

Steel G G & Peckham M J. Exploitable mechanisms in combined radiotherapy-chemotherapy: the concept of additivity.

Int. J. Radiat. Oncol. Biol. Phys. 5:85-91, 1979.

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Four conceptually different ways in which chemotherapy can improve the results of radiotherapy are described: spatial cooperation, independent cell kill, protection of normal tissues, or enhancement of tumour response. Problems in identifying a truly enhanced tumour response are considered, and it is shown that there usually exists a range of responses that could be termed "additive." The paper cautions against the ill-considered use of the terms "synergism" or "supra-additive." [The *SCI*[®] indicates that this paper has been cited in over 115 publications, making it the most-cited paper from this journal.]

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This paper was mostly written on an aeroplane between London and Washington. Michael J. Peckham and I had recently won one of the National Cancer Institute's (NCI) new Cancer Research Emphasis Grants (CREG) in the field of combined modality therapy, and as principal investigator I was required to attend regular working meetings of the CREG recipients.

Problems of terminology and the lack of agreed upon ways for evaluating results have bedevilled the fields of combined modality therapy and combination chemotherapy. There is something in the scientific and clinical mind that lights up at the thought of "synergism." Perhaps this is due to the hope of a magical gain in tumour response or perhaps the attraction of getting something for nothing. Whatever the reason, papers on experimental cancer therapy abound with claims for super-additivity and synergism, so much so that thoughtful and experienced investigators are often cynical when they hear such claims.

We sought to outline an approach to the evaluation of drug-radiation combinations that was rational and that enabled underlying

mechanisms to be identified. The effects on a cancer patient or tumour-bearing mouse of receiving both radiotherapy and chemotherapy are extremely complex. The paper set out four broad ways in which the addition of chemotherapy to radiotherapy might yield an improved therapeutic result: spatial cooperation, independent cell kill, protection of normal tissues, and enhancement of tumour response.

Although it may well be that the therapeutic gain demonstrated in the clinic so far has resulted from the first two of these mechanisms, the intellectually stimulating prospect is the last one. What does it mean to claim a better-than-expected response? If dose-effect relationships were always linear there would be no problem, for "additive" would have a unique meaning. But dose-effect relationships in radiobiology and chemotherapy are often far from linear. This led us to use the "isobologram" approach, which had been described previously.¹ We argued that in the case of possible situations that could be described as additive and that these can be graphically expressed as an "envelope of additivity."

As is not uncommon in scientific publication, some aspects of this paper were misunderstood. We were not seeking to establish a new criterion for additivity. We were trying to stress the *uncertainties* that are inevitably associated with this concept. Our additivity envelope was an expression of the range of uncertainty. Inevitably, there have been a number of subsequent publications that have tried to prove wrong the claims we were not making or that have elaborated them into even more complex theories.

For those who are seriously trying to compare therapies we would not recommend recourse to isobolograms. The best way is first to decide how best to quantify the critical normal tissue damage for combined treatment, then to apply combined treatments at two or preferably more radiation dose levels, simultaneously documenting tumour response and toxicity. The aim should be to identify, if necessary by interpolation, a combination treatment that is equitoxic with radiation alone or with some other reference treatment. At this point the treatment that gives the greatest tumour response is the better.

[For recent work in this field see reference 2.]

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1. Loewe S. The problem of synergism and antagonism of combined drugs. *Arzneim. Forsch.* 3:285-90, 1953. (Cited 145 times since 1955.)
 2. Steel G G. The search for therapeutic gain in the combination of radiotherapy and chemotherapy: review. *Radiother. Oncol.* (In press.)