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## STRESS AND IMMUNE FUNCTION : A BIBLIOGRAPHIC REVIEW

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### Résumé

**STRESS ET FONCTIONS IMMUNOLOGIQUES : UNE REVUE BIBLIOGRAPHIQUE.** — Des facteurs de stress liés à l'environnement sont impliqués dans l'étiologie d'importantes maladies du bétail y compris la gastroentérite transmissible du porcelet, la maladie de Newcastle et de Marek du poulet et la « fièvre des transports » des bovins. Malheureusement très peu de recherches ont été entreprises pour étudier la manière dont le stress modifie la résistance de l'hôte bien que l'atteinte du système immunitaire soit généralement admise. Huit facteurs de stress caractéristiques de l'élevage intensif ont été discutés : chaleur, froid, surpeuplement, mélange, sevrage, alimentation en quantité limitée, bruits et contraintes. Chacun de ces facteurs modifie le système immunitaire des animaux. Les changements observés dans la fonction immunitaire pourraient expliquer les bases physiologiques des interactions maladie-environnement. L'étude approfondie des modifications de la résistance de l'hôte induites par le stress pourraient aussi constituer la base scientifique pour une prophylaxie thérapeutique efficace. Des expériences mieux contrôlées sont nécessaires pour étudier la manière dont le stress modifie la sensibilité des animaux aux maladies infectieuses ou non.

The social and physical environment of animals and humans has long been implicated in the etiology of infectious diseases. Hippocrates emphasized the importance of the total environment when studying the cause of diseases (cited by Top, 1964). In domestic animals, several empirical observations suggest that stressful environmental conditions alter host resistance. However, controlled experiments on adverse environmental stimuli and animal health are

meager, and the results of some experiments are enigmatic. Yet, even though the effects of stress on animal health are incompletely understood, minimizing environmental stressors is often considered a panacea. Indeed, reducing stress is the basis for many herd health programs. A thorough understanding of animal health requires that the interaction between stress and disease be studied. Scientific information is needed to answer clinical problems that occur in the field. Current dogma must be evaluated in the perspective of new scientific studies.

Top (1964) reviewed historical, epidemiological and clinical evidence that emphasized the role of environment as one of the three

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important components of the doctrine of multiple causation. In many of these studies and others, the adverse effect of environment on the incidence of infectious diseases, such as influenza and poliomyelitis, was attributed to enhanced survival or transmission of pathogens outside the host (Lidwell *et al.*, 1965; Andrewes, 1964; Spicer, 1959; Armstrong, 1950; Wells, 1944). Direct environmental effects on host resistance were not clearly delineated.

There can be little doubt that temperature affects the transmission and proliferation of a microbe within and outside an animal's body. For example, environmental temperature may directly affect a parasite or a vector that is part of the life cycle of the parasite. If body temperature is changed by hot or cold weather, the virulence or generation time of certain pathogens may be altered. Cold weather may cause animals to remain indoors, which may indirectly enhance spread of the microbe. Cold weather may also dictate that ventilation rates be reduced, thereby causing an accumulation of microorganisms inside an animal structure. Social stressors, such as crowding and mixing, may cause open wounds or increase the rate of contact with an infected animal. However, the physical and social environment in which animals are raised can also directly affect host resistance. This concept has not been widely recognized by the scientific community.

Weather extremes are important, pragmatic stressors that affect the production of domestic animals. Therefore, most of the research emphasis with stress and animal health has been devoted to the study of hot and cold ambient conditions. Other diverse kinds of environmental stimuli that do not alter air or deep body temperature can also cause changes in immune function. Fear, frustration, maintenance of social dominance hierarchies and separation of neonatal animals from their mother cause alterations in the immune system. It is likely that all of these diverse types of environmental stimuli constitute a stressor, and that the nonspecific stress response directly alters specific immune events in the host. These stress-induced changes in immune function may cause alterations in the susceptibility of animals to disease.

There is increasing evidence that environmental stressors directly alter host resistance.

Relatively recent advances in immunology suggest that these changes in host resistance are mediated by changes in specific components of the immune system. Indeed, Soper *et al.* (1978) reported that mitogen-induced blastogenesis in dairy cows was reduced in the winter and elevated in the summer. This seasonal variation led the authors to conclude the following: « It has been assumed that the increased incidence of disease during the winter housing season was solely due to confinement of cattle, but the observations in this study suggest there may be a lessened immune response of the host during this time ».

Selye (1976) defined « stress » as the non-specific response of the body to any demand, and « stressor » as the environmental stimulus that provokes the stress response. As early as 1936, Selye described the reaction of laboratory animals to environmental stressors and characterized the General Adaptation Syndrome. Subsequent research in several laboratories showed that the symptoms of diverse types of acute stressors included adrenal hypertrophy, gastric ulcers, involution of the thymus and other lymphoid organs, lymphocytopenia, eosinopenia and neutrophilia. There is also evidence acute stressors cause thymic involution and atrophy of gut-associated lymphoid tissue (GALT) in calves (Hartmann *et al.*, 1976a). Now, over 40 years after Selye's initial report, it is well accepted that the thymus and lymphoid cells are intimately involved in host defense mechanisms against infectious diseases. Neonatal thymectomy increases the susceptibility of animals to infections, causes lymphopenia, retards skin graft rejections, reduces antibody synthesis to T cell dependent antigens and causes slow growth and diarrhea (Miller, 1961; 1962). Adult thymectomy may also reduce suppressor cell function (Janeway, 1973), alter helper function (Simpson and Cantor, 1975) and deplete theta-positive spleen cells (Cantor *et al.*, 1975). Therefore, the association between environmental stressors and lymphoid dysfunction may be the critical link between host resistance and environmental changes.

During the past decade, several reviews appeared which established the relationship between environment and disease (Siegel, 1971, 1980; Roberts, 1979; Chevillat, 1979; Thaxton, 1978; Weiner, 1977; Selye, 1976; Hudson *et al.*, 1974; Levi, 1971-1980;

Webster, 1970). Most of these papers dealt with the effects of thermal stressors, and two reports (Roberts, 1979; Thaxton, 1978) concentrated on immunological mechanisms. Weiner (1977) and Levi (1971-1980) also implicated social stressors in noninfectious and certain autoimmune diseases. For instance, at least seven noninfectious diseases in humans have been shown to be influenced by psychosocial factors: Grave's disease, essential hypertension, rheumatoid arthritis, ulcerative colitis, duodenal ulcers, bronchial asthma and regional enteritis.

Unfortunately, the literature on stress and immunity is scattered in diverse scientific journals. Therefore, the objectives of this review are to: firstly, establish a link between environmental stressors and the susceptibility of animals to disease; secondly, show that both physical (heat and cold) and emotional (avoidance learning and restraint) stressors alter host resistance; thirdly, demonstrate that several different kinds of stressors affect immune function, and fourthly, delineate problem areas and suggestions for future research. The physiological mechanisms that mediate these stress-induced changes in immune function are not emphasized, but certain stress-induced hormonal changes have been recently summarized (Stephens, 1980; Trenkle, 1978). Similarly, because the separation of « acute » and « chronic » stressors is somewhat arbitrary, and because a detailed description of experimental methods would be too bulky, the stressors in most of the publications were simply classified as heat, cold, weaning, etc. A detailed treatise of the effects of acute stressors, chronic stressors, acclimation and acclimatization should be addressed separately in another paper.

In the present review, eight stressors have been identified that typically occur on farm production units. These stressors have been demonstrated to affect certain components of antibody- and cell-mediated immunity in homeothermic animals. Experiments that were conducted *in vivo* have been emphasized. At the risk of gross oversimplification, tables 1 through 4 summarize these stress-induced changes across experiments, age, species, degree of stress and acclimation status. This summarization should be used only as a guide. Some references are provided in the tables, but a more complete documentation of these responses is provided in the text.

## Heat stress

### *Susceptibility to infection*

Heat stress increases the susceptibility of many animal species to infectious diseases. In a thorough study conducted by Juskiewicz *et al.* (1967), heat stress at 36 °C reduced the survival time of 12-week-old chickens inoculated with a virulent strain of *Pasteurella multocida* and generally increased nonspecific bacterial flora in various organs. Other reports showed that heat stress increased the susceptibility of mice to pneumococci (Larson *et al.*, 1939; Junge and Rosenthal, 1948), a hemolytic strain of streptococci (Colvin and Mills, 1939) and bacterial endotoxins (cited by Webster, 1970; Atwood and Kass, 1964). If there were a rapid change in air temperature after an infection with pneumococci, host resistance was reduced (McDowell, 1923). However, opposite results were obtained if rats were permitted to acclimate to a warmer temperature. An air temperature of 35 °C also reduced the mean lethal dose (LD<sub>50</sub>) of mice to bacterial endotoxin (Previte and Berry, 1962).

Interestingly, Arnold (1929) showed that heat stress increased the numbers of microbes passing through the stomach and small intestine. This finding suggested that the bactericidal capacity of the upper gut may have been compromised by heat stress. Bennett and Nicastrì (1960) pointed out that elevated body temperature activates latent herpes simplex virus in man, which leads to the appearance of fever blisters. These authors also cited early research which indicated that high temperatures increased mortality in animals that were infected with several gram-negative bacilli (e.g., dysentery, typhoid).

In some cases, the effect of elevated temperature on host resistance is less clear. In rabbits, the ultimate outcome of *Pasteurella multocida* infection depends on the degree of hyperthermia (Vaughn and Kluger, 1977). Furthermore, an elevated air temperature at 43 °C for two days does not reactivate an avian influenza virus in turkeys (Robinson *et al.*, 1979).

It is interesting that hyperthermia has been shown to enhance the resistance of mammals to several diseases. Host resistance to viral diseases seems to be particularly enhanced. In mice, elevated air temperature increased host resistance to rabies virus (Bell and Moore,

Table 1. — Generalized immune responses of homeotherms to elevated air temperature or body temperature.

Item	Response		References
	Increase	Decrease	
Susceptibility to endotoxin, streptococci, <i>P. multocida</i> , herpes simplex virus.	+		Juszkiewicz <i>et al.</i> , 1967 ; Atwood and Kass, 1964 ; Bennett and Nicastri, 1960 ; Walker and Boring, 1958 ; Colvin and Mills, 1939.
Susceptibility to pneumococci.	+	+	Junge and Rosenthal, 1948 ; Larson <i>et al.</i> , 1939 ; McDowell, 1923.
Susceptibility to tetanus toxin.	+	+	Ipsen, 1952 ; 1951.
		(immunized)	
Susceptibility to several viruses, including mycoplasmal pig pneumonia.		+	Bell <i>et al.</i> , 1977 ; Lycke <i>et al.</i> , 1971 ; Gordon, 1963 ; Marshall, 1959 ; Walker and Boring, 1958 ; Lillie <i>et al.</i> , 1937
Susceptibility to trypanosomes, mycoses, cryptococci, <i>M. marinum</i> .		+	Otieno, 1972 ; Marinkelle and Rodriguez, 1968 ; Mackinnon, 1968 ; Clark and Shepard, 1963 ; Kuhn, 1949 ; Kolodny, 1940.
LD <sub>50</sub> of endotoxin.		+	Atwood and Kass, 1964 ; Previte and Berry, 1962.
Virus-induced interferon.	+		Postic <i>et al.</i> , 1966.
Absorption of colostral immunoglobulin.		+	Stott, 1980.
Antibody synthesis.	+	+	Regnier <i>et al.</i> , 1980 ; Heller <i>et al.</i> , 1979 ; Thaxton, 1978.
Half life of immunoglobulin.	+		Casey, 1973.
Serum IgG <sub>1</sub> .		+	Kelley <i>et al.</i> , in preparation.
Concentration of peripheral blood lymphocytes.		+	Regnier and Kelley, 1981 ; Heller <i>et al.</i> , 1979
		no Δ	
		(calves, chronic)	Wegner <i>et al.</i> , 1976 ; Paape <i>et al.</i> , 1973 ; Kelley <i>et al.</i> , in preparation.
Phagocytosis.	+		Heller <i>et al.</i> , 1979 ; Donald, 1972.
Susceptibility to systemic anaphylaxis.		+	Morgan <i>et al.</i> , 1976 ; Gottschall <i>et al.</i> , 1944 ; Goldman, 1939.
Tuberculin sensitivity.		+	Kelley <i>et al.</i> , 1980.
Contact sensitivity.	+	+	Regnier and Kelley, 1981 ; (induction) (expression) Blecha, 1981 ; Kelley <i>et al.</i> , 1980 ; Blecha <i>et al.</i> , 1980 ; Pitkin, 1965.
SRBC evanescent DTH.	+		Blecha, 1981 ; Blecha <i>et al.</i> , 1980.
Mitogen blastogenesis.	+	+	Regnier and Kelley, 1981 ; ( <i>in vitro</i> ) (chickens) Kelley <i>et al.</i> , in preparation.
	+		(serum from calves)
Tumor growth.	+	+	Schechter <i>et al.</i> , 1978 ; Dickson and Ellis, 1974.

1974 ; Bell *et al.*, 1977), Coxsackie virus (Boring *et al.*, 1956 ; Walker and Boring, 1958), St. Louis encephalitis (Lillie *et al.*, 1937) and herpes simplex virus (Lycke *et al.*, 1971 ; Schmidt and Rasmussen, 1960 ; Armstrong, 1942). Similar results were obtained with canine herpes virus in puppies (Carmichael *et al.*, 1969), an attenuated myxoma virus in rabbits (Marshall, 1959) and transmissible gastroenteritis in pigs (Furuuchi and Shimizu, 1976 ; Shimizu *et al.*, 1978). Perhaps this reduction in susceptibility was related to interferon, because exposure of rabbits to an ambient temperature of 35 °C increased interferon titers elicited by Newcastle disease virus (Postic *et al.*, 1966). However, interferon induced by *Escherichia coli* endotoxin was unaffected.

Bennett and Nicastrì (1960) cited studies that were conducted late in the nineteenth century which showed that elevated air temperature enhanced the resistance of animals to staphylococci, pneumococci and anthrax bacilli. High temperature and humidity have also been suggested to reduce the incidence of mycoplasmal pig pneumonia (Gordon, 1963). In mice, an air temperature of 35 °C (moisture level unknown) reduced the mortality of animals that were infected with trypanosomes ; heat stress was more effective in reducing mortality with some species of the parasite than with others (Otieno, 1972). Identical results were also reported earlier in rats and mice (Kolodny, 1940 ; Amrein, 1967 ; Marinkelle and Rodriguez, 1968). In contrast, Kligler (1927) reported little effect of a moderate heat stress on *T. evansi* infection. Elevated air temperature enhanced the resistance of mice to *Mycobacterium marinum* (Clark and Shepard, 1963) and the incidence of cryptococcosis in mice was reduced by hyperthermia (Kuhn, 1949). Heat stress also enhanced the resistance of guinea pigs to an endemic typhus (Lillie *et al.*, 1937). Host susceptibility to several types of deep mycoses may be reduced as well (Mackinnon, 1968). However, a very moderate temperature of 27 °C had little effect on the susceptibility of guinea pigs to virulent tubercle bacilli (Baetjer and Lange, 1928).

#### *Explanations for enhanced resistance*

The conflicting reports of elevated air temperature on the resistance of animals to infectious diseases may have several

alternative explanations. In some of the reports cited above, it is likely that the elevated air temperature that was selected actually provided a thermoneutral or moderately warm environment for the animal being studied. The low air temperature may have therefore constituted an effective cold stress. Instead of concluding that high ambient temperature enhanced resistance, an alternative explanation would be that cold air temperature reduced host resistance. This confounding variable emphasizes the need for describing the age, acclimation status, physical environment and physiological thermoregulatory responses of the experimental animals.

The differential effect of heat stress on host resistance also depends on whether or not the animals are immune to the challenge organism at the time of exposure. In a series of well-controlled experiments, Ipsen (1952) reported that when mice were immunized at 35 °C with tetanus toxoid and then challenged with tetanus toxin at 25 °C, fewer mice died. This response was greatest at low doses of toxoid. However, elevated air temperature shortened the survival of non-immune mice to tetanus toxin, an effect which was particularly pronounced at sublethal doses (Ipsen, 1951). Presumably, elevated ambient temperature enhanced the pathological effects of the toxin. This detrimental effect was ameliorated if mice were vaccinated with the toxoid at a high temperature and challenged at a thermoneutral temperature. One simple explanation of these data could be as follows : if a non-immune mouse encountered tetanus toxin during the hot summer, death would probably occur. However, if the mouse survived this initial encounter with the toxin and was again exposed at normal temperatures, immunity would be enhanced. These data emphasize that the immune status of the experimental animals is important and should be thoroughly tested and reported.

Beneficial effects of high air temperature on host resistance may be explained by a direct reduction in the virulence of proliferation of microbes *per se*. Indeed, temperature is often used as a selection tool for the growth of different microbes *in vitro*. This topic is beyond the scope of this paper and has been reviewed recently by Rodbard *et al.* (1980). These authors, as well as Lwoff (1959), Carmichael and Barnes (1969) and Bennett and Nicastrì (1960), cited reports of the direct effect of temperature on the growth of several viruses

and bacteria, particularly poliomyelitis virus, pneumococci, gonococci and herpes simplex virus. In addition, Mackinnon (1968) discussed information which suggested that elevated temperature was particularly detrimental to several types of mycoses.

Effects of temperature on host resistance are probably not entirely explained simply by a direct effect on the microbe. Indeed, the hypothesis that fever or differences in body temperature among several animal species is entirely responsible for changes in the resistance of animals to disease because of the temperature preferendum of the invading microbe is quite speculative. With many of the studies cited above, growth of a microbe that was incubated at different temperatures *in vitro* may not reflect growth of a microbe in the cells of a hyperthermic or hypothermic animal that is responding to a thermal stressor (Bell *et al.*, 1977). Bennett and Nicastri (1960) clearly delineated the exacting conditions that must be demonstrated to prove that hyperthermia affects host resistance to infections. They gave several examples of diseases that ostensibly were not affected by body temperature. Although temperature of the host or of the host's tissues most certainly affects the growth of microbes, it is unlikely that changes in body temperature alone can explain the effects of hot and cold weather on host resistance.

Several lines of evidence suggest that the change in the resistance of heat- and cold-stressed animals is caused by stress-induced alterations in immune function. First, enhanced growth of a microbe does not always translate into clinical disease. For instance, Rodbard *et al.* (1980) noted that elevated temperature enhanced the growth of some strains of *Trypanosoma cruzi*, yet elevated ambient temperature also enhanced host resistance to this organism (Marinkelle and Rodriguez, 1968; Amrein, 1967; Kolodny, 1940). Indeed, because heat stress increased rectal temperature less than 1.3 °C. Marinkelle and Rodriguez (1968) concluded that heat stress did not affect the growth or virulence of trypanosomes. They concluded that heat stress altered the immune system. Rodbard *et al.* (1980) also noted that the rickettsial organism that caused typhus grew fastest at higher temperatures, but that only a reduced body temperature permitted growth of rickettsia in the peritoneal cavity. Further-

more, cold stress reduced the resistance of pigs to transmissible gastroenteritis (TGE) and of mice to *Salmonella typhimurium*, but growth of the microbes was relatively unaffected by air temperatures within homeothermic limits (Furuuchi and Shimizu, 1976; Miraglia and Berry, 1962). Also, both hot and cold conditions impaired the growth of *Mycobacterium leprae* in mice (Shepard, 1965), but only cold air resulted in clinical disease.

Other lines of reasoning suggest that changes in body temperature cannot entirely account for alterations in the resistance of heat- or cold-stressed animals. For example, hot or cold ambient temperatures may not always cause changes in core temperature, but may simply invoke thermoregulatory responses. Also, since temperature-sensitive mutants are available for many microbes, it would be likely that in the long run in hot or cold environments, a microbe would adjust to its surroundings and be able to survive (Rodbard *et al.*, 1980; Lwoff, 1959). Finally, several other stressors that do not alter body temperature also cause changes in the susceptibility of animals to infectious diseases. For example, both cold and psychological stressors reduce the resistance of mice to Coxsackie B virus. Therefore, it is likely that stress-induced changes in immune function are at least partly responsible for changes in the susceptibility of heat- and cold-stressed animals to several infectious diseases.

Hyperthermia could enhance host resistance by causing a secondary enhancement in certain components of the immune system. If thermal stress causes a large change in core body temperature, the effects of temperature on virulence of the microbe and changes in host resistance are difficult to separate. This problem can be approached by using non-infectious agents. Roberts (1979) recently presented an excellent review of the effects of changes in body temperature on disease-defense mechanisms of the host. However, many experiments were conducted by heating lymphoid cells *in vitro*. These studies may not yield similar results when animals are heated *in vivo*. This disparity could occur because heat stress does not always result in hyperthermia, and hyperthermia may occur without an increase in environmental temperature, as in the case of fever (Kluger, 1978). Indeed, it is very important to differentiate between animals

whose set point temperature does not change (acute thermal stressor) and animals that truly display a different set point temperature (fever; see review by Bernheim *et al.*, 1979). Therefore, because of thermoregulatory responses that occur *in vivo* in heat-stressed animals, results of *in vitro* studies may not be applicable to normal animals that are exposed to hot or cold weather. The van't Hoff effect may also explain some of the enhanced immune responses that occur *in vitro*.

#### *Blood leukocytes and antibody*

Heat stress has been shown to affect passively acquired, antibody-mediated immunity in bovine neonates. In dairy calves, elevated ambient temperature has been suggested as a cause of reduced absorption of colostral IgG<sub>1</sub> (Stott *et al.*, 1976). Lowered serum immunoglobulin was associated with a higher mortality rate and elevated serum corticosteroid concentrations. The latter correlation appears to be a spurious relationship because premature closure of the intestine cannot be induced by administration of exogenous corticoids (Stott, 1980).

Heat stress causes changes in active antibody-mediated immunity and peripheral blood leukocytes of several animal species. The combination of elevated ambient and dew point temperatures has been reported to reduce the ability of puppies to respond to a distemper virus vaccine but not to affect the antibody response to a hepatitis vaccine (Webster, 1975). Heat stress also increased the half-life of syngeneic (Casey, 1973) and xenogeneic (Stark, 1970) immunoglobulin in mice and reduced the number of leukocytes in the blood of chickens (Regnier and Kelley, 1981; Heller *et al.*, 1979; Nathan *et al.*, 1976). In cattle, hot air at relatively high humidity levels or adrenocorticotrophic hormone increased the number of blood leukocytes (Gwazdauskas *et al.*, 1980; Wegner *et al.*, 1976). However, this effect was achieved via a significant reduction in the lymphocyte: neutrophil ratio. Similar to other reports (Lee *et al.*, 1976; Paape *et al.*, 1973), recent results in our laboratory demonstrated that a less severe, chronic heat stress in young calves did not affect the number of peripheral blood lymphocytes, monocytes, neutrophils, eosinophils or basophils (Kelley *et al.*, manuscript in preparation). However, serum IgG<sub>1</sub> concentration was reduced by the two-

week exposure at 35 °C, and serum IgM was unaffected. Moderate heat stress with relatively low moisture content also reduced goblet cell numbers in the respiratory epithelium of calves (Jericho and Magwood, 1977), whereas the change in the number of goblet cells in the trachea of rats was increased by hot, dry air (Jones *et al.*, 1971).

In certain strains of New Hampshire and Athens Randombred chickens, a short, intermittent heat stress reduced both developing and circulating antibody (Thaxton and Siegel, 1970, 1972, 1973; Subba Rao and Glick, 1970; Thaxton *et al.*, 1968). This reduction depended on the time of immunization relative to initiation of stress. Subsequent research, however, has shown that this immunosuppression did not occur in outbred New Hampshire, Athens Randombred, White Rock or Leghorn breeds (Regnier *et al.*, 1980). Indeed, a more severe heat stress applied within four days of immunization caused an opposite effect: antibody titers to both sheep erythrocytes (SRBC) and *Escherichia coli* were elevated in Rhode Island Red × Leghorn chickens (Heller *et al.*, 1979). Paradoxically, this increase was associated with significantly elevated plasma corticosterone and ascorbic acid. Clearance of *Staphylococcus aureus* was also enhanced in the heat-treated chickens. Similarly, elevated ambient temperature has been reported to increase the clearance of carbon particles from the blood of rabbits (Donald, 1972).

Research with guinea pigs has clearly shown that hyperthermia reduces the severity of anaphylactic shock (Gottschall *et al.*, 1944; de Kruif and Simpson, 1941; Goldman, 1939). Morgan *et al.* (1976) demonstrated that heat stress reduced bovine serum albumin (BSA)-induced systemic anaphylaxis in chickens without reducing serum titers of anti-BSA antibodies. It is possible that the heat stress altered effector functions of a reagenic antibody without affecting the absolute amount of BSA antibody in the systemic circulation. This finding also suggested that other immune processes may have been altered by heat stress, such as antigen-antibody avidity, degranulation of mast cells and basophils or the synthesis, release or binding of vasoactive amines.

#### *Cell-mediated immunity*

When birds were exposed to a chronic, five-day heat stress at 36 °C, a significant sup-



pression in the expression of dinitrofluorobenzene (DNFB) contact sensitivity reactions and phytohemagglutinin (PHA) skin tests was observed in New Hampshire but not in White Rock chickens (Regnier and Kelley, 1981). Furthermore, peripheral blood leukocytes from heat-stressed birds of both breeds manifested an impaired capability to blast *in vitro* in response to the mitogen PHA (Regnier and Kelley, 1981). These results contrast with blastogenesis data obtained with heat-stressed calves, but the nature of the assays was different. In calves, mononuclear cells were separated from blood on Ficoll-Hypaque gradients, whereas in chickens the cells were cultured with whole blood. Therefore, it is unknown whether the cell population *per se* was affected in heat-stressed birds, or whether the immunosuppression was mediated by serum factors. The incubation of normal chicken peripheral blood lymphocytes at 40 °C also reduced mitogen-induced blastogenesis (Maheswaran and Thies, 1975). However, this latter report contrasts with the work of Lee (1978), in which an *in vitro* incubation at 41 °C enhanced blastogenesis of avian lymphocytes.

In mammals, the effects of elevated incubation temperatures *in vitro* are also equivocal. With rats, an incubation temperature of 40 °C has been reported to reduce mitogen-induced blastogenesis of peripheral blood lymphocytes (Hirsch *et al.*, 1977). However, when normal human lymphocytes were cultured *in vitro* at elevated ambient temperatures, a significant increase in mitogen- and antigen-induced lymphoblastogenesis was reported (Lauwasser and Shands, 1979; Smith *et al.*, 1978; Ashman and Nahmias, 1977; Roberts and Steigbigel, 1977). The production of leukocyte migration inhibition factor by human leukocytes *in vitro* was also enhanced by an incubation temperature of 38.5 °C (Roberts and Sandberg, 1979). These differences probably owed to species effects and to the degree of thermal exposure employed by the various investigators.

The direct effect of temperature on the rates of biochemical reactions, known as the van't Hoff effect (Belehradek, 1957), may also explain some of the enhanced responses that were recorded *in vitro*. This simple, positive feedback system could increase the rate-limiting component of an *in vitro* chemical reaction, which would result in greater proliferation or secretion rates of cells. However, with heat stress studies that were conducted

*in vivo*, physiological thermoregulatory mechanisms may have limited the van't Hoff phenomenon.

With mice, a corticoid-sensitive species, Pitkin (1965) suggested that a short, 60 min-heat stress reduced the expression of contact sensitivity reactions to dinitrochlorobenzene (DNCB). However, heat stress for longer periods may yield different results. A chronic five-day heat stress at 35 °C had little effect on the expression of DNFB contact sensitivity reactions in mice (Blecha, 1981). In contrast, heat stress enhanced the expression of evanescent delayed-type hypersensitivity (DTH) reactions with SRBC. When heat stress was applied during only the inductive phase of these reactions and mice were subsequently challenged at thermoneutral conditions, the *in vivo* dermal swelling to both DNFB and SRBC was significantly enhanced. These experiments indicated that heat stress in mice altered effector functions or the ontogeny of immune cells. This effect depended on the length of heat exposure and whether the animals were immune at the time of exposure (i.e., induction or expression).

New results (Kelley *et al.*, 1980) with four-week-old dairy calves revealed that hot ambient conditions (dry bulb = 35 °C; dew point = 21 °C) dramatically reduced the expression of DNFB-induced contact sensitivity reactions and dermal swelling in response to purified protein derivative (PPD) in animals sensitized with *Mycobacterium tuberculosis*. The effect of stress on induction of these responses was not investigated. These data demonstrated that the expression of cellular immune responses of calves was compromised during heat stress. However, PHA skin reactions and *in vitro* mitogen-stimulated blastogenesis of purified mononuclear cells were unaffected (Kelley *et al.*, in preparation). Plasma from heat-stressed calves enhanced mitogen-induced blastogenesis of mononuclear cells from normal calves. This enhancement was destroyed by heating the serum for 30 min at 56 °C. These results indicated that heat stress did not directly affect the metabolic machinery that was necessary for the proliferation of lymphoid cells. However, blood plasma from heat-stressed calves enhanced blastogenesis and may have altered the *in vivo* recruitment of lymphocytes and macrophages by specifically-sensitized immune lymphocytes.

### *Neoplasia*

Schechter *et al.* (1978) reported the local heating of a mammary carcinoma in rats reduced growth of both a primary tumor and peritoneal metastases. Local heating of the tumor induced a deep body temperature of 40.7 °C, or a hyperthermia of approximately 2 °C. However, when heat was applied to another part of the body that did not have tumor cells, growth of the tumor was unaffected. In contrast, Dickson and Ellis (1974) found that heating rats to a core body temperature of 41.5 °C for 1 h enhanced growth of distant metastases. Earlier work showed that local heating of the tumor was more effective than whole-body heating in retarding the growth of tumors (Dickson and Muckle, 1972). The authors speculated that whole-body heating may have adversely affected the immune system. Although these data are not extensively reviewed here, these results suggested that a locally-applied, moderate hyperthermia reduced tumor cell growth *in vivo*, but that an extremely high body temperature either depressed immune events that controlled tumor growth or directly stimulated the growth of some types of tumor cells.

Studies conducted *in vitro* also suggest that the ultimate outcome of heat treatment on tumor growth depends on the degree of heating. For instance, when spleen cells from normothermic rats were heated at 40.5 °C *in vitro* and immediately tested for their ability to kill tumor cells, cytotoxicity was reduced by 25 % (Schechter *et al.*, 1978). MacDonald (1977) also reported that the *in vitro* exposure of mouse cytotoxic lymphocytes to 43 °C destroyed the killing of allogeneic mastocytoma cells. However, when human lymphocytes were heated to only 40 °C, cytotoxic T-cell responses were enhanced (Smith *et al.*, 1978).

### **Cold stress**

#### *Susceptibility to infection*

Several experiments have demonstrated that the susceptibility of homeothermic animals to infectious diseases is increased during cold exposure. As early as the nineteenth century, Pasteur found that chilling birds by immersion in cold water reduced their resistance to anthrax, an effect which was apparently caused by reduced phagocytosis (cited by Rodbard *et al.*, 1980). Ram and Hutt

(1955) reported two well-controlled studies on the effect of cold air temperatures on the resistance of chicks that were experimentally infected with *Salmonella pullorum*. In the first experiment, 100 % of the infected chicks that were exposed to a reduced brooder temperature (28 °C) died, but the mortality was only 40 % in chicks inoculated with *Salmonella pullorum* and maintained at 35 °C. The second experiment demonstrated similar results, although they were less dramatic.

Soerjadi *et al.* (1979) recently expanded on these early studies. They infected young chicks with three doses of *Salmonella typhimurium* and exposed the chicks to a cold (20 °C) or warm (34 °C) air temperature. Cold air temperatures clearly increased the shedding of *Salmonella typhimurium* when birds were orally inoculated with 10<sup>3</sup> and 10<sup>5</sup> cells. However, this effect was masked when 10<sup>8</sup> cells were used, a treatment in which 75 % of the chicks on both treatments shed the organism. These workers also found that a 24 h-cold exposure (10 °C) increased the shedding of organisms in 12-day-old birds that were previously inoculated with *Salmonella typhimurium*, but this shedding was less pronounced in 20-day-old chickens. The increase in susceptibility of day-old chicks to salmonellosis induced by cold air temperatures was also recorded by other workers (Thaxton *et al.*, 1974 ; Bierer, 1961 ; Moore *et al.*, 1934). These changes in susceptibility may have been related to the maintenance of homeothermy in chickens (Thaxton *et al.*, 1974). In mammals, however, individually-housed mice maintained at 5 °C have lower resistance to *Salmonella typhimurium* and yet they remain normothermic (Miraglia and Berry, 1962 ; Previte and Berry, 1962).

Research conducted in Poland showed that inoculation of four-month-old chickens with a pathogenic strain of *Pasteurella multocida* and exposure to -1 °C slightly increased survival time (Juszkiewicz, 1967). Interestingly, compared to birds that were inoculated and maintained at 18 °C, there was less growth of *Pasteurella multocida* in the liver, spleen, kidneys and lungs of the cold-stressed birds. However, when birds were maintained at 36 °C (DP = 28 °C) for 6 h and inoculated in the hot conditions and then subjected to -1 °C, the stressed birds died earlier than the similarly infected birds that were maintained at 18 °C.

Furthermore, growth of pasteurilla in the organs was augmented in the stressed birds. While it is likely that the immune system was adversely affected, it is also possible that fluctuating air temperature increased mortality *per se*.

In pigs, an excellent series of experiments showed that cold stress increased susceptibility to transmissible gastroenteritis (Shimizu *et al.*, 1978). Eight- to twelve-week-old pigs were resistant to a virulent TGE virus when they were maintained at an air temperature of 30 °C. However, when ambient temperature was reduced to 4°C soon after inoculation with the virus, pigs became highly susceptible as evidenced by diarrhea, soft feces and villous atrophy. Pigs maintained at 4 °C had higher serum neutralizing titers of antibodies against the TGE virus. The authors also reported data which suggested that a fluctuating air temperature between 20 °C and 4 °C reduced the resistance of feeder pigs to transmissible gastroenteritis. Although body temperatures were not reported, studies in our laboratory indicate that an air temperature of 4 °C does not substantially alter rectal temperature of 8- to 12-weeks-old pigs. Since an air temperature of 30 °C to 40 °C is optimal for growth of the TGE virus *in vitro* (Furuuchi and Shimizu, 1976), it is unlikely that body temperature directly affected growth of the virus. Cold stress also increased the susceptibility of baby pigs to TGE (Furuuchi and Shimizu, 1976).

In accord with the above results, Armstrong and Cline (1977) showed that low ambient

temperatures increased the incidence of gastroenteritis induced by *E. coli* in weanling pigs. Blecha and Kelley (1980) also demonstrated that cold stress increased the incidence and severity of scouring in piglets that were not experimentally infected with pathogenic organisms. This occurred even though feed intake of the two groups of piglets was constant. Perhaps cold stress reduced the resistance of these piglets to indigenous, relatively avirulent organisms, thereby precipitating gastroenteritis. This hypothesis was supported by the data of Previte and Berry (1962) with mice. Alternately, cold stress may have altered normal physiological functions of the gastrointestinal tract which led to more diarrhea.

Roy *et al.* (1971) found that an environmental temperature of 14.5 °C or 21 °C had little effect on the number of young calves with lung lesions. Interestingly, with Jersey and Friesian calves, there was a negative relationship between relative humidity and lung lesions at 21 °C and a positive relationship between these two parameters at 14.5 °C. However, these correlations were low (< 0.25). It would be interesting to determine if this relationship remained when an index of the absolute level of moisture in the air, such as dew point temperature, was used as a variable in the statistical analysis.

Mortality was doubled in young calves when they were purchased during the winter months than when the calves were purchased during the rest of the year (Staples and

Table 2. — Overview of immune responses of endothermic animals in response to cold stress.

Item	Response		References
	Increase	Decrease	
Susceptibility to mycotic infections, <i>M. marinum</i> , <i>S. typhimurium</i> , <i>S. aureus</i> , <i>T. cruzi</i> , pneumococci, <i>P. bergii</i> , several viruses, (including TGE and influenza)	+		Soerjadi <i>et al.</i> , 1979 ; Shimizu <i>et al.</i> , 1978 ; Armstrong and Cline, 1977 ; Kiorpes and Yuill, 1975 ; Clark and Shepard, 1963 ; Miraglia and Berry, 1962 ; Previte and Berry, 1962 ; Marshall, 1959 ; Walker and Boring, 1958 ; Junge and Rosenthal, 1948 ; Saslaw <i>et al.</i> , 1946 ; Kolodny, 1940 ; Lillie <i>et al.</i> , 1937.

Table 2 (continued). — Overview of immune responses of endothermic animals in response to cold stress.

Item	Response		References
	Increase	Decrease	
Secondary infection	+		Juszkiewicz, 1967 ; Miraglia and Berry, 1963.
Susceptibility to <i>P. multocida</i> .	+	+	Juszkiewicz, 1967.
	(fluctuating tempera- ture)		
Diarrhea induced by <i>E. coli</i> .	+		Blecha and Kelley, 1980 ; Armstrong and Cline, 1977.
Susceptibility to tetanus toxin.	+	+	Ipsen, 1952 ; 1951.
	(immunized or low doses)		
LD <sub>50</sub> of tetanus toxin and endotoxin.		+	Previte and Berry, 1962 ; Ipsen, 1951.
Reactivation of influenza virus.	+		Robinson, 1979 ; Shope, 1955).
	(pigs) no Δ (turkeys)		
Virus-induced interferon.	+		Postic <i>et al.</i> , 1966.
Lung clearance.		+	Curtis <i>et al.</i> , 1976 ; Green and Kass, 1965.
Concentration of peripheral blood lymphocytes.		+	Regnier and Kelley, 1981 ; Kelley <i>et al.</i> , in preparation.
		no Δ (calves, chronic)	
Antibody synthesis.	+	+	Blecha and Kelley, 1981b ; Regnier <i>et al.</i> , 1980 ; Sabiston <i>et al.</i> , 1978 ; Thaxton, 1978 ; Subba Rao and Glick, 1977 ; Kiorpes and Yuill, 1975 ; Ste. Rose and Sabiston, 1971 ; Eiseman <i>et al.</i> , 1964.
Half life of immunoglobulin.		+	Sabiston and Ste. Rose, 1976 ; Casey, 1973 ; Trapani and Campbell, 1959.
Mitogen blastogenesis.		+	Regnier and Kelley, 1981 ; Woodward <i>et al.</i> , 1980a ; Kelley <i>et al.</i> , in preparation.
		(chickens ; serum from calves)	
		No Δ (leukocytes from calves)	
Tuberculin sensitivity.	+	+	Kelley <i>et al.</i> , 1980.
	(acute)	(chronic)	
Contact sensitivity.	+	+	Regnier and Kelley, 1981 ; Blecha, 1981 ; Kelley <i>et al.</i> , 1980 ; Blecha <i>et al.</i> , 1980 ; Suskind and Ishihara, 1965.
	(mice)	(cattle, chickens)	
SRBC evanescent DTH.	+	+	Blecha, 1981 ; Blecha <i>et al.</i> , 1980.
	(expression)	(induction)	
Acquisition of colostral immunoglobulin.		+	Blecha and Kelley, 1981a, 1980.
		no Δ (absorption)	Olson <i>et al.</i> , 1981, 1980.

Haugse, 1974). Temperature fluctuations were also associated with increased calfood mortality (Martin *et al.*, 1975a, b ; Margig *et al.*, 1976). The wetting of animals to create a chill increased the severity of pneumonic lesions in experimentally infected calves (Jennings and Glover, 1952). In this regard, cold stress reduced the clearance of bacteria from the lungs of mice (Green and Kass, 1965) and young pigs, but not older pigs (Curtis *et al.*, 1976). Adverse weather has also been shown to reactivate a latent influenza virus that was carried by lungworms in pigs (Shope, 1955) and to increase the susceptibility of monkeys to an influenza virus (Saslaw *et al.*, 1946).

Recently, Robinson *et al.* (1979) reported that a cold stress at -1 °C did not affect the susceptibility of turkeys to an avian influenza virus. The authors also found that a moderate (1 °C for 10 days) or severe (-18 °C for 4 days) cold stress did not reactivate the virus. In these experiments, however, the time of inoculation of the virus and initiation of cold stress was separated by five days. It is possible that cold stress exacerbates effects of the influenza virus only if initiation of the stress and exposure to the virus occur synchronously. It is also possible that the clinical symptoms caused by the stress response varies as a function of inoculation dose (Soerjadi *et al.*, 1979 ; Ipsen, 1952) or the virulence of the organism (Miraglia and Berry, 1962 ; Previte and Berry, 1962).

Effects of cold stress on laboratory animals have also been investigated. Cold air temperature typically increases the severity of mycotic infections in laboratory animals, an effect which has been attributed to reduced growth of the fungi at lower temperature (Mackinnon, 1968). Mice held at 4 °C had a greater mortality rate than controls when injected with Coxsackie virus (Boring *et al.*, 1956 ; Walker and Boring, 1958). This effect was clearly not mediated by adrenal cortical hormones or acclimation to cold. Similarly, in an excellent series of experiments, Previte and Berry (1962) found that acclimation did not improve the resistance of cold-stressed mice to *Salmonella typhimurium*. Unexplainably, in a study cited by Webster (1970), it was demonstrated that acclimation to cold stress ameliorated the pathologic effect of an infection with Coxsackie virus.

Cold-stress increased the incidence of secondary staphylococci infections in mice ; in-

terestingly, these infections did not localize, but appeared to invade the liver, heart, lungs, kidneys and spleen of cold-stressed animals (Miraglia and Berry, 1963, 1962). In mice, cold stress increased the incidence of *Plasmodium berghei* infection (McQuiston, 1979), increased the susceptibility of mice to avirulent *Salmonella typhimurium* and *Staphylococcus aureus* (Miraglia and Berry, 1962 ; Previte and Berry, 1962), increased mortality induced by *Serratia marcescens* endotoxin (cited by Webster, 1970 ; Previte and Berry, 1962) and *Mycobacterium marinum* (Clark and Shepard, 1963), enhanced the severity of lesions caused by an encephalitis virus (Lillie *et al.*, 1937), exacerbated the incidence of death caused by an attenuated strain of myxoma virus (Marshall, 1959) and increased the severity of *Bacillus enteritidis* infections (Kligler and Olitzki, 1931). An air temperature of 6 °C increased the number of blood parasites in rats infected with *Trypanosoma cruzi* (Kolodny, 1940). Similar results were obtained by Kligler and Weitzman (1926). Experimental treatments that were sufficient to lower rectal temperature by about 1 °C were also effective in increasing the number of rickettsiae in the peritoneal fluid of guinea pigs, rabbits and sheep (Castaneda, 1937). Low or fluctuating air temperature increased the susceptibility of rabbits (Kiorpes and Yuill, 1975) and dogs (Carmicheal *et al.*, 1969) to viral infections and reduced virus-induced interferon, but not endotoxin-induced interferon, in rabbits (Postic *et al.*, 1966). Cold stress also increased the susceptibility of hamsters to poliomyelitis (Teodoru and Schwartzman, 1956) and an endemic typhus in guinea pigs (Lillie *et al.*, 1937), but did not affect the susceptibility of mice to *Hymenolepis nana* (Weinmann and Rothman, 1967).

Extreme hypothermia increased the susceptibility of rabbits to an avirulent, but not virulent, pneumococcus infection (Muschenheim *et al.*, 1943). This effect may have been due to the temperature preferendum of the pneumococci (Bennett and Nicastrì, 1960). With mice, the reduction in resistance caused by exposure to an 18 °C air temperature only occurred when animals were treated with sulfadiazine ; cold stress alone seemed to enhance survival (Junge and Rosenthal, 1948). Indeed, extreme hypothermia has been reported to increase the survival time of mice infected with pneumococci (Eiseman *et al.*, 1964, 1956).

### *Antibody-mediated immunity*

Ipsen (1952, 1951) demonstrated that cold air temperatures could either enhance or reduce the susceptibility of mice to tetanus toxin, depending on whether or not the mice were immunized and the dose of toxin. For instance, more nonimmunized mice died at lower doses of tetanus toxin when they were cold stressed, which suggested that the LD<sub>50</sub> for cold-exposed mice was lower than that for normal mice. This suggestion was confirmed with bacterial endotoxins in cold-stressed mice: a 250-fold reduction in the LD<sub>50</sub> was observed with heat-killed *Salmonella typhimurium* and the LD<sub>50</sub> to the lipopolysaccharide of *Serratia marcescens* was reduced about 10 times (Previte and Berry, 1962). When high doses of the tetanus toxin were used in non-immunized mice, an opposite effect occurred: an air temperature of 10 °C enhanced survival to tetanus toxin. A similar effect occurred when mice were immunized at 25 °C but were challenged at 6 °C. Perhaps the elevated metabolic rate of the cold-stressed mice increased clearance of the toxin. However, when mice were immunized with the toxoid at 6 °C and challenged with high doses of toxin at 25 °C, mortality was increased. This effect was more pronounced at low doses of toxoid. These data suggested that cold air prolonged survival of mice to high doses of tetanus toxin in either normal mice or in mice that were immunized at normal temperatures. However, if mice were initially exposed to the toxin at 6 °C, recovered from the episode and encountered the toxin again at a normal temperature, the chance for survival was reduced.

Some strains of mice produce less antibody at cold temperatures (Sabiston *et al.*, 1978). Eiseman *et al.* (1964) also found that the exposure of mice to 6 °C dramatically reduced the hemolysin response to SRBC. However, other workers have reported that chronic cold stress had little effect on capability of rabbits (Northey, 1965) and mice (Chaffee and Martin, 1962) to synthesize antibody. It should be noted that the former author used an adjuvant at immunization.

Interestingly, in mammals, chronic cold stress generally increases antibody titers. For instance, cold stress enhanced the synthesis of antibodies to an intravenous injection of human albumin in rabbits (Ste. Rose and Sabiston, 1971). This contrasts with the earlier work of Northey (1965), who used protein an-

tigens in adjuvants. Cold exposure shortened the half-lives of IgG and IgM (Sabiston and Ste. Rose, 1976) and allogeneic antibody (Trapani and Campbell, 1959) in rabbits and IgG in mice (Casey, 1973). A two-week cold stress at -5 °C also slightly reduced serum IgG<sub>1</sub> levels in calves, but had no effect on IgM concentrations (Kelley *et al.*, in preparation).

Turnover rate of IgG and IgM was elevated in cold-stressed rabbits (Sabiston and Ste. Rose, 1976). This finding suggested that increased immunoglobulin synthesis caused by cold exposure could account for higher antibody titers. Kiorpes and Yuill (1975) rejected this hypothesis in their studies with a live virus. They explained that the immune response was unaffected and indicated that cold stress acted to simply increase the level of viremia, thereby providing a greater amount of antigen to stimulate antibody synthesis. However, recent results from our laboratory (Blecha and Kelley, 1981b) using a nonreplicating antigen (SRBC) showed that when five-week-old pigs were exposed to 0 °C for four days, both total and 2-mercaptoethanol-sensitive antibody titers were increased. Serum gamma globulin was also elevated. Similarly, Shimizu *et al.* (1978) reported that serum neutralizing titers to TGE were elevated in cold-stressed pigs. These data strongly suggested that a short cold stress directly stimulated antibody synthesis in the pig, which may have been mediated by the neuroendocrine system.

In chickens, an acute and chronic (28 days) cold stress enhanced the synthesis of antibody to SRBC and BSA in certain strains of birds (Subba Rao and Glick, 1977), whereas the antibody response to SRBC in other breeds of chickens was unaffected (Regnier *et al.*, 1980). A different type of chronic cold stress (six days) also did not affect the peak antibody response to SRBC (Regnier and Kelley, 1981). However, in the ectothermic chicken embryo, a cold incubation temperature (31 °C) reduced the synthesis of antibodies to a cellular antigen (Seto, 1972). Cold stress was most effective when applied within 24 h after immunization. An incubation temperature of 37 °C also reduced the capability of chicks to synthesize antibody later in life (Preda and Rusu, 1977).

A short cold exposure at 10 °C reduced the capability of newborn pigs to acquire colostrum immunoglobulin (Blecha and Kelley, 1981a). Cold stress did not reduce the absorption of

bovine colostral immunoglobulin by piglets (Blecha and Kelley, 1980). These results suggested that the absorption mechanisms were unaffected and that cold stress acted to weaken piglets, which impaired their opportunity to nurse and acquire colostral immunoglobulin. Extreme hypothermia reduced the rate of absorption of colostral immunoglobulin in dairy calves (Olson *et al.*, 1980), but a moderate cold stress had no effect on the absorption of immunoglobulin in newborn beef calves (Olson *et al.*, 1981). It is also possible that in the former study, extreme cold stress increased the rate of degradation of colostral immunoglobulin once it entered the systemic circulation, as indicated by the work cited above in mice and rabbits. This suggestion was also supported by the work cited above in mice and rabbits. This suggestion was also supported by the work of Siers *et al.* (1976), who showed that the percentage of blood proteins containing gamma globulin was lowered significantly by holding piglets at 5 °C for a little as one hour.

#### *Cell-mediated immunity*

The possible effect of cold stress on cellular immune events is relatively unknown. A reduction in mitogen responsiveness caused by lowered air temperatures *in vitro* has been suggested to cause a cellular immunodeficiency in the appendages of man, which may lead to certain kinds of local infections (Lauwasser and Shands, 1979). Duerschner *et al.* (1943) reported that extreme hypothermia reduced the expression of tuberculin skin test reactions in guinea pigs. Reduced skin reactions were accompanied with shorter survival times to virulent human tubercle bacilli and more deaths during the period of hypothermia.

Exposure of month-old dairy calves to ambient conditions of -5 °C for one week had little effect on the expression of PPD swelling in calves sensitized with *Mycobacterium tuberculosis* when compared with thermoneutral controls (Kelley *et al.*, 1980). Cold-stressed calves actually displayed significantly enhanced responses when compared to heat-stressed calves. Recent experiments in our laboratory also showed that an acute (12 h) cold stress enhanced the expression of PPD reactions in calves and increased the number of peripheral blood lymphocytes (unpublished). However, after two weeks of cold exposure, the expression of PPD reactions was reduced

when compared to thermoneutral controls. DNFB contact sensitivity reactions were also reduced at the end of both the first and second week of cold stress and PHA swelling was unaffected. Mitogen-induced blastogenesis of enriched peripheral blood mononuclear cell preparations from cold-stressed calves was not altered, but serum from cold-stressed calves reduced blastogenesis of normal mononuclear cells when compared with serum from calves that were heat stressed (Kelley *et al.*, in preparation). Cold exposure in calves had little effect on the number of circulating lymphocytes, monocytes, neutrophils, eosinophils or basophils (Kelley *et al.*, in preparation). These data suggested that cold stress did not directly affect mitogenesis of mononuclear cells in calves, but that serum factors may have caused an immunosuppression. Woodard *et al.* (1980a) also reported that cold stress had little effect on the blastogenesis of purified mononuclear cells from newborn beef calves. The three-day cold stress at 1 °C had little effect on the bactericidal activity of neutrophils or sera towards *Staphylococcus aureus* or *Escherichia coli* (Woodard *et al.*, 1980b) or on total complement hemolytic activity (Woodard *et al.*, 1980c).

A five-day cold stress at 1 °C reduced the expression of contact sensitivity responses and PHA skin test reactions in five-week-old chickens (Regnier and Kelley, 1981). When whole blood cultures from these stressed New Hampshire birds were stimulated *in vitro* with PHA, tritiated thymidine incorporation was reduced. A nonsignificant reduction was noted with White Rock broilers. As in calves, this reduction may have been caused by certain serum components in the blood of the cold-stressed birds. Also, cold stress in the New Hampshire birds caused a modest reduction in the number of peripheral blood lymphocytes.

With mice, cold air temperature has also been shown to affect cellular immune responses. When mice were exposed to 5 °C during the induction phase with DNFB and subsequently challenged at thermoneutral conditions, contact sensitivity reactions were enhanced (Blecha, 1981; Blecha *et al.*, 1980). This effect was also observed if the cold stress was continued through the expression phase (Suskind and Ishihara, 1965). Using a different DTH assay, evanescent DTH to SRBC (Liew, 1977), an enhanced response was again

observed if animals were exposed to cold air temperatures when challenged. However, cold stress that was applied only during the induction phase caused a reduction in the response to SRBC when mice were subsequently tested at a thermoneutral temperature. These results showed that cell-mediated immune responses in mice were generally augmented by cold stress. Completely opposite results were obtained, however, if cold stress was applied only when the animal was first exposed to SRBC. These findings suggested that the cellular immune response was dependent on whether the animal was stressed at the time it was first exposed to the antigen. These results may also ultimately explain the variation in cell-mediated assays between experiments and among different laboratories. Furthermore, immunological changes caused by cold stress may explain why some workers have observed both increases and decreases in the resistance of stressed animals to infectious diseases.

Hypothermia has been shown to reduce phagocytic activity in dogs (Gowen and Friou, 1961; Fedor *et al.*, 1956), in mice (Eiseman *et al.*, 1964) and in rabbits immune to *Diplococcus pneumoniae* (Kaufman and Northey, 1968). These experiments with phagocytosis should be interpreted with caution, however, because the degree of hypothermia was severe and used for a specific purpose under controlled laboratory conditions. If this degree of hypothermia was achieved in adult animals in cold weather, death would probably result. Furthermore, the animals' physiological and immune responses to induced hypothermia and chilling differ substantially (Eiseman *et al.*, 1964).

## Crowding

### *Resistance to infection*

Crowding refers to providing animals with limited living space and mixing refers to placing animals together that are unfamiliar with one another. Many of the effects of crowding are confounded with the development of new social interactions that are caused by mixing unfamiliar individuals.

The stress of crowding has been suggested to reactivate a latent rabies virus in guinea pigs (Soave, 1964) and an avian influenza virus in turkeys (Robinson *et al.*, 1979). One

experiment suggested that this reactivation of virus was mimicked by an injection of adrenocorticotrophic hormone (Soave, 1962), which is released from the adenohypophysis following most acute stressors. Crowded, nonimmunized mice were more susceptible to an LD<sub>50</sub> dose of *Salmonella typhimurium* than control mice (Edwards and Dean, 1977) and crowding also reduced the resistance of mice to the parasite *Microphallus pygmaeus* (Brayton and Brain, 1974). The stress of crowding after an acute infection with *Mycobacterium tuberculosis* reduced the survival time of mice when compared to mice that were crowded, infected and then returned to single housing conditions (Tobach and Bloch, 1956). Interestingly, the crowded male mice were more susceptible to a chronic tuberculous infection than the crowded females.

### *Immune function*

Solomon (1969b) reported that crowding rats at five to six per cage reduced both the primary and secondary antibody responses to flagellin. More recent studies confirmed these results with a typhoid-paratyphoid vaccine (Edwards and Dean, 1977). However, crowding had little influence on the capability of mice to synthesize antibodies to SRBC (Brayton and Brain, 1975). Crowding also reduced antigen-specific mitogenesis in male rats, but increased this response in female rats (Joasoo and McKenzie, 1976). This differential effect of crowding on male and female animals was similar to the results of Tobach and Bloch (1956), and may have been related to maintenance of a social dominance order. Mitogen-induced blastogenesis was unaffected by crowding.

### *Isolation*

As a matter of interest, Friedman *et al.* (1969) reviewed data which demonstrated that the stress of isolation could either enhance or reduce the susceptibility of mice, depending on the particular pathogenic agent. For instance, isolation had little effect on the growth of a Walker sarcoma in rats or the incidence of spontaneous leukemia in AKR/J mice. However, isolation increased the susceptibility of mice to encephalomyocarditis virus and decreased the susceptibility of mice



to *Plasmodium berghei*. The authors concluded that psychosocial factors clearly altered the resistance of animals to infectious agents, but that the ultimate outcome of the disease was dependent on several environmental factors.

The changes in host susceptibility that are caused by isolation may be related to changes in particular subsets of lymphoid cells that are altered by the stress response. Isolation reduced antigen-induced, but not mitogen-induced, lymphoblastogenesis in mice (Joasoo and McKenzie, 1976). Glenn and Becker (1969) also reported that the isolation of mice reduced the secondary antibody response to bovine serum albumin. However, recent results indicated that this effect depended on the previous social environment. For instance, when mice were isolated, exposed to psychosocial stimulation and then reisolated, antibody titers were reduced (Edwards *et al.*, 1980). Isolated mice actually synthesized more antibodies than those mice that were recently mixed.

## Mixing

### *Susceptibility to disease*

Davis and Read (1958) reported that the daily mixing of mice infected with *Trichinella spiralis* significantly increased the number of adult trichinella worms and larvae in stressed mice. Weinmann and Rothman (1967) also showed that fighting increased the susceptibility of both immune and nonimmune mice to the parasite *Hymenolepis nana*. Subordinate animals were the most susceptible. This experiment again suggested that social rank may influence host resistance.

It is also likely that the psychological effect of maintaining a social dominance order may account for many of the effects of mixing or crowding. For instance, Ebbesen and Rask-Neilson (1967) and Ebbesen (1968) reported that when DBA/2, BALB/c and CBA male mice were housed together, the survival time of male mice was shorter and splenic amyloid was higher than in females raised in groups. However, if a male was raised with several females, the male lived as long as the females. The enhancement of amyloidosis in grouped males did not appear to be related to the incidence of wounds, which led the authors to speculate that the maintenance of a dominance hierarchy in grouped males could

explain these results. This hypothesis was supported by other research. Sex-segregated housing in male mice enhanced growth of a murine sarcoma virus whereas fighting *per se* in females reduced growth of the sarcoma (Amkraut and Solomon, 1972). It is also interesting that Weinmann and Rothman (1967) noted an increase in the susceptibility of mice to *Hymenolepis nana*, even though mixing did not induce fighting.

Perhaps the most research with mixing and susceptibility to infectious diseases in the avian species has been reported by W.B. Gross. In an early report, he demonstrated that mixing chickens increased their resistance to pathogenic *Escherichia coli* organisms (Gross and Siegel, 1965). Later, Gross and Colmano (1969) found that an excess degree of social interaction caused by mixing chickens increased their resistance to bacterial infections caused by *Escherichia coli* and *Staphylococcus aureus*, but reduced their resistance to both *Mycoplasma gallisepticum* and Newcastle disease virus. These results are in general agreement with the work discussed by Friedman *et al.* (1969).

High social stress also reduced the resistance of birds to Marek's disease (Gross, 1972 ; Gross and Colmano, 1971) and increased the resistance to northern fowl mites (Hall and Gross, 1975) and *Eimeria necatrix* infection (Gross, 1976). Enhanced resistance to certain bacterial and coccidiosis infections may be mediated by the increased heterophile response of stressed birds (Siegel, 1980 ; Gross and Siegel, 1975 ; Gross, 1962). The responses of genetically-selected lines of birds to various types of infectious diseases have been recently summarized by Gross *et al.* (1980).

### *Immune system*

Research by Gross also showed that a high level of social stress that was induced by mixing reduced the synthesis of antibodies to *Escherichia coli* in certain artificially-selected lines of birds (Gross and Siegel, 1973). Other lines of birds exposed to low social stress had higher antibody titers. Mixing increased the rate of disappearance of antibodies from the systemic circulation of the visiting but not the resident birds of a nonaggressive family (Siegel and Latimer, 1975). This greater disappearance of antibodies did not occur in a larger, more aggressive family of chickens. In

mice, Vessey (1964) reported that mixing animals for a duration of 4 h daily reduced antibody synthesis to bovine serum. The author also demonstrated that subordinate mice had significantly lower antibody titers than dominant mice, which supported the work of Weinmann and Rothman (1967).

## Weaning

### *Disease and immune function*

Few data have been reported on the influence of weaning on the immune system of any species. Ader and Friedman (1965) demonstrated that mortality from a carcinosarcoma was increased in rats that were prematurely weaned. However, La Barba (1970) suggested an opposite effect with Ehrlich ascites carcinoma; early weaning increased survival time. Early weaning did not affect the outcome of an infection with an encephalomyocarditis virus (Friedman *et al.*, 1969).

In calves, Gwazdauskas *et al.* (1978) reported that antibody synthesis to heterologous erythrocytes was reduced when the antigen was injected within 24 h of weaning. This depression in antibody synthesis was related to increased serum glucocorticoid levels. Other researchers (Crookshank *et al.*, 1979) have also noted that weaning calves caused a moderate increase in serum cortisol and induced changes in some other biochemical parameters.

In a recent experiment (Blecha and Kelley, 1981b), it was shown that when pigs were injected with SRBC at 24 h prior to weaning, a significant reduction in antibody titers was observed one week later. Although the reduction was small, it was characterized mostly by a decrease in IgM synthesis. Paradoxically, pigs that were weaned two weeks prior to the controls had elevated circulating levels of gamma globulin. This may have been due to the removal of feedback inhibition by milk proteins, increased antigen exposure or a reduction in the catabolism of existing immunoglobulin.

Milk immunoglobulin, primarily in the form of IgA, continuously bathes the gut in nursing pigs, as in other species (Bourne, 1976; Porter, 1976; Wilson, 1974; Porter and Allen, 1972). Around one week of age, the pig begins to synthesize immunoglobulins locally (Porter *et al.*, 1970). There appeared to be an equal

number of IgA-secreting cells in the gut before and after weaning, which suggested that weaning *per se* had little effect on the number of IgA-secreting plasma cells. However, the associated stressors of mixing, transportation and relocation may combine to alter the number of IgA-secreting plasma cells, which may compromise local gut protection and exacerbate post-weaning diarrhea.

## Limit-feeding

### *Susceptibility to disease and cellular immunity*

Restricted feeding of gestating animals is a recommended management practice for many species of livestock. In several instances, this amounts to a 24 h fast. Much information is available on the influence of particular dietary components, such as protein (Chandra, 1980; Cooper *et al.*, 1974), on the immune system of animals. However, very little research has been conducted on the effect of limit-feeding on immune function.

Bistrián *et al.* (1975) reported that semistarvation reduced the number of circulating lymphocytes in humans. Contact sensitivity and *Candida* dermal reactions were also reduced by semistarvation. Similarly, food deprivation increased the susceptibility of mice to *Hymenolepis nana* (Weinmann and Rothman, 1967).

Food deprivation has been shown to alter other types of cellular immune reactions. Amkraut *et al.* (1973) used the popliteal lymph nodes to assess T-cell competence in a local graft vs. host reaction. By reducing the feed intake of rats to about 50 % of *ad libitum*-fed controls, a dramatic immunosuppression was observed. The authors stated that the reduced graft vs. host response was not completely restored when excess amounts of vitamins and minerals were fed. The immunosuppression could not be entirely accounted for by ACTH injections. Lymphocyte proliferation *in vivo* was not reduced in fasted animals, and may have even been enhanced. The authors speculated that limit-feeding affected the release of lymphokines or a donor suppressor cell population. Folch and Waksman (1974) lent some credence to this conclusion when they showed that spleen cells from rats deprived of water for 48 h showed loss of suppressor cell adherence to glass wool.

### *Antibody-mediated immunity*

Spalatin and Hanson (1974) reported that when food and water were withheld from chickens for one day, antibody titers to Newcastle disease virus were elevated when compared to chickens fed *ad libitum*, regardless of whether the vaccine was injected intramuscularly, administered in the drinking water, or inserted via a capsule into the crop. In most cases, however, survival of vaccinated chickens was not affected by food and water deprivation at immunization when the birds were subsequently challenged with virulent Newcastle disease virus (i.e., induction of immunity was unaffected by stress). Interestingly, when unvaccinated control birds were housed with vaccinated birds, spread of the virus was enhanced by food and water deprivation, as detected by a greater number of serologic responders, higher antibody titers and greater survival upon challenge with Newcastle disease virus. These results therefore suggested that the removal of food and water for 24 h enhanced shedding of Newcastle disease virus.

Nathan *et al.* (1977) reported different results with different antigens. They found that starvation for 48 h reduced the synthesis of antibodies to *Escherichia coli* and sheep erythrocytes. This effect occurred only when the birds were immunized within 24 h of deprivation. Nathan *et al.* (1977) also found that either a 24 h or 48 h fast reduced the number of peripheral blood leukocytes and weight of the bursa of Fabricius, spleen and thymus. Perhaps the disparity between their results and the data of Spalatin and Hanson (1974) can be explained by the longer fasting time in the former study. It is also likely that the nature of the antigen was related to this difference. Finally, Katayama *et al.* (1978) observed that a 24 h fast dramatically reduced various kinds of passive cutaneous anaphylactic reactions in guinea pigs. Results were similar, but less dramatic, in rats.

### **Noise**

#### *Resistance to disease*

When mice were first exposed to a noise level of 123 db, then inoculated intranasally with vesicular stomatitis virus and exposed to

noise during the subsequent four days, mortality rate was significantly higher than among control mice (Jensen and Rasmussen, 1963).

Similar results were obtained when mice were inoculated immediately before the second stress episode, but a slight increase in resistance was noted when mice were inoculated immediately after the second daily noise treatment. These data suggested that mice could successfully acclimate to noise stressors. Chang and Rasmussen (1965) found that high intensity noise reduced interferon production, but blood levels of vesicular stomatitis virus or antibody titers to this virus were not affected. When a susceptible strain of mice was subjected to bell-ringing noise and injected with a chemical carcinogen, there was a delay in tumor induction (Molomut *et al.*, 1963). However, there was no difference in the survival time of stressed and control mice. Sound stress also reduced the growth of a chemically induced rat mammary carcinoma (Pradhan and Ray, 1974).

#### *Immune function*

Jensen (1969) and Geber *et al.* (1966) reported that various levels of noise reduced blood leukocytes, such as eosinophils, in rodents. Hill *et al.* (1967) showed that intermittent noise, in combination with two other psychological stressors, reduced the synthesis of antibodies to bovine serum albumin in monkeys. Recently, Monjan and Collector (1977) reported that when male mice were exposed to intermittent noise at 100 db for one to three hours daily, spleen cell blastogenesis induced by concanavalin A and lipopolysaccharide and cytotoxicity towards P815 target cells were reduced for about three weeks. However, all of these responses were enhanced if the mice were exposed to the intermittent noise for a longer period of time. Eventually, blastogenic responses returned to normal, which suggested that the mice became acclimated to the noise. These results generally support the earlier experiments by Jensen and Rasmussen (1963). Interestingly, the clinical use of sonar, called echo sonography, reduced the synthesis of antibody to SRBC (Anderson and Barrett, 1979). This appeared to be due to both a lack of specific antibody of IgM class and a total IgM deficiency. Holt (1978) has briefly reviewed the effect of auditory stress on the immune system.

Table 3. — Effect of different stressors on immune function of homeothermic animals (mostly rodents).

Stressor Item	Response		References
	Increase	Decrease	
<i>Crowding.</i>			
Susceptibility to <i>S. typhimurium</i> , <i>Microphallus pygmaeus</i> .	+		Edwards and Dean, 1977 ; Brayton and Brain, 1974.
Susceptibility to <i>M. tuberculosis</i>	+	+	Tobach and Bloch, 1956.
	(female)	(male)	
Reactivation of virus.	+		Robinson <i>et al.</i> , 1979.
Antibody synthesis.	+		Edwards and Dean, 1977 ; Solomon, 1969.
Antigen-induced blastogenesis.	+	+	Joasoo and McKenzie, 1967.
	(female)	(male)	
<i>Mixing.</i>			
Susceptibility to <i>E. coli</i> , <i>S. aureus</i> , northern fowl mite, <i>Eimeria necatrix</i> .		+	Gross, 1976 ; Hall and Gross, 1975 ; Gross, 1972 ; Gross and Colmano, 1969 ; Gross and Siegel, 1965.
Susceptibility to <i>Trichinella spiralis</i> , <i>Hymenolepis nana</i> , <i>Mycoplasma</i> <i>gallisepticum</i> , Marek's disease, Newcastle disease virus.	+		Gross, 1972 ; Gross and Colmano, 1969 ; Weinmann and Rothman, 1967 ; Davis and Read, 1958.
Antibody synthesis.		+	Edwards <i>et al.</i> , 1980 ; Gross and Siegel, 1973 ; Vessey, 1964.
Half life of antibody.		+	Siegel and Latimer, 1975.
<i>Weaning.</i>			
Ascites carcinoma.	+	+	La Barba, 1970 ; Ader and Friedman, 1965.
Antibody synthesis.		+	Gwazdauskas <i>et al.</i> , 1978 ; Blecha and Kelley, 1981b.
Serum immunoglobulin.	+		Blecha and Kelley, 1981b.
<i>Limit-feeding.</i>			
Susceptibility to <i>Hymenolepis nana</i> .	+		Weinmann and Rothman, 1967.
Contact sensitivity.		+	Bistrián <i>et al.</i> , 1975.
Graft vs. host reaction.		+	Amkraut <i>et al.</i> , 1973.
Antibody synthesis.	+	+	Nathan <i>et al.</i> , 1977 ; Spalatin and Hanson, 1974.
Passive cutaneous anaphylaxis.		+	Katayama <i>et al.</i> , 1978.
Concentration of peripheral blood leukocytes.		+	Nathan <i>et al.</i> , 1977.
<i>Noise.</i>			
Susceptibility to vesicular stomatitis virus.	+	+	Jensen and Rasmussen, 1963.
	(acute)	(chronic)	
Virus-induced interferon.		+	Chang and Rasmussen, 1965.
Concentration of peripheral blood leukocytes.		+	Jensen, 1969 ; Geber, 1966.
Mitogen-induced blastogenesis.	+	+	Monjan and Collector, 1977.
	(chronic)	(acute)	
Spleen cell cytotoxicity.	+	+	Monjan and Collector, 1977.
	(chronic)	(acute)	

Table 4. — Effect of avoidance learning and physical restraint on immune function of laboratory animals.

Item	Stressor		Response		References
			Increase	Decrease	
<i>Avoidance learning.</i>					
Susceptibility to Coxsackie B virus, herpes simplex virus, polyoma virus.			+		Rasmussen, 1969 ; Friedman <i>et al.</i> , 1965 ; Johnson <i>et al.</i> , 1963.
Susceptibility to poliomyelitis.			+	+	Rasmussen, 1969 ; Marsh <i>et al.</i> , 1963.
Skin graft rejection.				+	Wistar and Hildemann, 1960.
Contact sensitivity.			+		Mettrop and Visser, 1971, 1969 ; Guy, 1952.
Symptoms of passive systemic anaphylaxis.				+	Treadwell and Rasmussen, 1961 ; Rasmussen <i>et al.</i> , 1959.
Concentration of peripheral blood lymphocytes.				+	Jensen, 1969 ; Marsh and Rasmussen, 1960.
Thymic and splenic involution.				+	Jensen, 1969 ; Marsh and Rasmussen, 1960.
Virus- and endotoxin-induced interferon.				+	Jensen, 1973 ; Jensen, 1968 ; Solomon <i>et al.</i> , 1967.
Tumor growth.				+	Newberry <i>et al.</i> , 1972 ; Marsh <i>et al.</i> , 1959.
<i>Restraint.</i>					
Concentration of peripheral blood lymphocytes.				+	Jensen, 1969 ; Marsh and Rasmussen, 1960.
Susceptibility to herpes simplex virus.			+		Rasmussen <i>et al.</i> , 1957.
Virus- and endotoxin-induced interferon.				+	Jensen, 1973 ; Jensen, 1968 ; Solomon <i>et al.</i> , 1967.
Contact sensitivity.			+		Blecha, 1981 ; Blecha <i>et al.</i> , 1980.
SRBC evanescent DTH.				+	Blecha, 1981 ; Blecha <i>et al.</i> , 1980.
Tumor growth.				+	Newberry <i>et al.</i> , 1976 ; Marsh <i>et al.</i> , 1959.

## Psychological stressors

### General comments

Although a sensory component is part of an animal's response to all physical stressors, adverse psychological encounters may directly alter immune function in the absence of physical stressors. For example, calves absorb more colostral immunoglobulin when they are with their dams than when they are separated from their mother (Fallon, 1978 ; Selman *et al.*, 1971). In this section, several experiments are discussed that involve a combination of physical and psychological stressors which are

thought to primarily elicit emotional states, such as fear and frustration. In these instances, several investigators have proposed that psychological or emotional stressors are involved in the etiology of infectious diseases, autoimmune diseases and tumor growth (Solomon, 1969a ; Rasmussen, 1969 ; Friedman *et al.*, 1969). In other cases, such as with broad retrospective surveys that have investigated the relationship of stress factors and the susceptibility of humans to infectious disease or cancer, the results are less clear (Andrews and Tennant, 1978 ; Fox, 1978 ; Rabkin and Struening, 1976).

### *Avoidance learning*

A chronic avoidance learning paradigm, consisting of a warning light-buzzer system and electric shock, increased the susceptibility of mice to Coxsackie B virus (Johnsson *et al.*, 1963; Friedman *et al.*, 1965), herpes simplex virus (Rasmussen *et al.*, 1957) and poliomyelitis and polyoma virus, but caused little change in the susceptibility to respiratory viruses (cited by Rasmussen, 1969). In contrast, a short (24 h) avoidance learning stress reduced the susceptibility of monkeys to poliomyelitis (Marsh *et al.*, 1963). The antibody response to vesicular stomatitis virus was unaffected by an avoidance learning paradigm, but clearance of the virus from the muscles of stressed mice was retarded (Yamada *et al.*, 1964). Solomon (1969b) confirmed that apprehension-electric shock had little effect on the capability of mice to synthesize antibody to flagellin. However, Solomon (1969b) demonstrated that a different type of psychological stressor reduced the primary, but not the secondary, response to this antigen.

The influence of psychological stressors on cellular immune events is almost unknown. A chronic avoidance learning paradigm (about three weeks) somewhat impaired survival time of skin grafts in mice (Wistar and Hildemann, 1960). However, a shorter, five-day avoidance learning stressor was suggested to enhance the expression of contact sensitivity reactions in sensitized guinea pigs (Guy, 1952). An acute, unavoidable electrical stressor also enhanced the induction of contact sensitivity reactions in guinea pigs (Mettrop and Visser, 1971, 1969). Serum corticoid levels were significantly elevated immediately after exposure to the electrical stressor. Although the data are meager, these results suggested that a short, acute psychological stressor enhanced contact sensitivity responses. Interestingly, restraint, cold and heat stress also enhanced contact sensitivity reactions in mice (Blecha, 1981; Blecha *et al.*, 1980).

Similar to the results observed with heat stress in chickens (Morgan *et al.*, 1976), mice that were subjected to an avoidance learning stress were less susceptible to passive anaphylaxis (Treadwell and Rasmussen, 1961; Rasmussen *et al.*, 1959). As with other stressors in rodents, avoidance learning caused adrenal hypertrophy, involution of the thymus and spleen, lymphopenia and leukopenia (Jensen, 1969; Marsh and Rasmussen, 1960). In the domestic pig, an unavoidable severe electrical

stress caused a moderate increase in leukocytes, which was characterized by a dramatic rise in neutrophils, a reduction in eosinophils and a moderate decline in lymphocytes (Ellersieck *et al.*, 1979).

Electrical stress can also affect interferon synthesis. Jensen (1968) showed clearly that a 4 h avoidance learning stress reduced interferon titers in mice. This reduction was also observed in adrenalectomized mice, which suggested that adrenal corticoids were not responsible for this reduction. Using an unavoidable random electric shock, Solomon *et al.* (1967) did not observe a reduction in interferon titers. Subsequent experiments by Jensen (1973) demonstrated that the stress-induced reduction in interferon titers that was caused by the stress of avoidance learning was not mediated by alpha adrenergic receptors or serotonin. Serum from stressed mice was also ineffective in reducing interferon levels of normal mice. Splenectomy abolished the stress-induced reduction in interferon.

Unexpectedly, when mice were shocked for 5 h prior to the induction of interferon with Newcastle disease virus, the interferon titer at 6 h after the stress was increased (Solomon *et al.*, 1967). Jensen (1968) did not observe this effect. Pretreatment with 3 mg.kg<sup>-1</sup> of hydrocortisone increased interferon titers when calves were inoculated with infectious bovine rhinotracheitis (IBR) (Cummins and Rosenquist, 1979, 1977). In contrast, however, cortisone pretreatment reduced interferon titers in mice (Rytel and Kilbourne, 1966). It should be noted that cortisol has been reported to increase and decrease interferon titers *in vitro* (DeMaeyer and DeMaeyer, 1963).

Physical immobilization of animals has also been shown to alter immune function. Immobilization causes leukopenia, adrenal hypertrophy and thymic and splenic involution (Jensen, 1969; Marsh and Rasmussen, 1960). In several well-controlled experiments, restraint reduced both virus-induced and endotoxin-induced interferon (Jensen, 1973, 1968), although Solomon *et al.* (1967) did not observe this effect. Restraint also increased the susceptibility of mice to herpes simplex virus (Rasmussen *et al.*, 1957).

Thaxton and Briggs (1972) reported that immobilization did not impair the capability of chickens to synthesize antibody to SRBC. However, recent work by Blecha (1981) showed clearly that restraint altered cellular immunological function in mammals. For in-

stance, when mice were restrained for a single 2.5 h period before immunization with SRBC (evanescent DTH), the cellular response was reduced when mice were subsequently challenged with SRBC in the footpad. However, enhanced reactions were observed with contact sensitivity reactions utilizing DNFB. If restraint was imposed immediately before challenge, similar results were obtained: the response to DNFB was augmented while the delayed reaction to SRBC was reduced. Since both of these tests, DNFB and SRBC, are thought to represent cellular immune events that occur *in vivo*, these data showed that a single acute stressor could either enhance or retard cell-mediated immune reactions. This probably occurred because the same stress differentially affected subsets or regulatory or effector cells that controlled these reactions.

### *Neoplasia*

La Barba (1970) and Crisp (1970) reviewed the effect of psychosocial factors on neoplastic diseases. Although the individual papers will not be discussed in detail, both authors presented evidence which showed that different kinds of cancer were influenced by psychosocial factors. More recent experiments have also supported the concept that psychological stressors alter the growth of some types of tumor cells.

Sklar and Anisman (1979) recently reported the effect of electric shock on growth of mastocytoma cells in mice. These workers found that tumors appeared earlier among mice that were subjected to one shock session that consisted of 60 shocks of a 6 min duration. Survival time was also reduced in the shocked mice. Tumor growth was unaffected when five or ten shock sessions were given, which suggested that the mice may have successfully acclimated to the stressor. Interestingly, when mice were given the opportunity to escape the shock, tumor growth was similar to non-shocked controls. Tumor growth was enhanced in the sham-treated mice that were not given the opportunity to escape the shock. These results indicated that the physical trauma of electric shock was not responsible for enhanced tumor growth. Instead, the emotional derangement associated with the inability to escape the shock exacerbated tumor growth.

Amkraut and Solomon (1972) also reported that an unavoidable electric shock given after

inoculation with a murine sarcoma virus enhanced tumor size. However, when the shock was administered before inoculation with the virus, tumor growth was retarded. Similarly, Marsh *et al.* (1959) and Pradhan and Ray (1974) found that tumor growth was retarded by the stressors of immobilization, electric shock and avoidance learning when the stressors were begun soon after induction of the tumor. Restraint and electric shock also reduced the number or growth of chemically-induced mammary tumors in rats (Newberry *et al.*, 1972, 1976). A different type of electric shock did not alter the survival of mice that were infected parenterally or intracerebrally with a leukemia tumor (Gershbein *et al.*, 1974). These workers also found that forced swimming reduced the growth of a Walker tumor in rats, but this stressor did not affect the rate of survival. Rashkis (1952) reported similar results. Finally, Peters and Kelly (1977) showed that appropriate corticosteroid or ACTH treatment reduced the number of tumor cells that were required for transplantation of a syngeneic neoplasm.

### **Other stressors.**

The influence of other types of controlled stressors on the immune response of animals has been studied. For instance, predator-induced stress increased the susceptibility of mice to *Hymenolepis nana* (Hamilton, 1974) and the physical handling of mice during early life increased their capability to synthesize antibody to the flagella of *Salmonella adelaide* (Solomon *et al.*, 1968). Transportation stress has been shown to reduce the number of plaque-forming cells formed *in vitro* (Gisler *et al.*, 1971). Acceleration and ether anesthesia gave similar results. This effect depended on the time of stress relative to immunization, and may have been due to an interaction of adrenal corticoids and growth hormone (Gisler and Schenkel-Hulliger, 1971). Space flight enhanced blastogenesis to both mitogens and antigens in rats (Mandel and Balish, 1977), and marathon running, but not moderate running, caused a transient reduction in mitogen- and antigen-induced blastogenesis in humans (Eskola *et al.*, 1978). The secondary antibody response to tetanus toxoid was unaffected by running. The stress of captivity and acclimation to captivity has also been suggested to

depress PHA-induced blastogenesis in Rocky Mountain bighorn sheep (Hudson, 1973).

Environmental stressors may be involved in the etiology of an infectious disease known as bovine pneumonic pasteurellosis (shipping fever). Various stressing agents, such as heat, cold and shipping, have been suggested to exacerbate symptoms of this disease complex and increase the frequency of isolation of *Pasteurella multocida* and *P. haemolytica* (Crookshank *et al.*, 1979; Irwin *et al.*, 1979; Andersen, 1978; Saunders and Berman, 1964; Hoerlein and Marsh, 1957). It should be noted that the transportation of cattle in pragmatic situations often includes the exposure of cattle to several other stressors, such as heat, cold, mixing, introduction to a novel environment and a change in diet. The effect of shipping on the immune system of calves has not been adequately investigated. However, some research has indicated that transportation and introduction to new environmental conditions impaired the capability of calves to synthesize antibody (Hartmann *et al.*, 1976b) and reduced mitogen-induced blastogenesis of peripheral blood mononuclear cells (Kelley *et al.*, 1981).

Hamdy *et al.* (1963) demonstrated that when pasteurella and parainfluenza type 3 virus were both present in calves, a single, alternating 30-min heat and cold stress enhanced clinical symptoms of shipping fever and the severity of pneumonic lesions. In two other experiments, a moderate thermal stress of 2 °C, 29 °C or alternating temperatures between 30 °C and 2 °C in two-to five-month-old calves had little effect on the incidence of pneumonia when calves were challenged with either IBR alone (Jericho and Darcel, 1978) or IBR and *Pasteurella haemolytica* (Jericho and Langford, 1978). However, in the latter experiment, rhinitis, tonsillitis and pneumonia were consistently produced when the IBR virus was passaged two additional times. Therefore, an alternate interpretation would be that a moderate thermal stress exacerbated the incidence of upper respiratory tract infections and pneumonia, an effect which depended on the virulence of the IBR virus. This conclusion is speculative, however, because a thermo-neutral control group of calves was not included in the study.

### Concluding remarks

1. Disease-environment interactions exist.

There is substantial scientific evidence to support the concept that diverse types of environmental stressors alter the susceptibility of animals to infectious diseases. The broad implication of this finding is that stress may trigger nonspecific physiological mechanisms that alter specific immunological events. It has not been widely accepted that environmental stressors directly alter immune defense mechanisms of the host. It is likely that stress-induced changes in the susceptibility of animals to many diseases are mediated mostly by changes in immune function.

2. Evidence suggests that environmental stressors increase the susceptibility of animals to relatively avirulent microbes. The effect of environmental stressors on host resistance depends on the type and virulence of pathogen to which the animal is exposed, the nature and duration of the stressor, age and species of the animal, time of stress relative to time of exposure to the pathogen and whether the animal is immune to the pathogen. Careful research is needed to clearly define the relative importance of each of the above parameters, as well as to learn how acclimation or habituation influences the animal's immune system. Finally, it is important to learn whether these stress effects are independent or whether biologically-relevant interactions exist.

3. Stress does not always lead to a reduction in host resistance. Elevated ambient temperature enhances host resistance to some viral diseases and social stress reduces the growth of some tumor cells and enhances host resistance to some bacterial pathogens. The physiological and immunological mechanisms that are responsible for the stress-induced immunoenhancement and immunosuppression should be understood. *In vivo*, adrenal corticoids have been associated with both enhanced and depressed immune responses. Stress-induced changes in other hormones should also be studied, particularly with corticoid-resistant species.

4. Recent experiments have shown that several types of environmental stressors dynamically alter cell-mediated immune events. The effect of stress on cellular responses is dependent on the time of stress relative to the induction or expression of the response and on the type of cells that are involved in the cellular immune event. These data imply that



the effects of stress on the pathogenesis of a disease depends on whether the animal has been previously exposed to the pathogen (i.e., immune). Furthermore, a single stress episode at the time of the first exposure to antigen (induction) can alter subsequent cellular immune events when the non-stressed animal is exposed several days later to the same antigen (expression). It is likely that the changes in cellular immunity that are caused by the stress response may explain why some investigators have reported both increases and decreases in the susceptibility of animals that have been subjected to a single stressor.

5. The effect of stress on the capability of animals to synthesize antibodies is equivocal. For instance, different degrees of heat stress have been shown to decrease, increase and cause no change in the capability of birds to synthesize antibodies. It is assumed that this paradox is due to breed differences. However, it is also possible that this disparity owes to the degree of heat stress imposed on the birds.

6. Evidence is presented which indicates that both natural and specific host defense mechanisms are altered by environmental stressors. The effects of stress on natural defenses have hardly been investigated. It is possible that environmental stressors could alter several non-specific mechanisms, such as anatomic barriers, the inflammation process or intracellular lysozymes.

7. Investigations into the effects of stress on animals should employ cells or serum from animals that are stressed *in vivo*, not cells or serum from normal animals that are stressed *in vitro*. The stressor should be clearly defined and well-controlled. Studies should also be conducted to determine which effector lymphocytes (i.e., helper, suppressor, cytotoxic), types of cells (i.e., macrophages, neutrophils, mast cells) or antibody functions (i.e., opsonization, antibody-dependent, cell-mediated cytotoxicity, neutralization) are affected by environmental stressors.

8. More emphasis should be placed on the influence of psychological stressors on the immune system of domestic animals. Substantial evidence supports the hypothesis that psychological stressors alter the susceptibility of animals to disease and that many of these changes are mediated by alterations in host defense.

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#### Summary

Environmental stressors are involved in the etiology of important livestock diseases, including transmissible gastroenteritis in young pigs, Newcastle's and Marek's disease in chickens and shipping fever in cattle. Unfortunately, very little research has been conducted to learn how stress alters host resistance, although it is generally assumed that the immune system of the host is affected. This paper identifies eight stressors that typically occur in modern livestock production units: heat, cold, crowding, mixing, weaning, limit-feeding, noise and restraint. All of these stressors have been shown to alter the immune system of animals. These changes in immune function may ultimately explain the physiological basis of disease-environment interactions. A thorough understanding of stress-induced changes in host resistance will also provide the scientific basis for effective prophylactic therapy. More controlled experiments are needed to learn how stress alters the susceptibility of animals to infectious and noninfectious diseases.

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