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TO BOND OR NOT TO BOND: CHEMICAL VERSUS PHYSICAL THEORIES OF DRUG ACTION

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In 1903, Arthur Cushny, Professor of Materia Medica and Therapeutics at the University of Michigan, published an article in the Journal of the American Medical Association entitled “The Pharmacologic Action of Drugs: Is It Determined by Chemical Structure or by Physical Characters?” To a chemist today, this question might seem odd. The physical properties of a drug and its chemical structure are, after all, intimately related, and even if one wants to distinguish between closely integrated physical and chemical properties, surely both are involved in drug action. Physical properties such as solubility and chemical reactivity due to the presence of certain molecular structures can and do both influence pharmacological effects.

At the turn of the twentieth century, however, the understanding of the nature of chemical bonding and of cellular structure and function was still in its infancy, and many chemists and pharmacologists sought a simplified answer to Cushny’s question. There was thus significant controversy over whether the physical or the chemical properties of a substance could best explain its pharmacological action, and over the value of attempts to relate the physiological activity of a drug to its chemical structure.

The fact that drugs may exert a selective action on specific organs of the body had long been recognized empirically and expressed vaguely in the traditional designation of certain remedies as cordials (acting on the heart), hepatics (acting on the liver), etc (2). As early as the seventeenth century, the noted chemist Robert Boyle had tried to explain the specific effects of drugs in terms of the mechanical philosophy by suggesting that since the different parts of the body have different textures, it is not implausible that when the corpuscles of a substance are carried by the body fluids throughout the organism, they may, according to their size, shape and motion, be more fit to be detained by one organ than another (3).

Attempts were also made in the sixteenth and seventeenth centuries, under the influence of Paracelsus and his followers, to explain drug action in more chemical terms. The iatrochemists, for example, tended to attribute most physiological and pathological phenomena (including pharmacological action) to acid-base interactions (4). It was not until the nineteenth century, however, when chemistry had become firmly established as a science, that the chemical approach could be given a clearer and more specific expression. Around mid-cen-