ON THE CHOICE OF MATERIAL FOR GENETICAL STUDIES

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I should like today to discuss some examples of the ways, often unpredictable, in which the choice of material for study has influenced the history of genetics. Much of what I have to say will be familiar to most of you, and much of it will probably also be discussed by other participants in this symposium, but I should like to put it together from a somewhat unusual point of view.

I shall first consider some cases in which progress was delayed by the choice of material that was unfavorable for reasons that could not be foreseen.

The first example is that of MENDEL'S choice of the hawkweeds (Hieracium) for the work described in his second paper on genetics (MENDEL 1870). In this paper MENDEL described the taxonomic difficulty of the material, and gave the following reasons for undertaking his study:

"Regarding the question whether and to what extent hybridization plays a part in the production of this wealth of forms, we find very various and conflicting views held by leading botanists. While some of them maintain that this phenomenon has a far-reaching influence, others...will have nothing to do with hybrids in Hieracia.... "

"The question of the origin of the numerous and constant intermediate forms has recently acquired no small interest since a famous Hieracium specialist has, in the spirit of the Darwinian teaching, defended the view that these forms are to be regarded as arising from the transmutation of lost or still existing species."

The quoted passage is of interest because of the recent suggestion that MENDEL would not have dared to discuss evolution because of the opposition to it in the Catholic church. This passage shows that he not only discussed it but specified that he had spent much time in the monastery garden in an attempt to test it. He rightly concluded that his experiments had not answered the questions he had asked; for present purposes the point is that he had asked important questions and had chosen what appeared to be excellent material to study them. As we now know, the material was actually about the worst he could have chosen, for a reason that he could not have guessed--namely that it usually reproduces by apomixis,--i.e., that the seedlings arise from purely maternal tissue, without the occurrence of meiosis or segregation.

The next example is that of GALTON's choice of Bassett hounds for his statistical study of parent-offspring correlations for discrete variations. He was looking for data to use in such a study, and his friend SIR EVERETT MILLAIS offered him the use of his extensive pedigree data on Bassetts (GALTON 1908). The animals were listed as "bicolor" or "tricolor." Apparently most or all of the dogs of this breed have the familiar black-and-tan pattern, and also have an irregular

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pattern of white spotting. As in so many mammals (horses, cattle, mice, etc.) the extent and distribution of the white areas is extremely variable and is only partly determined by the genetic composition of the individual, since the two sides of an animal are often quite different. In the Bassetts an animal was listed as tricolor if a tan area was present, i.e., if any region normally tan was left pigmented by the variable extent of the white areas. If all the potentially tan areas were in fact white, the animal was a bicolor. In other words, the character was not a good discontinuous one, but only a rather indirect measure of a weakly inherited continuous variability.[1] No wonder the results GALTON obtained were quite different from MENDEL's!

One may surmise that, if GALTON had not known MILLAIS, he would have been led to use the data recorded in the British Stud Book. If he had tabulated these data, he could scarcely have failed to see that chestnuts mated together gave only chestnuts, that a gray always had at least one gray parent, that grays (which are almost always mated to non-grays) produced offspring half of which were gray, and that bay or brown stallions were of two kinds--one that often had chestnut offspring and one that never did.

If he had gotten this far he would surely have reached the Mendelian solution, for he was already prepared by his particulate interpretation of the nature of the hereditary material, his acceptance of WEISMANN's conclusion that the hereditary material must be halved in the formation of the gametes, and his mathematical turn of mind.[2]

If this had happened, genetics might have been spared the unfortunate and acrimonious controversy of the early years of this century between the Mendelians and the biometricians.

HUGO de VRIES was one of the outstanding biologists of his time. His "Intracellular Pangenesis" (1889) was one of the important works in the history of genetics, and in several respects, foreshadowed the Mendelian approach. He also carried out a series of beautiful quantitative studies on the effects of various chemicals on plasmolysis, and understood, and stated quantitatively, the relation between monovalent and divalent metals and acid radicals on osmotic pressure; it was his quantitative data that led VAN T'HOFF and ARRHENIUS to develop the ionic theory of electrolytes. His mutation theory (1901) played a large part in the development of modern ideas about genetics, and he was one of the original group that found and

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[1] If some of the animals were genetically black, rather than black and tan, these would also contribute a second, genetically distinct, kind of bicolor.

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[2] OLBY (1965) has suggested that GALTON did in fact derive the Mendelian ratio of 1:2:1 in 1875. This paper has been criticized by LINTS and DELCOUR (1968--see also a reply by OLBY [1968]). It is clear that GALTON was discussing somatic cell divisions and not sexual reproduction. The account is in a letter to DARWIN, and GALTON seems never to have published it--presumably because he came to realize that his analysis applied only to a single cell-division, whereas there were many successive ones in the case he was discussing.

The passage does show, however, that GALTON knew how to use the binomial theorem--which makes it even more clear that he was prepared to understand and appreciate the Mendelian approach.

appreciated MENDEL's paper in 1900.[3]

The surprising thing is that, in spite of this distinguished record, de VRIES made only slight contributions to the development of genetics, in the post-Mendelian period, even though he continued a very active research program, and published many books and papers for the next 30 years. The reason is clearly that he got involved with the wrong material for the time--namely Oenothera. He could not have forseen that the various special and unusual properties of this plant made it unprofitable to study at this stage of the development of genetical techniques and theory.

Having considered three cases where investigators were unlucky in their choice of material, I should now like to describe an example of a lucky stroke a case where the material turned out to be even more favorable than could have been anticipated.

Drosophila was first used as an object for genetical studies only because it was easy and relatively inexpensive to breed in the laboratory, and because large families and many generations could be produced relatively quickly. With an annual plant one can usually get one generation a year; with laboratory rodents there are more generations, but what one gains in this respect is offset by what he loses from the small size of individual families. The gain from the use of Drosophila is rather better than a 20-fold speeding up.

This was the obvious advantage of the material, but at first it was more than balanced by the absence of clear-cut variations-in current terminology, of marker genes. In fact, the earliest studies (by CASTLE and his students [1906], by MOENKHAUS, by LUTZ, and by MORGAN) were concerned with the effects of inbreeding and selection on fertility and other quantitatively varying characters, which could not be analyzed effectively at that time or even now without the use of marker genes.

About 1909 MORGAN began to use Drosophila in an attempt to induce mutations. It seems clear that he was interested in the mutation process itself, and not in the accumulation of marker genes for other kinds of study. But the first clear-cut and easily classified mutant that he got was white eyes, and the fact that this was the first known sex-linked gene in a form where the male is heterozygous for sex changed the whole direction of the work especially since the attempt to induce mutations was a failure owing to the lack of efficient methods of detection and the relatively low frequency of occurrence of "visible" mutant types.

Nevertheless, the search for mutant types did lead to the careful examination of many individuals in the hope of finding new variants. It was not then realized that such a procedure would almost certainly lead to the accumulation of a whole series of usable marker genes but in fact it did do so, and the first great disadvantage of the material disappeared as Drosophila gradually came to have at least as many usable marker genes as any other organism.

As it turned out, the material had some unforseen advantages. When MORGAN began his work with Drosophila melanogaster it was known that the chromosome number was low though there were supposed to be five pairs rather than the actual four; but it was not realized how

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[3]I should like here to point out that in my "History of Genetics" (STURTEVANT, 1965, p.27) I did de VRIES an injustice, by mistranslating a passage in his second French paper of 1900. I quoted him as saying, about MENDEL's paper: "This memoir, very beautiful for its time, has been known to me and then forgotten." It should have read".....has been misunderstood and then forgotten." There is no implication that de VRIES had seen the paper earlier, and I made some unjustified inferences from my mistranslation.

convenient this low number was to prove. As the work progressed,
the cytological study of the material became more important, but it
was difficult and discouraging because of the small size and lack
of visible detail in the metaphase chromosomes and in the meiotic
stages. Perhaps the most dramatic unexpected advantage of the genus
became apparent as a result of the analysis of the salivary gland
chromosomes in 1933. The first analysis was that of HEITZ and BAUER
on other Diptera, and in the same year PAINTER showed that Drosophila
was also favorable. The material was thus transformed from one of
the poorest and most difficult cytological objects to one of the best.
The resulting advances were quick and spectacular.

The early studies of Drosophila uncovered one property that was at
first felt to be something of a nuisance-namely, the absence of cross-
ing over in the male. This did somewhat slow down the early studies,
but the genetic techniques were soon adapted to it, and it is now
recognized as one of the most useful special properties of Drosophila,
since it makes possible the indefinite retention, use, and study of
whole chromosomes that would otherwise be likely to be continually
changed by crossing over.

There are, of course, other cases where what appeared to be a
disadvantage of the material has been exploited to the point where it
was recognized as an advantage. One of the most striking is that of
"endomixis," better called autogamy, in Paramecium aurelia, which
SONNEBORN has so extensively and successfully utilized as a research
tool.

I should now like to consider a few cases where wisely chosen
material has given results of great importance in the history of
genetics, with few major surprises due to special properties of the
organisms studied.

The first such example is that of MENDEL's peas. The advantages,
known to MENDEL, were that numerous plants could be grown in a rela-
tively small space; that crosses could be made although self-fertili-
zation is the rule, so that F_2 could be produced by simply leaving
the flowers alone, without bagging or artificial pollinating; and
that numerous distinct true-breeding strains were available, 34 of
which he tested for constancy before he began his crosses.

The paper is remarkably complete. The needed tests were all
carried out, and there were no loose ends left. Here MENDEL was lucky,
since his letters to NÄGELI show that, in the year after the work was
completed, the ravages of the pea-weevil made it impossible to grow
peas successfully at Brünn.

It appears from his letters to NÄGELI that MENDEL himself studied
maize, which "behaved exactly like Pisum." In the 1890's it was stu-
died by CORRENS and by de VRIES, both of whom were intrigued by the
inheritance of endosperm characters-which each separately worked out.
Both gave Mendelian interpretations in 1900. But the extensive use
of the material came later, in this country, with the work of SHULL
and of EAST and EMERSON, and their respective students.

It appears that these later choices of the material were influen-
ced chiefly by two peculiarities of maize: the fact that the male and
female inflorescenses are separate, and the fact that it is an impor-
tant crop plant. The first fact meant that large-scale controlled
pollinations (either crosses or selfings) were more feasible than with
other material then in use. The second fact meant that the techniques
for growing large numbers in the field had been worked out; that large
numbers of inherited differences were available; and that technical
and financial support for the work could be found.

I am not going to elaborate on the further history of maize
genetics, which two of the participants in this symposium are so much
more competent to discuss, as are several members of the audience. I

should like to point out, however, that it seems to me that the element of luck has played little part in the maize story. It has come about as a result of a wise choice of material and its exploitation by a group of gifted and hard-working investigators.

I certainly do not want to give the impression that the study of maize has been simply a dull grinding out of results that could be largely foreseen. It hardly needs saying that it has been an exciting story, full of the surprises that are the spice of a research man's life. But, I think, these surprises have not, in general, often arisen from unforeseen special properties of the maize plant itself.

One of the outstanding students of maize was, of course, L. J. STADLER, in whose honor this meeting is being held, and he was also responsible for another striking example of a wise choice of material for the study of a particular problem. I refer to his use of barley (STADLER 1928) for his original study of the effects of radiation on mutation. The great advantage of this object was that each of the several stalks of the mature plant was represented by a single cell in the irradiated seeds, so that induced recessives could be recovered in the next generation by selfing individual stalks. The absence of such a recessive from the progeny of the other stalks of the same plant identified it as induced, and served as an automatic control.

The next example that I should like to discuss is that of Neurospora. The work of DODGE (1927) showed that the products of meiosis, the ascospores, were linearly arranged in the ascus, and could be dissected out in order, thus leading to the recovery of all four products, and to a distinction between the first and second meiotic divisions. Further, the nuclei of the plants grown from the ascospores were haploid. These properties made the material very useful for studies of segregation, recombination, and crossing over, and such studies were carried on by LINDEGREN, DODGE, and others with great success. There were, however, two serious difficulties inherent in the material. The dissection of the ascospores from the asci is a very difficult and laborious business, which few people have the skill and patience to carry out on a large scale. The other difficulty was that the plant turned out to be a difficult and unsatisfactory cytological object.

Meanwhile the physiological work of ROBBINS and others showed that Neurospora could be grown on a simple chemically defined medium. It was this property, together with its genetic advantages, that led BEADLE and TATUM (1941) to choose it for their experiments in bio-chemical genetics-the spectacular success of which is too well known to need elaboration here. The point I wish to make is that this was a striking example of a wise, rather than a lucky, choice of material.

As was pointed out above, Drosophila may produce rather more than 20 generations per year, whereas an annual plant usually produces one, or sometimes two. This difference results in a difference in pro-cedure. In the design of experiments the Drosophila worker does not hesitate to use a few extra generations if they will make his experi-ment more elegant or more conclusive-or even make it possible.

In the case of bacteria and bacteriophage there is a comparable jump. It would be possible to produce more than 20 successive genera-tions here while Drosophila was producing one-but this is not prac-tical, since it would get the experiment out of phase with the investigator's daily rhythm, and would leave him no time to plan and analyze his experiments, or even to eat and sleep. In practice, about a 10-fold speed-up occurs; but owing to the haploid nature of the material, and the fact that segregation immediately follows mating, one generation is, for most purposes, equivalent to two generations of a diploid higher organism. That is to say, the speeding up in going from Drosophila to bacteria or bacteriophage is about the same as in going from an annual plant to Drosophila.

This again results in a difference in research methods, since the duration of a generation is no longer a limiting factor in experimental design.

If one starts from the position in an annual plant and applies this same factor of rather more than 20 in the opposite direction, he finds himself at the generation interval of another important genetical object, man. Here again this jump has important consequences for research methods.

Fifteen years ago I wrote (STURTEVANT 1954), "Man is one of the most unsatisfactory of all organisms for genetic study. The time interval between successive generations is long, at best individual families are too small to establish ratios within them, and the test-matings that a geneticist might want cannot be made. Obviously, no geneticist would study such a refractory object, were it not for the importance that a knowledge of the subject has in other fields."

This statement irritated some of my friends-and rightly so. I was thinking only in terms of the methods of study used with other organisms, and was forgetting the obvious advantages of man. For no other organism do we have such detailed and extensive knowledge of structure and its variability, of embryology, evolution, pathology, behavior, biochemistry, geography, and population structure. Even in 1954 I should have remembered that these advantages had led to major advances in basic genetics, exemplified by the work of GARROD in biochemistry, of LANDSTEINER and his followers in immunology, and of BERNSTEIN and others in population genetics, to name only a few examples. Since 1954 there has, of course, been a rapidly increasing flow of such basic advances made with human material.

In this account I have put a good deal of emphasis on the element of luck in the choise of material for study. Should we then conclude that the choice of material is simply a gamble, and unknown properties may either block the project or make it more successful than could be foreseen? Obviously this conclusion is not justified-though it is not possible to wholly eliminate the element of luck.

The more information one can gather about the general properties of a proposed research object, the better is the chance of a wise choice-which is one of the best reasons for a broad training and the development of skill in the use of a library.

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Dr. Sturtevant in a happy moment at the Symposium.

Dr. Anderson, Mrs. Sturtevant, Dr. Sturtevant and Dr. Coe at the reception.

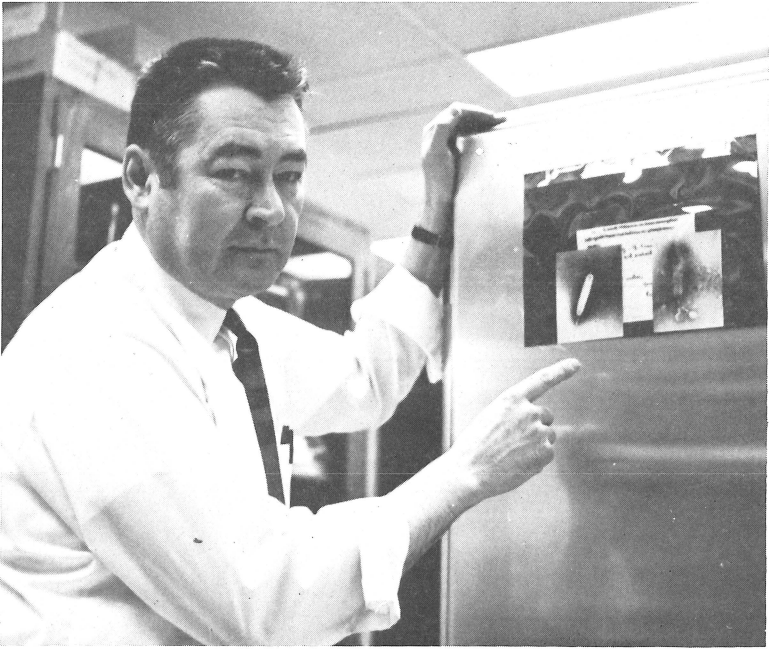STADLER SYMPOSIA VOL. 1 and 2 (1971)

From left to right: Dr. Anderson, Dr. Sturtevant and Dr. Stern, the
three men who made the most fundamental discoveries in
recombination and the mapping of genes.

From left to right: Dr. Sturtevant, Mr. R. Athwal, Mrs. Sturtevant and Dr. Doyle.

Dr. H. P. Riley (left)with Dr. E. R. Sears(right).

Dr. Doermann lecturing.

From left to right: Dr. Gilmore, Dr. Kikudome, Dr. Fogel, Dr. Goldman.

The participants of the Second Stadler Genetics Symposium in front
of the Fine Arts Auditorium. In the foreground from left to right:
Beadle, Sager, Peacock, Fogel, Rick, and Margulis, the six speakers.