Thus, both the incidence of restraint erosions and the change in behavioral arousal during restraint appear to be strongly influenced by the rats' body temperature. On the other hand, it is possible that these behavioral characteristics are secondary to the presence of painful gastric erosions rather than to hypothermia, per se.

To further evaluate the relation between erosion pathogenesis and body temperature we determined whether the extent of the fall in body temperature was correlated with the amount of mucosa eroded during restraint. Specifically, we predicted that, for each rat, body temperature at the end of the restraint period would correlate inversely with the total length (in millimeters) of its gastric erosions. We reviewed lesion length and temperature data on 322 restrained rats studied in various experiments in our laboratory. We found a correlation of $r = -.795$ ($P < .001$). This finding further supports the proposition that thermoregulatory failure is a critical variable in restrain erosion pathogenesis.

Although our data show that a specific set of behavioral responses (increased "arousal" during restraint) characterizes rats that are susceptible to gastric erosions, they fail to show that these behaviors affect the probability of erosion production. Instead, the findings demonstrate a relation between impaired thermoregulation and erosion production, and suggest that the behavioral changes during restraint are also, but independently, a consequence of these body temperature changes.

Our data provide a model for the study of how specific risk factors relate to pathophysiologic changes. The data show that a risk factor—early maternal separation—affects a system that is important in gastric erosion pathogenesis—body temperature regulation. However, the effect on the thermoregulatory system was elicited only under a special condition, namely restraint.

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10. The EEG and EMG electrodes were implanted according to M. A. Hofer [*Dev. Psychobiol.* **9**, 189 (1976)], except that they were soldered to plastic adapters (Plastic Products, Inc.) for later attachment to the recording cable.
11. The activity platform (Lafayette Instruments) was calibrated for each animal so that it recorded head turns, grooming, and the body twitches that characteristically occur during paradoxical sleep.
12. Criteria for scoring states were adapted from D. Jouvet-Mournier, L. Astic and D. Lacote [*Dev. Psychobiol.* **2**, 216 (1970)]. Eye movements were not recorded because the characteristic body twitches that occur in the 30-day-old rat during rapid eye movement sleep were easily detected by the activity platform. Sleep and wakefulness were determined by standard EEG and EMG criteria, scoring 30-second epochs. During wakefulness an epoch was scored as "active" if the activity platform showed movements for 15 seconds or more; it was scored as "quiet" if there were fewer than 15 seconds of movement. The activity platform was calibrated for each animal to reflect drinking, grooming, and face-washing as well as more vigorous activities such as walking. Records were scored blind and inter-rater reliability was 92.3 percent. Details of recording and scoring will be described elsewhere (S. H. Ackerman, M. A. Hofer, H. Weiner, in preparation).
13. The effects of food deprivation alone can be considered independently. We previously reported (*1*) that in rats tested at postnatal day 30 the addition of restraint to food deprivation produces significantly more gastric erosions than food deprivation alone. We have tested a total of 194 15-S rats with 48 hours of food deprivation as "control" groups for various experiments. Gastric erosions were noted in 38 (19.6 percent). Out of a comparable group of 185 15-S "control" rats, food-deprived for 24 hours and then restrained for 24 hours, 158 (85.4 percent) developed gastric erosions. In the present study, we obtained electrophysiologic and behavioral measures during food deprivation alone. We found some points of overlap with the same measures obtained during restraint; but the relationship is complex and will be reported in detail elsewhere.
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Prostaglandin Restoration of the Interferon Response of Hyporeactive Animals

Abstract. *Virus-infected animals and those bearing various types of malignancies progressively lose their ability to respond to interferon inducers. The interferon response of virus-infected animals could be restored to normal levels when inducers were administered with certain prostaglandins. This suggests that prostaglandins may enhance the therapeutic efficacy of interferon inducers as antiviral and antineoplastic agents.*

Interferon is an antiviral substance produced by animal cells in response to an invading virus or other suitable stimulus. The interferon produced then diffuses to other cells, organs, and tissues and establishes an intracellular state that inhibits virus replication. Since its discovery in 1957 (*1*) considerable effort has been directed toward developing methods of using the interferon system as a means of treating viral and neoplastic diseases. Recent clinical trials suggest that interferon may have a beneficial effect on a number of viral infections and neoplastic processes (*2*). One approach being taken toward the utilization of this substance has been the development of agents capable of stimulating the host's own cells to produce interferon. A variety of compounds are now known to be effective interferon inducers, and several are currently being evaluated in man. However, one obstacle to the development of these agents has been that animals progressively lose their ability to respond to inducers as a consequence of certain viral infections and various neoplastic processes (*3*). This reduced ability to respond could limit the therapeutic effectiveness of such compounds.

It was reported (*4*) that mice infected with encephalomyocarditis (EMC) virus developed a suppressed ability to respond to interferon inducers and that peritoneal cells collected from these animals and induced in vitro were also hyporeactive. Both systems were therefore available for evaluating the effect of various substances on both the development and maintenance of hyporeactivity. Since prostaglandins have been implicated in regulation of various cellular processes the effect of this group of agents on the ability of normal and hyporeactive cells and animals to produce interferon in response to inducers was investigated.

In initial studies mice were injected intraperitoneally with a 100 percent lethal inoculum of EMC virus [1000 plaque forming units (PFU)]. Ninety-six hours later peritoneal cells were collected from normal and EMC virus-infected mice. Cells were suspended at 1×10^6 cells per milliliter in minimum essential medium (MEM, Microbiological Associates) con-

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taining 5 percent fetal calf serum (Reheis Chemical), 100 units of penicillin and 50 μg of streptomycin per milliliter. Suspended cells (1 ml) were added to 35-mm plastic petri dishes (Falcon). Cells then were challenged with 0.1 ml of MEM alone, 1×10^7 PFU of Newcastle disease virus, or 3×10^7 PFU of Chikungunya virus. One-half hour after the addition of inducers, plates in duplicate received the prostaglandins (PG) E_1, $F_{1\alpha}$, or A_1 (*5*) at concentrations of 5 to 0.5 μg/ml (Table 1). Plates were returned to 37°C for 18 hours at which time growth medium was collected and after being held at a *p*H of 2.0 for 4 days at 4°C was assayed for interferon on murine L_{929} cells by using a vesicular stomatitis virus plaque reduction assay (*6*).

The results indicated that each of the prostaglandins enhanced the ability of hyporeactive cells to produce interferon (to near normal levels) in response to both inducers but had little if any effect on the ability of normal cells to respond. In cases where there was an effect the response of normal cells was slightly suppressed by prostaglandins. In subsequent studies the response of hyporeactive cells was found to be enhanced by other prostaglandins including PGE_2, $PGF_{2\alpha}$, and PGA_2 at concentrations varying from 2 to 0.05 μg/ml, depending upon the prostaglandin and time of addition with regard to inducer. Prostaglandins were able to enhance the interferon response of hyporeactive cells when added from 2 hours before to 4 hours after inducer.

The effect of prostaglandins on the response of the intact animal was then investigated. Mice were injected intraperitoneally with a 100 percent lethal inoculum of EMC virus (1000 PFU) or Semliki forest virus (SFV, 100 PFU) and their serum interferon response to four different inducers administered with or without prostaglandins was investigated (Table 2). Ninety-six hours after infection the mice were challenged with Newcastle disease virus (1×10^7 PFU, injected intraperitoneally), polyriboinosinic acid · polyribocytidylic acid [poly(I) · poly(C)], (100 μg, intraperitoneally), tilorone hydrochloride (250 mg/kg, postorbitally) or 2-amino-5-bromo-6-methyl-4-pyrimidinol (ABMP, 1000 mg/kg, postorbitally) (*7*). Prostaglandin E_1, $F_{1\alpha}$, or A_1 was injected intraperitoneally 30 minutes after inducer at a dose of 1.0 mg/kg. Mice were bled by cardiac puncture 4 hours after they received poly(I) · poly(C), 6 hours after they received Newcastle disease virus or ABMP, and 24 hours after tilorone administration. Serum was collected and assayed for interferon. The results (Table 2) indicate that the response of hyporeactive, virus-infected mice was enhanced when inducers were administered in conjunction with prostaglandins. The response of normal mice, however, was slightly suppressed or unaffected by prostaglandins. In subsequent studies the response of hyporeactive, virus-infected mice was enhanced when the same inducers were injected intraperitoneally with other prostaglandins including PGE_2, $PGF_{2\alpha}$, and PGA_2 at concentrations ranging from 2 to 0.05 mg/kg. In addition, prostaglandins had an enhancing effect when administered from 4 hours before to 4 hours after inducer depending upon the in-

Table 1. Effect of prostaglandins on the ability of peritoneal cells from normal or hyporeactive (EMC virus-infected) mice to respond to interferon inducers in vitro. Prostaglandins were added to cells 30 minutes after inducer (Newcastle disease virus, NDV, or Chikungunya virus, CV). Growth medium was collected 24 hours after the addition of inducer and was assayed for interferon.

Concentration of prostaglandin (μg/ml)	Peritoneal cells			
	Hyporeactive		Normal	
	NDV	CV	NDV	CV
	Prostaglandin E_1			
5	750*	150	1100	1130
2	2100	1200	1300	1200
1	3200	1150	1700	1500
0.5	1500	1300	1800	1200
	Prostaglandin $F_{1\alpha}$			
5	1300	910	1800	1150
2	950	800	1900	1100
1	450	560	1440	1200
0.5	380	720	1990	1100
	Prostaglandin A_1			
5	2000	820	1500	950
2	1500	930	2100	1300
1	2700	780	1360	1200
0.5	240	1100	1700	1300
	Placebo (phosphate buffered saline)			
	250 ± 90	<50	2000 ± 150	1400 ± 180

*Interferon response (expressed in units per milliliter) ±1 standard deviation. Each value represents the mean of three separate experiments.

Table 2. Enhancement of the serum interferon response of hyporeactive (SFV or EMC virus infected) but not normal mice when inducers were administered with prostaglandins. Inducers were administered 96 hours after EMC or Semliki forest virus (SFV) was injected. Prostaglandins (1 mg/kg) were injected intraperitoneally 30 minutes after the inducers.

Prostaglandin	Inducer								
	PBS	Poly(I)·poly(C)		Tilorone		ABMP		NDV	
		Interferon	Percentage	Interferon	Percentage	Interferon	Percentage	Interferon	Percentage
				Normal mice					
E_1	<50*	1200	52†	6000	130	2200	92	2400	130
$F_{1\alpha}$	<50	1920	83	4500	98	2400	100	1600	89
A_1	<50	1650	71	4600	100	2800	120	1900	105
PBS	<50	2300		4600		2400		1800	
				Mice infected with EMC					
E_1	100	2200	440	4500	1500	8100	2300	1300	650
$F_{1\alpha}$	120	3500	700	1600	530	2100	600	1800	900
A_1	110	3000	600	1100	370	1200	340	1250	620
PBS	75	500		300		350		200	
				Mice infected with Semliki forest virus					
E_1	500	1200	170	1400	480	1200	270	1300	500
$F_{1\alpha}$	390	1250	180	2000	690	900	200	400	150
A_1	420	2000	280	1650	570	1100	240	750	290
PBS	350	700		290		450		260	

*Serum interferon response (units per milliliter). Each value represents the mean of two separate experiments. Serum was collected 4 hours after poly(I) · poly(C) or phosphate buffered saline (PBS), 6 hours after Newcastle disease virus (NDV) or ABMP, and 24 hours after tilorone administration. †Percentage of PBS treated control.

ducer and concentration of prostaglandin used.

The results presented here indicate that the state of hyporeactivity that develops in virus-infected mice is reversible and that by judicious selection of inducers and prostaglandins the response of hyporeactive mice could be restored to near normal levels. These results are significant in that they not only suggest that the therapeutic efficacy of inducers may be significantly enhanced by coadministration with prostaglandins but that the state of hyporeactivity that develops in virus infections or neoplastic diseases is probably mediated by a specific cellular event that is influenced in some fashion by prostaglandins. The possibility that the effect seen was due to modulation of cyclic nucleotide levels was considered. However, direct addition of dibutyryl adenosine 3′,5′-monophosphate, isoproterenol, theophylline, carbachol, or dibutyryl guanosine 3′,5′-monophosphate had no significant effect upon the responsiveness of cells from EMC- or SFV-infected mice or on the response of the intact animals themselves (*8*). These results suggest that prostaglandins restored the cellular interferon response through an unidentified process not involving cyclic nucleotides.

In further studies (*8*), mice infected with influenza A_2 or Friend leukemia viruses (*8*) developed an infection-induced state of hyporeactivity, and the interferon response of these animals was enhanced or restored by coadministration of prostaglandins with inducers. These results indicate that the restoration was a fairly general phenomenon. It was not restricted by the inducer or prostaglandin used, and the interferon response of mice infected with any of four viruses was enhanced. Enhancement was selective, however, in that the response of normal cells was generally not affected although hyporeactive cells were. At present, the mechanism by which hyporeactive cells are rendered more responsive is not fully understood, although it does not appear to be linked to overt manipulation of cellular macromolecular synthesis or increased uptake of inducer (*8*).

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8. D. A. Stringfellow and R. R. Gorman, in preparation.

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Atmospheric Dust: Climatological Consequences

Idso and Brazel (*1*) conclude from various radiation measurements for a range of dust-loading events at Phoenix, Arizona, that a buildup of anthropogenically produced tropospheric aerosols must inexorably tend to warm the planet's surface. We question the conclusion for several reasons.

Some of the results raise the question of measurement error. For the dust event of 22 February 1977, figure 1C in (*1*) shows that the dust loading, as indicated by the ratio of diffuse to normal-incidence solar radiation, rose sharply at 1100 hours, remained high until 1300 hours, and did not return to the unperturbed level until 1400 hours. The infrared radiation from the sky (figure 1B) rose sharply at the same time, 1100 hours, but fell sharply to the unperturbed level by 1200 hours. On 15 April 1977, the infrared radiation from the sky lagged behind the dust loading.

Idso and Brazel's raw data do not imply a warming effect, at least in two of the three cases presented (22 February and 15 April). On those dates increased dust levels gave rise to a change in net all-wave radiation (darkened circles of figure 1) such that the net incoming radiation (incoming visible minus outgoing infrared) was reduced. This represents a local cooling effect at the ground—reduced incoming solar radiation more than outweighed the change in infrared radiation. The inference of a climatological warming rests on the argument that infrared changes are felt over the entire area ($4\pi R^2$) of the earth's surface, whereas the solar radiation, being effectively unidirectional, falls normally on the cross-sectional area (πR^2). This might be correct if the measurements were all taken with the sun in the zenith (that is, zenith angle $\theta = 0°$). They were in fact taken at zenith angles between 40° and 70°. Since incoming normal flux is proportional to $\cos\theta$, in the flat atmosphere approximation, measured solar radiation should be divided by 4 $\cos\theta$ to obtain an approximation for a global average.

A second critical aspect is the location on figure 2 in (*1*) of the point representing the present state of the atmosphere. It does not have to be moved far to the right to make it fall in a region where the curve of figure 2 is falling rather than rising, implying cooling with increasing dust. Idso and Brazel chose an initial point corresponding to clear conditions in Phoenix, but is this realistic for a real world that is about 50 percent cloud-covered, 80 percent ocean, and has a haze level that receives sizable contributions from sea salt, terpenes, and sulfates? In other words, the earth, in its entirety, may actually have an average diffuse/direct value nearer to 0.1, say, in which case addition of aerosols, according to Idso and Brazel's curve, would lead to cooling on a global scale.

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With respect to the first question raised by Herman *et al.*, the net solar and net all-wave radiation data of figure 1, A and B, were acquired at a site 4 km distant from the site of the diffuse and normal-incidence solar radiation measurements of figure 1C, and this spatial separation could conceivably create discrepancies. However, we see no discrepancy on 11 January or on 15 April. On 22 February there is an apparent discrepancy, but on closer examination we see that it is due to a faulty delineation of the dust event in the solar and all-wave radiation data. That is, in comparing all 3 days, it is evident that in our report the net solar and net all-wave radiation traces for 22 February are too flat over the midday period.

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