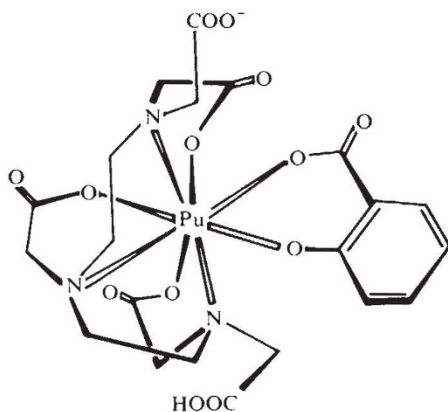


the known chemistry of mixed ligand chelate formation, as we describe elsewhere⁵, the choice of suitable combinations is straightforward. For example, Martell *et al.*⁶ demonstrated, using potentiometric titrations, that Th(IV) formed very stable mixed ligand chelates with EDTA, salicylate and catechol (10^{11} – 10^{13} times more stable than EDTA alone). As expected, Pu(IV) reacted similarly.

We reject the suggestion, unsupported by experimental evidence, that alternative explanations besides mixed ligand complexes are responsible for our results. Our experiments^{4,5}, including ultrafiltration, solvent extraction, and *in vivo* reversal of salicylate antipyresis by Zn and Cu EDTA, provided experimental evidence for mixed ligand chelate formation. The proposed mixed ligand chelate of Pu with DTPA and salicylate is depicted by the following structure:



The requirements for biological transport emphasised by May and Williams have long been known. It is not necessarily true, however, that highly charged polyaminopolycarboxylic acids are confined to extracellular spaces. A very small but adequate fraction of these chelants penetrate intracellular space as shown by sustained excretion of metals following single treatment^{7,8}. Charged metal ions, for example, chromate, can also penetrate cell membranes and reach cell interiors⁹. May and Williams' proposal that synergistic chelation therapy occurs when one drug mobilises the metal and the other traps it in plasma is inapplicable to our systems, as compounds such as salicylate and catechol by themselves do not react with Pu(IV) in *in vivo* conditions.

Although computer simulation studies of speciation in biological fluids have a certain value, they are unnecessary in our therapeutic investigations, as even simple non-computer calculations readily show that the very strong mixed ligand chelates used by us bind >99% of the total metal. Indeed, this is shown in their own calculations¹⁰, even with single chelants, and computer calculations used previously¹¹ by one of us. The ability of complexing

agents to bind metals in the blood stream does not necessarily coincide with the ability to remove metals deposited in the tissues¹².

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Evolution of the 3', 5' internucleotide bond

DHINGRA AND SARMA¹ posed the question "Why do nucleic acids have 3', 5' phosphodiester bonds?". They concluded from a detailed NMR investigation of the conformations of dinucleoside monophosphates that 2', 5'-linked oligomers are unlikely to form helical structures that are stabilised by base-stacking. Thus 2', 5'-linked nucleic acids would be less suitable for participation in present day biochemical operations that involve helix formation. Dhingra and Sarma considered a polymer as a set of repeating dimer structures and did not consider the perturbations that could be introduced by the presence of a complementary strand. There is, of course, evidence that 2', 5'-linked oligomers can complex with 3', 5'-linked complementary polymers, although the melting temperatures of these complexes do tend to be lower than in the case of an all 3', 5'-linked complex².

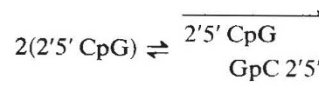
We considered this same question some years ago, and predicted³ that the 2', 5' bond in a helical oligonucleotide would be more susceptible to non-enzymatic chain breakage than would the 3', 5' bond. A large difference in kinetic stability was subsequently demonstrated experimentally for a triple helix of oligoadenylates and poly U in mildly basic solution⁴. Thus during the early chemical evolution of nucleic acids, it seems reasonable to suppose that there was a strong selective pressure for the 3', 5' bond, and against the 2', 5' bond.⁵

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SARMA AND DHINGRA REPLY—Since the publication of our paper in *Nature* we have carried out extensive NMR studies in 100% water on self-complementary 2', 5'-dinucleoside monophosphates, that is



to monitor the Watson-Crick hydrogen bonding protons. The data showed that 2', 5'-linked dimers have little proclivity to form Watson-Crick hydrogen bonded miniature double helices under conditions in which their 3', 5' analogues have been shown¹ to form such complexes. The study has revealed that the availability of a complementary dimer does not introduce enough perturbations to the intrinsic stereochemistry of 2', 5' systems to induce the formation of miniature double helices. In this connection, it is important to note that in the reported crystal structure of 2', 5' ApU no miniature double helices have been observed², contrary to the crystal structure findings on 3', 5' ApU and 3', 5' GpC^{3–8}, but like 3', 5' UpA⁹.

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