two viruses capable of infecting endothelial cells to unmask receptors for the Fc fragment of IgG (and to a lesser extent for C3b) is likely to be of pathophysiologic importance. White blood cells activated by C5a or by immune complexes [as may occur in IgG aggregate anaphylaxis, chronic serum sickness, lupus erythematosus, and idiopathic pulmonary fibrosis (*12*)] marginate and attach to endothelial cells in vivo (*13*). Furthermore, endothelial cells infected with certain viruses have the capacity to bind PMN's, and the PMN's thus bound become adherent for other PMN's (*3*). White blood cell aggregates, such as those formed in anaphylaxis (*15*), might be expected to unmask Fc receptors on endothelial cells. The stagnant or reduced blood flow created by the mechanical blockage caused by white cell aggregates and emboli would provide favorable conditions for binding the Fc portion of aggregated IgG or immune complexes (both present in the plasma of anaphylactic subjects). In turn, endothelial cell–bound immune complexes would provide further stimulus for complement activation and complement-linked immune lysis. Presumably, this series of reactions would occur most prominently at the level of the microcirculation where mechanical blockage of blood flow would be most pronounced and where, in fact, the inflammatory response to, for example, anaphylaxis is most pronounced (*15*).

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Effect of Indomethacin on Intestinal Tumors Induced in Rats by the Acetate Derivative of Dimethylnitrosamine

Abstract. *Over the course of 20 weeks, Sprague-Dawley rats developed intestinal tumors in response to an intraperitoneal injection of the acetate derivative of dimethylnitrosamine. The same agent did not induce tumors in Lobund-Wistar rats. The number of tumors was significantly smaller in rats given drinking water containing indomethacin (beginning 14 days after the injections) than in control rats given drug-free water.*

It has been reported that DMN-OAc, the acetate derivative of dimethylnitrosamine, induces intestinal tumors in Sprague-Dawley rats after a single intraperitoneal injection (*1, 2*). Sprague-Dawley rats were more susceptible to tumor induction than Fischer 344 and Buffalo strain rats and, among them, males were more susceptible than females. A dose-related induction of intestinal tumors in Sprague-Dawley rats was demonstrated 20 weeks after one, five, and ten doses of 1,2-dimethylhydrazine (DMH; 30 mg per kilogram of body weight) were administered by gavage at weekly intervals. In further experiments with the same protocol, DMH did not induce intestinal tumors in Lobund-Wistar rats; methylazoxymethanol acetate (MAM), the active metabolite of DMH, induced tumors in both strains (*3*). Subsequently it was demonstrated that the number of rats with tumors induced by five doses of DMH could be reduced significantly by oral administrations of indomethacin, a nonsteroidal anti-inflammatory drug that blocks the synthesis of prostaglandins (*4*). In Sprague-Dawley rats that received a single dose of DMH, the antitumor effect of indomethacin was even more significant (*4*). Indomethacin also had an antitumor effect in rats that had been inoculated with a single dose of MAM.

To determine the effect of indomethacin on tumors induced by another carcinogen, we gave male Sprague-Dawley and Lobund-Wistar weanlings single intraperitoneal injections of DMN-OAc (13 mg/kg). Both strains were from a closed

Table 1. Induction of intestinal tumors by DMN-OAc.

Rat strain	Rats with tumors	Tumors in colon	Tumors in small intestine	Mean number of tumors per rat
Sprague-Dawley	28 of 39	19	34	1.4
Sprague-Dawley	8 of 9	6	13	2.1
Lobund-Wistar	0 of 10	0	0	
Sprague-Dawley	6 of 12	1	7	0.66
Lobund-Wistar	0 of 11	0	0	

Table 2. Effect of indomethacin on induction of intestinal tumors by DMN-OAc.

Treatment	Rats with tumors	Tumors in colon	Tumors in small intestine	Mean number of tumors per rat
Indomethacin	1 of 7	0	1	0.14*
Control	6 of 8	5	7	1.5
Indomethacin	0 of 5	0	0	
Control	8 of 10	7	7	1.4

*$P < .05$, Student's t-test.

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colony that had been propagated for 36 generations in this laboratory and in which "spontaneous" intestinal tumors have not been observed. The rats were maintained in plastic boxes under room conditions (72°F, 70 percent humidity, and a 12-hour light-dark cycle). They were fed sterilized Tek-Lad food (L-485) and provided with ground corncob bedding.

After 20 weeks intestinal tumors were found in 28 of the 39 Sprague-Dawley rats (average, 1.4 tumors per rat) (Table 1). More tumors developed in the small intestine than in the colon. None of the Lobund-Wistar rats developed tumors. Their unique resistance to the carcinogenic effects of DMH and DMN-OAc warrants further study, especially since the latter agent may be a direct carcinogen.

We then injected 30 Sprague-Dawley rats with DMN-OAc and, 14 days later, fed groups of them indomethacin (20 mg/liter) in their drinking water. Fresh indomethacin was provided at 3-day intervals. Control rats were given drug-free water. (It was calculated that the drug-treated rats consumed 3 mg of indomethacin per kilogram per day). All the rats were killed 20 weeks after the injections. In the two trials, the number of indomethacin-treated rats with intestinal tumors was significantly smaller than the number of control rats with tumors (Table 2). The control rats had tumors similar in size, number, and distribution to those described by Joshi *et al.* (*1*) and Berman *et al.* (*2*) and to those observed in the preliminary trials noted above.

It has been determined that DMN-OAc is inactivated within 48 hours after its injection into rats (*5*). Since the indomethacin treatments were started 14 days after the rats were injected with the carcinogen, the antitumor effect may be interpreted less as chemoprevention than as therapy or antipromotion. The results are in agreement with the antitumor effects of indomethacin in rats that were given DMN and MAM (*4, 6*).

Thus, indomethacin has a therapeutic or antipromotional effect against autochthonous intestinal tumors induced by DMH (*4*), MAM (*4, 7*), *N*-methyl-*N*-nitrosourea (*8*), and DMN-OAc. An interpretation of this effect is based on the production of prostaglandins by intestinal tumors (*9*). Agents that block the synthesis of prostaglandins may prevent development of the tumors. However, prostaglandins may not actually have a role in the cytostatic action of anti-inflammatory drugs (*7*).

Indomethacin has retarded the growth of transplanted tumors (*10*). The more precise effect on autochthonous tumors supports the proposition that primary tumors should be used in the assessment of putative anticancer agents. In this respect, indomethacin has been of some therapeutic value in humans with desmoid tumors (*11*). It is important to determine whether the antitumor activity of indomethacin is curative or suppressive, and whether it is effective on advanced intestinal tumors.

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Functional Characteristics of the Blood of the Deep-Sea Hydrothermal Vent Brachyuran Crab

Abstract. *Hemocyanin in the whole blood of the hydrothermal vent brachyuran crab,* Bythograea thermydron, *has a moderate oxygen affinity* (P_{50} = *6.6 millimeters of mercury at 2.6°C;* p*H 7.5), which unlike that of other hemocyanins is independent of temperature over the range 2° to 30°C; carbon dioxide and* p*H have independent effects on the oxygen affinity of this pigment. The* p*H effect on affinity is moderate* ($\Delta log\ P_{50}/\Delta pH = -0.34$), *whereas increased carbon dioxide, which can act both directly and by changing* p*H, has a much larger effect* ($\Delta log\ P_{50}/\Delta pH = -0.81$). *This blood has a moderately high degree of cooperativity (Hill cooperativity coefficient,* n, *was 2.8) and a large oxygen-carrying capacity for a crustacean (4.5 milliliters of oxygen per 100 milliliters of blood). These properties characterize an oxygen transport system whose function appears to be largely independent of the wide range of environmental conditions encountered around the vents.*

The brachyuran crab, *Bythograea thermydron*, is an active scavenger around the recently discovered deep-sea hydrothermal vents, at a depth of 2500 m (*1, 2*). Although typically found foraging among the vestimentiferan tube worms that are aggregated close to the vent fissures, the crabs have been observed throughout the vent area (*3*). Because of the rapid mixing of water emerging from the fissures (up to 22°C, anoxic, 350 μm of H_2S, *p*H 6.5) with the surrounding bottom water (2°C, 110 μm of O_2, no H_2S, *p*H 7.5), environmental conditions in the vent area are extremely variable in any one spot and change dramatically within distances of a few centimeters, exposing the crabs to an extreme range of physical and chemical conditions over intervals of the order of minutes (*1, 4*).

We examined the oxygenation characteristics of the whole blood of *B. thermydron* to gain insight into how animals live in this strange environment. We present data indicating that the hemocyanin of the hydrothermal vent crab has oxygenation characteristics that are in some ways unique and that suit this animal to an active life-style in the variable environment of the vents.

The crabs were collected by the submersible *Alvin* during November and December 1979 at the Galápagos Rift Valley sites Garden of Eden, Rose Garden, and Mussel Bed (*5*). Blood samples were taken with a hypodermic syringe from the arthrodial membranes at the bases of the walking legs of live animals that were freshly captured or had been maintained in pressure vessels at 250 atm and 5°C. Absorption spectra were obtained from fresh blood diluted with Millipore-filtered seawater and scanned from 760 to 320 nm. The spectra showed the large peak at 340 nm characteristic of crustacean hemocyanins.

Oxygen equilibrium curves of a small subsample of the fresh whole blood (2 to

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