MIF within the lungs. MIF was first identified about 30 years ago as a factor that inhibited macrophage migration at sites of inflammation. More recently, it was found to be identical with a pituitary factor that antagonizes the effects of corticosteroids and potentiates the effects of endotoxin[11,12]. In endotoxemic rodents, MIF can be detected in alveolar macrophages, lymphocytes, ciliated airway epithelium, hepatocytes and renal tubular epithelium[13], and circulating levels of MIF increase markedly, suggesting that MIF production may be upregulated in patients with gram negative sepsis. As an endogenous inhibitor of glucocorticoid action, MIF may modulate the delicate balance between the proinflammatory effects of acute phase cytokines such as TNFα and IL-1β, and the anti-inflammatory effects of adrenal steroids, which also increase in the circulation following sepsis and trauma.

The authors document an increase in circulating and intrapulmonary MIF concentrations in patients with ARDS, and the antiglucocorticoid effect of MIF on TNFα and IL-8 production by alveolar cells from these patients. Thus, as part of the fundamental inflammatory response in ARDS, lung macrophages elaborate a factor that has the potential to prolong the inflammatory response by blocking the effects of endogenous corticosteroids (see figure). This concept has important implications for the role of corticosteroids as treatment for ARDS. Although initial treatment with high-dose corticosteroids is not beneficial[14], limited clinical reports suggest that some patients with sustained ARDS may improve with late steroid treatment[15]. Among the potential benefits of steroids are amelioration of the intrapulmonary inflammatory response, and lessening of the fibrotic response that causes lasting disability[16].

The NIH-sponsored ARDS Network, a collaborating group of clinical centers in the United States organized to perform large scale clinical trials, is planning to test the efficacy of corticosteroids in patients with ARDS that persists for more than seven days. The Donnelly study suggests that one important variable that should be considered is the cytokine balance in the lungs of the patients entered into such trials. As high intrapulmonary concentrations of MIF in some patients might influence the outcome of treatment, the clinical results of the trial may be difficult to interpret without a better understanding of the nature of the intrapulmonary inflammatory response. Indeed, one shortcoming of many of the negative trials of new treatments for sepsis and ARDS is the relative lack of information about the inflammatory processes in the blood and critical organs of the patients randomized in the protocols.

More information is needed about the critical cytokine balances that are present in the lungs of patients before and during the course of ARDS. Parts of the puzzle are becoming clear, but critical pieces must still be worked into place. Continuing studies of the balance between pro- and anti-inflammatory cytokines may help to identify those patients who are at highest risk of developing ARDS, and those patients who are destined to have the worst clinical course. These are the patients who will benefit most from new anti-inflammatory therapies.

Author is supported in part by NIH grants HL30452, GM37696 and AI29103, and by the Medical Research Service of the Department of Veterans Affairs.

1. Donnelly, S.C. *et al.* Regulatory role for macrophage migration inhibitory factor (MIF) in the acute respiratory distress syndrome (ARDS). *Nature Med.* **3**, 320–323 (1997).
2. Hudson, L.D., Milberg, J.A., Anardi, D. & Maunder, R.J. Clinical risks for development of the acute respiratory distress syndrome. *Am. J. Respir. Crit. Care Med.* **151**, 293–301 (1995).
3. Bachofen, A. & Weibel, E.R. Alterations of the gas exchange apparatus in adult respiratory insufficiency associated with septicemia. *Am. Rev. Respir. Dis.* **116**, 589–615 (1977).
4. Steinberg, K., Maunder, R.M., Milberg, J., Martin, T.R. & Hudson, L.D. Evolution of bronchoalveolar cell populations in the adult respiratory distress syndrome. *Am. J. Respir. Crit. Care Med.* **150**, 113–122 (1994).
5. Milberg, J.A., Davis, D.R., Steinberg, K.P. & Hudson, L.D. Improved survival of patients with acute respiratory distress syndrome (ARDS). *JAMA* **273**, 306–309 (1995).
6. Pittet, J.F., Mackersie, R., Martin, T.R. & Matthay, M.A. Biological markers of acute lung injury: prognostic and pathogenetic significance. *Am. J. Respir. Crit. Care Med.* (in the press).
7. Donnelly, S.C. *et al.* Interleukin-8 and development of adult respiratory distress syndrome in at-risk groups. *Lancet* **341**, 643–647 (1993).
8. Goodman, R.B. *et al.* Inflammatory cytokines in patients with persistence of the acute respiratory distress syndrome. *Am. J. Respir. Crit. Care Med.* **154**, 602–611 (1996).
9. Pugin, J., Ricou, B., Steinberg, K.P., Suter, P.M. & Martin, T.R. Proinflammatory activity in bronchoalveolar lavage fluids from patients with ARDS, a prominent role for interleukin-1β. *Am. J. Respir. Crit. Care Med.* **153**, 1850–1856 (1996).
10. Donnelly, S.C. *et al.* The association between mortality rates and decreased concentrations of interleukin-10 and interleukin-1 receptor antagonist in the lung fluids of patients with the adult respiratory distress syndrome. *Ann. Intern. Med.* **125**, 191–196 (1996).
11. Bernhagen, J. *et al.* MIF is a pituitary-derived cytokine that potentiates lethal endotoxemia. *Nature* **365**, 756–759 (1993).
12. Calandra, T. *et al.* MIF is a glucocorticoid-induced modulator of cytokine production. *Nature* **377**, 68–71 (1995).
13. Bacher, M. *et al.* Migration inhibitory factor expression in experimentally induced endotoxemia. *Am. J. Pathol.* **150**, 235–246 (1997).
14. Bernard, G.R. *et al.* High-dose corticosteroids in patients with the adult respiratory distress syndrome. *New Engl. J. Med.* **317**, 1365–1370 (1987).
15. Meduri, G.U. *et al.* Corticosteroid rescue treatment of progressive fibroproliferation in late ARDS. *Chest* **105**, 1516–1527 (1994).
16. McHugh, L. *et al.* Recovery of function in survivors of the acute respiratory distress syndrome. *Am. J. Respir. Crit. Care Med.* **150**, 90–94 (1994).

Pulmonary and Critical Care Medicine, 111B
Seattle VA Medical Center
1660 S. Columbian Way
Seattle, Washington 98108, USA

Estrogens, progestins and coronary artery reactivity

Certain progestins may oppose the favorable effects of estrogen on the cardiovascular system of postmenopausal women (pages 324–327).

J. KOUDY WILLIAMS & MICHAEL R. ADAMS

CORONARY HEART DISEASE (CHD) is the leading cause of death and a major cause of disability among postmenopausal women in most Western societies[1]. Although a direct causal relationship has not been shown, it has been established that risk of CHD is reduced by as much as 50 percent in postmenopausal women who take 0.625 mg of conjugated equine estrogens (the estrogens most commonly given to American women; CEE) or the equivalent daily[2]. Although estrogen use is associated with a reduced risk of CHD, when taken long-term it has been reported to increase the risk of endometrial and breast cancer. To offset this effect postmenopausal women on hormone replacement therapy are recommended to take estrogen in combination with either progesterone (the

natural hormone) or synthetic progestin derivatives. However, the impact of the co-administration of a progestin on the cardioprotective effects of estrogen is unclear. On page 324 of this issue Miyagawa *et al.*[3] show that co-administration of estradiol-17β with the synthetic progestin medroxyprogesterone acetate (MPA) diminishes estrogen-induced protection against coronary vasoconstriction in ovariectomized rhesus monkeys. By contrast, estradiol-17β combined with progesterone protected against coronary vasoconstriction. These results suggest that certain progestins may oppose favorable effects of estrogens on the cardiovascular system.

Although some types and doses of progestins have been shown to have deleterious effects on plasma lipid and lipoprotein concentrations, it should be pointed out that sex hormone effects on lipid concentrations explain only about 30 percent to 50 percent of their CHD risk effects[4]. It has been hypothesized that the remaining effects of sex hormones may be mediated in the artery wall. Our studies indicate that MPA diminishes the vasodilator effects of CEE in response to acetylcholine independently of plasma lipid and lipoprotein concentrations[5,6]. The Miyagawa study is significant because the investigators compare the effects of estradiol-17β and progesterone versus estradiol-17β and MPA on coronary artery responses to constrictors (serotonin/thromboxane) released during platelet activation, a situation that may very well occur *in vivo* at the site of a coronary artery plaque rupture.

Why do progesterone and MPA have seemingly contrasting effects on vascular reactivity and atherogenesis? There are no definitive studies that identify a mechanism(s) by which progesterone and MPA affect vascular reactivity differently. However, the example of well-characterized anti-estrogenic effects of progestins on the reproductive system may be instructive. The extent of the anti-estrogenic effects of a progestin on pathophysiologic processes of the endometrium, for example, depend on several factors, including dose, potency (or type), and route or pattern of administration. Although the effects of progestins on arterial walls remain unclear, there is evidence suggesting that estrogens may modulate vascular reactivity through mediating nitric oxide production, low density lipoprotein oxidation, ion channel activity, and expression of vasoactive biomolecules such as endothelin. Some, or all, of these processes may be targets antagonized by progestins.

Do other progestins have vascular effects similar to MPA? Progestins are known to differ in their potency. Because MPA is more potent than progesterone, it may more effectively antagonize the vascular benefits of estrogen. Furthermore, progestins also differ in their androgenicity. MPA has more potent androgenic properties than progesterone. We have found that a nonandrogenic progestin, nomegestrol acetate, does not diminish the beneficial effects of estrogen on coronary dilator responses in monkeys, thus supporting the notion that relative androgenicity may play a role in determining a progestin's effects on vascular reactivity. Progestins also differ in their capacity to stimulate glucocorticoid release, which may also explain differential effects on vascular reactivity.

The dose of hormone and hormone kinetics are very important factors in the interpretation of data from animal models. Care must be taken to approximate the dose of hormone in the animal to that given to women. However, it cannot be ruled out in the Miyagawa study, and other studies using animal models, that the kinetics of metabolism may be different in monkeys and people. If this is so, blood and tissue concentrations of the hormones may differ between species. Thus, the results of the current study are important because they suggest that a particular progestin or estrogen may act differently at the same tissue site.

New approaches to hormone replacement therapy may involve developing estrogens that prevent cardiovascular disease and osteoporosis but do not increase the risk of breast and uterine cancer. For example, 17 alpha-dihydroxyequilenin (one of the estrogens in CEE) has little effect on the uterus of monkeys, but does benefit the cardiovascular system[7]. Furthermore, certain plants, such as soybeans, contain a significant amount of isoflavones, compounds with structures similar to estradiol that bind weakly to the estrogen receptor. These plant "estrogens" have beneficial effects on vascular reactivity of coronary arteries[8] but have few effects on breast and uterine tissue[9].

The public health importance of these issues cannot be underestimated. Despite epidemiologic evidence that hormone replacement therapy reduces the risk of CHD, osteoporosis, and possibly dementia in postmenopausal women, in the United States less than eight percent of this group take hormone replacement therapy. Poor compliance is accounted for, in large part, by fear of cancer (associated with unopposed estrogen) and side effects (such as menstrual bleeding). The perfect hormone replacement therapy might be one that affords cardiovascular and bone protection without causing unwanted side effects or increasing the risk of breast or uterine cancer. To date, no such therapy exists. The Miyagawa study is an important contribution to our understanding of the interactive effects of estrogens and progestins on the cardiovascular system. Future research may focus on the development of estrogens (such as 17 alpha-dihydroequilenin and soy "estrogens") that do not have harmful effects on the breast and uterus, and progestins (such as nomegestrol acetate) that may not reduce the beneficial effects of estrogen on cardiovascular tissue.

1. Gorodeski, G.I. & Utian, W.H. Epidemiology and risk factors of cardiovascular disease in postmenopausal women. in *Treatment of the postmenopausal woman: Basic and clinical aspects* (ed. Lobo, R.A.) 199–221 (Raven, New York, 1994).
2. Wenger, N.K., Speroff, L. & Packard, B. Cardiovascular health and disease in women. *New Engl. J. Med.* **329**, 247–256 (1993).
3. Miyagawa, K., Rosch, J., Stanczyk, F. & Hermsmeyer, K. Medroxyprogesterone interferes with ovarian steroid protection against coronary vasospasm. *Nature Med.* **3**, 324–327 (1997).
4. Barrett-Connor, E. & Bush, T.L. Estrogen and coronary heart disease in women. *JAMA* **265**, 1861–1867 (1991).
5. Williams, J.K., Adams, M.R., Herrington, D.M. & Clarkson, T.B. Short-term administration of estrogen and vascular responses of atherosclerotic coronary arteries. *J. Am. Coll. Cardiol.* **20**, 452–457 (1992).
6. Williams, J.K., Honore, E.K., Washburn, S.A. & Clarkson, T.B. Effects of hormone replacement therapy on reactivity of atherosclerotic coronary arteries in cynomolgus monkeys. *J. Am. Coll. Cardiol.* **24**, 1757–1761 (1994).
7. Washburn, S.A. *et al.* Effects of 17 alpha-dihydroxy equilenin sulfate on atherosclerotic male and female rhesus monkeys. *Am. J. Obstet. Gynecol.* **175**, 341–351 (1996).
8. Honoré, E.K., Williams, J.K., Anthony, M.S. & Clarkson, T.B. Soy isoflavones enhance coronary vascular reactivity in atherosclerotic female macaques. *Fertil. Steril.* **67**, 148–154 (1997).
9. Foth, D. & Cline, J.M. Effects of mammalian and plant estrogens on mammary glands and uteri of macaques. *Am. J. Clin. Nutr.* (in the press).

Department of Comparative Medicine
Bowman Gray School of Medicine
Wake Forest University
Winston-Salem, North Carolina 27157–1040, USA