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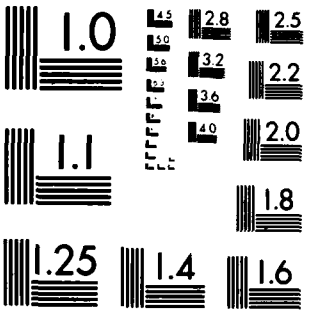

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)
This is an invited editorial for The New England Journal of Medicine which discusses a new finding, i.e., that a mediator released by phagocytic cells during severe trauma or infection serves to initiate proteolysis of skeletal muscle. The mediator causes PGE_2 formation in muscle which in turn activates lysosomal proteases. The importance of this sequence is discussed in terms of host survival and defensive mechanisms. Interrelationships among the mediators are also discussed.

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an Editorial by

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United States Army Medical Resarch Institute of Infectious Diseases

Fort Detrick, Frederick, Maryland 21701

This is an invited editorial

scheduled for publication in the

March 10, 1983 issue of

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The accelerated catabolism of skeletal muscle protein which accompanies severe trauma and infection can now be ascribed to the actions of endogenously produced mediators. Reports (1,2) in this issue of the Journal have identified these actions using in vitro preparations of rat skeletal muscle as a bioassay. Rates of proteolysis in these muscle preparations were quantitated by measuring free amino acid release into the media.

Clowes et al (1) isolated and partially characterized a small glycopeptide from the plasma of traumatized or septic patients. When compared to control samples of normal plasma, mediator-containing samples were found to induce significantly greater rates of bioassay muscle proteolysis. Intermediate rates of amino acid release were generated by plasma from patients who had undergone noncomplicated elective surgery. Further, the magnitude of in vivo proteolysis in the uninjured leg muscles of septic or traumatized patients was estimated by measuring arterio-venous differences in the plasma concentrations of representative free amino acids. Leg muscle proteolysis in individual patients correlates well with their plasma bioactivity in the assay system.

Although evidence for a circulating proteolytic mediator was indirect in the study of Clowes et al (1), additional support for the presumptive role of circulating mediators was found by Baracos et al (2), who studied the actions of highly purified human leukocytic pyrogen (LP) in a similar rat muscle bioassay system. LP produced a rapid increase in muscle proteolysis without affecting the synthesis of new muscle protein. Baracos et al (2) also showed that LP-induced proteolysis was mediated through the synthesis of prostaglandin E_2 (PGE_2) in muscle. Both the accumulation of PGE_2 and the

proteolytic action of LP could be blocked by incubation of assay muscle with indomethacin, a drug known to inhibit PGE_2 synthesis. Baracos et al (2) demonstrated further that the LP-induced acceleration of muscle proteolysis could be blocked through a different mechanism by an experimental drug, Ep-475. This agent appears specific in its ability to inactivate the lysosomal cathepsins B, H, and L in intact skeletal muscle. The findings suggested that the proteolytic actions of LP in skeletal muscle were caused by an increased production of PGE_2 which, in turn, activated thiol proteases in muscle cell lysosomes (2). Alternatively, naturally occurring cathepsin inhibitors in muscle (3) might be deactivated.

Endogenous peptide mediators are formed and released when mobile phagocytic cells are suitably stimulated. LP-induced fever is mediated in hypothalamic thermal regulatory centers via a localized formation of PGE_2 in neuronal cells (4). The action of LP on skeletal muscle would thus appear to employ the same secondary messenger. Further work will be required to determine if the glycopeptide mediator identified in plasma by Clowes et al (1) is structurally related to LP, if it is produced by activated phagocytes, and if it works by a similar molecular mechanism.

The findings (1,2) extend the concept that activated phagocytic cells can produce hormone-like mediators to signal distant tissues. Mediator activities are reflected by a variety of names (5), including LP, endogenous pyrogen (EP), leukocytic endogenous mediator (LEM), neutrophil releasing factor, lymphocyte activating factor, and most recently interleukin-1. However, the molecular structure is not known for any of these mediators and their relationships are uncertain.

Many of the generalized, but diverse, metabolic and physiologic responses which accompany severe trauma, infection, or inflammatory states have been ascribed to the action of endogenous mediators (5,6). Such responses include the experimentally demonstrated generation of fever, the production and release from bone marrow of neutrophils, the accelerated hepatic uptake of amino acids from plasma, the hepatic synthesis of intracellular enzymes and metal-binding proteins, the hepatic production of acute-phase plasma proteins, the hepatic sequestration of iron and zinc, and the stimulation of phagocyte and lymphocyte populations to greater activity (5,6). Mediator activities that can be demonstrated in vitro using cultured cell or tissue preparations would appear to be independent of intervening CNS or hormonal controls.

Acceleration of skeletal muscle proteolysis was previously included on theoretical grounds (5) within this list of mediator-induced responses. It seemed logical that mediator release might activate a mechanism for generating the free amino acids needed for host defenses. It remains possible that another consistent response to illness, i.e., anorexia, is also initiated by an endogenous mediator.

Muscle proteolysis during severe illness is of positive value for survival. In this regard, skeletal muscle provides a metabolically dynamic protein bank and potential source of free amino acids (7,8). This role of skeletal muscle protein is beneficial, because each of the different immunological and nonimmunological host defense mechanisms is based, ultimately, on the ability of body cells to synthesize new proteins. With severe trauma, infection, or inflammation, the labile source of amino acids in muscle can be tapped for high priority defensive needs of the host. On the

other hand, if the pool of labile nitrogen becomes depleted, as in cachectic diseases or severe protein malnutrition, the patient becomes especially vulnerable to superimposed infections, often by opportunistic microorganisms (7).

In addition to the reutilization of amino acids for synthesis of new proteins, branched-chain amino acids released during proteolysis can be metabolized within muscle as direct sources of energy. Some other amino acids, similarly released or synthesized within muscle cells, travel via plasma to the liver where they may become substrates for gluconeogenesis (7). The additional glucose is used, in turn, to initiate and sustain the heightened consumption of oxygen which accompanies fever (7). The Journal papers (1,2) should stimulate compariosns of muscle proteolysis due to various cachectic illnesses, to glucocorticosteroids and other hormones (8), and to previously identified muscle protease regulators (3). Differences or similarities of cardiac muscle must also be ascertained in comparison to responses of striated skeletal muscle.

Unfortunately, variously named mediator substances have not been available in sufficient purity or quantity to allow for broad testing in all bioassay systems by which mediator activities have previously been explored. The possibility that a single mediator initiates all recognized host responses seems remote in view of physicochemical and immunological differences between partially purified species of LP (9). Further, a single mediator could not account for disease-related differences in clinical fever patterns, WBC responses, and acute-phase protein fluctuations. However, since laboratory production of variously named mediators employs similar cells and methods, it

is possible that different mediator species are all members of a closely related family (6).

Despite more than three decades of study, these endogenous mediators have not been precisely identified or characterized. Formidable obstacles to progress remain. The need to obtain mediators in vitro from living phagocytic cells limits the size of production runs. Biological characterizations still depend upon relatively insensitive bioassay systems. Large mediator losses occur during purification and standardization. Specific structural characterization and workable quantities of mediators will be required to determine individual physiologic roles.

Hopefully, these obstacles can be overcome. Recently, Flynn et al (10) identified mononuclear phagocytes in human placentas as sources for mediator production. Recombinant DNA technologies offer a possible future production method. Bioassay systems should be made more sensitive, use cultured tissue or cells to minimize expenditures of purified mediator, or be replaced by physiocochemical quantitation or immunoassay. The latter should improve when well characterized mediators and specific, high affinity polyclonal or monoclonal antibodies are produced.

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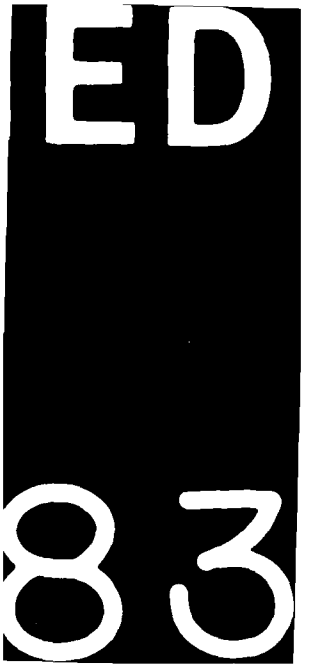
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