pA, a new scale for the measurement of drug antagonism

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Commentary by

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This is the first of a set of three papers in the Journal that were to transform the study of drug antagonism (see also Schild, 1949, and Arunlakshana & Schild, 1959). At the time it was written, there was a pressing need for methods that would allow the effectiveness of drugs to be measured and expressed in a consistent and reproducible fashion. As Schild noted in his introduction, the requirement was particularly great for antagonists because of the multiplicity of methods then used and the lack of information about their reproducibility. In this important paper he proposed and validated a new measure of antagonist action, pA. The key principle is that the same submaximal response to an agonist is measured first in the absence of antagonist and then in its presence, using a greater concentration of agonist. This was an important departure from early attempts to quantitate drug antagonism by determining the reduction that the antagonist caused in the response to a standard application of agonist. The results of such measurements had proved rather irreproducible, not only from laboratory to laboratory but even between different preparations of the same tissue.

Schild was always meticulous in his acknowledgement of the contributions of others, and he makes it clear that his new scale for the expression of drug antagonism was based on the work of Clark & Raventos (1937) who had already recognised the advantages of assessing the effectiveness of antagonists in terms of the multiple by which the agonist concentration had to be increased to overcome the effect of a certain concentration of antagonist. This factor was described as the *dose ratio* by Gaddum *et al.*, (1955). Schild extended the concept by suggesting that a useful index of the effectiveness of an antagonist would be the value of pA_x, the negative logarithm of the concentration of the antagonist that reduces the effect of a multiple dose (x) of an agonist to that of a single dose. Here x is the dose ratio. Though this was to prove an important advance, the paper became a landmark at least as much because of its detailed description of how best to measure the action of antagonists and also because of its searching discussion of the pharmacological applications of such methods. Three points merit particular mention.

1. Schild showed that pA values provided a means of quantifying not only the overall effectiveness of an antagonist but also some of the characteristics of its action, namely, its time dependence and its variation with concentration. It has to be appreciated that Schild defined pA as an *experimental* measure of antagonist action, independent of theory. Hence pA increases with time following the application of an antagonist. Also, pA_x values may or may not vary with the magnitude of the response measured depending on the antagonist's mechanism of action. Moreover, pA values can be calculated whether or not the antagonism is competitive (though their interpretation is much less certain for noncompetitive antagonism, as Arunlakshana & Schild were to discuss in 1959). It follows that the term pA_2 should not be regarded simply as another way of expressing the negative logarithm of the dissociation equilibrium constant for the combination of an antagonist with its binding site: this relationship holds only for reversible competitive antagonism, at equilibrium, as shown by Arunlakshana & Schild (1959).

2. The paper described in the greatest detail how the action of antagonists could be evaluated using the isolated guinea-pig ileum preparation, and the procedures that Schild introduced were to be widely adopted. His 'automatic assay apparatus' allowed tissues to be exposed to agonist at reg-

ular and precisely timed intervals that would not be affected by the whims or distractions of the experimenter. Schild gave great attention to the details of the equipment and made every effort to ensure that his kymograph tracings would reflect accurately the responses of the tissue.

3. Perhaps most importantly, Schild showed how pA_x measurements could provide a reproducible and statistically satisfactory index not only of the activity of antagonists but also of their relative selectivity in blocking the responses to agonists of different classes. His famous 'ladder' illustration of Fig. 7 allowed both potency and selectivity to be assessed at a glance.

As noted, the pA scale was defined in terms of experimental observations, independent of theory. But tucked away in the second of the two small-print sections on p. 197 is a most important prediction: that for simple competitive antagonism, a nine-fold increase of antagonist should be surmountable by a five-fold rise in agonist, between pA_2 and pA_{10}. Hence the difference between pA_2 and pA_{10} should be 0.95. Here again Schild is meticulous in his attribution and choice of words. He writes that this result 'can be shown' from the mass action equation developed by Gaddum (1937) for a first order reaction. Clearly, his starting point was the Gaddum equation in its simplest form, based on one-for-one competition between agonist and antagonist for a uniform population of binding sites. It is evident that Schild had already appreciated that the assumption of straightforward competition of this kind implied a simple quantitative relationship between the dose ratio and the concentration of antagonist. Further, by then he knew what this relationship was. He was to publish it two years later (Schild, 1949) in the form.

$$x - 1 = K_2 B_x$$

Here x is the dose ratio, K_2 is an affinity constant, and B_x is the concentration of antagonist that gives rise to a dose ratio of x. This was to become widely known as the Schild equation and it is considered further in the commentary on the third of Schild's papers on the quantitative study of drug antagonism (Arunlakshana & Schild, 1959).

References

ARUNLAKSHANA, O. & SCHILD, H.O. (1959). Some quantitative uses of drug antagonists. *Br. J. Pharmacol.*, **14**, 48-58.

CLARK, A.J. & RAVENTOS, J. (1937). The antagonism of acetylcholine and of quaternary ammonium salts. *Quart. J. Exp. Physiol.*, **26**, 375-392.

GADDUM, J.H. (1937). The quantitative effects of antagonistic drugs. *J. Physiol.*, **89**, 7-9P.

GADDUM, J.H., HAMEED, K.A., HATHWAY, D.E. & STEPHENS, F.F. (1955). Quantitative studies of antagonists for 5-hydroxytryptamine. *Quart. J. Exp. Physiol.*, **40**, 49-74.

SCHILD, H.O. (1949). pA_x and competitive drug antagonism. *Br. J. Pharmacol.*, **4**, 277-280.