Correspondence

Discriminatory indices in rheumatoid arthritis

Sir, In the 2 recent studies by Bird et al. and Dixon et al., the value of various biochemical parameters as discriminatory indices of clinical response in rheumatoid arthritic patients treated with alclofenac and penicillamine was described.

With particular reference to the measurement of serum sulphydryl (SH) levels, greater attention to the precise methodological assay technique used could, I propose, provide some clarification in the resultant interpretation of the specific function that the SH moiety has in pathogenic and therapeutic biochemical mechanisms in rheumatoid disease. The method used in the aforementioned reports, while utilising the same spectrophotometric SH reagent, namely, Ellman's DTNB, differs in several pertinent respects from that used in a comparable study which was referred to in their paper. The most important difference in experimental assay technique is the choice of pH, the rate of SH reaction being critically dependent on the concentration of the reactive S— anion. It has been shown that it is possible to discriminate between slow-reacting protein —SH groups, e.g., serum albumin, which react fully at alkaline pH only, and low-molecular-weight thiols, e.g., glutathione and penicillamine, which react fully at both alkaline and acid pH values. Hence, as compared to the measurement of serum SH levels at 1 pH value only, namely, pH 7-4, the selection of 2 distinct acidic and alkaline pH values, namely, pH 6-5 and pH 7-6, enables the separate contribution of 2 different populations of 'fast' and 'slow' reacting serum SH groups to be more specifically and accurately assessed.

As has been previously reported, it is of interest to note that whereas penicillamine causes a significant increase in the 'slow' reacting protein —SH type group levels equivalent to normal values, minimal increases in serum SH are detectable at pH 6-5, thus indicating no comparable increase in thiol type 'fast' reacting SH groups, despite the actual administration of the free thiol drug. By contrast, however, in alclofenac treated rheumatoid patients, the observed increase in serum SH reactivity is largely confined to that measured at pH 6-5 with no comparable increase in the 'slow' protein —SH type levels determined at pH 7-6. Since alclofenac per se contains no SH moiety, the rise in serum SH reactivity may be attributed to 2 possible mechanisms. Either the normally very low serum concentration of free physiological thiols, e.g., glutathione and cysteine, has increased dramatically, or alternatively the formation of albumin-bound ligand drug complexes may have produced alloplastic conformational and electrostatic perturbations in the albumin molecule with consequently heightened chemical reactivity of the mercaptable SH moiety.

Subsequent studies have also confirmed the ability of antirheumatic drugs, e.g., penicillamine and aurothiomalate, to increase serum SH levels both in vivo and in vitro, whereas nonsteroidal anti-inflammatory drugs appear to enhance serum SH reactivity only in vitro. However, because of the different methodology used, i.e., assay at a single alkaline pH and not utilising measurement of the initial rapid SH reactivity, direct comparisons with the in-vivo studies measuring the 'fast' reacting serum SH levels at pH 6-5 are not, unfortunately, possible. The ability of 'gold' treatment to normalise serum SH levels is of especial interest in relation to the proposal that the therapeutic efficacy of aurothiomalate in rheumatoid arthritis is dependent on the thiomale thiol carrier portion of the drug molecule. In addition to serum SH changes, penicillamine administration has also been shown to produce an increase in cellular levels of free glutathione in erythrocytes.

The important role of SH/SS redox reactions in the maintenance of enzymatic activity, membrane integrity, free radical scavenging, and protein conformational stability points to the uniquely ubiquitous function that the SH group displays in cellular physiology. The development and application of specific discriminatory assays and techniques for identifying and measuring thiol levels and alterations in reactivity of specific protein —SH groups offers perhaps one way by which the role of autodisulphide dysfunction in the pathogenesis of rheumatoid disease and possible therapy may be elucidated.

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References

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Synovial fluid in antiquity

Sir, We enjoyed Dr Alarcon-Segovia’s paper1 on the description of synovial fluid and therapeutic arthrocentesis by the Nahuatl Indians of Mexico in pre-Columbian times. We cannot agree, however, with the statement contained therein that Paracelsus is generally considered to be the first to have noted the presence of viscid liquor in the joint cavity. Numerous references to the existence of such fluid in the movable joints are found in the writings of the ancients, beginning with the Hippocratic texts *Of the Places of Man* and *On the Articulations*.5 Galen described the function of synovia as a joint lubricant in his treatise *On the Function of the Parts of the Human Body*,6 and in his commentaries on Hippocrates he stresses the importance of examination of the joint fluid: ‘The physicians must examine the nature of the humor which, in a small quantity, envelops the joints, because many swellings of joints do not become purulent due to this humor. This, namely, is a thick humor. . . . Some physicians have already examined these swellings by incising them.’7

Much of the early information concerning joint fluid was derived from observations of traumatic injuries, and both Paracelsus and his followers, including Severinus (1542–1602), credit wound surgeons with the origin of the term synovia, which was also known by them as Gliedwasser (joint-water) and Gluttwasser (glow-water).8

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References


Venous thrombosis in SLE

Sir, The article by Gladman and Urowitz1 confirmed a susceptibility to venous thrombosis of patients with systemic lupus erythematosus (SLE). Similar observations have been made by Peck, Hoffman, and Franck.8 Neither of these studies was able to define any specific characteristics which pre-disposed patients to venous thrombosis, although it is noteworthy that 3 of the 17 cases described by the former authors had a circulating anticoagulant. They did not state whether this feature was sought in every instance.

We have recently described 4 patients in whom recurrent or extensive venous thrombosis was associated with the presence of the lupus coagulation inhibitor.3 This paradox has been previously noted,4 and in our view is more than a chance association. In our cases further thrombosis was prevented by continuous warfarin treatment over an average period of 6 months. Interestingly, anticoagulation reduced the partial thromboplastin times and made it more difficult to demonstrate the inhibitor. There were no haemorrhagic complications during treatment. We believe that severe venous thrombosis in SLE should suggest the possibility of the lupus circulating anticoagulant, which, if demonstrable, is an indication for long-term anticoagulation.

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