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Authors

Cooper, Dan Michael
Radom-Aizik, Shlomit
Schwindt, Christina
et al.

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HIGHLIGHTED TOPIC | *Exercise and Inflammation***Dangerous exercise: lessons learned from dysregulated inflammatory responses to physical activity****Dan Michael Cooper, Shlomit Radom-Aizik, Christina Schwindt, and Frank Zaldivar, Jr.***Pediatric Exercise Research Center, Department of Pediatrics, University of California, Irvine, California*

Cooper DM, Radom-Aizik S, Schwindt C, Zaldivar F Jr. Dangerous exercise: lessons learned from dysregulated inflammatory responses to physical activity. *J Appl Physiol* 103: 700–709, 2007. First published May 10, 2007; doi:10.1152/jappphysiol.00225.2007.—Exercise elicits an immunological “danger” type of stress and inflammatory response that, on occasion, becomes dysregulated and detrimental to health. Examples include anaphylaxis, exercise-induced asthma, overuse syndromes, and exacerbation of intercurrent illnesses. In dangerous exercise, the normal balance between pro- and anti-inflammatory responses is upset. A possible pathophysiological mechanism is characterized by the concept of exercise modulation of previously activated leukocytes. In this model, circulating leukocytes are rendered more responsive than normal to the immune stimulus of exercise. For example, in the case of exercise anaphylaxis, food-sensitized immune cells may be relatively innocuous until they are redistributed during exercise from gut-associated circulatory depots, like the spleen, into the central circulation. In the case of asthma, the prior activation of leukocytes may be the result of genetic or environmental factors. In the case of overuse syndromes, the normally short-lived neutrophil may, because of acidosis and hypoxia, inhibit apoptosis and play a role in prolongation of inflammation rather than healing. Dangerous exercise demonstrates that the stress/inflammatory response caused by physical activity is robust and sufficiently powerful, perhaps, to alter subsequent responses. These longer term effects may occur through as yet unexplored mechanisms of immune “tolerance” and/or by a training-associated reduction in the innate immune response to brief exercise. A better understanding of sometimes failed homeostatic physiological systems can lead to new insights with significant implication for clinical translation.

inflammation; innate immunity; leukocyte; asthma

FOR INVESTIGATORS who study the biology of exercise, it is only natural that their research would largely be focused on the health benefits of physical activity. Given the near epidemic increase in diseases and conditions like Type 2 diabetes, hypertension, and even certain malignancies—all of which are preventable in large measure by altering physical activity behavior (43, 80, 115), it may be hard to imagine the value of examining the much smaller problem of pathophysiology induced by exercise. But exercise can be dangerous and is associated with chronic musculoskeletal injury, bronchoconstriction, and, on rare occasion, anaphylaxis and sudden death. Moreover, as has been illustrated in the history of the development of vaccines and immunization, investigating the deleterious health consequences of failed homeostatic physiological systems leads to fundamental and useful biological knowledge. In this review, we examine the lessons learned from dangerous exercise, particularly in the sense that exercise can elicit an immunological “danger” type of stress and inflammatory response (86) that, under certain circumstances, becomes dysregulated and detrimental to health.

THE STRESS AND INFLAMMATORY RESPONSE TO EXERCISE

What is striking about dangerous exercise is that in almost every instance, the interrelated stress, inflammatory, and immune systems play a significant role. A key concept that has emerged over the past several decades is that exercise, even in healthy people, leads to a robust inflammatory response characterized by mobilization of leukocytes and an increase in their numbers in the central circulation, and an increase in circulating potent inflammatory mediators like IL-6, the latter a pleiotropic cytokine (11, 103) produced by immune cells (44), a variety of tissues [like adipocytes (125)], and directly from the active muscle tissue (104, 125, 129, 131). Brief exercise stimulates innate immunity at the systemic level, as well as setting the stage for local, muscle inflammatory responses.

It has been known for decades that individual bouts of exercise lead to an increase in circulating leukocytes and even stem cells (1, 10, 24, 91, 114, 158). This is a remarkably reproducible, substantial, somewhat dose-dependent phenomenon known to exist in children and adults, as well as in other mammals (34, 55, 64, 105). Lymphocytes, monocytes, and natural killer (NK) cells increase rapidly with the onset of exercise but begin to decrease immediately on its cessation. Circulating neutrophils increase more slowly and may remain

Address for reprint requests and other correspondence: D. Cooper, 101 The City Drive, Orange, CA 92868 (e-mail: dcooper@uci.edu).

elevated for up to several hours, long after the initiating bout of exercise ends (93, 112, 155). We now know that exercise as brief in duration as 6 min can mobilize leukocytes (120); thus the physical activity-related increase in these critical circulating innate immune cells happens frequently in the daily lives of many humans and other mammals.

In 1999, Ostrowski and coworkers (97) presented a model of the immune and inflammatory response to exercise in healthy people. They noted that strenuous exercise led to increased circulating levels of proinflammatory mediators, but simultaneously, "... cytokine inhibitors and anti-inflammatory cytokines restrict the magnitude and duration of the inflammatory response to exercise." Moreover, the idea that initial stimulus of the inflammatory system "awakens" both pro- and anti-inflammatory response pathways is seen not only in exercise, but in other conditions, like sepsis and burn injury (107, 111), as well.

Until fairly recently, the potential biological significance of exercise-induced immune responses was either ignored or minimized as simply another typical manifestation of the global response to all sorts of physiological and psychological "stress or danger" stimuli mediated in common through neuroadrenergic activity and chemical mediators like cortisol, growth hormone, epinephrine, and norepinephrine, all of which can alter immune function (82, 83, 96, 99, 119). However, the emerging view is that while exercise clearly elicits a brain "danger" response, central stimulation of neuroadrenergic pathways alone do not account for all of the inflammatory and immune responses known to accompany brief bouts of exercise (130). Indeed, in studies that have attempted to compare the inflammatory response to exercise with psychosocial stress, exercise was found to alter immune mediators far more profoundly (50). Unlike psychosocial stress, exercise is accompanied by target tissue metabolic signals (e.g., profound change in pH, lactic acid, temperature, PO_2 , and PCO_2) that themselves can independently alter immune mediators [like heat shock proteins (38, 73)] and leukocyte function (76). There is even evidence that exercise may be accompanied by translocation of gut bacteria into the central circulation, causing a classic antigen-mediated systemic immune response (18, 58, 85). Finally, in recent years, Pedersen, Febbraio, and their collaborators have made the groundbreaking discovery that working muscle tissue itself produces immune mediators like IL-6 and IL-8 (2, 37).

We now know that the change in numbers of circulating immune cells following exercise is also accompanied by a change in the gene-expression profile of these cells (25, 39). In our laboratory, Connolly et al. (25) showed that a relatively brief bout of heavy exercise significantly altered the expression of hundreds of genes in peripheral blood mononuclear cells (PBMCs). Following 30 min of heavy exercise, we found changes in PBMC genes reflecting a range of responses including pro-inflammatory responses, e.g., prostaglandin D_2 synthase (PTGDS) (145), cathepsin W (CTSW) (72), MIP 1 β (CCL4) (109), and heat shock 70-kDa protein 1B (HSPA1B) (118); anti-inflammatory responses, e.g., dual-specificity phosphate 1 (DUSP1) (75), interleukin-1 receptor antagonist (IL1RA) (53), cystatin (CST7) (70), and aldo-keto reductase family 1, member C3 (AKR1C3) (113); and even growth factors, e.g., epiregulin (EREG) (160), early growth response-1 (EGR-1) (32), and endothelial growth factor (ECGF1) (156).

The bulk of the gene responses were transient and returned to baseline, or even below baseline, by 1 h of recovery. Whether these documented changes in the gene expression in circulating immune cells in response to exercise occur because of direct effects on the cells themselves, or, alternatively, by mobilizing cells with different gene expression profile patterns from various depots, is not known. Whatever the mechanism may prove to be, while exercise can quickly stimulate pro-inflammatory gene responses in PBMCs, anti-inflammatory signals are also put into play that rapidly quench the development of a potentially deleterious inflammatory state within circulating immune cells.

DANGEROUS EXERCISE

The usual balance between the pro- and anti-inflammatory exercise responses is occasionally upset, however, and when it is, disease may result. In the following, we review several examples of failed homeostatic inflammatory responses to exercise.

Injury and overuse. Musculoskeletal sports injuries range from the common condition of delayed-onset muscle soreness to frank breaks, tears, and dislocations, and invariably involve acute inflammation (22, 102, 106, 146). Indeed, as shown in Fig. 1, Carp and coworkers (22) recently demonstrated that even local musculoskeletal (work-related) injuries can lead to increases in systemic levels of mediators like TNF- α and IL-1 β that indicate inflammation. It is, however, not at all clear if the initial inflammatory response is beneficial or harmful and, consequently, whether or not the early inflammation should be treated (15, 152). As noted by Tidball (141), muscle repair in response to injury consists of a "complex picture in which inflammatory cells promote both injury and repair, through the combined actions of free radicals, growth factors, and chemokines." In a recent elegant study, Tidball and Wehling-Hendricks (142) compared the different regulatory functions of macrophages that infiltrate damaged muscle early after the insult (in the first 2 days) with those that appear in the muscle during *days 2–4*. Remarkably, their studies demonstrated that the later invading macrophages played more active roles in stimulating muscle repair, perhaps through interacting with resident satellite cells, while the early-invading macrophages played key roles in removing damaged tissue.

Thus the optimal balance of immune/inflammatory responses in sports injuries may depend not only on the profile of infiltrating types of leukocytes but even on the conditions (systemic? local?) that might differentiate functional pathways within a leukocyte subpopulation itself. Since these inflammatory/immune cells in the tissues likely originate from circulating immune cells in the circulation, it is reasonable to speculate that factors within the circulation might alter the function of these cells upon reaching target tissues. Interestingly, Lessner and coworkers (79) demonstrated that in the case of atherosclerotic lesions, growth of plaques was augmented through recruitment of monocytes from the circulation. The interaction of circulating immune cells, their tissue counterparts, and growth and repair in response to exercise remains a poorly investigated area.

With overuse syndromes or repeated injuries, the inflammatory response becomes chronic and can exacerbate, rather than ameliorate, the underlying injury (9). A number of investiga-

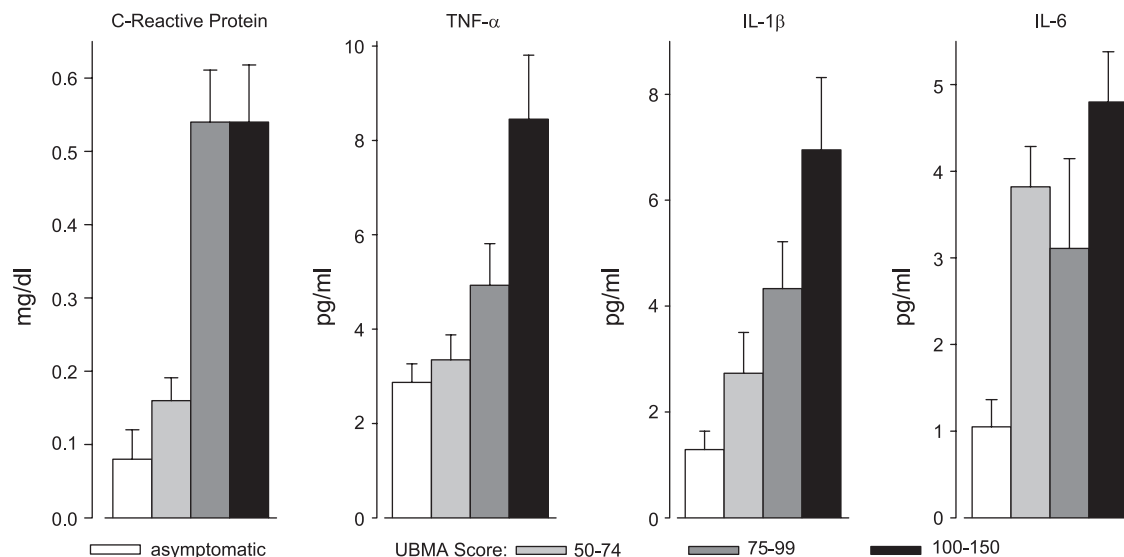


Fig. 1. Evidence that regional musculoskeletal injury can lead to a systemic inflammatory response. Twenty-two individuals with a history of upper-extremity, work-related musculoskeletal injury due to overuse of no longer than 12 wk duration were included. Using the upper-body musculoskeletal assessment (UBMA), in which higher scores indicate greater severity of the work-related disuse injury, these investigators found that increasing injury severity was significantly associated with increasing systemic levels of inflammatory indicators: C-reactive protein, TNF- α , IL-1 β , and IL-6. Whether this chronic inflammatory state also influences immune cells rendering them more reactive to additional exercise is not known. Data are from Carp et al. (22).

tors have focused on innate immune cells, namely neutrophils, as agents of continuing tissue damage in sports injuries because of their propensity to produce reactive oxygen species (16, 157) and other inflammatory agents like HOCl (67, 144), the latter through continued activation of the neutrophil myeloperoxidase pathway. Neutrophils infiltrate muscle acutely following heavy exercise (92, 108), and there is evidence that inhibiting neutrophil reactive oxygen species (ROS) production (experimentally, by blocking the CD11b neutrophil receptor, one of the pathways that initiates ROS production) attenuates tissue damage resulting from muscle exposure to ROS (144).

The idea that the neutrophil transforms from a useful responder in the acute phases of the inflammatory process to an agent of ongoing injury in the chronic state (20) is, intriguingly, echoed in recent research on the harmful role of the neutrophil in chronic lung disease (62, 65, 154) and rheumatoid arthritis (RA). With regards to the latter, Cross and coworkers (26) and Ontonello et al. (98) showed that neutrophil apoptosis is delayed in affected inflamed joints. The mechanisms that alter neutrophil function in RA are complex but may involve chronic hypoxia [mediated through HIF-1 (151)]. As a consequence, the dysregulated neutrophils exacerbate, rather than ameliorate, chronic inflammation by the ongoing release of potentially damaging cytokines. Exercise is accompanied by regional and systemic acidosis (149), heat (57), and reduced P_{O_2} (117), all of which can stimulate factors like HIF (52, 61). Whether chronic inflammation associated with sports injuries leads to a similar transformation in immune cells such as occurs in chronic lung disease or RA is not known. Clearly, understanding how exercise might alter immune cell apoptosis will be a fruitful area for future research in this field.

Anaphylaxis. Exercise-associated allergic responses are wide-ranging, including potentially life-threatening, but fortunately rare, anaphylaxis (153); exercise-induced asthma (6, 135); and exercise-associated urticaria (31). Anaphylaxis is the most extreme example of dysregulated immune responses. The

word itself, coined by its discoverer Charles Richet in 1913, referred to the aberrant and deadly immune response he had observed in a previously sensitized animal model that had been exposed to a triggering antigen. Richet demonstrated a biological response gone awry, quite the opposite of the hoped-for prophylaxis seen with successful immunizations (116). In classic anaphylaxis, a small amount of initiating antigen (e.g., from a bee sting) cross-links antibody molecules in a sensitized individual, activates immunoglobulin receptors on inflammatory cells (e.g., mast cells and basophils) causing them to release mediators that increase vascular permeability, impair smooth muscle function, and lead to a range of symptoms including hypotension, urticaria, and wheezing. If untreated, anaphylaxis can culminate in shock and death (19). Current research suggests that anaphylaxis can be IgE dependent (most common) or independent of IgE (40).

A perplexing feature of exercise-associated anaphylaxis is that the antigen responsible for triggering a massive systemic allergic response has yet to be identified. The aggregate of case reports and the few attempts to challenge individuals with a history of exercise anaphylaxis suggest that the response can be elicited with relatively brief exercise protocols such as the Bruce treadmill test and that, like other causes of anaphylaxis (e.g., food allergies), the mechanism of exercise-induced anaphylaxis seems to be related to IgE (63). An additional intriguing observation is the association of exercise anaphylaxis with the ingestion of a meal, particularly meals that include wheat (12, 23, 140), up to several hours before the instigating bout of exercise. How the previous ingestion of a meal is linked to exercise-induced anaphylaxis is still not known. We propose a possible mechanism in our construct of exercise modification of previously activated leukocytes (EMPAL), as shown schematically in Fig. 2. In this model, food-sensitized gut-associated immune cells are relatively innocuous when they remain within the local circulations of the gut and portal and splenic systems. However, when these sensitized cells are released into

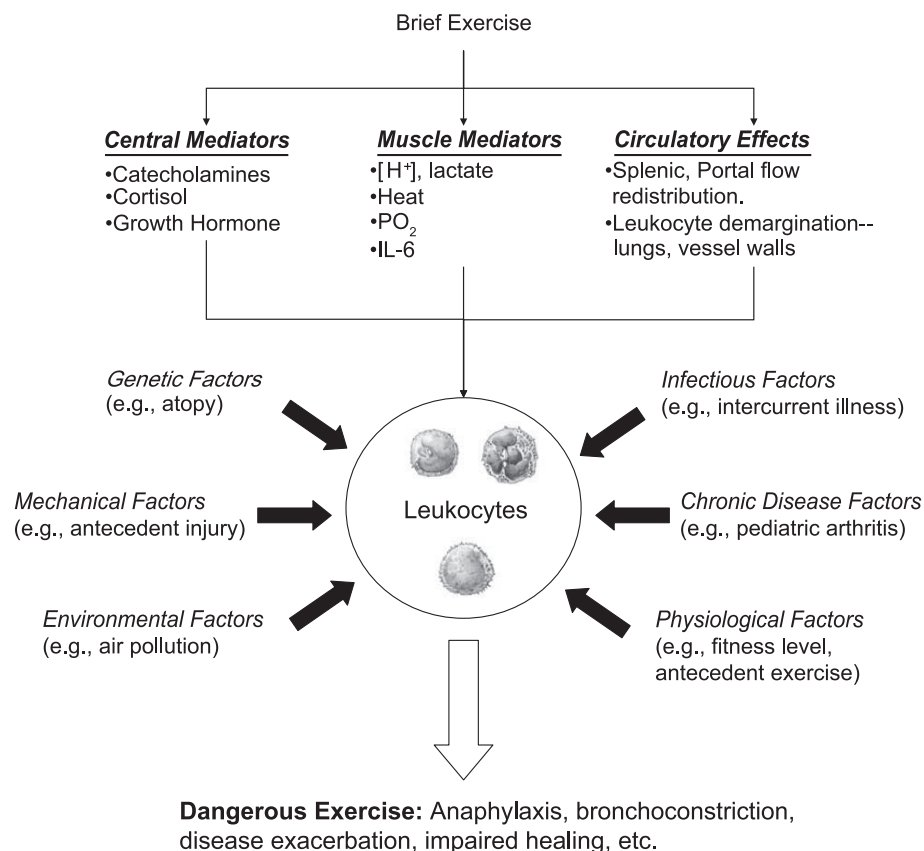


Fig. 2. Exercise modulation of previously activated leukocytes (EMPAL), a possible mechanism of dangerous exercise.

the circulation as a result of exercise-associated redistribution of blood flow (133), the stage is then set for a more profound immune response like anaphylaxis.

Exercise-induced bronchoconstriction. An imbalance of the pro- and anti-inflammatory leukocyte responses to exercise may also play a role in a significant clinical manifestation of asthma, exercise-induced bronchoconstriction (EIB)—the transient reduction in lung function due to airway obstruction that occurs after vigorous exercise. EIB is a common feature of asthma (particularly in children), estimated to occur in about 60–80% of asthmatic children (27), and exercise is the most common stimulus for inducing an attack in asthmatic children (5). There are recent data suggesting that EIB may be high in athletes (69). Despite the clinical importance of the phenomenon, the mechanism of EIB remains controversial, and EIB is often underdiagnosed (7, 17, 21, 122). The fact that many of the exercise-induced immune responses in healthy people involve increases of some of the same mediators [e.g., ICAM (3, 128)] and leukocytes [e.g., neutrophils (13)] that play a role in bronchoconstriction in asthmatics leads to the notion that leukocyte responses might be involved in the mechanism of EIB.

Controversy has surrounded the mechanisms responsible for EIB for decades (49, 88). Two theories, both resulting from airway dehydration associated with exercise, have predominated: 1) airway thermal flux (i.e., cooling and rewarming); and 2) increased airway osmolarity. These events, it is hypothesized, trigger an inflammatory response in the airway. There are inconsistencies, however, with clinical and experimental observations regarding both mechanisms (7). Moreover, de-

spite some promising results in the early 1980s, the research into the role of inflammatory cells and cytokines in EIB had dwindled (29, 77, 78) until fairly recently.

There is now a growing body of data suggesting that leukocytes may be abnormal in asthmatics. For example, Mann and Chung (84) recently demonstrated increased expression on circulating neutrophils of the adhesion molecules CD11b and CD35 and of resistance to the effects of prednisolone, all evidence for increased neutrophil activation. Gounni and coworkers (51) demonstrated that there exists a subpopulation of circulating neutrophils in asthmatic subjects that express the IgE receptor FcεRI and that when engaged, this receptor activates the neutrophils. The authors speculated that these neutrophils may play a role in asthma airway pathology by contributing to local inflammation and aggregation of lymphocytes.

There is also substantial data demonstrating abnormalities in lymphocytes in children (as young as 24 mo) and adults with asthma. In particular, lymphocytes obtained from peripheral blood in asthmatics demonstrate a predominance of T-helper lymphocyte type 2 (T_H2, IL 4 producing) immune responses relative to T_H1 (IFN-γ producing) (33, 124). Moreover, Tsumori and colleagues (147) showed that T cells from asthmatic subjects, in particular T_H2 cells, preferentially migrate to bronchial tissue (see Fig. 3), and de Blic and colleagues (28) found that bronchoalveolar lavage samples obtained from highly symptomatic children with asthma show substantially increased ratios of the protein products IL-4/IFN-γ. Thus there is a direct line of evidence linking altered T-cell cytokine production from lymphocytes found in the circulation to levels

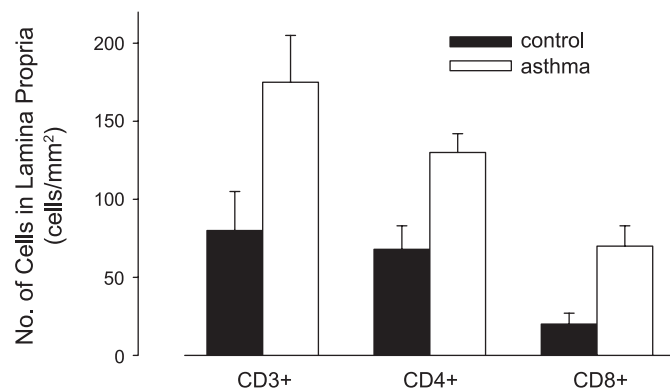


Fig. 3. Evidence that peripheral immune cells are abnormal in asthmatic subjects. Using immunoincompetent SCID mice, these investigators implanted human bronchiolar tissue and peripheral blood mononuclear cells (PBMCs). They found highly significant increases in the number of PBMCs that had infiltrated into the tissue when comparing asthmatic with control subjects. Moreover, the asthmatic PBMCs produced higher quantities of IL-4 mRNA, suggesting a predominance of T helper type 2 (T_H2) lymphocytes. We propose that exercise might contribute to this imbalance, leading to exercise-induced bronchoconstriction (EIB). [Data redrawn from Tsumori et al. (147).]

of cytokines produced by T cells within the airways of patients with asthma.

Recently, Umetsu and DeKruyff (148) have delineated a potential role in allergic asthma for invariant T-cell receptor natural killer T cells ($iNKT$) that aggregate in the lungs of allergic individuals. Unlike in other chronic inflammatory lung diseases such as sarcoidosis, the asthma-associated $iNKT$ cells residing in the lung secrete IL-4 and not IFN- γ , hence are T_H2 -type cells, and more likely play a mechanistic role in bronchoconstriction. While the role of these cells in the pathophysiology of asthma is not fully understood, Umetsu and DeKruyff suggest that possible activation of CD4+ NKT cells in the periphery might be activated by asthma triggers and stimulate circulating effector T_H2 cells. Much work needs to be done on the impact of exercise on these newly discovered leukocyte links to asthma and allergy.

LESSONS LEARNED FROM DYSREGULATED IMMUNE RESPONSES TO EXERCISE

EMPAL. Given the fairly robust and powerful immune and inflammatory response that occurs in healthy people with exercise of sufficient intensity and duration, how is it that the dangerous, deleterious consequences of exercise (asthma, ana-

phylaxis) are not more common? Obviously, for most people, the exercise-associated pro-inflammatory responses are blunted almost immediately by anti-inflammatory mediators stimulated simultaneously by the bout of physical activity. One theme that does emerge from the examples described above and from the recent literature is that exercise could become dangerous when and if an individual's leukocytes had been rendered more responsive than normal to the additional immune stimulus of exercise.

In this scenario (Fig. 2), prior activation of leukocytes is sufficient to upset the normally balanced immune/inflammatory stimulation by exercise, and, consequently, the circulating immune cells "behave badly." In the case of food-induced exercise anaphylaxis, as noted above, our model suggests that food-sensitized immune cells [possible lymphocytes or macrophages (136)] are relatively innocuous until they are redistributed from gut-associated circulatory depots, like the spleen, into the central circulation where they interact with larger numbers of immune cells, including basophils and mast cells, and cause a systemic response.

In the case of asthma, the prior activation of leukocytes may be the result of genetic or environmental factors. As noted, there is increasing data supporting the idea of an imbalance between the T_H1 and T_H2 lymphocytes in asthmatic subjects (90) that may be worsened with exercise (54). In addition, a particularly relevant group is the TIM genes (T cell, immunoglobulin, mucin domain-containing molecules), which play a role in determining T_H1 or T_H2 function of lymphocytes (71). The genetics of asthma and atopy is the subject of much current research, speculation, and debate (68, 121). Many of the suspected genes are involved in regulation of immune cell function through mediators like TNF and IL-4. We identified the set of genes that were found to be both affected by exercise in PBMCs [Connolly et al. (25)] study and that have been associated with asthma [from a recent meta-analysis by Ober and Hoffjan (94)]. We found seven genes that overlapped in these two studies (Table 1), providing a potential road map for investigation into physiological pathways that might link exercise with bronchoconstriction (66, 100, 101, 137, 138).

It is now clear that EIB is worsened when people exercise under conditions of excessive air pollution. As noted recently by McConnell et al. (87), "incidence of new diagnoses of asthma is associated with heavy exercise in communities with high concentrations of ozone; thus, air pollution and outdoor exercise could contribute to the development of asthma in

Table 1. Seven genes that are both linked to asthma and whose expression in PBMCs is influenced by 30 min of exercise in healthy adults

Gene Name	Gene Symbol	Role in Asthma
T-box 21	<i>TBX21</i>	Influences naive T-cell development
Adrenergic, β_2 -, receptor, surface	<i>ADRB2</i>	Potentially important source of variability in the response to β_2 -agonist drugs
Prostaglandin D ₂ receptor (DP)	<i>PTGDR</i>	Involved in the control of inducible cyclooxygenase (COX-2) and its metabolites
Signal transducer and activator of transcription 4	<i>STAT4</i>	Mediates responses to interleukin-12 in lymphocytes and regulating the differentiation of T helper cells
Arachidonate 5-lipoxygenase	<i>ALOX5</i>	Encodes 5-lipoxygenase; involved in leukotriene role in aspirin-sensitive asthma
Prostaglandin E receptor 2 (subtype EP2), 53 kDa	<i>PTGER2</i>	Involved in the control of the inducible cyclooxygenase (COX-2) and its metabolites
Chemokine (C-C motif) ligand 5	<i>CCL5</i>	Promotes T_H2 dominance

The genes listed were found to significantly increase expression following exercise in young adult men [data from Connolly et al. (25)] and were observed to be linked with asthma in at least one published study [data from Ober and Hoffjan (94)]. PBMC, peripheral blood mononuclear cells; T_H2 , T-helper type 2 lymphocyte.

children.” This idea is corroborated by recent work from Frampton and coworkers (45) (Table 2) showing that exposure to ultrafine particles in air pollution (<100 nm) in combination with exercise can influence activation of circulating lymphocytes and expression of key adhesion molecules like ICAM-1 on other leukocytes. These authors also found that the effect of the ultrafine particles on circulating leukocytes was different in asthmatic subjects compared with nonasthmatic controls. Thus we speculate that one contributing mechanism to EIB may be the combined influence of environmental stress and genetic predisposition rendering circulating leukocytes more susceptible to the innate immune signal from brief exercise.

Intercurrent illness, acute or chronic, activates the immune system, and with exercise, exercise modulation of previously activated leukocytes may occur. Surprisingly, despite much popular focus about whether physical training with intercurrent illnesses like colds and flu is dangerous, there is very little research on what happens to immune function when exercise is performed in the face of active immune responses to viral illness. School guidelines about when children can return to play following acute common illnesses such as asthma are varied and inconsistent (4). Inflammatory mediators like IL-6 or TNF- α are associated with the symptoms of fatigue and malaise commonly experienced in influenza (59), and most infected individuals just do not want to exercise (likely, a wise choice, physiologically). Nonetheless, there is evidence that exercise can on occasion exacerbate intercurrent illness with potentially serious consequences, such as myocarditis (46, 47).

A similar lack of research surrounds the immune effects of exercise in people with chronic inflammatory diseases and conditions. In cystic fibrosis, a disease characterized by chronic infection and persistently elevated levels of inflammatory cytokines like IL-6, exercise leads to larger acute increases in IL-6 than observed in controls in both children and adults (56, 143). In systemic lupus erythematosus, a systemic autoimmune disease (134), brief exercise leads to abnormal cortisol, prolactin, and CD4+/CD8+ T-cell responses (110). In pediatric arthritis, particularly systemic forms, strenuous exercise may

actually exacerbate symptoms and lead to episodes of disease flare-up with pain and, on occasion, systemic manifestations of disease, including fever and malaise (personal observation and Ref. 8). Obesity is now known to be associated with chronic low-grade inflammation with elevated circulating leukocytes and cytokines in both children and adults (150, 159). Intriguingly, obesity is now clearly associated with asthma (14), as well as with the incidence and severity of exercise-induced bronchoconstriction (30, 60). Collectively, these clinical examples do suggest that exercise in the context of the chronically ill individual could potentially lead to deleterious consequences through mechanisms that involve a pathological combination of exercise stimulation of immune signals with leukocytes previously affected by other stress, inflammatory, or immune mediators.

SUMMARY: IS EXERCISE AN “IMMUNIZATION”?

This review of the existence of substantial immune-modulated pathophysiological effects of exercise substantiates the idea that the immune and inflammatory consequences of physical activity may play a role in the health benefits of exercise and leads to the question, “Is exercise an immunization?” In the most general sense, immunizations promote health by altering the immune system in a manner that prevents disease. Vaccinations specifically stimulate immunity with modified antigens that “educate” the immune system but without causing disease. Is exercise a powerful enough immune modulator that, like a killed or attenuated virus, actually causes a robust enough innate immune response to invoke the creation of specific memory cells in adaptive immunity to generate a long-term alteration in future immune responses?

There are increasing data suggesting that exercise, more specifically, levels of fitness and associated body composition, can alter the immunological response to vaccination. Smith and coworkers (126), for example, showed in vivo an age-related reduction in the primary antibody and memory T-cell response in humans to a novel antigen. Remarkably, the age-related

Table 2. Summary of UFP exposure effects on circulating leukocytes

Protocol	Adhesion Molecules	Lymphocyte Subsets and Activation	Leukocyte Counts
UPREST ($n = 12$ healthy subjects): 2-h exposure to $10 \mu\text{g}/\text{m}^3$ UFPs or filtered air at rest	No effects	No effects	No effects
UPDOSE ($n = 12$ healthy subjects): 2-h exposure with intermittent exercise for each subject ($10 \mu\text{g}/\text{m}^3$ UFPs; $25 \mu\text{g}/\text{m}^3$ UFPs, and filtered air)	Decreased monocyte CD54 Decreased PMN CD49d (males)	Increased CD25+ T-cells (females)	Decreased monocytes and basophils (females)
UP50 ($n = 16$ healthy subjects): 2-h exposure to $50 \mu\text{g}/\text{m}^3$ UFPs and air with intermittent exercise as in UPDOSE	Decreased monocyte CD18 and CD54 (males) Decreased PMN CD18 and increased CD11a	Increased CD25+ T-cells	Decreased eosinophils
UPASTHMA ($n = 16$ asthmatic subjects): 2-h exposure with intermittent exercise as in the UPDOSE ($10 \mu\text{g}/\text{m}^3$ UFPs and air)	Decreased monocyte CD11b. Decreased PMN CD54 and increased CD62L (males) Decreased eosinophil CD11b	Decreased CD4+ T-cells	Decreased eosinophils and basophils

The combination of exercise and exposure to ultrafine particles (UFP) had marked effects on circulating immune cells. PMN, polymorphonuclear leukocyte. Data are from Frampton et al. (45).

impairment was attenuated in those older individuals who had maintained a physically active lifestyle, but the mechanisms for this beneficial effect remain unknown. Edwards and co-workers (35) suggested that acute eccentric exercise might influence the antibody response to the influenza vaccine by acting as a local adjuvant. They found that the antibody response was enhanced by exercise in women but reduced in men. In contrast, exercise increased the cell-mediated response in men but not in women. Again, the mechanisms for these intriguing effects are not yet understood. Finally, earlier work in the authors' laboratory (36), demonstrated a reduced specific antibody response to tetanus in obese, physically inactive children and adolescents. Factors such as a lower vaccination dose relative to body size, or reduced absorption from the injection site due to increased adipose tissue or related to reduced immune response due to the chronic low-grade inflammation expressed by the higher levels of IL-6 could all have contributed to this finding.

Recently, several investigators have begun to focus on the longer term effects of exercise and physical activity on the cell-surface expression of toll-like receptor 4 (TLR-4) on immune cells (41, 42, 48, 74, 89). The TLRs are transmembrane proteins responsible for recognizing pathogens and are seen as a link between innate immune function (the latter, clearly stimulated by exercise) and adaptive immunity (132). Collectively, these observations suggest that exercise can downregulate surface expression the TLR-4 on immune cells. Thus these observations may explain how repeated exercise can lead to a sort of immune "tolerance," part of the mechanisms through which the immune and inflammatory signals of exercise are balanced. In the right dose, might this exercise-induced tolerance help ameliorate conditions like EIB? Although some data are compelling, whether being physically fit protects against EIB has not yet been conclusively determined (81).

Exercise could also modify immune responses indirectly through the well-described anatomic and metabolic adaptations to repeated physical activity. Increased muscle mass, improved oxygen delivery to working muscle, and more mitochondria could all act in concert to lessen the muscle-derived stress signals noted above: heat, hypoxia, and acidosis. Might some of the established health-promoting effects of exercise (reduction of cardiovascular disease risk) result from exercise alterations of the immune system? Obviously, much work needs to be done in all of these areas.

What is clear from the existence of dangerous exercise is that the immune responses caused by exercise are real and robust. Like pharmaceutical therapies, prescribing exercise as therapy, an activity that is gaining in acceptance throughout the medical community (e.g., 95, 123, 127, 139), must be predicated on understanding the risks and benefits of exercise as thoroughly as possible. Only in this manner can the "right" dose be achieved. Finally, a greater understanding of dangerous exercise is likely to yield new knowledge that is useful not only in the context of exercise physiology but also in shedding new light on the role of the immune system as it adjusts to daily life perturbations such as physical activity.

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