Magellanic Clouds, all the data presented here combine to show that the rate of processing interstellar material through stars is less for the small Magellanic Cloud than for the Galaxy. This fact is in agreement with the low metal content inferred from the other available data. Most encouraging of all, however, is the fact that, so far, results on the Magellanic Clouds confirm the picture presented in the beginning of this article for our own Galaxy. We must expect in the future, it seems, that wherever we encounter low densities we will encounter stars of low metal content. High-density regions produce stars of high metal content, and therefore the stellar content can be quite different from galaxy, and can even be different from region to region within one extragalactic system.

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Poliomyelitis Immunization

Mass use of oral vaccine in the United States might prevent definitive evaluation of either vaccine.

David Bodian

The apparent unfolding of two unprecedented phenomena in the field of poliomyelitis this summer in the United States highlights the problem of policy making with respect to the use of killed poliovirus vaccine and live oral attenuated poliovirus vaccine. Unfortunately, widespread misconceptions concerning the potentialities of both vaccines, published in scientific journals and in the lay press, have made policy making by medical and public health agencies difficult, if not dangerous. An example is the Summary Statement of the Council on Drugs, American Medical Association, concerning the present status of poliomyelitis vaccination in the United States—a statement recently approved by the House of Delegates, AMA, which has received wide publicity (*1*). This document contains assumptions concerning the effects of killed and oral attenuated poliovirus vaccines which in some instances are unproved, and in others have been proved to be erroneous. In addition, the document does not present an adequate picture of the present status of poliomyelitis immunization in this country, at least as far as our major source of information is concerned, the Surveillance Reports of the U.S. Public Health Service.

The first of the phenomena in question is the new order of magnitude of reduction of incidence of paralytic poliomyelitis in the United States. At the date of writing, the absence of the early summer seasonal rise of cases constitutes a phenomenon unknown in this country since epidemic poliomyelitis began to take its heavy toll in 1916. The second phenomenon is the indication this summer that the dissemination of poliovirus types I and II has been radically reduced in the country as a whole. The only reasonable explanation for these phenomena is the ecological effect of the killed poliovirus vaccine program, instituted only 6 years ago.

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Proposed Oral Vaccine Program

By far the most serious step taken by the AMA Council on Drugs has been to propose that a mass vaccination program, involving previously vaccinated as well as unvaccinated individuals, is needed in this country in order to eliminate poliomyelitis as a significant public health problem. Whether poliomyelitis is now a significant health problem in the United States is debatable in itself, but the Council also appears to have overlooked the fact that there is not available enough oral attenuated poliovaccine of all three types to back up this proposal of the AMA at this time, and that the proposal thus contains the seed of futility and embarrassment. In a field where public disappointment has been more frequent than necessary, a premature proposal is worse than none.

Moreover, there are many with long experience in this field who do not feel that mass immunization programs with oral poliovirus vaccines are desirable in this country at this time, even if such vaccines were available. In view of the fact that paralytic poliomyelitis has been eliminated as a major public health problem with the use of inactivated poliomyelitis vaccine, and that residual case incidences are in the range of what may be an irreducible minimum, it would appear sensible to await definitive results of programs with oral attenuated vaccines in other countries rather than to superimpose a new program upon a currently successful one. Proposals for country-wide mass vaccination programs appear to ignore the fact that we do not as yet have defini-

tive analyses of the extent of public response and of results of previous oral-vaccine trial programs in communities in this country, such as Cincinnati, Ohio; Dade County, Florida; Harrisburg, Pennsylvania; and Allegheny County, Maryland. Such analyses are essential before it can be decided whether the community effort required in a mass nationwide trial would be consonant with the results to be expected.

Most of all, little thought has been given to the implications of the fact that the field use of even licensed products, such as vaccines, is really part of the process of verifying a scientific hypothesis regarding safety and efficacy. The use of a product in hundreds of thousands, or millions, of human beings introduces an order of magnitude of testing which far exceeds the sensitivity of animal tests or preliminary small-scale human trials. Not only is the order of magnitude different, but new and unforeseeable variables are almost always introduced when large-scale use by human beings follows apparently favorable results in preliminary tests.

The licensing of a product, therefore, does not eliminate the need for further observation of results or for final evaluation. In a sense the public, lay and medical, retains an important stake in ascertaining whether the inactivated poliovirus vaccine program, which represents an enormous investment of devoted effort, is successful, and to what degree. The proposed "change-over" to mass vaccination with oral vaccine would eliminate the possibility of a definitive evaluation of either program and therefore can truly be said to be unscientific or antiscientific in its disregard of the importance of verification.

"Change-over"

The AMA's Reference Committee on Public Health has assumed that a "change-over from Salk vaccine to oral vaccine" is inevitable. However, in a free society it can be safely predicted that if two vaccines are available, both will be used. For this reason the effect of a "change-over" requires critical examination in the light of the inevitable confusion which will result unless the proper role of each type of vaccine is accurately assessed, and unless the importance of evaluating each type is recognized.

A grand strategy of poliomyelitis immunization in this country should be firmly based upon established scientific principles, and yet must anticipate the unexpected. With the inactivated vaccine the unexpected crises, all of which followed the successful field trial of 1954, were the Cutter incident in 1955; difficulties in inactivation in 1955; inadequate potency of the type I and, especially, the type III component, in 1956 to 1958; false positive results in the monkey safety tests due to latent neurotropic virus infections in test animals in the period 1954 to the present; and a series of problems arising from the isolation of a large number of simian viruses from the tissue cultures of monkey kidneys used for production of vaccine virus and for safety testing. All of these problems were surmounted through a cooperative scientific approach by industry and by the National Institutes of Health and its scientific advisers. All affected the potential supply of vaccine and the willingness of industry to continue production.

Three important crises have already arisen in the live-virus vaccine trials. The first involved evidence implicating one widely used trial vaccine as the cause of cases of paralytic poliomyelitis (*2*). The second involved the discovery that a hitherto undetected simian virus was present in experimental vaccine lots (*3*). The third, and as yet unresolved, crisis pertains to doubts concerning the genetic stability of one of the type III oral poliovirus vaccine strains (*4*). Yet the American Medical Association has approved, for the first time, an unlicensed product still being tested and has recommended its mass use in the United States. The need for such haste at this time, when poliomyelitis incidence in the United States is at an all-time historic low, is far from apparent. It is difficult to escape the suspicion that the policy-makers in the American Medical Association have been misled by the widely held misconceptions concerning the evidence relating to the effects of both types of vaccine.

Areas of Controversy

This unfortunate situation, from the point of view of medical science, has been accentuated by the fact that promotional statements by at least one manufacturer concerning oral live attenuated poliovirus vaccines have far outstripped scientific evidence but have been widely disseminated, quoted, and even accepted by responsible investigators. Apart from the argument that it is obviously easier to administer, the most cogent arguments advanced in favor of oral attenuated poliovirus vaccine, as contrasted with inactivated vaccine, are that the oral vaccine (i) is more effective and provides more lasting immunity; (ii) has superior capacity to combat epidemics in progress; (iii) has superior capacity to inhibit virus excretion in immunized persons; and (iv) can eradicate polioviruses from large areas, including continental masses, if used in simultaneous mass programs over a short period of time.

Despite the many field trials of oral vaccines in many countries since the pioneering work of Koprowski and his colleagues in 1952 (*5*), every one of these points remains controversial, because of the lack of conclusive scientific evidence.

It may be appropriate to comment on specific statements of the report of the Council on Drugs, AMA, in relation to the foregoing points, which are subject to challenge from the scientific point of view.

The Council asserts that inactivated vaccines have reduced the risk of paralytic poliomyelitis by 80 percent or more, yet the best available information from U.S. Public Health Service Surveillance Reports indicates a higher than 90 percent efficacy in individuals who have had the now recommended four doses of inactivated vaccine (*6*). A serious step such as a "change-over" to oral vaccine ordinarily would be expected to be preceded by adequate evidence of equal or superior efficacy of the new vaccine. No such evidence exists.

Another statement repeats an old but as yet unproved speculation. The Council on Drugs states: "The persistence of immunity induced by the oral poliovirus vaccines may be of much longer duration than is the case with Salk vaccine; and, in fact, the persistence of immunity may conceivably approach that induced by natural infection in type, degree, and duration." Scientific evidence for such an assumption, however reasonable it may sound, does not yet exist. Substantial evidence of good persistence of antibody levels due to killed vaccines has, however, been reported (*7*). The balance of evidence indicates that the persistence of an antibody response is largely unrelated to

the nature (live or killed virus) of the poliovirus antigen.

The capacity of any vaccine to combat epidemics in progress is so difficult to measure that it may seem futile to challenge the concept that oral poliovirus vaccines are tailor-made for the purpose. Neither the oral live poliovirus vaccine nor the inactivated vaccine has been given an adequate test. In view of the rapid antibody response to large doses of inactivated vaccine reported by Barnett and Baron (*8*) and also observed, though not reported, by me, it seems remarkable that large doses of inactivated vaccine have thus far not been used in early stages of expected outbreaks of poliomyelitis. Parenteral immunization would not be inhibited by the interfering effects of the common summer outbreaks of alimentary virus infections, some of which are known to inhibit "takes" with the oral live virus vaccine.

In relation to the possible effect of oral vaccines in eliminating poliovirus carriers, the Council states: "Natural infection [the context implies oral attenuated as well as naturally occurring polioviruses] not only confers lasting protection against paralytic attack following subsequent reinfection with the same type of poliovirus, but it also renders such individuals relatively incapable of spreading the virus to contacts." It is, however, well known that persons vaccinated with oral vaccine do spread virus to contacts soon thereafter. Subsequently, there is a period of resistance to alimentary reinfection, but there is no evidence that oral attenuated polioviruses are able to confer more than temporary alimentary resistance to naturally occurring poliovirus strains. Adequate studies of long-term resistance are lacking.

In contrast to the statement of the Council quoted above are its categorical statements denying any capacity of the killed poliovirus vaccine to affect the spread of poliovirus. "Thus, although Salk vaccination can be expected to reduce greatly the relative risk of paralytic poliomyelitis among adequately vaccinated individuals, the procedure cannot be expected to have a great effect on the incidence of alimentary poliovirus infection among either vaccinated or unvaccinated individuals, and therefore the eradication of the disease as a community health problem." Also, "It [the inactivated vaccine] does not protect against poliovirus infection in the alimentary tract." These statements ignore experimental evidence which led to the prediction of an effect of killed vaccine on virus excretion and spread (*9, 10*), as well as evidence developed in the field in the past few years (*11, 12*). The sweep of the statements is especially incomprehensible since the evidence is clear that even low levels of serum antibody are capable of preventing throat infections with polioviruses in human beings (*11*) as well as in chimpanzees (*10*).

Current Incidence

In addition, at the present time, as mentioned before, there appears to be a reduction in the incidence of paralytic cases beyond the effect to be expected from protection of vaccinated individuals alone, suggesting an effect of the killed poliovirus vaccine program on the spread of virus. Moreover, this year the startling reversal of the frequency of isolation of type I and type III polioviruses at least raises the question of immunological pressure on the formerly dominant type I virus population as a result of mass immunization with killed poliovirus vaccine. It is well known that the type II component of killed poliovirus vaccine is of such high potency that individuals receiving a series of three or more doses may have high antibody levels exceeding levels resulting from a natural infection. There is not only experimental evidence that high serum antibody levels are capable of preventing throat infections with virulent poliovirus and of inhibiting fecal virus excretion, but evidence from the field that type II poliovirus has virtually disappeared from the United States. A similar effect may be operating to reduce the amount of type I virus in the United States, whereas an effect on type III virus may be delayed by the poor potency of the type III component during the period 1956 to 1958.

Role of Oral Vaccine

In contrast to developing evidence that killed poliovirus vaccine can, and perhaps is, eliminating poliomyelitis as a public health problem, and is drastically reducing the spread of polioviruses, is the widely held notion that only a mass program of oral poliovirus vaccine administration can accomplish such a feat. I am not aware of any evidence that can remove this notion from the sphere of speculation and controversy, at least as far as the United States is concerned. First of all, a mass vaccination program throughout the country is not likely to be acceptable to health officers of all the states or to the public, especially now that the need for such a formidable program is in doubt, and in the absence of near-total acceptance, the possibility of increasing rather than decreasing the spread of poliovirus exists. If the AMA proposal for mass immunization with oral vaccine were accepted, in the face of the extraordinarily low incidence of poliomyelitis now observed, a subsequent further decrease in poliomyelitis would prove nothing, and an increase in poliomyelitis, for whatever reason, would serve as a boomerang, since it would be impossible to certify that such an increase was not due to reversion of vaccine strains to a virulent form, however doubtful one might be that this was the case.

Since there is no evidence of diminution of immunity due to inactivated vaccine in the 8 years since it has been used on a large scale, the proposal of the American Medical Association to include previously immunized as well as unvaccinated individuals in mass oral vaccination programs therefore seems quite unnecessary if not rash. Mass immunization programs with oral vaccine are entirely reasonable in nonimmunized countries and communities. In this country, at this time, it seems to me that the use of the oral vaccine can only be justified in nonvaccinated individuals who choose this vaccine in preference to inactivated vaccine. In a previous review of this problem I phrased the proper role of the oral vaccine in this country as that of an additional tool in a "mopping-up" operation, to attempt to reach those persons who have not been reached by the inactivated-vaccine program (*13*). Evidence that the more easily administered oral vaccine actually has succeeded in reaching a significant number of those who have failed to take advantage of the killed-virus vaccine is still to be revealed by studies of trials in communities in the United States. It would not be surprising if analysis of experimental trials of oral vaccine in communities in this country were to reveal that the greatest response to an oral vaccine program will come from those families who have already responded to killed-virus vaccine and are therefore least in need of protection against poliomyelitis.

Summary

I would summarize the foregoing discussion by asserting, first, that the superiority of the live oral attenuated poliovirus vaccines over the inactivated vaccines now in use remains to be demonstrated, except for convenience of administration. Second, the proposal to introduce live oral poliovirus vaccine by means of country-wide mass immunization programs is irresponsible in the sense that such a procedure would eliminate the possibility of a definitive evaluation of either vaccine in this country, and moreover is unlikely to accomplish more than can be accomplished by a more conservative approach. Third, even after licensing, a new vaccine product must be considered to be on trial, since new variables enter the scene when large-scale manufacture and large-scale use begin. In this connection it is of importance that the margin of safety of live-attenuated-poliovirus lots now in production is not large, as measured by the only laboratory test available—neurovirulence in monkeys. In comparison with unacceptable trial strains, about which questions of safety have been raised after field use, the acceptable strains have measurably less neurovirulence, but the differences are not great, and approval of each lot will require careful scrutiny for evidence of even slight degrees of reversion in neurovirulence during production.

Finally, there is a place for both types of vaccine in the control of poliomyelitis throughout the world. How and where each type should be used is a scientific problem which can best be resolved with careful assessment of all the available evidence concerning vaccine characteristics in relation to the ecology of poliomyelitis. From the point of view of a scientific evaluation of the results of the present vaccination program in this country, it appears that a quip I made in 1960 (*13*)—we may now have too many poliomyelitis vaccines!—has come home to roost.

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Science and the News

Congress Presses Funds on National Institutes of Health

Congress has been force-feeding medical research through the National Institutes of Health for a decade with funds that now make up fully half of all dollars supporting biomedical studies in this country. The practice continued last week as the Senate and House compromised by appropriating $738 million for NIH for fiscal 1962, 26 percent more than the Administration asked and 34 percent more than NIH had last year (see Table 1). The money bill was typical of congressional action since 1953, when Congress appropriated $59 million; since then it has provided an average of 25 percent above Administration requests, and 33 percent above its previous year's appropriation.

This generosity—congressional health champions justify it as an "investment" rather than "expenditure"—has caused considerable uneasiness, largely on two grounds: some regurgitation in the medical field itself, as heard in sporadic reports that NIH officials are "out beating the bushes" for ways to spend their "embarrassing riches," and the alarming casualness with which Congress opens the federal purse strings. This year two more factors made its actions rather striking: the apparent failure of the new Democratic Administration to recapture control of the NIH budget by anticipating and heading off the predictable congressional increases pushed by Representative John Fogarty and Senator Lister Hill, both Democrats; and the expected $5 to $6 billion national deficit which caused President Kennedy to explicitly ask Congress "to refrain from adding funds or programs, desirable as they may be," in order to preserve fiscal integrity.

Congress begins action on NIH budgets in the House health subcommittee headed by Fogarty, a former bricklayer from Rhode Island. The House usually raises the request a few millions or tens of millions. Then the Senate, through a subcommittee chaired by Senator Hill, son of a small-town doctor from Alabama, adds a whopping hundred million or so. Both bills pass their respective bodies after considerable debate. A compromise between bills is reached in conference, and now with cursory debate, both houses adopt it. The numbers this year were as follows: Kennedy asked $583 million (up $35 million from fiscal 1961 appropriations); the House gave $641 million; the Senate gave $835 million; the 50-50 compromise was $738 million.

That the increases were planned before Congress held extensive hearings (2000 pages of testimony came fourth) is seen in an exchange on the first day that Fogarty's committee considered the NIH budget. Lead-off witness was the surgeon general of the Public Health Service, Luther L. Terry (named, incidentally, after Senator Hill's father). NIH is part of the health service.

Fogarty: "If the committee decided to increase the appropriation by $100