Free Research versus Design Research[1]

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THERE IS A CHOICE before us between free and design research, or as I see it, between supporting the man or the experimental design. Let us support the man.

I bring up a discussion of this choice because I believe it is of vital concern to us as members of one of the committees of the National Research Council, whose chief function it is to pass on research projects. We have much power in our hands. How we use it may affect the entire future of scientific research in America.

We are participants in a great revolutionary movement. For the first time, we as scientists are beginning to hold the responsibility for our future in our own hands. We are asked to pass not only on the scientific merits of the work of our colleagues, but on its anticipated merits for financial support. This movement started both in this country and abroad during World War I and picked up momentum during and after World War II. It has now become firmly established. Before that, scientists received support almost entirely from individual philanthropists, foundations, other organizations, and university funds. Scientists themselves had little to do with the disposition of funds. Now support comes in large part from the various government agencies—a few large public organizations—and funds for research are channeled almost exclusively through committees of scientists.

We, on this and similar committees, hold the purse strings. We distribute or withhold the life-giving funds for research. This gives us much power and responsibility—more than we may realize. We exercise our power in voting on projects; we fulfill our responsibility by trying to vote fairly, intelligently.

This means in the first place that we must try to get as much first-hand information about the man, the project, the setting, as we can; that we do not content ourselves with hearsay; and in the second place, and more importantly, that we try to work out in our minds the philosophy of the future of research—what do we expect from research? and how can we get it? by supporting individual workers, by supporting teams of workers, or by supporting experimental designs? These questions we must answer.

How do we meet this responsibility now? Have we stopped to consider that in most instances all we know about a project is what we see written on a piece of paper—the application blank—words. We do not know the man, we may never have even heard of him. We know nothing about his ability, ideals, or sincerity; about the project we know only what we see in the application. This means that in most instances we must vote the way most of us bet on horses at the races: because we like the name, the number, or the stable.

Under the circumstances we do the best we can. We pick out the one tangible part of the application—the experimental design—how the man plans to work out his project. We are asking more and more questions; aware of this, applicants elaborate their designs in more and more detail. Accordingly this part has come to play a progressively more important role. A vicious cycle has set in. In making an application for a grant before World War II, a few lines or at most a paragraph or two sufficed for the experimental design; now it may extend over 6–8 single-spaced typewritten pages. And even then committee members may come back to ask for more details. How far we have gone in this direction I have seen in this and other committees. We have all seen members with excellent records of research question research plans, often of other recognized scientists, in such detail that, had it been done to themselves in their earlier and more active years, they would most certainly have protested violently. Although done in good faith, this questioning of details by committee members often serves no other purpose than the inflation of our egos, especially when the applicant is a man of some importance.

Under these circumstances, passing the buck has come to be practiced very widely. Projects are passed from committee to committee—to my knowledge in one instance, six committees—largely because at no place along the line did anyone believe that he had adequate information to come to a firm decision. This is a wasteful, time-consuming, discouraging practice.

The researcher has come to play a less and less important part; comparatively little is known about his background, setting, facilities, his sincerity, above all about his imagination, determination, and ability to carry on independent research. He is gradually being reduced to the status of a technician who must follow out in detail a definite plan of research.

We seem to forget: that in the past great discoveries have with few exceptions been made by individual workers, often working in great isolation; that some of the most important discoveries have been made without any plan of research—largely by acci-

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dent or in dreams, as in the instance of Loewi's Nobel prize-winning discovery; that discoveries have resulted from a general state of what Alan Gregg has called puzzlement—puzzlement at discrepancies in findings—a state of mind which would not lend itself to any accurate verbal description; that there are researchers who do not work on a verbal plane, who cannot put into words what they are doing—whose thinking functions in terms of experiences, subconscious observations—who don't know what they have been after until they actually arrive at their discoveries.

We seem to forget too: that experimental designs only serve a purpose in most instances of confirming what is already known, filling in gaps, adding decimal points; that experimental designs are useful tools devised by statisticians to check on ideas, but that they are not substitutes for ideas; that there may be little relation between a man's ability to devise wonderful experimental designs and his ability to do research; that good researchers use research plans merely as starters and are ready to scrap them at once in the light of actual findings; that experimental designs breed "team research." Research plans are laid out in detail. Men must be found to fit into them. Good research men may be taken away from their own work benches, often never to return. Actual work is often delegated to technicians. Opportunities for getting first-hand information are reduced to a minimum. Opportunities for independent thinking are sacrificed. Often no one person takes responsibility. "Team research" serves a purpose in developing and applying ideas; it rarely produces new ideas. It usually discourages the real researcher and encourages men who on their own would otherwise never have entered research.

In trying to fulfill our responsibilities we must take into account two other factors: the source and amounts of the funds and the fact that we are facing the possibility of full-scale warfare. Our funds come from the public treasury through one or more channels; they are greater than ever before, greater than any of us would have dreamed of before World War II. The cry is still for more and more funds. Do we want quality or quantity in our research?

Large funds encourage great enterprises—great experimental designs. They encourage great "teams of workers." They take good research men away from their work benches to direct many technicians. The use of such large sums from the public treasury for research must be justified—public-spirited men are likely to want to know how the funds have been used. This means that we, members of this and similar committees, as men who are responsible for the distribution of funds from the public treasury, are naturally prompted to play safe, not to gamble with public funds. Sensitive to these responsibilities we feel ourselves urged to ask for details of designs, expenditures—we hesitate to give the researcher a free hand. We have to ask ourselves whether this is a wise, farsighted policy.

Most importantly in many instances we must face the problem of how a project fits into the war needs. When the needs are immediate, it is the project, the design, that counts. Who does the work is often relatively unimportant. It becomes a technical job. Great pressures are being brought from many angles to produce results for immediate use. Shall we sell the day to serve the hour?

What can we do? First of all let us get all the facts we can about the worker, visit him ourselves whenever possible and see him at work. Try to convince ourselves of his ability and sincerity. Find out how his project fits into his scheme of things. See the setting and the facilities offered by his university or community.

Let us try to adjust the funds to his needs.

Let us try to help improve the conditions of research for the individual worker. This means longer grants—fewer reports—less paper work.

Let us not ask men for detailed reports until they have completed their jobs. Half-finished reports only clutter up other men's minds and create confusion in the literature.

Let us try to give the funds for research with as few strings attached as possible, without asking a man exactly what he is going to do and why.

Let us not mistake experimental design for ideas.

Let us encourage researchers to return to their work benches; to make first-hand observations; and let us question whether a proposed "team research" is a product of experimental design or whether it grows out of genuine supplementation of contributions.

Let us remember what Arthus (*1*) said, "Indeed it is not in the turmoil of social life, not through academic chats nor laboratory gossip that we come to see the light, that interpretations become clear, that experiments are conceived, and conclusions reached. It is through solitary, profound, and sustained meditation. In order to make some progress in the experimental sciences one must meditate a great deal." He should have added that ideas do not often come from big conferences and meetings. Let us not take men away from their work for many useless conferences. Let us give them time to think consecutively.

Let us be careful how we handle a researcher's ideas. They belong to him. When he puts them on application forms, let us not broadcast them, scatter them far and wide to scrupulous and unscrupulous hands. Public agencies do this now with the result that authorship of ideas is often forgotten or ignored. The researcher's satisfaction comes from finishing a job—his own. He is human. It may have taken him years to work out his ideas. In wartime, yes, all ideas must be pooled and as quickly as possible. But not in peacetime.

Let us try to educate public agencies and legislators to see the importance of backing individuals—of betting on them—giving them greater freedom. Government agencies can do this. They have done it in Great Britain.

Let us discourage the great practice of passing the buck, avoiding responsibility by passing projects from committee to committee, rather than by getting first-hand information.

The choice before us, experimental design or free research, the project or the man, has many ramifications, but it concerns the mainspring of the entire operation, the future of research in America. Let us support the man.

Reference

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Inactivation of Vaccinia Virus by a Diffusible Component from Hydrolyzed Hyaluronic Acid

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PREVIOUS STUDIES from this laboratory have shown that various preparations of hyaluronic acid inactivated vaccinia virus grown in cell culture, and that this effect was markedly increased when the acid was hydrolyzed by hyaluronidase added to the culture medium (*1*). Experiments have, therefore, been carried out to identify the virus-inactivating component or components. In this preliminary note we describe experiments showing that: (a) the virus-inactivating substance is freely diffusible through a cellophane membrane; and (b) the substance, or one of its components, is in all probability glucuronic acid or a glucuronide.

The procedure in 10 basically similar experiments was as follows: an 0.5% solution of purified umbilical cord hyaluronic acid was prepared in 0.1 *M* acetate buffer pH 6.0 containing 0.1 *M* NaCl and dialyzed overnight at 4° against approximately 10 volumes of the same buffer. A purified preparation of dialyzed testicular hyaluronidase (activity 1000 TRU/mg;[4] final concentration 1 : 1000) was then added to the hyaluronic acid and the mixture incubated for 48 hr at 37° in the presence of toluene. A sample of the hydrolyzate was removed and stored at − 20° C, and the remainder dialyzed in cellophane tubing against distilled water at 4° until, as judged by colorimetric tests (*2, 3*), no further N-acetyl glucosamine or glucuronic acid diffused through the membrane. The diffusate (material passing through cellophane) was concentrated to the original volume by lyophilization. The four materials (i.e., hyaluronic acid, hydrolyzate, dialyzate, and diffusate) were sterilized by heat (10 min at 75° C) or filtration and tested together for viral inactivation against dermo or Levaditi vaccinia virus. Tests were carried out on: (*a*) rabbit skin; (*b*) cell cultures; (*c*) the chlorioallantoic membrane of chick embryos; and (*d*) the hemagglutination reaction. Reducing substances, glucosamine, and glucuronic acid were estimated in each fraction. Approximately 50% of the original N-acetyl glucosamine and glucuronic acid present in the hydrolyzate was recovered in diffusible form.

The most striking results were obtained in rabbit skin, and a summary of a typical experiment is given in Table 1. In this experiment equal volumes of diluted virus and test material were incubated at pH 6.0 for 4 hr at 37°; the same virus suspension was incubated with buffer alone as a control. Groups of 4 rabbits then received 0.5 ml of each mixture intradermally, the development of lesions being recorded after 3, 5, and 7 days. Typical lesions developed after 3 days from control injections and in those where virus had been treated with either hyaluronic acid, hydrolyzate, or dialyzate; in the two latter cases the lesions were fre-

TABLE 1

INACTIVATION OF VACCINIA VIRUS BY DIFFUSATE FROM HYDROLYZED HYALURONIC ACID: INTRADERMAL INOCULATION IN RABBITS

(All materials dissolved in 0.1 *M* acetate buffer, pH 6.0)

Test material	Virus dilution*	Type of lesion†
Hyaluronic acid‡	10^{-2}	+++
Hydrolyzate	10^{-2}	+++++
Dialyzate	10^{-2}	+++++
Diffusate	10^{-2}	—
Buffer control	10^{-2}	++++

* Dermo virus, egg-passage strain.

† ++++ Edematous, necrotic lesion, approximately 3–5 cm in diameter; +++ similar lesion without visible necrosis; — no visible or palpable lesion.

‡ Wyeth Institute of Applied Biochemistry, batch 215–2.

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[3] With the technical assistance of Robert A. Roosa and Arthur G. Tyrol, Jr.

[4] Kindly supplied by J. Seifter from the Wyeth Institute of Applied Biochemistry.