnosed with cancer, using wet mounts stained with Kinyoun, saccharose and ZnSO4 procedures stained with Lugol's iodine. Seven patients with DS and three with FS had more than one parasite. Pathogenic intestinal parasites were seen in 26% of DS and 15% of FS. Of the frequent parasites, Entamoeba histolytica was found in 12 DS and in 2 FS ($p = 0.01$), Giardia lamblia in three DS and six FS and Hymenolepis nana in eight DS and 10 FS. Other pathogenic parasites were found only in DS: Cryptosporidium sp. in five patients, Ascaris lumbricoides in two, Strongyloides stercoralis in two and Isospora sp. in one. Cryptosporidium and Isospora were only identified by wet mounts stained with Kinyoun while other parasites were identified by flotation procedures. Since six (3%) of our patients had coccidia, the laboratory must perform special techniques for their detection. In epidemiologic settings where there is a high prevalence of intestinal parasitic infections the coproparasitoscopic studies should be performed and antiparasitic treatment provided before starting chemotherapy.

Hashimoto, H., S. M. Messerli, et al. (2009). "Ivermectin inactivates the kinase PAK1 and blocks the PAK1-dependent growth of human ovarian cancer and NF2 tumor cell lines." Drug Discov Ther **3**(6): 243-6.

Ivermectin is an old anti-parasitic antibiotic which selectively kills nematodes at a very low dose (0.2 mg/kg) by inhibiting their GABA (gamma-aminobutyric acid) receptor, but not mammalian counterpart. Interestingly, several years ago it was reported by a Russian group that Ivermectin can suppress almost completely the growth of human melanoma and a few other cancer xenografts in mice at the much higher doses (3-5 mg/kg) without any adverse effect on mice. However, its anti-cancer

mechanism still remained to be clarified at the molecular levels, that would determine the specific type of cancers susceptible to this drug. The first hint towards its anti-PAK1 potential was a recent finding that Ivermectin at its sublethal doses dramatically reduces the litter size (number of eggs laid) of the tiny nematode C. elegans. Interestingly, either a PAK1-deficiency (gene knock-out) or treatment with natural anti-PAK1 products such as CAPE (caffeic acid phenethyl ester) and ARC (artepillin C), the major anti-cancer ingredients in propolis, also causes the exactly same effect on this nematode, suggesting the possibility that the kinase PAK1 might be a new target of Ivermectin. This kinase is required for the growth of more than 70% of human cancers such as pancreatic, colon, breast and prostate cancers and NF (neurofibromatosis) tumors. Here we demonstrate for the first time that Ivermectin blocks the oncogenic kinase PAK1 in human ovarian cancer and NF2-deficient Schwannoma cell lines to suppress their PAK1-dependent growth in cell culture, with the IC50 between 5-20 muM depending on cell lines.

Heyns, C. F. and A. van der Merwe (2008). "Bladder cancer in Africa." Can J Urol **15**(1): 3899-908.

Accurate epidemiological data about the incidence and mortality of bladder cancer are unavailable for most African countries. Transitional cell carcinoma (TCC) of the bladder is probably less common in rural African regions than in industrialized countries, due to lower levels of exposure to carcinogenic chemicals. In areas with endemic schistosomiasis (bilharzia) caused by parasitic schistosomes (blood flukes), most bladder cancer cases are comprised of squamous cell carcinoma (SCC). However, with increased urbanization, industrialization, and cigarette smoking in many African countries, there is an increasing incidence of TCC relative to SCC of the bladder. SCC of the bladder presents in patients who are on average 10 to 20 years younger than those with TCC. In Egypt and other North African countries, SCC is more common in men (the male to female ratio ranges from 3:1 to 5:1), probably because boys and men performing agricultural work are more exposed to schistosomiasis-infested water. In some sub-Saharan countries, SCC of the bladder is equally common in men and women, probably due to equal schistosomiasis exposure of girls and boys, and because women obtain household water and perform most agricultural tasks. Although SCC of the bladder often presents at a locally advanced stage, the tumors are usually well differentiated, with a relatively low incidence of lymphatic and hematogenous metastases. Patients with localized SCC are ideal candidates for cystectomy and orthotopic neobladder construction, because they are relatively young and healthy, and there is no risk of urethral recurrence, unlike with TCC. Unfortunately, many patients in Africa still present with advanced and inoperable bladder cancer, and many do not have access to healthcare facilities that can provide a cure and a good quality of life by means of radical cystectomy and neobladder construction.

Ishii, A., H. Matsuoka, et al. (1994). "Parasite infection and cancer: with special emphasis on Schistosoma japonicum infections (Trematoda). A review." Mutat Res **305**(2): 273-81.

This article contains a review of current knowledge on the association of parasite infections and cancer formation, especially that of Schistosoma japonicum (Trematoda) in man and experimental animals. The association of S. haematobium infection and bladder cancer is well known and documented. However, S. japonicum infection has also been reported to be associated with cancer, in this case hepatocellular carcinoma and/or colorectal cancer. Pathological records and analyses have shown a correlation between this infection and cancer, and pathohistological descriptions have been numerous, together with clinical case reports. Epidemiological analyses have been conducted in China and Japan and support a role of S. japonicum infection as one of the risk factors in cancer formation, along with others, such as hepatitis virus infection and alcoholic intake. Experimental results have also shown that cancer appears early and in larger numbers in experimentally infected animals given a known carcinogen. In spite of these positive end-point associations, the mechanism of schistosome-mediated enhancement of carcinogenesis is obscure. A suggestive observation is that in S. japonicum-infected mice carcinogen-metabolizing hepatic activity including P-450 was decreased so that an administered carcinogen persisted for a longer period than in uninfected mice. Further studies, both epidemiological and experimental, are needed to firmly establish the relationship between schistosome infection and cancer.

Johnston, W. W. (1986). "Cytologic diagnosis of lung cancer. Principles and problems." Pathol Res Pract **181**(1): 1-36.

This diagnostic seminar discusses the current status of the principles and problems of cytology as it is applied to the diagnosis of lung cancer. This discussion is divided into four major parts. Part I presents a discussion of cytopreparatory techniques and cytology of the lung in the absence of cancer. The cytology of benign proliferations which may mimic cancer is emphasized. The role of cytology in the diagnosis of pulmonary infectious organisms is noted.

Part II discusses lung cancer as manifested in specimens of sputum, bronchial washings, and bronchial brushings. Part III presents some data on the validity of cytology with respect to role of specimen number and type in lung cancer diagnosis and cell typing in lung cancer. The continued usefulness and importance of multiple specimens of sputum for lung cancer diagnosis are documented. Part IV presents a brief synopsis of fine needle aspiration biopsy of lung cancer.

Lowenfels, A. B. and P. Maisonneuve (2006). "Epidemiology and risk factors for pancreatic cancer." Best Pract Res Clin Gastroenterol **20**(2): 197-209.

Pancreas cancer is considered an 'orphan' cancer because of its relative low incidence. Unfortunately even with early diagnosis, mortality rates are high, explaining why, despite the low incidence, it ranks eighth in a world listing of cancer mortality. International incidence rates vary in different countries, implying that environmental factors are important. Of these factors, smoking is the most well documented etiologic agent, explaining about 25% of all cases. Dietary factors may be important, but it has been difficult to define specific items which either increase or decrease the risk of pancreatic cancer. Since the incidence of pancreas cancer is so strongly age-dependent, we can anticipate an increasing number of patients as the population of most Western countries ages.

Madhusudhan, K. S., S. Gamanagatti, et al. (2007). "Pulmonary infections mimicking cancer: report of four cases." Singapore Med J **48**(12): e327-31.

Lung infections infrequently simulate cancer, and their differentiation, based on imaging findings, can sometimes be difficult. The infections may be fungal, mycobacterial, parasitic or, rarely, viral. A biopsy is required to prove the infectious nature of the lesions. A specific diagnosis is necessary for initiation of appropriate therapy. We report four cases of chronic pulmonary infections, which were wrongly diagnosed as bronchogenic carcinoma based on radiological features. We also reviewed the existing literature.

Mansky, P. J. (2002). "Mistletoe and cancer: controversies and perspectives." Semin Oncol **29**(6): 589-94.

Extracts and preparations from the tree parasitic plant mistletoe (Viscum album L.) have been used in the treatment of cancer for decades. Numerous preclinical and in vitro studies have reported immunostimulatory, cytotoxic, and proapoptotic effects. Translation of these effects into clinical response continues to pose a problem. While a number of clinical studies have found improvement in quality of life (QOL), data on the efficacy of mistletoe to prolong survival are conflicting and of variable quality. Clinical trial data regarding the toxicity and pharmacokinetics of mistletoe components with known in vitro or preclinical activity are lacking. Mistletoe is a widely used form of complementary and alternative medicine (CAM) for cancer treatment, and research into its use poses the challenges of translation of preclinical data into demonstrable clinical efficacy and investigating CAM approaches as a component of complex cancer treatment systems.

Mantovani, M. S., M. F. Bellini, et al. (2008). "beta-Glucans in promoting health: prevention against mutation and cancer." Mutat Res **658**(3): 154-61.

The polysaccharides beta-glucans occur as a principal component of the cellular walls. Some microorganisms, such as yeast and mushrooms, and also cereals such as oats and barley, are of economic interest because they contain large amounts of beta-glucans. These substances stimulate the immune system, modulating humoral and cellular immunity, and thereby have beneficial effect in fighting infections (bacterial, viral, fungal and parasitic). beta-Glucans also exhibit hypocholesterolemic and anticoagulant properties. Recently, they have been demonstrated to be anti-cytotoxic, antimutagenic and anti-tumorogenic, making them promising candidate as pharmacological promoters of health.

Menon, B. S., M. S. Abdullah, et al. (1999). "Intestinal parasites in Malaysian children with cancer." J Trop Pediatr **45**(4): 241-2.

In this prospective study, we examined stool specimens from children with cancer receiving chemotherapy who were admitted for fever to the Universiti Sains Malaysia Hospital in Kota Baru, Kelantan. Stool specimens were examined for ova and cysts of parasites. Over a period of 15 months, there were 129 febrile episodes in 50 children with cancer and, in all, 237 stool specimens were examined. Sixty-six per cent of febrile episodes were associated with neutropenia and 9 per cent were associated with diarrhoea. Stool parasites were found in 42 per cent of children. The most common were helminths, followed by protozoa. Trichuris trichiura was the most common parasite (24 per cent), followed by Ascaris lumbricoides (22 per cent). Hookworm was found in 2 per cent. Giardia lamblia was found in 6 per cent of children, Blastocystis hominis in 4 per cent, and Cryptosporidium parvum in 2 per cent.

Miller, R. W. (1978). "Environmental causes of cancer in childhood." Adv Pediatr **25**: 97-119.

Although it is commonly said that only a small proportion of childhood cancers are caused by environmental exposures, much has been learned about exogenous carcinogens through study of their effects or noneffects in children: 1. Ionizing radiation poses some risk no matter how small the dose. 2. Concepts about the viral etiology of cancer have had to be adapted to fit observations in children concerning candidate viruses. 3. Transplacental chemical carcinogenesis has become a reality and poses an increasing threat as chemical pollution worsens. 4. Questions have been raised about the risk of breast feeding in (at present) rare instances when the mother has been heavily exposed to chemicals that are excreted in the fat of breast milk. 5. A few drugs administered to children induce cancers within the pediatric age-span. The pediatrician must take action not only against exogenous agents that induce cancer while the patient is under his care, but also against exposures that begin in utero and lie latent or accumulate throughout life to give rise to cancers in the years or decades ahead. There is much more to carcinogenesis than the effects of the environment. Important information has been gained about the origins of cancer and about human biology in general through studies of children who are unusually susceptible to certain forms of neoplasia. Knowing the mechanisms involved may lead to new modes of treatment, to screening tests for environmental carcinogens or to methods for detecting cancer early enough for treatment to be life-saving.

Ming-Chai, C., C. Chi-Yuan, et al. (1980). "Evolution of colorectal cancer in schistsosomiasis: transitional mucosal changes adjacent to large intestinal carcinoma in colectomy specimens." Cancer **46**(7): 1661-75.

In this study of 454 colorectal carcinoma colectomy specimens, (289 were associated with and 165 were unassociated with schistosomiasis. Schistosome infestation was found to play an etiologic role in bowel malignancy in patients having diffuse involvement of the large intestine and a history of ten years or more of colitic symptoms. Diminutive polyps, pseudopolyps, ectopically proliferating glands, disintegrated muscularis mucosae, denudation, and multicentric carcinoma were frequently encountered in the schistosomiasis-associated (SA) group, whereas papillary and adenomatous polyps were most common in the schistosomiasis nonassociated (SN) group. Pseudopolyposis, ectopically regenerating glands, and multicentricity are thought to be predisposing factors in the development of colorectal cancer. This sequence of events is analogous to the development of carcinoma in ulcerative colitis.

Monceviciute-Eringiene, E. (1996). "Cancer and malignant resistance of cells as phenomena of adaptation to damaging factors." Med Hypotheses **46**(5): 459-62.

I propose the hypothesis that mechanisms of general biological persistent resistance to damaging factors are closely related to the development of tumour cells. This phenomenon is characteristic of bacterial variants whose resistance to antibiotics and other chemotherapeutic drugs appears through L-transformation. As somatic cells are exposed to carcinogens and develop into tumour cells, they also acquire resistance to the toxic effects of carcinogens through multistage malignant transformation. Many cancerous cells, which have acquired persistent resistance to chemotherapy drugs or irradiation, often reappear locally or in metastases after courses of treatment. Thus, these cells undergo a kind of repeated development of malignancy. After a certain remission period, they begin to multiply more intensively locally, and are more likely to spread by metastasis. All resistant cells have the following characteristics: simplified metabolism, genetic, biochemical and morphological properties; lower requirements from their nutrient medium; rapid growth; parasitic qualities; invasiveness. It is as if they regress into a more primitive mode of existence (atavism) to survive under unfavourable circumstances. Somatic cells, resistant to carcinogens and the cells which undergo progression to more malignant types under the influence of drugs become similar to unicellular organisms or to forms of the latter which are resistant to damaging factors. The more primitive the cells become, the better they survive. Thus, cancer is a special case of the general resistance of cells to damaging factors.

Monceviciute-Eringiene, E. (2005). "Neoplastic growth: the consequence of evolutionary malignant resistance to chronic damage for survival of cells (review of a new theory of the origin of cancer)." Med Hypotheses **65**(3): 595-604.

In the present review, a new theory that the mechanisms of general evolutionary persistent resistance to damaging factors are closely related to the development of tumour cells is introduced. Evolutionary resistance and its variability have an immense power to drive and control the process of carcinogenesis and the success of microbial and antitumour chemotherapy. First, this phenomenon of adaptation is characteristic of microbial cells whose resistance to antibiotics and other chemotherapeutic drugs is manifested through ATP-dependent transmembrane transporters. The structure and function of some multidrug transporters of resistance are conserved from microorganisms to mammals.

When somatic cells are exposed to carcinogens and develop into tumour cells, they also acquire resistance to the toxic effects of carcinogens through these same transmembrane transporters (P-glycoprotein, glutathione S-transferases and other products of evolutionary resistance-related genes arisen for detoxification and exportation of cytotoxic xenobiotics and drugs). Cancerous cells acquire a persistent evolutionary resistance to chemotherapy drugs or irradiation through the same ATP-dependent transporters encountered in prokaryotic and eukaryotic cells. The mechanism of acquired resistance of cells to damaging factors, which becomes manifested during tumorigenic process formation, is a general biological law of primary significance in carcinogenesis. This resistance can be called malignant as, once formed, it does not disappear, as does also a clone of malignant cells. In tumorous cells, the mutagenic processes, morphological and functional modifications are a mechanism of secondary significance in carcinogenesis, contributing to formation of damage-resistant cells. This mechanism characterizes the processes of simplification arising in damage-resistant cells. Such cells acquire parasitic features. To survive under unfavourable conditions, they get adapted as if returning down the evolutionary stairs back to a more primitive stage of atavistic regression, which is characteristic of primitive forms of existence. Therefore they cease obeying the growth-regulating mechanisms in the organism and acquire the potential of unlimited division and accelerated growth (metastases) as do unicellular organisms or their forms resistant to damaging factors in the environment and in the host organism. Thus, cancer is a natural self-protective response of the damaged cells to the biological, physical and chemical damage and oxidative stress. This response has been developed in the process of evolution under the impact of the general biological Darwinian law of nature--to survive through variability and adaptation to the changed environmental conditions. Thus, malignization is the consequence of an evolutionary variety of the general biological resistance of cells to damage and stress in order to survive.

Muller, J., D. Sidler, et al. (2008). "Thiazolides inhibit growth and induce glutathione-S-transferase Pi (GSTP1)-dependent cell death in human colon cancer cells." Int J Cancer **123**(8): 1797-806.

Thiazolides are a novel class of broad-spectrum anti-infective drugs with promising in vitro and in vivo activities against intracellular and extracellular protozoan parasites. The nitrothiazole-analogue nitazoxanide (NTZ; 2-acetolyloxy-N-(5-nitro 2-thiazolyl) benzamide) represents the thiazolide parent compound, and a number of bromo- and carboxy-derivatives with differing activities have been synthesized. Here we report that NTZ and the bromo-thiazolide RM4819, but not the carboxy-thiazolide RM4825, inhibited proliferation of the colon cancer cell line Caco2 and nontransformed human foreskin fibroblasts (HFF) at or below concentrations the compounds normally exhibit anti-parasitic activity. Thiazolides induced typical signs of apoptosis, such as nuclear condensation, DNA fragmentation and phosphatidylserine exposure. Interestingly, the apoptosis-inducing effect of thiazolides appeared to be cell cycle-dependent and induction of cell cycle arrest substantially inhibited the cell death-inducing activity of these compounds. Using affinity chromatography and mass spectrometry glutathione-S-transferase P1 (GSTP1) from the GST class Pi was identified as a major thiazolide-binding protein. GSTP1 expression was more than 10 times higher in the thiazolide-sensitive Caco2 cells than in the less sensitive HFF cells. The enzymatic activity of recombinant GSTP1 was strongly inhibited by thiazolides. Silencing of GSTP1 using siRNA rendered cells insensitive to RM4819, while overexpression of GSTP1 increased sensitivity to RM4819-induced cell death. Thiazolides may thus represent an interesting novel class of future cancer therapeutics.

Nakashima, T., K. Okuda, et al. (1975). "Primary liver cancer coincident with Schistosomiasis japonica. A study of 24 necropsies." Cancer **36**(4): 1483-9.

The etiologic relationship of parasitic liver disease to primary liver cancer has long been debated. For this reason, a review of 4611 necropsies was carried out to determine the frequency with which hepatocellular carcinoma occurred in association with schistosomiasis. Of 227 cases of hepatocellular carcinoma, 24 (10.6%) were associated with schistosomiasis japonica. This was significantly higher than the incidence of this carcinoma without schistosomiasis (2.78%). The majority of the 24 cases exhibited the features of a mixed macronodular and micronodular cirrhosis (Gall's posthepatitic cirrhosis); this was super-imposed upon and caused a masking of schistosomiasis fibrosis. By radioimmunoassay hepatitis B antigen was positive in 27% of these cases. A review of the literature indicated that chronic schistosomiasis, on its own, is unlikely to be the cause of primary liver cell carcinoma. Histologic features resembling post-hepatitic cirrhosis combined with a high frequency of hepatitis B antigen suggest that viral hepatitis rather than S. japonicum is the more likely etiologic factor involved, or has a synergistic effect on carcinogenesis.

Ohashi, K., H. Winarno, et al. (2003). "Indonesian medicinal plants. XXV. Cancer cell invasion

inhibitory effects of chemical constituents in the parasitic plant Scurrula atropurpurea (Loranthaceae)." Chem Pharm Bull (Tokyo) **51**(3): 343-5.

Six fatty acids (1-6), two xanthines (7, 8), two flavonol glycosides (9, 10), one monoterpene glucoside (11), one lignan glycoside (12), and four flavanes (13-16) were clarified by a bioassay-guided separation as chemical constituents of Scurrula atropurpurea (Loranthaceae), a parasitic plant of the tea plant Thea sinensis (Theaceae). Among these constituents, it was found that the alkynic fatty acid octadeca-8,10,12-triynoic acid (6) exhibits a more potent inhibitory effect on cancer cell invasion in vitro than flavanes [(+)-catechin (13), (-)-epicatechin (14), (-)-epicatechin-3-O-gallate (15) and (-)-epigallocatechin-3-O-gallate (16)].

Ohshima, H. and H. Bartsch (1994). "Chronic infections and inflammatory processes as cancer risk factors: possible role of nitric oxide in carcinogenesis." Mutat Res **305**(2): 253-64.

Infection by bacteria, parasites or viruses and tissue inflammation such as gastritis, hepatitis and colitis are recognized risk factors for human cancers at various sites. Nitric oxide (NO) and other oxygen radicals produced in infected and inflamed tissues could contribute to the process of carcinogenesis by different mechanisms, which are discussed on the basis of authors' studies on liver fluke infection and cholangiocarcinoma development. A similar mechanism could apply to other suspected and known cancer-causing agents including Helicobacter pylori infection (stomach cancer) or asbestos exposure (lung mesothelioma). Studies on the type of tissue and DNA damage produced by NO and by other reactive oxygen species are shedding new light on the molecular mechanisms by which chronic inflammatory processes may initiate or enhance carcinogenesis in humans.

Oliveira, J., L. Ralton, et al. (2007). "The synthesis and the in vitro cytotoxicity studies of bisnaphthalimidopropyl polyamine derivatives against colon cancer cells and parasite Leishmania infantum." Bioorg Med Chem **15**(1): 541-5.

Bisnaphthalimidopropyl derivatives (BNIPSpd, BNIPDaoct, BNIPDanon, BNIPDadec, BNIPDpta and BNIPDeta) were synthesised in yields ranging from 50% to 70% and their cytotoxicity against colon cancer cells (Caco-2) and the parasite Leishmania infantum determined using the MTT assay. Cytotoxicity within Caco-2 cells was manifested with IC(50) values between 0.3 and 22 microM. Compounds with the central longer alkyl chains exhibited the highest cytotoxicity. Against L. infantum, IC(50) values were encompassed within a narrower concentration range of 0.47-1.54 microM. In the parasites, the presence of nitrogen in the central chain and the length of the central alkyl chains did not especially enhance cytotoxicity. This may be due to the way these compounds are transported in the cells.

Ouaissi, A. and M. Ouaissi (2005). "Molecular basis of Trypanosoma cruzi and Leishmania interaction with their host(s): exploitation of immune and defense mechanisms by the parasite leading to persistence and chronicity, features reminiscent of immune system evasion strategies in cancer diseases." Arch Immunol Ther Exp (Warsz) **53**(2): 102-14.

A number of features occurring during host-parasite interactions in Chagas disease caused by the protozoan parasite, Trypanosoma cruzi, and Leishmaniasis, caused by a group of kinetoplastid protozoan parasites are reminiscent of those observed in cancer diseases. In fact,although the cancer is not a single disease, and that T.cruzi and Leishmania are sophisticated eukaryotic parasites presenting a high level of genotypic variability the growth of the parasites in their host and that of cancer cells share at least one common feature, that is their mutual capacity for rapid cell division. Surprisingly, the parasitic diseases and cancers share some immune evasion strategies. Consideration of these immunological alterations must be added to the evaluation of the pathogenic processes. The molecular and functional characterization of virulence factors and the study of their effect on the arms of the immune system have greatly improved understanding of the regulation of immune effectors functions. The purpose of this review is to analyze some of the current data related to the regulatory components or processes originating from the parasite that control or interfere with host cell physiology. Attempts are also made to delineate some similarities between the immune evasion strategies that parasites and tumors employ. The elucidation of the mode of action of parasite virulence factors toward the host cell allow not only provide us with a more comprehensive view of the host-parasite relationships but may also represent a step forward in efforts aimed to identify new target molecules for therapeutic intervention.

Ouaissi, M. and A. Ouaissi (2006). "Histone deacetylase enzymes as potential drug targets in cancer and parasitic diseases." J Biomed Biotechnol **2006**(2): 13474.

The elucidation of the mechanisms of transcriptional activation and repression in eukaryotic cells has shed light on the important role of acetylation-deacetylation of histones mediated by histone acetyltransferases (HATs) and histone deacetylases (HDACs), respectively. Another group belonging to the large family of sirtuins (silent

information regulators (SIRs)) has an (nicotinamide adenine dinucleotide) NAD(+)-dependent HDAC activity. Several inhibitors of HDACs (HDIs) have been shown to exert antitumor effects. Interestingly, some of the HDIs exerted a broad spectrum of antiprotozoal activity. The purpose of this review is to analyze some of the current data related to the deacetylase enzymes as a possible target for drug development in cancer and parasitic diseases with special reference to protozoan infections. Given the structural differences among members of this family of enzymes, development of specific inhibitors will not only allow selective therapeutic intervention, but may also provide a powerful tool for functional study of these enzymes.

Patton, S. E., M. C. Hall, et al. (2002). "Bladder cancer." Curr Opin Oncol **14**(3): 265-72.

Bladder cancer is a common and chemotherapy-responsive tumor, related to tobacco smoking, environmental arsenic exposure, industrial dye exposure, and parasitic schistosomiasis exposure. Both reduction of carcinogen exposure and chemoprevention, possibly with cyclooxygenase 2 inhibitors, should reduce the incidence. The search for the ideal screening and monitoring test continues with some promising new candidates, including survivin. Although 10-year survival can be achieved in 87% of early-stage patients with muscle-invasive disease rendered T(0) and 57% of those rendered T(1) at second look after transurethral resection bladder tumor, most still require radical cystectomy. Continued improvements in surgical techniques permit gains in quality of life after the procedure. Ten-year survival can still be achieved with cystectomy in the face of grossly positive lymph nodes in 32% of T(2) and 10% of T(3) patients. A recent meta-analysis indicates that preoperative irradiation is unlikely to be beneficial, but definitive chemoradiation can produce significant 5-year survival rates in nonoperative candidates and those desiring bladder preservation. The Intergroup now has preliminary data from a Southwest Oncology Group-based trial showing a significant benefit for neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin. The regimen of gemcitabine and cisplatin is equally efficacious with less toxicity than methotrexate, vinblastine, doxorubicin, and cisplatin. It has been adopted as the standard arm in a phase III trial for advanced bladder cancer, comparing it with the triplet of gemcitabine, paclitaxel, and cisplatin. Other active agents in bladder cancer include ifosfamide, carboplatin, docetaxel, and vinorelbine, and various doublets of these agents are being tested in phase II trials, with promising results.

Persing, D. H. and F. G. Prendergast (1999). "Infection, immunity, and cancer." Arch Pathol Lab Med **123**(11): 1015-22.

A significant percentage of human cancers worldwide are associated with infections due to known viruses, including human papillomaviruses (cervical cancer and other skin cancers), human T-lymphotropic viruses (adult T-cell leukemias and lymphomas in endemic areas), hepatitis B virus (liver cancer), and Epstein-Barr virus (Burkitt lymphoma and nasopharyngeal carcinoma). The fraction of human cancers attributable to infection may now need to be revised in light of the fact that new viral associations have been discovered and other nonviral associations have been identified. This article addresses the increasingly recognized role of infectious agents as precipitants of human neoplasia and the possibility that novel diagnostic, therapeutic, and chemopreventive strategies may emanate directly from research directed at identifying and understanding these agents.

Pidcock, N. B., E. H. Cooper, et al. (1984). "Immunoglobulin A, G and E levels in Egyptians with cancer: influence of schistosomiasis." Int J Cancer **33**(6): 771-5.

The main patient series consisted of 415 Egyptians attending the Cairo Cancer Institute and comprising 286 bladder cancer, 97 breast cancer, 14 head and neck cancer and 18 gastrointestinal cancer cases. Also included in the study were 36 patients with active schistosomiasis and 89 health controls. Serum IgA, IgG, IgG subclasses, IgE, Schistosoma and Ascaris-specific IgE (RAST) and the acute-phase protein CRP were measured in all, or sub-sets, of the main patient group. The well-established increase in IgE and IgG levels, and the more recently reported increase in the levels of IgG3 and IgG4 subclasses in patients with schistosomiasis, were also found in bilharzial bladder cancer, indicating that humoral immunity persists in cancer-bearing patients. However, the plasma protein profile in bilharzial bladder cancer is further modified by significant increases in the levels of IgA, IgG, IgG1, IgG2 and CRP when compared to levels in patients with Bilharzia in the absence of neoplastic change. Patients with cancers not associated with parasitic infestation also had significant increases in their serum levels of IgG1, IgG2, IgG, IgE and CRP when compared to healthy Egyptian controls, but 41% of these non-bladder cancer patients showed IgE responses to previous parasitic infestations suggesting that any immunological response to cancer would be on the background of a variable non-specific increase of IgE.

Richards, K. L., B. Zhang, et al. (2009). "Genome-wide hypomethylation in head and neck cancer is more pronounced in HPV-negative tumors and is associated with genomic instability." PLoS One **4**(3): e4941.

Loss of genome-wide methylation is a common feature of cancer, and the degree of hypomethylation has been correlated with genomic instability. Global methylation of repetitive elements possibly arose as a defense mechanism against parasitic DNA elements, including retrotransposons and viral pathogens. Given the alterations of global methylation in both viral infection and cancer, we examined genome-wide methylation levels in head and neck squamous cell carcinoma (HNSCC), a cancer causally associated with human papilloma virus (HPV). We assayed global hypomethylation levels in 26 HNSCC samples, compared with their matched normal adjacent tissue, using Pyrosequencing-based methylation assays for LINE repeats. In addition, we examined cell lines derived from a variety of solid tumors for LINE and SINE (Alu) repeats. The degree of LINE and Alu hypomethylation varied among different cancer cell lines. There was only moderate correlation between LINE and Alu methylation levels, with the range of variation in methylation levels being greater for the LINE elements. LINE hypomethylation was more pronounced in HPV-negative than in HPV-positive tumors. Moreover, genomic instability, as measured by genome-wide loss-of-heterozygosity (LOH) single nucleotide polymorphism (SNP) analysis, was greater in HNSCC samples with more pronounced LINE hypomethylation. Global hypomethylation was variable in HNSCC. Its correlation with both HPV status and degree of LOH as a surrogate for genomic instability may reflect alternative oncogenic pathways in HPV-positive versus HPV-negative tumors.

Rolston, K. V., S. Rodriguez, et al. (1997). "Pulmonary infections mimicking cancer: a retrospective, three-year review." Support Care Cancer **5**(2): 90-3.

Pulmonary infections can mimic or occasionally co-exist with pulmonary neoplasms. In order to determine the frequency and nature of these infections, we conducted a retrospective analysis, covering a 3-year period, of patients who were referred to our center with presumed lung cancer but turned out to have pulmonary infection instead. The overwhelming majority of patients (93.3%) referred to "rule out" lung cancer were documented as having a neoplastic process, and only 1.3% had an infection. Fungal infections (histoplasmosis, cryptococcosis, coccidiomycosis) accounted for 46%, mycobacteria for 27%, bacteria for 22%, and parasitic lesions (dirofilariasis) for 5% of these infections. The most common clinical manifestations were cough and chest pain, and the most common radiographic finding was a solitary pulmonary nodule. There were no specific clinical or radiographic features predictive of either infection or neoplastic disease. All patients responded to specific anti-infective therapy with or without surgical excision. Our data indicate that pulmonary infections mimic neoplasms very infrequently. However, establishing a specific diagnosis is critical, since the management and outcome of these two processes are entirely different.

Saenz, M. T., M. C. Ahumada, et al. (1997). "Extracts from Viscum and Crataegus are cytotoxic against larynx cancer cells." Z Naturforsch C **52**(1-2): 42-4.

The effects of hexanoic extracts of Viscum cruciatum Sieber parasitic on Crataegus monogyna Jacq. (I), Crataegus monogyna Jacq. parasitized with Viscum cruciatum Sieber (II), and Crataegus monogyna Jacq. non-parasitized (III), and of a triterpenes enriched fractions isolated from I, II and III (CFI, CFII, CFIII respectively), on the growth of HEp-2 cells have been evaluated. All the samples demonstrated significant cytotoxic activity against cultured HEp-2 cells, and all of them showed a stronger in vitro activity than 6-mercaptopurine solution used as a positive control. With the hexanoic extracts I, II and III almost similar activity was obtained, but the hexanoic extract I showed comparably better results. Almost complete inhibition was observed with triterpenes-enriched fractions CFI, CFII and CFIII, at the dose 6 micrograms/ml, after 72 h of treatment. The most intense response was obtained with the triterpenes-enriched fraction CFIII (from Crataegus monogyna non-parasitized), where the inhibition was 93%, but the fraction CFI and CFII showed similar inhibition (92% and 83%).

Salluh, J. I., F. A. Bozza, et al. (2005). "Cutaneous periumbilical purpura in disseminated strongyloidiasis in cancer patients: a pathognomonic feature of potentially lethal disease?" Braz J Infect Dis **9**(5): 419-24.

Cutaneous manifestations in disseminated strongyloidiasis are infrequent but should raise the suspicion for its diagnosis. We retrospectively evaluated the charts of six patients with cancer and a proven diagnosis of disseminated strongyloidiasis. All patients had received prophylaxis with albendazole before starting antineoplastic therapy, which included high-dose steroids. They presented with septic shock, acute respiratory failure and characteristic purpuric periumbilical skin lesions. Strongyloides larvae were identified in tracheal aspirates (n=5), gastric aspirates (n=4), lung (n=2) and skin biopsies (n=2). All patients

died despite antihelminthic therapy and intensive care support.

Samoszuk, M. (1997). "Eosinophils and human cancer." Histol Histopathol **12**(3): 807-12.

Eosinophils are rare granulocytes that are normally associated with allergic diseases or responses to various parasitic infections. Many types of human cancer, however, are also associated with extensive eosinophilia, either within the tumor itself, or in the peripheral blood, or in both locations. Special techniques such as autoflourescence or immunohistochemistry are sometimes needed to detect the presence of intact and degranulating eosinophils within the tumors. With the help of these techniques, extensive eosinophilia is most often seen in hematologic tumors such as Hodgkin's disease and certain lymphomas; however, many other types of cancer such as colon, cervix, lung, breast, and ovary also contain eosinophilia if diligently sought. Although the presence or absence of eosinophilia within these tumors does not appear to have a major influence on the prognosis of the patient, eosinophils may play an important role in the host interaction with the tumor, perhaps by promoting angiogenesis and connective tissue formation adjacent to the cancer. In addition, tumor-related eosinophilia provides some interesting clues into tumor biology, particularly with regard to production of cytokines by the tumor cells.

Scagliotti, G. V. and G. Selvaggi (2006). "Antimetabolites and cancer: emerging data with a focus on antifolates." Expert Opin Ther Pat **16**(2): 189-200.

Antimetabolites, especially antifolates, play an important role in the treatment of a variety of both malignant, and non-malignant diseases, such as rheumatoid arthritis, and bacterial and parasitic infections. Recently, new antimetabolites have become an area for anticancer drug expansion. Gemcitabine has emerged as an important new agent in several tumour types, including non-small cell lung cancer, pancreatic, bladder, breast and ovarian cancers. Capecitabine is an intriguing new prodrug, offering tumour selectivity and prolonged tumour exposure to 5-FU. More potent thymidylate synthase inhibitors have also been developed; raltitrexed and pemetrexed are now commercially available for the treatment of mesothelioma, non-small cell lung cancer and other solid cancer types. This review will describe the most recent findings and their potential clinical applications.

Schenkel, E., V. Berlaimont, et al. (1995). "Improved high-performance liquid chromatographic method for the determination of polyamines as their benzoylated derivatives: application to P388 cancer cells." J Chromatogr B Biomed Appl **668**(2): 189-97.

A simple reversed-phase HPLC method was developed for the determination of eight polyamines or monoacetylpolyamines, as their benzoylated derivatives. Interfering products, inherent to the benzoyl chloride derivatization technique (benzoic acid, methyl benzoate and benzoic anhydride), were identified. A new derivatization procedure for their total elimination was developed without any loss of sensitivity and selectivity. Not only the HPLC method was validated, but also the choice of an internal standard was investigated. The results show that it is possible to use this HPLC assay to determine the polyamine content in P388 cancer cells. Furthermore, the method is now being used to evaluate the uptake of various polyamines by P388 cancer cells and by other cancer and parasitic cells.

Schwartz, D. A. (1980). "Helminths in the induction of cancer: Opisthorchis viverrini, Clonorchis sinensis and cholangiocarcinoma." Trop Geogr Med **32**(2): 95-100.

Opisthorchis and Clonorchis parasitize the bile ducts of millions of persons in the Far East. The most important aspect of infection with these flukes is their ability to initiate cancer. Numerous studies have shown these flukes to occur in association with cholangiocarcinoma far more frequently than can be explained by chance. Experimental studies in animals have confirmed the carcinogenic potential of these parasites. Although the pathogenesis remains unclear, the initial carcinogenic event is probably a function of the length and severity of infection, the host's immune response, and such variables as ingestion of dietary carcinogens.

Shacter, E. and S. A. Weitzman (2002). "Chronic inflammation and cancer." Oncology (Williston Park) **16**(2): 217-26, 229; discussion 230-2.

A substantial body of evidence supports the conclusion that chronic inflammation can predispose an individual to cancer, as demonstrated by the association between chronic inflammatory bowel diseases and the increased risk of colon carcinoma. Chronic inflammation is caused by a variety of factors, including bacterial, viral, and parasitic infections, chemical irritants, and nondigestible particles. The longer the inflammation persists, the higher the risk of associated carcinogenesis. This review describes some of the underlying causes of the association between chronic inflammation and cancer. Inflammatory mediators contribute to neoplasia by inducing proneoplastic mutations, adaptive responses, resistance to apoptosis, and environmental changes such as stimulation of angiogenesis. All these changes

confer a survival advantage to a susceptible cell. In this article, we discuss the contribution of reactive oxygen and nitrogen intermediates, prostaglandins, and inflammatory cytokines to carcinogenesis. A thorough understanding of the molecular basis of inflammation-associated neoplasia and progression can lead to novel approaches to the prevention and treatment of cancer.

Sherman, P. W., E. Holland, et al. (2008). "Allergies: their role in cancer prevention." Q Rev Biol **83**(4): 339-62.

The nature of the biological relationships between cancers and allergies has intrigued researchers and health care providers for five decades. Three hypotheses have been proposed: antigenic stimulation predicts positive associations between cancers and allergies (i.e., allergy sufferers are more likely to get cancer), whereas immunosurveillance and prophylaxis predict inverse associations (i.e., allergy sufferers are less likely to get cancer). Immunosurveillance predicts inverse associations for cancers of all tissues and organ systems, and prophylaxis predicts inverse associations specifically for cancers of tissues and organ systems that interface with the external environment. To comparatively evaluate these hypotheses, we comprehensively reviewed the literature on cancer and allergies. We located 148 papers published from 1955 through 2006 that reported results of 463 studies of relationships between patients' histories of 11 specific allergies and cancers of 19 tissues and organ systems, and 183 studies of patients' histories of multiple allergies in relation to various types/sites of cancers. Analyses of these studies revealed that (1) frequencies of positive, inverse, and null allergy-cancer associations differed considerably among cancers of different tissues and organ systems; (2) more than twice as many studies reported inverse allergy-cancer associations as reported positive associations; (3) inverse associations were particularly common for cancers of the mouth and throat, brain glia, colon and rectum, pancreas, skin, and cervix but (4) particularly rare for cancers of the breast, prostate, and brain meninges, and for myeloma, non-Hodgkin's lymphoma, and myelocytic leukemia; (5) lung cancer was positively associated with asthma but inversely associated with other allergies; (6) inverse associations with allergies were more than twice as common for cancers of nine tissues and organ systems that interface with the external environment compared to cancers of nine tissues and organ systems that do not interface with the external environment; and (7) eczema, hives, and allergies to animal dander and food were most frequently inversely associated with cancers of tissues that interface with the external environment. Taken together, these results are more consistent with the prophylaxis hypothesis than the two alternatives. IgE is a widespread and ancient immunoglobulin isotype in mammals, occurring among all known marsupials, monotremes, and eutherians. The IgE system and its associated allergy symptoms may serve a common protective function: the rapid expulsion of pathogens, dangerous natural toxins, and other carcinogenic antigens before they can trigger malignant neoplasia in exposed tissues.

Sithithaworn, P., M. R. Haswell-Elkins, et al. (1994). "Parasite-associated morbidity: liver fluke infection and bile duct cancer in northeast Thailand." Int J Parasitol **24**(6): 833-43.

Infection with the liver fluke, Opisthorchis viverrini, remains a major public health problem in Northeast Thailand, where approximately one-third of the population is infected. The northeast region is largely populated by Laos-descendent Thais who enjoy eating raw fish, which harbour the infective stage of the fluke. The parasite has maintained its presence in the population despite the widespread use of praziquantel and dissemination of health education material throughout the region by vigorous government-sponsored programs in recent years. The most severe consequence of liver fluke infection is cholangiocarcinoma, i.e. cancer of the bile duct epithelium. Although mortality due to the parasites alone appears to be uncommon, cholangiocarcinoma arising as a result of infection is one of the leading causes of death in the region. This paper reviews the pathogenesis of infection and the geographic, hospital-based and community studies which demonstrate the close relationship between infection and cancer. In addition, data from the Cancer Registry of Khon Kaen, Northeast Thailand and population-based studies using ultrasonography to visualize early tumours which illuminate the very high frequency of the cancer among heavily infected individuals and communities are discussed. Finally, the paper will close with a brief commentary on the prospects for control of the parasite and its likely impact on the frequency of cancer given the current epidemiological situation of liver fluke infection.

Stentiford, G. D., K. S. Bateman, et al. (2007). "Enterospora canceri n. gen., n. sp., intranuclear within the hepatopancreatocytes of the European edible crab Cancer pagurus." Dis Aquat Organ **75**(1): 61-72.

Only 1 genus (Nucleospora) within 1 family (Enterocytozoonidae) of the Microsporidia contains species that are parasitic within the nuclei of their host cells; to date, all described intranuclear Nucleospora spp. parasitise fish. This study describes the first

intranuclear microsporidian parasite of an invertebrate, the European edible crab Cancer pagurus L. (Decapoda: Cancridae). Infected crabs displayed no obvious external signs, and maximum apparent prevalence of infection within a monthly sample was 3.45%. Infected hepatopancreatic tubules were characterised by varying numbers of hypertrophic and eosinophilic nuclei within epithelial cells. Parasite stages appeared as eosinophilic granular accumulations causing margination of host chromatin. In advanced cases, the tubule epithelia degenerated, with parasites and sloughed epithelial cells appearing in tubule lumens. All life stages of the parasite were observed within host nuclei. Uninucleate meronts were not detected, although binucleate stages were observed. Multinucleate plasmodia (sporogonal plasmodia) contained up to 22 nuclei in section, and late-stage plasmodia contained multiple copies of apparatus resembling the polar filament and anchoring disk, apparently associated with individual plasmodial nuclei. As such, aggregation and early assembly of sporoblast components took place within the intact sporogonial plasmodium, a feature unique to the Enterocytozoonidae. Liberation of sporoblasts from plasmodia or the presence of liberated sporoblasts was not observed in this study. However, large numbers of maturing and mature spores (measuring 1.3 +/- 0.02 x 0.7 +/- 0.01 microm) were frequently observed in direct contact with the host nucleoplasm. Considering the shared features of this parasite with microsporidians of the family Enterocytozoonidae, and the unique presence of this parasite within the nucleoplasm of decapod crustacean hepatopancreatocytes, this parasite (Enterospora canceri) is proposed as the type species of a new genus (Enterospora) of microsporidian. Molecular taxonomic work is now required, comparing Enterospora to Enterocytozoon and Nucleospora, the 2 other genera within the Enterocytozoonidae.

Stentiford, G. D., M. Green, et al. (2002). "Infection by a Hematodinium-like parasitic dinoflagellate causes Pink Crab Disease (PCD) in the edible crab Cancer pagurus." J Invertebr Pathol **79**(3): 179-91.

The edible crab (Cancer pagurus) supports a large and valuable fishery in UK waters. Much of the catch is transported live to continental Europe in specially designed live-well ('vivier') vehicles. During the winter of 2000/2001, many trap-caught crabs from Guernsey, Channel Islands, UK, were reportedly moribund and pink in colour. These crabs generally died before and during vivier transportation. We provide histological, immunological, and molecular evidence that this condition is associated with infection by a Hematodinium-like dinoflagellate parasite similar to that previously reported in C. pagurus and to an infection causing seasonal mass mortalities of the Norway lobster (Nephrops norvegicus). Pathologically, every altered host bore the infection, which was characterised by very large numbers of plasmodial and vegetative stages in the haemolymph and depletion of reserve cells in the hepatopancreas. Due to the hyperpigmentation of the carapace and appendages, we have called this infection 'Pink Crab Disease' (PCD). Similar Hematodinium infections cause 'Bitter Crab Disease' in tanner and snow crabs, which has had a negative effect on their marketability. At present, little is known about the seasonality, transmission, and market impact of this infection in C. pagurus.

Tarin, D. (2006). "New insights into the pathogenesis of breast cancer metastasis." Breast Dis **26**: 13-25.

Synthesis and integration of macroscopic and microscopic findings on the pathogenesis of breast cancer and metastasis with recent cellular and molecular research on these topics provides a modern re-evaluation of the disease, which is relevant to clinical efforts and further research. At a microscopic level, tumors are not merely aggregates of malignant cells but are maladjusted living entities, which recruit host stromal cells such as fibroblasts, endothelial cells, etc. with which they intermingle and interact. The result is the formation of an expanding, distorted but recognizable caricature of the histology of the organ from which they are derived, which destroys adjacent normal tissue. The acquisition of metastatic capability endows the tumor with unique powers to parasitize other organs of the living host, with which it shares near complete genetic identity. This exceptional situation renders the parasitic cells almost invisible to host defences and poses a grave threat to host survival. The disseminated cancer cells present to the host defences very much the same problem that a guerilla army presents to orthodox military forces, because the disorderly tumor cells are difficult to distinguish from normal ones and are distributed in small units, in a large terrain. Recent evidence of disturbed molecular interactions between the colonizing and host populations offers the idea that one might be able to deploy classical counter-insurgency concepts based upon the dual approach, firstly of denying support from the indigenous population, by using drugs and secondly, of infiltrating the cells from within, using targeted genetic vectors. Both of these therapeutic approaches are not yet within our grasp, but we have recognized the nature of the adversary and will eventually be able to design tools to undermine its drive and progress.

Thun, M. J., S. J. Henley, et al. (2004). "Inflammation and cancer: an epidemiological perspective." Novartis Found Symp **256**: 6-21; discussion 22-8, 49-52, 266-9.

Many chronic inflammatory conditions increase the risk of cancer in affected tissues. Clinical conditions that involve both inflammation and increased cancer risk include a broad range of immunological disorders, infections (bacterial, helminthic, viral), and chronic chemical and mechanical irritation. For example, the inflammatory bowel diseases, ulcerative colitis and Crohn's disease, predispose to the development of cancers of the large bowel and/or terminal ileum; chronic infection with the bacterium Helicobacter pylori causes atrophic gastritis, dysplasia, adenocarcinoma and an unusual form of gastric lymphoma; and parasitic infection with schistosomes and other trematodes cause cancers of the urinary bladder and the intrahepatic and extrahepatic biliary tract. Chronic reflux of gastric acid and bile into the distal oesophagus causes chemical injury, Barrett's oesophagus and oesophageal adenocarcinoma. Chronic cholecystitis and gallstones predispose to cancer of the gallbladder. Besides these clinical syndromes, subclinical inflammation may promote the development of certain tumours. The expression of COX-2 and lipid mediators of inflammation increases during the multistage progression of these tumours. Non-steroidal anti-inflammatory drugs (NSAIDs), which inhibit COX-2 activity and tumour development in many experimental and clinical settings, are inversely associated with certain cancers in epidemiological studies. Despite their promise, however, anti-inflammatory drugs are not yet recommended for the prevention or treatment of any cancers. Numerous questions must be resolved concerning their molecular and cellular targets of action, efficacy, safety, treatment regimen, indications, and the balance of risks and benefits from treatment in designated patient populations.

Traversa, D., S. Avolio, et al. (2008). "Copromicroscopic and molecular assays for the detection of cancer-causing parasitic nematode Spirocerca lupi." Vet Parasitol **157**(1-2): 108-16.

Spirocerca lupi (Nematoda, Spirurida) is a life-threatening parasitic nematode of dogs that is presently emerging in several countries. Nonetheless, canine spirocercosis is neglected and underestimated, mainly due to diagnostic limitations inherent to clinico-pathologic, diagnostic imaging and laboratory methodologies. Given the significant benefit of improved diagnosis, the present work evaluated the reliability of a recently described copromicroscopic approach, the FLOTAC technique, as well as a PCR-based assay with that of traditional coproscopic techniques to diagnose S. lupi infection. Ninety-four faecal field samples were collected from two endemic areas (i.e. 29 and 65 from Kenya and Israel, respectively) and processed using different coproscopic examination techniques. In particular, set I (Kenyan samples) comprised the modified flotation with Sheather's sugar solution and merthiolate-iodine-formalin technique, while set II (Israeli samples) comprised a flotation technique with zinc sulphate solution, a modified sugar flotation procedure and the FLOTAC method. All samples were also subjected to a semi-nested PCR protocol specific for a region internal to the mitochondrial cytochrome c oxidase subunit 1 gene of S. lupi. The coproscopic examinations showed low sensitivity and high variability, demonstrating the unreliability of the conventional methods for detecting S. lupi eggs. Nonetheless, the FLOTAC technique scored the highest number of positives and significantly higher number of S. lupi eggs per microscopic field compared to the other coproscopic methods. Additionally, of the coproscopically negative samples, 9 (45%) Kenyan and 21 (38.2%) Israeli samples scored molecularly positive using the PCR-based approach. The potential implications and perspectives for canine spirocercosis of these coproscopic and molecular diagnostic methodologies evaluated herein are discussed.

Trudeau, C., S. Yuan, et al. (2001). "A novel parasite-derived suicide gene for cancer gene therapy with specificity for lung cancer cells." Hum Gene Ther **12**(13): 1673-80.

The enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRT) expressed by the parasite Trypanosoma brucei (Tb) can convert allopurinol, a purine analogue, to corresponding nucleotides with greater efficiency than its human homologue. We have developed a retroviral system that expresses the parasitic enzyme and tested its capacity to activate the prodrug allopurinol to a cytotoxic metabolite. Cytotoxicity assays demonstrated that five non-small cell lung carcinoma cell lines transduced with the construct were sensitized to the prodrug by 2.1- to 7.6-fold compared with control values. This selectivity was not observed in seven other cell lines also expressing the construct, such as breast carcinoma. Assays indicated that enhanced cytotoxicity to allopurinol correlated with induction of apoptosis in lung cancer cells. The selectivity of this suicide gene was not explained either by the TbHGPRT expression or by the allopurinol accumulation. Our study shows that this novel system may represent a therapeutic tool for gene prodrug targeting of lung cancer, considering the fact that allopurinol is well tolerated in humans.

Tsutsumi, Y. and Y. Fujimoto (1983). "Early gastric cancer superimposed on infestation of an Anisakis-like larva: a case report." Tokai J Exp Clin Med **8**(3): 265-73.

This report describes a 73-year-old male with early gastric cancer (type IIc) superimposed on infestation of a parasitic larva. Eosinophilic granulomas surrounding a dead worm were seen in the submucosa just beneath the intramucosal tubular adenocarcinomatous lesion measuring 1 X 1cm at the anterior wall in the acid-secreting area. The cancer cells showed lowered and altered mucin production in comparison with the surrounding non-cancerous fundic mucosa. The parasite was identified as an Anisakis-like larva by the presence of typical lateral chords. An immunohistochemical examination revealed that the cancer cells were more strongly positive for IgA and secretory component than the surrounding non-cancerous mucosa, and that IgG, IgA and IgM were detected in plasma cells around the granulomas but IgE and IgD were not. The possibility that the Anisakis-like larva preferentially infested the cancerous mucosa because of the change in mucin, local defect in acid secretion and/or other structural alterations in the area is discussed.

Velimirovic, B. (1992). "Infection and cancer: current state of art." Eur J Epidemiol **8**(5): 715-22.

Empirical evidence of the association of cancer with parasitic and viral infectious agents has been recognized earlier. Today, viruses are thought to account for about 10% of all cancers and they take a central place in experimental cancer research. This area has expanded tremendously with modern molecular biology techniques, the knowledge of gene expression, cellular enzyme and mechanisms of transformation. However, the last proof of causality is not yet available. Serologic, virologic, experimental and protective evidence is needed to confirm the assumptions in this rapidly developing field of research. The prevention of hepato-cellular carcinoma by effective vaccines now available is, in the opinion of the WHO, at least theoretically possible.

Waku, M., L. Napolitano, et al. (2005). "Risk of cancer onset in sub-Saharan Africans affected with chronic gastrointestinal parasitic diseases." Int J Immunopathol Pharmacol **18**(3): 503-11.

Gastrointestinal Schistosomiasis and Amebiasis are uncommon in the western world, while such infections are frequent in the African community. In addition to the problems associated with the clinical symptoms of these parasitic infections, it is important to stress the increase in cancer of the Gastro-Intestinal (GI) tract. In this study we evaluate the prevalence of cancer in patients affected by chronic inflammatory diseases caused by the above named parasites. In three years, from January 2000 to December 2003, we observed a total of 1199 subject. Of these, 950 presented with complaints of diarrhoea, vomiting, abdominal pain, melena, hematemesis, rectal discharges and alteration of bowel habits. A total of 818 patients were evaluated in Uganda (Mulago and Arua hospitals) and 381 at Luisa Guidotti Hospital in Zimbabwe. An exhaustive clinical history was collected for each patient and then physical and laboratory examinations were performed. The clinical files of all patients previously admitted to the respective hospitals were obtained and the information taken from these files was then integrated with our clinical findings. Subjects who were found free of gastro-intestinal disease after examinations and did not have a clinical history of infective GI disease but presented with other pathologies, were regarded as control group. The control group was composed of 249 subjects. The subjects who were positive on examination underwent further investigations. The number of patients affected by schistosomiasis and amebiasis were 221 and 224 respectively. The number of patients who suffered from aspecific enterocolitis was 454, intestinal tuberculosis was present in 21 patients and we found 30 patients with esophageal candidiasis. Patients who had the above mentioned GI diseases were then divided into 3 groups. First group was composed of patients who had a clinical history of infective GI diseases and were re-admitted for similar symptoms, and on examination were positive for the presence of the same infective GI diseases. Such patients were placed in the Chronic group. The second group was formed of patients who had previously undergone treatment for infective GI diseases but on readmission were found free of infective GI disease, and this group was described as the Cured group. They had symptoms associated with other pathologies. A third group, which we described as the Acute group was composed of patients who did not have any previous case of GI infection and were admitted for the first time. Such patients were found positive on examination for infective GI diseases. In the 950 patients, we found a total of 45 tumors. The tumors were prevalent (42 tumors) in the chronic group. In 34 patients the tumor was in the colo-rectal region, in 3 patients in the stomach, in 4 patients in the esophagus and 1 patient had cancer in the small bowel. Our results show a strong association between the chronic infection of the GI tract and the likelihood to develop tumors. However, it is not clear which biological mechanisms are implicated in such transformations. They may depend on the chronic inflammation of the GI mucous which permits the

entrance of carcinogenic materials or on the effects of mutagenic products produced by the parasites or both.

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