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# Animal Models in Drug Development: Historical Aspects

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*Abstract.* The historical aspects of drug development and evaluation are anecdotically related. Clinical trials have proven the effectiveness of animal tests in the vast majority of cases, and the effort has been well spent. Similar or more noteworthy success may be obtainable with model systems in the study of prostatic cancer.

*Key Words.* Drug Development – Animal models – Historical aspects

In the post-World War II years, along with the many other resurgent scientific developments of that golden age, the pharmaceutical industry developed techniques for the mass animal screening of compounds for potential use as drugs. These biological tools went with great concurrent advances of chemistry as a science which permitted the wholesale synthesis of new chemical entities which could be tested for biological activity.

The result was that the drug cabinets of the world were restocked with drugs that had real pharmacological activity for good or ill, depending on how they were used or abused.

The chemical approach was a two-pronged one. One, from all sorts of sources ideas were generated that a certain type of compound might exert some interesting pharmacological activities. So a dozen or maybe 100 of a desired chemical type would be made and tested. More often than not the theory on which they were made proved unfounded. But with surprising frequency they revealed unexpected pharmacological activity which in itself was useful or which led to developments in other fields. When successful results were written up, a chain of reasoning was often implied that the compound came into being by a series of logical Socratic steps. It sounded better that way. But I was there on some of the occasions. And it might have been more logical to report: I reached into a pickle barrel and pulled out a plum.

The second approach was that of pure chemistry. The medicinal chemist would visualize – and the virtuosos of the field had great creative imagination – an entirely new type of chemical structure which he thought he could make with no idea of what it might do. These would be made and tested for biological activity – purely as a shot in the dark.

It seemed to me in the early 50's that every time we shook a scientific bush an interesting new drug was dislodged.

Thus we got steroids of a bewildering variety, antihistamines, diuretics, antihypertensives, antidiabetics, the psychotropics, and of greatest life-saving importance, the antibacterials.

What we did not get were good antiviral agents. And what we also did not get were good anti-cancer drugs. Is there a relation between these two failures? I only ask the question. Since retirement I don't get paid for providing answers.

What we saw in all of this was analogous to the social and economic development of new geographical frontiers. The soil was fertile, the natural resources great. Like our oil fields, however, this productive well is being pumped dry. I am sure that new drugs will still emerge from this type of hit-or-miss, relatively unsophisticated approach, but the productivity curve is down; that which came easily is now harder to come by. We are still finding new active compounds but, in most cases, ones which are no better than what we already have; and lastly, the political climate in which the search is made is becoming more and more frustrating and preclusive.

The alternative approach that is being evolved as a practical necessity is to study a lesser number of compounds more finely targeted in design to achieve some specific biochemical purpose and similarly to sharpen the focus of testing methods to pinpoint highly specific, generally enzymatic, pharmacologic activity.

At present many types of compounds can be screened for specific desired activity in relatively simple in vitro systems. These have an advantage in that the test may suggest something of the mechanism of action.

But sooner or later, before the compound goes into man, it has to go into a whole animal. For one thing one has to learn what the drug does to physiological processes other than those it was designed to affect. Particularly one must estimate its potential toxicity. If the reasons for this are not self-evidently compelling, there is the added one that the FDA will put you in jail if you do not do it.

A good battery of screening methods will pick out something like 1–5 compounds from 100 that seem to be worth the sizable investment of further developmental efforts requisite to trial in man. Many of these will die along the way before they get to man and most of them after early human trials. My guess is that from 5000 starting entities, one compound will end up as a prescribable drug. This is a distressingly long-odds business – one that would turn a Las Vegas odds-maker to agriculture for a living.

I review this bit on non-oncologic history to highlight a parallel attempt, I am sure the most mammoth biological screening program in all history, to find anti-cancer drugs by similar means.

As I have indicated, the pharmaceutical houses made little headway in looking for anti-cancer drugs. Then in 1955, the NCI decided to look harder and wider under the aegis of the so-called Cancer Chemotherapy National Service Center (CCNSC).

I was on one of their early panels but did not last long because some klunk from a profit-making organization used grant money to buy drapes for his office and other such amenities.

In the uproar all professional for-profiteers were unceremoniously eliminated from the program – most of us before we could even get our hands on a dollar. I do not know how nor when the iron curtain was cracked. Evidently, however, the proscription against those who live in sin with self-supporting organizations – which have the privilege of paying the tax bills – is now less stringent.

The CCNSC program still lives as part of the Division of Cancer Treatment. Its history to date has recently been recorded [2]. In the course of its two decades, it has screened by one or another method relevant to cancer, nearly 300,000 synthetics and over 200,000 natural product extracts (from an unsigned report from the Division of Cancer Treatment, dated December, 1976). I have seen (but cannot document) that one in 40,000 of these compounds was active by some criterion, but that ratio is getting better. Still we are dealing in a long-odds business.

In its early stages the CCNSC would screen anything it could get its hands on from any source, and I believe properly so. My company used to send them compounds and extracts in large numbers as did many other chemical houses.

The screening methods, originally in vivo against an assortment of animal tumors, have undergone extensive continuous revisions. Those recently listed as used in the past or available for use now in selected circumstances, numbered over 120 [1].

In practice, the number of routine initial tests now used for a new substance is small, but special tests are employed that are tailored to the nature of the compound and its anticipated type of action. The single initial in vivo "pre-screen" test is against mouse leukemia P388 – thought to be the most usefully predictive of any now available.[1] In other words, as is true in other fields, blind screening has yielded to reasoned, targeted screening. In FY '75, 39,370 materials were studied to varying extents, of which 18 have been selected for clinical development. This is a "hit" rate of a little less than one in 2,000 – at least better than the over-all program average. Eight of these 18 compounds were related to known active agents.[2]

An elaborate comparison has now been made[2] of the results of animal tests relative to subsequent results of clinical trials against 17 solid human tumors. The conclusion was that, depending on the type of tumor, the animal tests gave correct predictions in from 70 to 90 % of the cases. Thus, the animals might give false negatives or false positives in something approaching 25 % of the cases.

It would be appropriate but difficult to give some quantitative inventory of the success of this program. It certainly has contributed to cancer chemotherapy as practiced today. It is something of an international effort since the intention is to exploit contributions from any source. Any measure of progress is to be hailed. The costs relative to the modest successes have certainly been high. Obviously we have come up with no success comparable to that achieved over the same period in, for instance, the control of the hypertensive diseases. All of this stands as a monument to the enormous difficulty of the problem rather than to an ineptitude of the many contributors to the greatest drug hunt in history. One gets the impression of intelligent, imaginative management of the program.

This brings us to the specialized screening systems reviewed here today. At the first meetings of this Panel the urgent need for better testing methods and animal models as guides to better therapy for prostatic cancer was repeatedly stressed. This workshop will survey the results to date.

I believe it will show that the progress made has been one of our most notable successes. Tools are being provided by which chemo- and other types of therapy, targeted for prostatic cancer, can receive preliminary evaluation, probably of a much more meaningful sort than available before. If so, the effort has been well spent.

[1] Schepartz, S. A., Memo to Suppliers of Compounds, Feb. 13, 1976.

[2] Annual Report, Division of Cancer Treatment, FY '76.

## References

1 VENDITTI, J.: Protocols for screening chemical agents and natural products against animal tumors and other biological systems. Cancer Chemother. Rep. *3:* 1–88 (1973).

2 ZUBROD, C. G., et al.: The chemotherapy program of the National Cancer Institute: History, analysis and plans. Cancer Chemother. Rep. *50:* 349–539 (1976).

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