SCIENTIFIC MEETING

THE RELATIONSHIP BETWEEN CHEMICAL STRUCTURE AND THERAPEUTIC ACTIVITY

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Arguments whether the physical properties or the chemical properties of any active substance are the more important are largely a waste of time, as both are linked together *via* the molecular structure. The physical properties must be such as will ensure the substance arriving at the seat of action, but once this is attained some "molecular fit" appears to be necessary for the required activity. In fact, some of Pauling's work gives scientific backing to the simile of the lock and key advanced by Fisher.

During comparatively recent times the new conception has been advanced that, in certain attacks on invading organisms, the remedial compound exerts its activity by interference with an essential metabolite. The names of Woods and Fildes are prominent in this respect, the best example being that of the sulphonamides, for which the essential metabolite is *p*-amino-benzoic acid. Progress along this route is to be expected, since it gives a definite direction to research. Difficulty will be encountered from the fact that most cells, whether they belong to an invading organism or the host, are very similar in their essential requirements. Though immediate practical results in the introduction of new substances to medicine will in the near future, in all probability, result from the empirical method, fundamental information will have to take into account the biochemical aspect.

The acridine antiseptics and the synthetic œstrogens provide examples for discussion. During the 1914-18 war the acriflavine type of substance was established as being of great importance in the treatment of wounds, since compounds of this class have the important property of being as active *in vivo* as *in vitro*. In 1935 the two compounds available were both derivatives of 2: 8-diaminoacridine, and the preparation of all the isomeric mono and diamino derivatives of the acridine nucleus and comparison of their potency was undertaken. It was found that the 2 and 5 positions were the most active, but that the 5 position appeared to induce increased toxicity. Whenever a 1 (or 8) amino substitution appeared the compound was entirely inactive, a result which has been explained *via* hydrogen bonding. The 2:7-derivative appeared to possess the best properties of a compound of this type in that, although it exhibited a high toxicity against the invading organisms, it was only very slightly toxic against the host. The work of Manifold and Russell on the use of this compound with brain tissue gives support. Albert has since carried this work farther, and claims that for an acridine derivative to be active its *p*K as a base should be above a certain value, and also that the possibility of tautomerism within the molecule concerning the nitrogen grouping might be of importance. A recent preparation, as yet not published, of 1-dimethylamino-acridine, which cannot give rise to hydrogen bonding, and has a *p*K above the minimum as suggested by Albert, but which is inactive, suggests that the last word has not been said in this respect.

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NEW REMEDIES

Tivlolac* is a solution of colloidal calcium and vitamin D for injection, subcutaneously or intramuscularly, in allergic states such as urticaria, allergic rhinorrhœa, migraine and asthma, or in vasomotor disorders such as chilblains or angioneurotic œdema. It may also be employed prior to tonsillectomy and dental extraction to reduce capillary hæmorrhage, and it may be given to hasten bony union where this is delayed owing to known calcium deficiency. The average dose is 1 ml. daily for 2 days, followed by a similar dose at 4 to 6-day intervals. Tivlolac contains 0·05 per cent. of colloidal calcium and 5000 I.U. of vitamin D in 1 ml., and is issued in boxes of 6 and 12 ampoules of 1 ml., and in rubber-capped bottles containing 15 and 30 ml. S. L. W.

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With regard to the synthetic œstrogens, it was suggested that the high activity of the stilbœstrol which resulted from the work of Robinson, Dodds *et al* was due to molecular simulation of œstradiol. To probe this contention 3-monohydroxy, 4-monohydroxy and 3:4-dihydroxy-$\alpha\beta$-diethylstilbene were prepared and tested for œstrogenic activity. The 4-hydroxy compound was very active, an activity which was highly potentiated by the introduction of a second 4-hydroxy group; the 3-hydroxy derivative showed little activity, and the 3:4 dihydroxy showed a lower activity than the 4-monohydroxy compound. These results proved that molecular simulation could not be the whole story, and with any derivative of diethylstilbene a *para*-hydroxy group was of paramount importance. Further exploration of the molecular skeleton, $\alpha\beta$-diethylstilbene, has resulted in obtaining an activity similar to that of deoxycorticosterone in 4-hydroxy-4-ωhydroxyaceto-$\alpha\beta$diethylstilbene and recently cardiatonic activity in a 4-butenolide.

It will be observed that the examples chosen illustrate the empirical method of attack, but that once an activity has been obtained further work of a systematic character may be prosecuted within the group. Many thousands of different researches, having for their aim the production of something of use in medicine, have produced the comparatively few important synthetic compounds in use to-day, but, although many of the researches lead to a negative result, they none the less contribute to the knowledge of the relationship between chemical structure and therapeutic activity.