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Nobel Prize in Medicines 1957

Daniel Bovet

The Nobel Prize in Physiology or Medicine 1957 was awarded to Daniel Bovet "for his discoveries relating to synthetic compounds that inhibit the action of certain body substances, and especially their action on the vascular system and the skeletal muscles"

Presentation Speech by Professor B. Uvnäs, member of the Staff of Professors of the Royal Caroline Institute

Your Majesties, Your Royal Highnesses, Ladies and Gentlemen.

The work of Daniel Bovet should be considered in its context, bearing in mind what had been found out about biological amines between about 1920 and 1930. It had been thought that nerve impulses reached peripheral organs rather in the way that signals are transmitted along a telegraph wire to a receiver. However, Otto Loewi and Henry Dale demonstrated, in work gaining them a Nobel Prize, that nerve impulses released small amounts of highly active substances at the nerve endings. Amines such as acetylcholine, adrenaline, and, as Ulf von Euler has shown more recently in Stockholm, noradrenaline, are substances of this type which transmit the peripheral effects of nerve impulses. It was also

discovered that another amine, histamine, was released in much larger quantities than normal in allergic reactions. The well-known symptoms of such allergies as hay-fever, eczema, asthma, etc., appear depending upon the site of histamine production.

The discovery of the role played by biological amines, so far as chemical transmitters were concerned, opened up new paths for research. Pharmacologists and chemists could see the possibility of producing substances whose actions would reproduce or inhibit those of the biological amines. It was becoming possible, thanks to these products, not only to interfere in experimental physiological phenomena, but even in the pathological processes of illness in clinical medicine. Daniel Bovet concentrated his research on the problem of pharmacologically blocking the amines mentioned above, and he succeeded in producing substances which specifically inhibited their effects.

As early as 1937, Bovet and Staub succeeded in producing the first antihistamine, thymoxidiethylamine, capable of preventing anaphylactic shock in animals which, unneutralized, was fatal. This first histamine antagonist was, it is true, too toxic to be used clinically, but virtually every antihistamine that is used throughout the world today to oppose symptoms of allergy is derived from it.

From what we know at present, no antihistamines exist in Nature. But, on the other hand, there do exist substances which can prevent nerve impulses taking effect. Venetian ladies of the sixteenth century knew they could make themselves more seductive by bathing their eyes with a lotion of belladonna. The characteristic dilation of the pupil is produced by the alkaloid of belladonna, atropine, which blocks the effects of acetylcholine released at nerve endings in the musculature of the iris. The nerve impulses lose their effect and the pupil is paralysed. In the same era the South American Indians knew a vegetable preparation, curare, which they used - if I dare express myself thus - on slightly different hunting grounds. Curare is a poison which suited the use they made of it - on the tip of an arrow - extremely well. It paralyses its prey by blocking, in the way that atropine does, the transmitter substance - here again acetylcholine - which links the motor nerve to the muscle fibres. Given orally, curare is completely inactive. Nature has equally produced

substances which can inhibit the effects of adrenaline and noradrenaline, these two amines which are released at the nerve endings of sympathetic fibres. The most important of these so-called sympathicolytic substances are the alkaloids which are found in ergot.

The alkaloids of ergot, as well as those of curare, have extremely complicated chemical structures and do not lend themselves to synthesis. They are little used for experiment and still less used in the field of clinical medicine on account of their toxicity and the unpredictable character of their effects.

For a number of years, Bovet and his co-workers studied in animals the relationships between chemical structure and biological effect, as could be observed in the alkaloids of curare and ergot. Proceeding by systematic variations and successive simplifications of chemical structure, work which involved the elaboration of new methods of biological testing and the production of hundreds of new synthetic chemical compounds, they succeeded, by degrees, in obtaining simple chemical compounds which proved themselves, from the point of view of specificity and the absence of undesirable side-effects, much more useful than naturally occurring substances.

The interest which the appearance of products capable of paralysing muscle presents in practical medicine is bound to the evolution of modern surgery, which has made it possible to perform more and more complicated surgical procedures. Operations of this type often require complete muscular relaxation. Anaesthesia must therefore be deep and long, and for this reason it carries risks which can be more dangerous than the surgery itself. We owe to Bovet's research the general muscle relaxants which we use today. We can, in this way, use a light level of anaesthetic and reduce the hazards to which the patient is subjected. Sympatholytic compounds have not yet found any application in general medicine. The future will tell whether the hopes placed in them will be fulfilled and whether they will be of value in the treatment of hypertension and other vascular conditions for which we think a reduction in nervous control would be desirable.

Apart from the importance of Bovet's work in experimental neuropharmacology, his observations have exerted a very stimulating influence in one rapidly growing branch of

pharmacology: I speak of psychopharmacology. Biological amines are the transmitters of nerve impulses in the different tracts of the brain, just as they are the chemical agents which link nerve fibres to peripheral organs. In other words, it should be possible to find drugs which specifically affect brain function. Already, in fact, we posses a number of compounds of this type. Lysergic acid is one of the active components of the ergot alkaloids. A compound closely related to lysergic acid, namely lysergic acid diethylamide (LSD), has a really dramatic effect on mental activity, as one Swiss chemist quite accidently verified. The absorption of a fraction of a milligram of this compound is enough to produce gross distortion of both visual and auditory perception, and mental states resembling those seen in the acute psychoses and certain other mental illnesses. It is fascinating, and at the same time frightening, to know that we can, with minute quantities of simple chemicals, modify the mental state, the soul of a human being. But there is another side to this picture. It allows us to cherish the well-founded hope that in the near future we shall have effective means at our disposal for fighting mental illness which at present is one of the most terrible scourges of mankind.

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