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Sela M, Fuchs S & Arnon R. Studies on the chemical basis of the antigenicity of proteins. 5. Synthesis, characterization and immunogenicity of some multichain and linear polypeptides containing tyrosine. *Biochemical J.* **85**:223-35, 1962.
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The paper describes a large number of linear and multichain synthetic polypeptides that are immunogenic and capable of provoking specific precipitable antibodies, thus starting the use of synthetic antigens for a better understanding of immunological phenomena. Experiments described threw light on several definitive chemical features necessary to endow a molecule with immunogenicity, such as composition, shape, size, and accessibility. [The *SCI*® indicates that this paper has been cited in over 215 publications.]

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My PhD thesis at the Weizmann Institute of Science (under the supervision of Ephraim Katchalski-Katzir) was concerned with the synthesis of polytyrosine, poly-*p*-aminophenylalanine, and polymeric azo dyes derived from them. These should serve as synthetic models for azoproteins, of which one rare example was the attachment of haptens to proteins, by Landsteiner. Reading his book on *The Specificity of Serological Reactions*, I stumbled upon his statement that gelatin is probably not antigenic because it does not contain tyrosine.[1]

This led me to studies on the increase of the antigenicity of gelatin upon attachment of tyrosine peptides, which I continued with Ruth Arnon (her PhD thesis). These showed that limited tyrosylation enhanced immunogenicity without significantly changing specificity, whereas more extensive tyrosylation converted gelatin into a potent immunogen provoking primarily antibodies to tyrosyl peptides.[2] By the way, it was then that we clearly defined the notion of immunogenicity and distinguished it from antigenic specificity.

Several years earlier, inspired by a lecture in Rehovot by "Mr. Polymer," Herman Mark, on new developments in the field, I synthesized a new family of polymers, the multichain polyamino acids.[3] Assuming that gelatin is not necessary for immunogenicity, we now used, with Arnon, the water-soluble multichain poly-DL-alanine as the carrier for peptides of tyrosine and glutamic acid and showed that the resulting copolymer, denoted (T,G)-A--L, led to specific antibodies in experimental animals.[4]

Our preliminary communication on a "synthetic antigen" was rejected by *Nature* on the grounds that the journal does not publish papers that are part of a series. Sara Fuchs joined us, and part of her PhD thesis is summarized in the resultant paper, discussed here. Tens of linear and multichain polyamino acids were synthesized and tested for their immunogenicity and antigenic specificity. We learned a lot about the role of size, composition, and shape, as well as the accessibility, of those parts of the molecule crucial for immunogenicity in the nature of the immune response.

The availability of synthetic antigens permitted a systematic elucidation of the molecular basis of antigenicity, as well as other immune phenomena, and permitted the unequivocal proof for the genetic control of the immune response. This seems to me the main reason for the importance of this paper, as many laboratories became interested in the synthetic approach to immunological phenomena.[5] Arnon and Fuchs, both in the Department of Chemical Immunology at the Weizmann Institute, played a major role in this development, and in the early 1970s, together with Arnon, we developed the notion of synthetic vaccines of the future as a natural corollary of the present study.[6] Another offshoot of the paper is the synthetic "Cop 1," a copolymer of Ala, Lys, Glu, and Tyr, cross-reactive immunologically with the basic encephalitogen of the brain, investigated now clinically as a candidate drug for multiple sclerosis.[7]

I have been at the Weizmann Institute of Science for the past 36 years and have just returned to the Department of Chemical Immunology after a 10-year tour of duty as president of the institute. The study reported in the paper under discussion here, as well as studies resulting from it, were rewarded with several prizes, both to me and to Arnon.

1. **Landsteiner K.** *The specificity of serological reactions.* Cambridge, MA: Harvard University Press, 1945. 310 p.
2. **Arnon R & Sela M.** Studies on the chemical basis of the antigenicity of proteins. 2. Antigenic specificity of polytyrosyl gelatins. *Biochemical J.* 75:103-9, 1960. (Cited 75 times.)
3. **Sela M, Katchalski E & Gehatia M.** Multichain polyamino acids. *J. Amer. Chem. Soc.* 78:746-51, 1956. (Cited 60 times.)
4. **Sela M & Arnon R.** A specific synthetic polypeptide antigen. *Biochim. Biophys. Acta* 40:382-4, 1960. (Cited 40 times.)
5. **Sela M.** Antigenicity: some molecular aspects. *Science* 166:1365-74, 1969. (Cited 225 times.)
6. ———. Totally synthetic antigens as potential vaccines. (Miescher P A, Bolis L & Ghione M, eds.) *Immunopharmacology.* New York: Raven Press, 1985. p. 81-9.
7. **Bornstein M B, Miller A J, Teitelbaum D, Arnon R & Sela M.** Multiple sclerosis: trial of a synthetic polypeptide. *Ann. Neurology* 11:317-19. 1982.

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