ANTAGONISMS AND ANTAGONISTS

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Numerous definitions are offered for the term "drug antagonism" which at first sight appears self-explanatory to so many; they all differ from one another, are unsatisfactory (*e.g.*, 21; *cf.* also 145) and lack general applicability (*cf.* 75). Such a situation alone would justify an attempt to clarify the general problem of drug antagonism and would recommend a most elementary approach. Accordingly, this review of the problem will be guided by a small number of considerations resulting from application and adaptation of the few basic concepts of pharmacology.

1) If drug *effect* designates the resulting alteration of a physiological function and drug *action* the underlying alteration of the conditions of that function (93), antagonism is primarily a problem of *combined drug effect*; the "Why?" of a phenomenon cannot be studied without adequate knowledge of the "What?", the phenomenon itself. With the here premised contradistinctive definition of the terms action and effect at hand, their frequently synonymous and vicarious use will be avoided and the word "response", which some use synonymously with "effect", others however as a term reserved for the context of biostatistical sensitivity gradation, and many quite indiscriminately for either of these two very different magnitudes (*cf.* 145), will be dispensed with altogether.

2) "Antagonism" refers to a modification of one or more components of the effect spectrum of a drug combination. The spectrum of a binary combination is the fusion product of the spectra of the two partner drugs, but combined effects must also be classified as *genera* (93) according to their provenience. To name only those most important in the present context: The *homergic* effects, represented in each of the partner spectra; the *heterergic* effects, represented in only one, and the *coalitive* effects, represented in neither of the partner spectra; and the *homodynamic* effects, a genus, in which the same effect, as well as an identical mechanism of action, is traceable to either partner (88, 90, 93).

3) Since all attempts at definining antagonism turn around such comparative expressions as "lesser" or "weaker", antagonism is a *quantitative* problem of combined drug effect; *i.e.*, a problem of the quantitative relationship between dose and effect—a relationship customarily visualized by the *dose-effect curve*. In a combination, the place of the dose abscissa is taken by the *combined-dose field* containing all the combined-dose pairs, and therefore the correlated effect intensities are no longer depicted on a two-dimensional curve but on a three-dimensional *space surface* (86, 90). Antagonism is a problem of the shape of this space surface.

4) The shape of the dose-effect surface can be conveniently depicted in the cartographer's manner in the dose field by *isobols*, that is: by lines connecting those dose pairs which are equi-effective in regard to an adequately selected endpoint of a combined effect (54, 86, 90, 93, 95). The family of isobols for various endpoints of the same effect is presented in a "*graded isobologram*", and

graded isobolograms for all pertinent effects of a combination, when assembled in one graph, form "*multiple isobolograms*" (91–94).

5) The course of the isobols is essentially different for each genus of combined effect (see Figure 1). The isobols of *homodynamic* effects connect the two respective endpoint doses on the partner axes in a straight diagonal and all isobols in a family are parallel when the dose axes are adjusted by use of a proportionality factor. The *homergic* isobol also interconnects the partner axes but is arcuate and deviates NE- or SW-ward[1] from the diagonal, and the members of the family may differ greatly in their course. All *heterergic* isobols run rectangularly out into the dose field from their endpoint on the respective dose axis and are parallel (90, 93; see also 54, p. 398). *Coalitive* effects, though they exhibit very characteristic isobols (88), will not be discussed in this succinct review from the viewpoint of antagonism.

Thus, these five sets of elementary considerations end up in affording quasi altitude maps of typical dose-effect relations of combined drugs. They should greatly help in viewing the essence of the problem, but one cannot expect an all-embracing answer from this small atlas of basical situations. Quite contrariwise, all they seem to tell is that (a) in the enormous variety of appearances of homergic effect the hand of antagonism would be hard to recognize, and (b) the behavior of homodynamic and heterergic effects seems so invariably predelineated that no change could occur,—unless there enters an interfering factor not foreseen in those schematic maps of Figure 1.

Indeed, the reality of experimentally obtained isobolograms exhibits a multitude of such interferences. They can readily be demonstrated even in the first isobologram in history, fifty-five years older than the term isobol and the resumption of isobolographic viewing, namely, in Fraser's presentation of his experiments on the combined lethal effect of physostigma and atropia (45, 46; for a more complete, slightly rearranged presentation see 93). The isobol, which over the entire east half of the original graph follows a diagonal course, exhibits a sharp north deflection in the range of lowest atropine and highest physostigmine doses. With admirable clearsightedness Fraser pointed already to interference by a supervenient effect as the factor responsible for the anomalous course. His attention was turned to the sector of (S-ward) *reversal* from the deflection, whereas in the present context it will suffice to point to an effect of the lower dose range of atropine as the major, antagonistically interfering factor; however, even this seemingly simple isobologram raises questions which today are still under discussion (see 2).

More adequate for analysis than this single isobol—which, moreover, deals with such an equivocal ("coenostigmic"; *cf.* 93) endpoint as death—is of course a *graded* isobologram. One plotted, *e.g.*, from Läser's data on the combined effect of vitamin B_1 and acetylcholine upon the amplitude of the isolated frog heart (81; see the isobologram in 93, figure 8) shows that all of the family of isobols of negative inotropic acetylcholine effects are deflected E-ward from their straight-vertical course by the interference of a heterergic B_1 effect. The

[1] To simplify orientation in isobolographic maps, the directions of the compass are employed in this review.

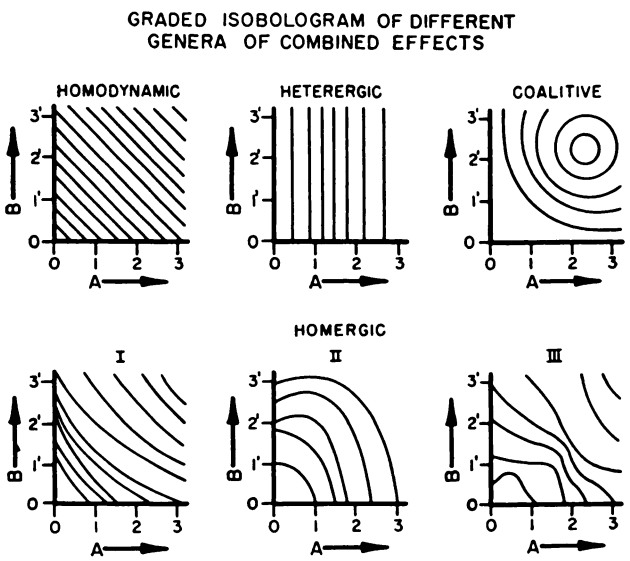

FIG. 1. Graded Isobolograms of different genera of combined effect.—Schematic presentation of the course of isobols for different endpoints of the same combined effect, namely (upper row), of homodynamic, heterergic, and coalitive effects, and (lower row) of three forms of homergic effect, I = synergistic, II = antagonistic course of isobols, III = "synergo-antagonistic" course as calculated for "effect summation."—Abscissae: doses (in arbitrary units) of partner drug A; ordinates: doses of partner drug B.—For further explanation see text.

isobologram teaches that such deflected isobols are neither rectilinear nor necessarily similar in the geometrical sense. Moreover, though the isobologram may not bear out all of the investigator's conclusions, it makes many of them clearer than the multiple log dose-effect curve, by which Läser presents his results.

Still more instructive are *multiple* isobolograms, such as those depicting equieffectiveness in regard to various of the effects of the combinations of phenobarbital with pentylenetetrazol (91, figure 3) and with nikethamide (U.S.P.) (92, figure 1). The heterergic isobols for threshold convulsions of the two convulsant drugs run in a quite unruly fashion [N.B. at variance with that same isobol in the trimethadione-pentylenetetrazol combination (94)]. When they are depicted together with some isobols for heterergic effects of phenobarbital origin (see 93, figure 7), the three phases of their "undulating" (123) course may appear explained by triple interference: phenobarbital, at low dosage, deflecting the convulsant isobol E-ward, antagonistically; at a higher dosage, in the range of its prehypnotic excitatory effect, in the opposite direction; and in the range of its still higher hypnotic doses again antagonistically E-ward. Attention may also be drawn to the antagonistic N-ward deflection of the hypnotic effect by pentylenetetrazol and an opposite S-ward deflection by nikethamide.

Into the discussion of these three examples the term antagonism has almost

automatically infiltrated. It is, however, not fortuitous that the examples are all from the genus of heterergic effects. Applied to these, the word antagonism indeed obtains a clear conceptual background. The vague comparative "lesser" looses its "dangling" character and refers to a correctly defined level of comparison. In heterergic combined effects, the measurable, by definition rectangular, straight-line isobol of the "active" partner is the given reference for any deviation induced by an interfering effect of the theoretically "inactive" second partner.

All this does not hold true for the homergic combined effect; here the level of comparison is not accessible to measurement. Even in the absence of extra interference, homergic effect is the product of imperspicuous interference between the two participating partner effects, and from this pre-existent status a further modification cannot be experimentally delineated (see also 122). Indeed, in regard to homergic effects, it has long become an agreement of convenience to employ an entirely *extraneous* reference of comparison, namely the behavior of homodynamic effect, and to call homergic effects antagonistic when their isobols deviate NE-ward from the diagonal, and synergistic, when they deviate SW-ward (86, 93, 151; see also 54, p. 398; 95). It is obvious that the course of a homergic isobol, called "antagonistic" under this agreement, may coincide for a long stretch with a synergistically, W-ward, deflected heterergic isobol from the spectrum of partner A. This creates a dilemma that may sometimes not be solved even by careful study of the spectrum of partner B; nor is it a completely satisfactory solution to call the rectangular triangle NE of the homodynamic diagonal as a hypotenuse an area of "relative antagonism" (86, 150–152) or of "relative synergism" (54, p. 398).

Thus, quite confusingly the term antagonism is applied in an entirely different sense to each of the two major genera of combined effect. Still other sources of confusion are indicated in the examples discussed. First: One effect of the same combination may behave antagonistically, another synergistically. Second: The same effect of the same pair of partners may be antagonistic in one dose area and synergistic in another. Two further examples may illustrate this complication. The first one is based on a general consideration: Whereas homodynamic effects comply with the rule of *dose additivism* [(90); = iso-additivism (47)], there is a wide-spread, though untenable assumption (*cf.*, *e.g.*, 61, p. 11) that all homergic effects follow the rule of *effect summation* [= hetero-additivism (47)]. If, on the basis of this assumption, one adds the effects coordinated to each dose pair of two partners having even only slightly different dose-effect curves, he ends up with the graded isobologram of the homergic example III of Figure 1, in which the family of isobols represents all possibilities from synergistic via undulating, *i.e.*, synergo-antagonistic, to antagonistic course. The other, particularly interesting example is taken from Ariëns' and de Groot's investigations (5, 10). When their experimental data are employed to plot a graded isobologram (as presented in 93, figure 9), a family of isobols is obtained for various endpoints between 0 and 100% of maximum intensity of combined contracturing effect of two of their di-onium compounds, M 129 (abscissa) and M 115 (ordinate), upon the frog rectus abdominis. Under the definitions used

above, all isobols for endpoints <35 indicate an either homergic or homodynamic effect, all those for endpoints ≮35 indicate heterergic effect; moreover, all isobols except that for endpoint 35 express antagonism, the heterergic isobols by deviating to NW from the horizontal, the homergic isobols by deviating to NE from the rectilinear diagonal course of unvaried homodynamic effect. The shift from homergism to heterergism, which marks the interesting behavior of this drug combination, points to a "dualism of *effect*", namely, to a second ("cryptantergic"; see below) effect of M 129, which interferes with the combined contracturing effect. To be sure, this viewing of the effect phenomena is well compatible with the experimenters' thoughtful hypotheses of a "dualism of *action*".

This last combination exemplifies a melange of synergism and antagonism only in a terminology in which the word synergism is merely employed to designate homergism. Nevertheless all adequately extensive experimental studies of combined effects indicate how frequently the often derided term "synergo-antagonism" (87, pp. 221–227; 90) is the only one fitting the phenomena observed. This, together with many other ambiguities pointed out above, makes it obvious that the word antagonism can only be useful when employed with all the attributes of reference of the individual case. Among these references to be specified are, as previously discussed, the physiological type of the combined effect, its genus and the combined-dose range. Another important specification should not be forgotten, namely, that of the timing of the administration of each of the partner doses. The significance of this temporal factor was already known to Fraser (45, 46). Nevertheless his isobol, as well as later ones of homergic effects, which exhibit a similarly excessive and asymmetrical deviation, raises the question of adequate synchronization with regard to the "times of peak effect" of the two partner doses. This problem is discussed elsewhere (89, 92, 93), and Zipf (151) has reported instructive experiments in which rather small alterations of the time interval between the injections of the partner doses meant a shift from a diagonal or even synergistic to an antagonistic course of his isobols.

It is no cure for these complications if one shifts the emphasis from the *drama* to the *personae dramatis*, by favoring the term *antagonist*. In homergic effects, it is *a priori* impossible to say which of the partner drugs is the antagonist and which is antagonized. This may at first sight appear different in heterergic effects. However, they fall into two major classes which could perhaps best be distinguished by the adjectives *enantiergic* and *cryptantergic*; "enantiergic" applying to the cases of *mutual* antagonism where each of two manifest partner effects differs from the other only by the sign, such as depression *versus* stimulation of the same function; "cryptantergic" applying to unilateral antagonism, where the effect spectrum of the second partner drug carries no manifest indication of a potentiality of interference. In this case, the cryptergic partner may justly, though not without due specifications, be designated as the antagonist, whereas in the class of enantiergic antagonisms an alternating emphasis on any one of two antagonists might only detract from consideration of the two partners' focal relationship, the *reciprocity* of their interference. It may be mentioned

that, in a graded isobologram of both the heterergic (+) and (−) effects, this reciprocal antagonism results in a "neutralization zone" extending the subthreshold area near the zero point of the combined-dose field more or less radially far out into the field, and that the presence of such a band of ineffective doses most characteristically distinguishes enantiergic from cryptantergic effects (see 93).

Any attempt at further classification of antagonistic phenomena would lead beyond the frame of this brief survey of antagonistic *effects*. Clarification of the processes of antagonistic *action* is, to be sure, the ultimate aim. However, an understanding of the physiological *outcome* is, in general, the prerequisite for the understanding of those more intimate *mechanisms* conditioning the effect phenomena. Discussion of the fortunate circumstances which sometimes allow to circumvent this prerequisite must be dispensed with here. So must also a discussion of the all-too frequent belief that *biostatistics* can open an avenue of approach to problems of combined effect; its role may be stated in one sentence (for details compare 93): In the study of antagonism, as in all comparable problems, biostatistics plays an important part when applied in its due place, namely, when it is employed as the tool to find the behavior of the "normal" individual,—"the probit 5 individual" (93)—within the natural population of test objects with varying drug sensitivity, and a most precarious role when employed in the fallacious belief that the gradation of sensitivity, for instance the percentage scale of individuals exhibiting an endpoint effect, can replace the yardstick of *intensity* of effect,—which, after all, is the only measure of antagonism as a quantitative phenomenon.

A. J. Clark (31, p. 239) who played such a leading part in this field summarized his opinion on the problems of antagonistic *action* in the statement: "Imperfect knowledge",—and that includes: imperfect conceptual clarity,—"appears to be the most probable reason for any apparent simplicity in processes of drug antagonism." If the present review has succeeded in demonstrating that this holds true for antagonistic *effects* as well, it may have served to clarify by illuminating complexities.

DRUG ANTAGONISM AND pA_x

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Clark and Raventos (32) suggested a method of estimating the activity of drug antagonists in terms of "the concentration which altered by a selected proportion, *e.g.* 10-fold, the concentration of an active drug needed to produce a selected effect". The negative decimal logarithm of this (molar) concentration has been termed pA_x where x is the proportion selected (131). Since pA_x is a null measure which involves no change in response it is independent of the method of experimentation and can be determined equally well in perfused and isolated preparations (13). Its usefulness as an empirical measurement