

This Week's Citation Classic®

Koj A. Acute-phase reactants: their synthesis, turnover and biological significance. (Allison A C, ed.) *Structure and function of plasma proteins*. London: Plenum Press, 1974. Vol. 1. p. 73-125; and Addendum. p. 127-31.
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This chapter in a book devoted to biochemistry, physiology, and medical aspects of plasma proteins describes the family of proteins synthesized by hepatocytes in response to infection, injury, and inflammation. Particular emphasis is laid on metabolism of acute-phase proteins and mechanisms regulating their induced synthesis. [The *SCI*® indicates that this book chapter has been cited in over 435 publications.]

Trends in the Acute-Phase Response

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January 23, 1989

As a postdoctoral fellow in the National Institute for Medical Research at Mill Hill, London, I was introduced to the studies of plasma protein synthesis and turnover by the late Arthur S. McFarlane, then head of the Division of Biophysics. He devised ingenious methods of labelling proteins *in vitro* with radioactive iodine and *in vivo* with ¹⁴C-carbonate. In cooperation with Erwin Regoeczi, A. Hugh Gordon, and Anthony C. Allison (then at the Clinical Research Centre) we soon demonstrated that rabbits injected with bacterial endotoxin¹ or large doses of vitamin A (supposed to labilize lysosomes) show increased synthesis of certain plasma proteins. Similar results were obtained with the perfused liver isolated from injured rats. The concept of trauma-inducible "acute phase" plasma proteins was already outlined,² but the mechanisms responsible for induction remained totally unknown. Before my return to Kraków, Allison suggested I write a critical review on the subject. The monograph was at first limited to fibrinogen and

appeared in Polish as my habilitation thesis,³ but, during the next two years, it grew into a comprehensive chapter, covering a dozen proteins and thus appropriate for a book to be edited by Allison. Because of restricted access to literature in Kraków, I had to rely on reprints sent by the authors responding to my requests based on careful reading of *Current Contents*®. At that time circulation of reprints was much wider than now and they were often accompanied by personal letters with useful comments from the authors. For several reasons publication of the book by Plenum Press was delayed until 1974, and thus I felt compelled to prepare an addendum, which turned out to be not very useful and responsible for misquotations of the last page number of my review.

In subsequent years studies on acute-phase reactants developed rather slowly until the beginning of the 1980s, when the field was literally "invaded" by immunologists and molecular biologists. All of a sudden the regulation of synthesis of acute-phase proteins in tissue culture became a classical model of investigating gene expression in eukaryotic cells,^{4,5} and the search for the hepatocyte stimulating factors resulted in the discovery of several inflammatory cytokines, including interleukin 6, known formerly as interferon- β_2 or B-cell stimulatory factor 2.^{6,7}

It is interesting that a chapter published in a not easily accessible book has been so widely cited. I can only guess at the reasons: that this review appeared at just the right time, it contained personal opinions and a critical evaluation of the field, and it provided exhaustive coverage of the literature. Whatever the reason, it is certainly rewarding to see that the time devoted to the search, selection, and digestion of innumerable references has not been in vain.

1. Koj A & McFarlane A S. Effect of endotoxin on plasma albumin and fibrinogen synthesis rates in rabbits as measured by the ¹⁴C-carbonate method. *Biochemical J.* 108:137-46, 1968. (Cited 65 times.)
2. Owen J A. Effect of injury on plasma proteins. *Advan. Clin. Chem.* 9:1-41, 1967. (Cited 75 times.)
3. Koj A. Wpływ urazu na szybkość syntezy fibrynogeny (The effect of injury on the rate of fibrinogen synthesis). *Monografie Biochemiczne* 22:1-56, 1969.
4. Gordon A H & Koj A, eds. *The acute-phase response to injury and infection: the roles of interleukin 1 and other mediators*. Amsterdam, The Netherlands: Elsevier, 1985. 339 p. (Cited 40 times.)
5. Fey G A & Fuller G M. Regulation of acute phase gene expression by inflammatory mediators. *Mol. Biol. Med.* 4:323-38, 1987.
6. Gaultie J, Richards S, Harnish D, Lansdorp P & Baumann H. Interferon beta-2/BSF-2 shares identity with monocyte derived hepatocyte stimulating factor and regulates the major acute phase protein response in liver cells. *Proc. Nat. Acad. Sci. USA* 84:7251-5, 1987.
7. Koj A. The role of interleukin 6 as the hepatocyte stimulating factor in the network of inflammatory cytokines. *Ann. NY Acad. Sci.* (In press.)

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