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THE PATENT SYSTEM: ITS ECONOMIC AND SOCIAL BASIS

STUDY OF THE SUBCOMMITTEE ON PATENTS, TRADEMARKS, AND COPYRIGHTS OF THE COMMITTEE ON THE JUDICIARY UNITED STATES SENATE EIGHTY-SIXTH CONGRESS, SECOND SESSION

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FOREWORD

This study was prepared by Victor Abramson, economic adviser to the U.S. Treasury Department, for the Subcommittee on Patents, Trademarks, and Copyrights as part of its study of the U.S. patent system, undertaken pursuant to Senate Resolution 240 of the 86th Congress. Covering a report actually prepared in 1947 for the Patent Survey Committee, a Presidential Commission appointed to examine the patent system, it is now being published for the first time, with minor revisions, in connection with the study program being conducted under the supervision of John C. Stedman, associate counsel of the subcomittee. It will be followed by a companion study, also prepared by Mr. Abramson, entitled "Patent Abuse—A Plan for Its Control."

The need for a thoroughgoing and realistic analysis of the economic forces that underlie the patent system has long been apparent, and the subcommittee has attempted to meet this need to some extent. Several of its studies and much of its inquiry have been directed to the economic workings of the system. These previous efforts to understand and analyze the economics of the patent system reached their peak with the publication earlier of our Study No. 15, prepared by Prof. Fritz Machlup, entitled, "An Economic Review of the Patent System." "The Patent System: Its Economic and Social Basis," by Mr. Abramson, provides a valuable addition to the literature on this subject. It takes on added significance in providing the economic foundation for the concrete proposals that the author makes in his companion study on patent abuse.

Mr. Abramson is well qualified by background and experience to deal with this subject. As a long-time economist with Brookings Institution he gave extensive attention to the role of Government in the economic life of the Nation, including its administration of the patent system. His work in this field culminated in his coauthorship of a landmark study entitled "Government and Economic Life." During World War II, he acted as an economic adviser to the Alien Property Custodian, in which capacity he devoted much attention to the administration of enemy-owned patents and patent rights seized pursuant to the Trading With the Enemy Act. These experiences made him a natural selection for the post of economic adviser to the Patent Survey Committee.

In publishing this study, it is important to state clearly its relation to the policies and views of the subcommittee. The views expressed by the author are entirely his own. While the subcommittee welcomes the report for consideration, its publication in no way signifies agreement with the statements contained in it. The publication does, however, testify to the subcommittee's belief that the study represents a valuable contribution to patent literature and is in the public interest.

JOSEPH C. O'MAHONEY,
Chairman, Subcommittee on Patents, Trademarks and Copyrights, Committee on the Judiciary, U.S. Senate.

September 8, 1960.

PREFACE

This report, together with a companion study, Economic Report No. 2, entitled "Patent Abuse—A Plan for Its Control," was prepared in 1947 for the Patent Survey Committee, a Presidential commission charged with the task of examining the patent system and suggesting appropriate measures of reform. It has been revised editorially and its legal citations brought up to date, but essentially the analysis and proposals are in their original form.

This report is designed to provide a frame of ideas for the specific measures of patent reform presented in Economic Report No. 2. While it may be separately read, in view of its limited purpose no effort has been made to cover exhaustively the history either of our own or other patent systems. Nor have other views of the theory of patents or their functions been systematically examined, although they have, I hope, been taken into account.

Throughout the preparation of both reports, I was greatly benefited by a number of enlightening discussions and many provocative suggestions from W. Houston Kenyon, Jr., counsel to the Patent Survey Committee. Mr. Kenyon also furnished a legal analysis of the patent system which formed the principal basis of the legal sections of Economic Report No. 2, and advice in phrasing the recommendations of that report so as to make them more intelligible to lawyers. I drew heavily on the extensive experience of Mr. P. J. Federico of the U.S. Patent Office to clarify in my own mind many questions which were troublesome to me. The Department of Justice, through the cooperation of the late Mr. Wendell Berge, head of the Antitrust Division, and under the direction of Mr. E. Houston Harsha, contributed valuable case materials.

I will have to take responsibility for the conclusions reached and the recommendations made.

VICTOR ABRAMSON.

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THE PATENT SYSTEM: ITS ECONOMIC AND SOCIAL BASIS

CHAPTER I

THE ROLE OF PATENTS IN A COMPETITIVE SYSTEM

A. EARLY ORIGINS

It may appear as a surprising fact that the English patents for inventions, which later furnished the model for our own patent system, first came to prominence as an instrument through which the Crown exerted national power to control industry and commerce. In an adapted form, patents survived the emergence of a system of competitive enterprise, and eventually counted among their advocates some of the leading writers in the liberal tradition. Today patents occupy an important role in every industrialized society which places any significant reliance upon private enterprise.

In England, patents grew to importance during the reign of Elizabeth beginning in the middle of the 16th century. At that time advances in the arts were infrequent and interchange of new ideas was slow. England was in many respects industrially less advanced than France and the Lowlands, and it appeared that the best opportunity to develop new industries and trades was to encourage craftsmen to migrate to England to teach their skills, and tradesmen to come for the purpose of opening up new commerce. Patents were used to provide such encouragement, and they were thus granted for "first importation" and for technology new only in England, as well as for "new inventions" in the narrower sense.

At the beginning, the chief problem was to break down the existing monopolies of manufacture and commerce held by the towns and guilds. Patents were used as a means of asserting national power to protect new workmen and traders coming in from abroad, and often merely granted to them permission to practice their arts or trades in the fields or territories then monopolistically controlled by local groups. As national power grew, however, and industry and commerce expanded, patents emerged as an instrument of industrial regulation. They came also to be used increasingly for revenue purposes, and as a means of bestowing personal favors, and they were extended to cover industries and trades already well established. Their use to encourage "invention," even in the sense of "first importation," diminished in importance, and their grant in monopolistic forms increased.

Opposition to patents arose from many sources in the latter part of the 16th century. The accumulation of capital and the influx of Protestant refugees representing a new source of labor brought pres-

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sure for greater freedom of enterprise. And there were outcries against the arbitrary and high-handed tactics of patentees and the high prices which many of them were charging for necessities. The towns and guilds, when they could not reach agreement with patentees, resented the latter's intrusion, but they were already declining in power. The sentiment grew that patents, far from encouraging enterprise, were proving a burden.[1]

As patents grew in number and came to be used for many purposes, the courts applied to them an important distinction under the common law. Those which were granted for new manufactures or for introducing new trades were held to be lawful, but those in industries or trades already established were declared contrary to the common right of every citizen to enter those fields as a means of earning a living.[2] The courts had no means, however, of preventing the issuance of unlawful patents and they remained common, and in many instances were successfully enforced, up to the enactment of the Statute of Monopolies (1624) in the reign of James I.

This statute provided that all monopolies before or thereafter granted should be "utterly void" and should be judged according to the common law. It exempted from its operation, however:

> * * * letters-patent and grants of privilege * * * of the sole working or making of any manner of new manufactures, * * * to the true and first inventor and inventors of such manufactures, which others, at the time of making such letters-patent and grant, shall not use, so as also they be not contrary to the law, nor mischievous to the state, by raising prices of commodities at home, or hurt of trade, or generally inconvenient. * * *

Patents for inventions thus for the first time received express legislative sanction in an act which sought to outlaw monopolies generally, and they have since that time enjoyed a favored position among monopolies.

Other forms of monopoly were not, however, wholly eliminated. The Statute of Monopolies did not deal with charters, and after its enactment, this latter form of monopoly grant continued for a long time to be employed for many of the purposes for which patents had been used.[3] They were particularly important in encouraging risky ventures such as settlement of the New World or the conduct of trade with distant lands then growing in volume.

In the limited role assigned to patents by the Statute of Monopolies, they flourished with the progress of the Industrial Revolution. The basic new inventions of that period gave a strong impetus to research, and from that time forward patent control of industrial technology formed a vital and universally accepted part of the economic scene. The vast increase in production potential which these inventions brought, and the improvements in transportation and communica-

[1] For excellent accounts of the early history of patents, see, William Hyde Price, "The English Patents of Monopoly," particularly at 3–46 (1906), and George Unwin, "The Gilds and Companies of London," 293–319 (1908).

[2] See the two famous cases of *Darcy* v. *Allein*, 77 English Reports 1260 (King's Bench, 1602), and *The Clothworkers of Ipswich*, 1 Alde. P.C. 6 (King's Bench, 1614); and discussion in William C. Robinson, "The Law of Patents," at 9–12 (1890).

[3] See Price, op. cit. supra note 1, at 36; George Unwin, "Industrial Organization In The Sixteenth and Seventeenth Centuries," ch. V (1904); and William Cunningham, "The Growth of English Industry and Commerce: Vol. II; The Mercantile System" (6th ed. 1925–29).

tion which followed, unloosed strong pressures for free access to the new opportunities which were then opening up. And the period between the middle of the 18th century and the middle of the 19th century saw the rise of a competitive economic system and the development of a social philosophy to support it.[4] But the grant of patents for inventions won the firm support of many of those who shaped the thought of the times in favor of unhampered freedom of enterprise.[5]

In our own country the history of patents followed closely that in England. During the colonial period capital was scarce and enterprise extremely hazardous, and patents were granted, though infrequently, for new industries based on known technology as well as for new inventions.[6] The attitude toward patents was colored, however, by their abuse in the hands of the Crown. There was little discussion of the patent question in the Constitutional Convention. But a proposal for the adoption of a patent system received unanimous support,[7] and it was provided in article I, section 8 of the Constitution that Congress should have power—

> * * * to promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries.

In the early years of our national history the need for skilled artisans was great. We were in the same position in which England had been two centuries earlier. There was a particular desire to secure knowledge of the new technological developments then taking place in England. This was difficult because export of the new machines was closely controlled as was information concerning the inventions themselves. Those who succeeded in leaving with essential drawings, or who could duplicate these machines from their own knowledge, found a profitable market for their information in this country. There were suggestions that the Government should provide bounties to encourage the immigration of these men, and tariffs to protect the industries which they built up.[8] And Washington in his first inaugural address urged "the expediency of giving effectual encouragement, as well to the introduction of new and useful inventions from abroad as to the exertion of skill and genius at home." But our patent system, following the pattern of the Statute of Monopolies, limited these grants strictly.

The act of 1790,[9] which established in all essentials (except examination procedure which was not added till 1836) our patent system

[4] See, for example, Paul J. Mantoux, "The Industrial Revolution in the Eighteenth Century" (Rev. ed. 1947); Eli F. Heckscher, "Mercantilism," 2 vols. (1935); and Heckscher, "Mercantilism," Econ. Hist. Rev., 44–54 (1936).

[5] See, for example, Jeremy Bentham, "The Rationale of Reward," at 92 (1825); and John Stuart Mill, "Principles of Political Economy," book V, ch. X (1848).

[6] See, for example, Victor S. Clark, "History of Manufactures in the United States," vol. I, 1607–1860 (1929).

[7] See Walton Hamilton, "Patents and Free Enterprise," TNEC Monograph No. 31, at 23–27 (1941).

[8] See, for example, Alexander Hamilton, "Report on Manufactures," (1791), particularly at 42–43 and 60–62, as reprinted in S. Doc. No. 172, 63d Cong., 1st sess. (1913).

[9] Compare B. E. Lanham and J. Leibowitz, "Classification, Searching, and Mechanization in the U.S. Patent Office," 40 Jour. Pat. Off. Soc'y 86–87 (1958), which describes these early laws as follows:

"The 1790 act required as a condition precedent to the grant of a patent that satisfactory evidence of novelty, utility, and invention be established, which requirements are in existence at the present time. A 'prior art search' was thus necessary, and since it was apparently limited to the relatively few patents issued by American Colonies and States as well as among books on mechanics and industrial arts, no need for classification of the searchable material was then necessary.

"The first U.S. patent was issued on July 31, 1790, and the total was 57 on February 21, 1793, when a new Patent Act replaced the earlier one. The new act substituted a 'registration' system for the 'examination' system, and that unfortunate replacement continued until the act of July 4, 1836, was passed."

as we know it today, provided that, upon petition, any person could secure the grant of a patent, but only if he had—

> * * * invented or discovered any useful art, manufacture, engine, machine, or device, or any improvement therein not before known or used * * * [which was deemed] * * * sufficiently useful and important * * *.

The powers conferred under patents were to comprise—

> * * * the sole and exclusive right and liberty of making, constructing, using and vending to others to be used, the said invention or discovery * * *.

And no express obligations concerning use or licensing were imposed beyond the requirement of disclosure:

> * * * so particular * * * as not only to distinguish the invention or discovery from other things before known and used, but also to enable a workman or other persons skilled in the art or manufacture * * * to make, construct or use the same, to the end that the public may have the full benefit thereof, after the expiration of the patent term * * *.

The grant of patents even for new inventions was not, however, without opposition. Madison, in 1788, raised the question whether it might not be wise to reserve the right to abolish patent grants at a price.[10] And Jefferson challenged the claims that these grants were supported in natural law, which at that time was looked to as the foundation for all forms of property right:

> If nature has made any one thing less susceptible than all others of exclusive property, it is the action of the thinking power called an idea, which an individual may exclusively possess as long as he keeps it to himself; but the moment it is divulged, it forces itself into the possession of every one, and the receiver cannot dispossess himself of it. Its peculiar character, too, is that no one possesses the less, because every other possesses the whole of it * * *. Inventions cannot, in nature, be a subject of property. Society may give an exclusive right to the profits arising from them, as an encouragement to men to pursue ideas which may produce utility, but this may or may not be done according to the will and convenience of the society, without claim or complaint from anybody.[11]

When he had gained experience in the administration of the patent statutes, however, Jefferson came eventually to favor the grant of patents for inventions.

Two principal factors account for our adoption of a patent system at a time when public distaste of monopoly was strong. An inventor's right to retain his discoveries in secrecy was generally acknowledged to be supportable in natural law.[12] At the same time, the public dis-

[10] See "5 The Writings of James Madison," at 274 (Hunt ed. 1900–1910).
[11] Letter of Aug. 13, 1813, reproduced in "The Writings of Thomas Jefferson," vol. 13 at 333–334 (Mem. ed., 1904).
[12] William Robinson, op. cit. supra note 2, at 38. As Mill stated "* * * I have seen with real alarm several recent attempts * * * to impugn the principle of patents * * * which, if practically successful, would enthrone free stealing under the prostituted name of free trade, and make the men of brains, still more than at present, the needy retainers and dependents of the men of money bags." J. S. Mill, "Principles of Political Economy," book V, ch. X, p. 549 (5th London ed., 1877).

closure of inventions was thought of as socially beneficial. Through disclosure, duplication of inventive effort could be reduced, there would be inspiration for new lines of research, and when the patent expired all might use the invention freely. It had been established at common law that these benefits of disclosure could justify the public in granting patents, and the same view took hold in this country.[13]

The other consideration which served as the basis for our patent system is summed up in the Constitution: "to promote the progress of science and useful arts." In a sense, this is the more fundamental thought, since it implies a continuing need to confer unusual private powers in order to foster invention. While the rationale of our patent system was not fully developed at the time of its founding, the essential factors which constitute its economic and social justification have not changed. What has changed is the precise form best suited to our present needs. Before undertaking a detailed examination of experience under our patent system, it will be helpful to indicate in general terms the economic and social considerations by which its performance must be judged.

B. ECONOMIC AND SOCIAL CONSIDERATIONS

It is clear that the patent monopoly has from the beginning occupied a unique role in our system of private enterprise. In other fields of endeavor, we have relied for the satisfaction of our wants either on competition or on regulated monopoly. Patents are the sole instance of publicly conferred, yet virtually unregulated, private powers of exclusion. This distinctive phase of our public policy reflects essentially the fugitive character of inventions, which makes their private control difficult; and the absence of natural tendencies toward monopoly, which makes their close public control unwarranted.

Inventors confront problems in their efforts to derive personal benefits from their labors which differ materially from those which face other producers. Other producers can effectively control the use and disposition of their products through mere possession, and additional supplies will be costly to reproduce. Inventions, however, consist only of ideas which rivals can often acquire without cost to themselves, perhaps through simple inspection of a marketed product. Where this occurs, no one will be under any constraint to take invention costs into account in setting production rates or selling prices of products which embody or utilize the invention. As a result, output and prices will fail to reflect invention costs, and no one will be able to gain a return for the effort which has gone into the invention. To put the thought another way: the "supply" of an invention, once conceived, is difficult to control, and ordinarily can be expanded at negligible cost and without pertinent limit. By contrast, the supply of other products can readily be limited, and their prices are much more responsive to their costs. This difference in supply conditions, which stems from the fugitive nature of inventions, lies at the heart of the distinc-

[13] William Robinson, op. cit. supra note 2, at 58-66.

tive treatment which inventions have been accorded in our public policy.[14]

The problem of public policy is to determine the desired supply of new inventions, and the safeguards to inventive effort which must be erected in order to insure that supply. A limited number of new inventions is assured to society even without any special stimulus. Accident or observation unrelated to deliberate inventive effort will provide some inventions. Others will be produced by those with an "instinctive bent" for invention, or who find sufficient reward in the joy of the effort or the satisfaction of accomplishment.[15] Purely economic factors will also support some inventive effort without assured safeguards. Where changes take place in the relative prices or availability of labor, materials, or capital, it may become profitable for business firms to undertake adaptations not requiring costly research, designed to economize the scarce or costly factor or utilize more effectively the plentiful or cheap factor.[16] The obsolescence of existing equipment may spur a search for means to reduce losses. And the competitive advantages which lie in market priority, or the hope of at least temporary secrecy, may lead to a degree of inventive effort.

By any social test, however, the community's needs for new industrial technology are unlikely to be satisfied through such incidental efforts or incentives. If, in determining adequacy of supply, we apply to inventions the same test that we do to most other products under our free enterprise system, we will measure performance according to cost-price relationships. By this standard, it will be in society's interest to assure, as a minimum, the supply of any invention whose costs of creation can be recovered through savings made possible in manufacture, or through the profitable sale of a new product. So long as the hazard remains that the profit potentialities of inventive effort may be dissipated through competitive use of the invention, this social aim cannot be achieved.[17] For some with inventive skill will be attracted to this work only if their prospective incomes appear as great as in other fields open to them; while others will be more likely to direct their inventive activities to the satisfaction of social needs if they can see in this manner a way of increasing their incomes.[18]

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[14] Fritz Machlup contends that the difference between material and intangible goods has "nothing to do with the problem" of Government intervention to support the private value of inventions. Machlup, "An Economic Review of the Patent System," Senate Patent Study No. 15, at p. 58 (1958). It is his view that: "What really matters is the difference between 'variable' and 'sunk' costs." "Sunk" costs, however, are common to nearly all industrial and commercial ventures. Where inventions differ from most other forms of production is precisely in their intangible nature. It is because of this fact that in the short period the price-determining, variable costs of expanding supply are negligible, and in the long period there is no fixed investment ("sunk" cost) which requires replacement. These conditions do not prevail where "sunk" costs are embodied in tangible instruments of production, which are subject to attrition through use, are costly to reproduce, and the output of which is inherently limited and can easily be controlled. Professor Machlup appears to acknowledge these points in the illustrations which he himself refers to as "unrealistic," cited by him at p. 59 of his study.

[15] See Joseph Rossman, "The Psychology of the Inventor" (1931); S. C. Gilfillan, "The Sociology of Invention" (1935); and A. P. Usher, "A History of Mechanical Inventions" (1929, rev. ed. 1954).

[16] See J. R. Hicks, "Theory of Wages," at 121–130 (New York 1948); A. C. Pigou, "Economics of Welfare," at 412, 671–680 (4th ed. 1952); essay on "Invention", in Sir Josiah Stamp, "Some Economic Factors in Modern Life" (1929); and Hugh Dalton, "Some Aspects of the Inequality of Incomes" (1920).

[17] Professor Machlup contends that because of a "Headstart" inventors can make "some money" without patent protection. Senate Patent Study No. 15, supra note 14, at 59–60. He does not indicate, however, whether he believes this incentive would suffice to supply society with all the inventions whose social costs could be justified by their social usefulness. Indeed, he seems to despair of ever solving this problem, despite the fact that he deems it possible to determine the direction of socially desirable reforms (p. 80).

[18] See F. W. Taussig, "Inventors and Money-Makers" (1915); and Arnold Plant, "Economic Theory Concerning Patents for Inventions," (N.S.) Economica 30–51 (1934).

One caution must be expressed in applying this social test to inventions. It is valid only where conditions of demand and supply are in some degree competitive; or, if any significant degree of monopoly prevails, only where this control is subjected to some form of public regulation. In the course of this report, and in Economic Report No. 2,[19] we shall suggest limitations over the use of patents designed to achieve the maximum degree of competition, both in the provision and use of inventions, consistent with the social purposes of our patent system.

With these thoughts in mind, we may now examine the way in which a patent system works to provide a supply of new inventions, and its limitations as shown through experience. A patent conveys to an individual the power of exclusion over the use of an invention. With this power in hand the patentee is able to limit the commercial use of his invention, and so to preempt some part of the market value of products manufactured with its aid. Unavoidably, the use of other forms of capital, and of labor and materials, will be affected by this power of exclusion, because inventions make their contribution to social progress through improved effectiveness in the use of these other factors of production.

From the social point of view, patents are not an ideal means of encouraging inventive effort. They may come into the hands of firms which, technically, are less advantageously equipped than their competitors to use the invention. The patentee may have investments in competing technology or in competing lines of manufacture which make it temporarily unprofitable for him to employ an invention which his competitors would exploit immediately.[20] More fundamentally, patentees, since they enjoy a degree of monopoly power, are unlikely to exploit inventions to the extent warranted by their usefulness to society, and may be overcompensated in terms of their costs.[21] Production by any monopolist is likely to be at a lower level, and his prices higher, than would prevail if the industry were competitive. Moreover, the production policies of a monopolist are likely to leave some opportunities unexploited, thus forcing other productive resources into socially less useful lines of manufacture, or to work with inferior technology.

The actual strength of the monopoly represented by a patent, it should be said, is limited by the competing technology accessible to rival firms. A patent is granted on a technical and not a market basis. That is, the grant is for a scientific achievement, and the monopoly is confined to the advance made over the prior art. While the patentee is protected against "equivalents," this protection also is judged on a technical basis. Thus, marketwise, there may be close competition between patented inventions, or with unpatented technology. Insofar as this is true, the monopoly of an individual invention is socially of less consequence.

[19] "Patent Abuse—A Plan for Its Control" to be published at a future time.

[20] See Hicks, and Pigou, op. cit. supra note 16. The owner of several competing patents may even be able to survive competitively if he shifts from the use of a better to a poorer invention.

[21] However, even under the protection of a patent an inventor may be unable to recover the full social value of his invention, because of his inability to share in the benefits he creates for other inventors, or in the economies made possible in other lines of manufacture or distribution. See Pigou, op. cit. supra note 16, at 183–185.

The precise degree of monopoly power which should be assured under patents, in order to secure a socially adequate supply of new technology and products, is difficult to judge. Inventive activity takes place under conditions of greater uncertainty than are found in most lines of production, since inventors cannot know beforehand either the effort required to reach a successful result, or the prospective commercial value of the outcome. This risk may attract those who prefer a gamble over a sure thing, even though the prospect of loss may be greatly out of proportion to the prospect of gain.[22] Others, however, may require the hope of high reward, if their reluctance to undertake such risks is to be overcome. The exact effects of patents are not predictable. High profits on successful inventions may draw so many to inventive activity that returns generally will fall below those in less hazardous enterprise,[23] with a consequent misdirection of productive resources. The high returns occasionally experienced, however, may do no more than generate self-limiting competition which provides a supply of inventions while holding profits generally in check.[24]

Despite these hazards and limitations of a patent system, the choice of means to foster invention remains a matter of alternatives. The other choices—publicly conducted or publicly subsidized research—appear less satisfactory. Apart from the inventions designed directly to satisfy public needs,[25] the production requirements of private industry and private consumer wants constitute the proper guides to inventive effort. Where demands are private, a more vigorous and sensitive adaptation to need is more likely through private incentives than through direct public provision.[26] There are, of course, fields of scientific inquiry guided neither by commercial nor public considerations, but to the support of such research a patent system has little to contribute.

The support of invention through public subsidy would entail serious administrative difficulties. If the subsidy were indiscriminate, no correspondence could be achieved between public outlays and public benefits. Yet, if the reward were fashioned according to some standard of value, there would be need to rely on experience to determine worth; and if worth of the invention were measured by actual market realization, it would vary with the extent of promotion and the rates set for competing inventions.[27] Compensation could be

[22] See Alfred Marshall, "Principles of Economics," at 400 (8th ed. 1936); and Adam Smith, "Wealth of Nations," book I, ch. X (1776).

[23] See Frank Knight, "Risk, Uncertainty and Profit" (1921).

[24] See Merton, "Fluctuations in the Rate of Industrial Invention," 49 Quarterly Journal of Economics 454-474 (1935); Simon Kuznets, "Secular Movements in Production and Prices" (1930); and Edward H. Chamberlin, "The Theory of Monopolistic Competition," at 57-64 (5th ed. 1946).

[25] J. K. Galbraith in "The Affluent Society" (1958), particularly ch. XIX, argues persuasively for expanded research supported by public funds where the results cannot be specialized to or sustained by any marketable product. While views may differ on the extent or forms of public needs for new inventions, any deficiencies which may exist in the public sector will probably call for corrective measures different from those which would apply to the private sector. Nor is it likely that reform of the patent system, which operates essentially by influencing private incentives, will prove the most effective means of meeting deficiencies in the public sector. Direct procurement or subsidy appear most appropriate where the need to be served is public rather than private.

[26] For an analysis of the considerations which make this very likely to be true in the case of inventions see Pigou, op. cit. supra note 16, at 396-401.

[27] For an early analysis of some of these problems, see John Stuart Mill, "Principles of Political Economy," book V, ch. X (1848).

confined to inventions determined to be of unusual value to the community. However, if this were done, those who failed to secure governmental compensation would be without a source of return. These uncertainties of reward, it seems certain, would materially retard the flow of new inventions.

C. RECOMMENDATION NO. E–1

It may be concluded that a patent system in some form is the most practicable means under a system of private enterprise to provide a socially adequate supply of new industrial technology. In its present form, our patent system is not wholly satisfactory for this purpose. Its weaknesses and limitations will be described in greater detail in later chapters of this report and in Economic Report No. 2. Before proceeding to that task, we shall undertake in the next chapter to define the essentials of a sound patent system.

CHAPTER II

THE ESSENTIALS OF A SOUND PATENT SYSTEM

The more extreme advocates of the patent system have credited it with a large share of our economic and technical progress. Its severest critics, citing evidence of abuse, have marked it a failure. There is a measure of truth in both views, but in the present analysis no effort will be made to appraise the gains and losses we have experienced under our patent system. Our concern will be the limitations and defects of the patent system and the measures of reform likely to produce a socially more satisfactory result, on the presumption that a patent system in some form will serve a useful purpose. There are certain ideal standards which may guide this appraisal, and these will be outlined later in this chapter. Since others judge the patent system by different standards, however, certain of the more common of these opposing views are briefly discussed.

A. SOME POPULAR MISCONCEPTIONS

1. The restrictive effects of patents are regarded by some as a virtue. They point to the inventive effort and the industrial diversification stimulated by the inaccessibility of patented technology to competitors as a social gain. By this standard, there would be almost no limit to the fragmentation of industry into isolated monopolies, and mere innovation would take its place alongside the test of inventive contribution which we now apply as a proper basis for the grant of patents. Governmental license, and not private enterprise, would then chiefly determine the use of the Nation's productive resources throughout the economy.

It is the search for new technology undertaken in anticipation of patents, and not the search impelled by limitations over the use of known technology, that the patent system is properly designed to foster. Society could, in fact, afford a greater volume of inventive effort if a way could be found to encourage inventions without according powers to limit their use. For these powers, far from benefiting society, constitute a social cost of the patent system, since they diminish output by inhibiting the use of the best technology. It may be found desirable to grant such powers as the most practicable means of fostering invention, but if so they must be carefully limited according to that need. And that need is itself limited because of the competing demands for the use of the Nation's scarce resources. It is only because commitments made under the patent system must be honored, if that incentive is to prove effective in fostering invention, that any publicly conferred powers over the use of known technology are socially justified.

2. Even those who hold a more positive view of the functions of a patent system sometimes argue that it is useful as a means of preserving competition, particularly the competitive position of small-

scale enterprise. This surely is a perversion of the concept of competition. Society's essential safeguard for the best use of its resources under a competitive system lies in the freedom it insures to serve market demands. Limitations over that freedom, with few exceptions, impair the effective performance of competition. While limitations over the size of individual firms may at certain points perhaps enliven competition, measures designed to shelter existing firms of any size can only obstruct the operation of competitive forces. In any event, patents cannot effectively serve this purpose. If there is any bias in the patent system, it is, as we shall see, in favor of the larger firms. At best, only a limited number of smaller firms are likely to be protected by this means.

3. Some regard patents as designed chiefly to encourage independent, rather than group, inventive effort. They view corporate research as confined to "routine contributions," as contrasted with the "inventive genius" which often characterizes the work of independent inventors.[28]

There is evidence that corporate research is directed principally to the development of improvements and the perfection of known inventions for commercial use.[29] Such research is not, however, socially less useful than that which may be regarded as more fundamental; nor does it stand less in need of support through patents. Like the work of inventive geniuses, it requires prolonged and systematic study by experts, and is clearly beyond the probability of ready conception by skilled artisans.[30] While, as we pointed out in the preceding chapter, a certain volume of corporate research will be supported by the desire to avert the obsolescence of specialized production facilities, a business firm cannot ordinarily afford to spend money on research if its competitors will have free and immediate access to the results. The work of inventive geniuses is much more likely to be spontaneous. Moreover, the adaptation of inventions for commercial use is vital if the public is to benefit fully from scientific progress.

4. The view of the patent system which differs most fundamentally from the standards we shall suggest looks upon patents as essential to the commercial exploitation of new inventions, principally because of the uncertainties which prevail where new products are to be marketed. It is true that monopoly powers, such as those conferred under patents, do improve the chance of high profits and diminish the risk of low profits, thus making it more attractive to hazard investment where market prospects are uncertain. More is required, however, to establish the social need for monopoly to exploit as well as foster inventions.

We have, under our private enterprise system, limited entry in the "public utilities." In those industries, the conditions of supply make competition insupportable, and monopoly powers have been both granted and regulated in order to insure adequate service to the public. (For further discussion see ch. IV.) No such general justification for monopoly holds true in the exploitation of patented inventions. Nor

[28] See *Potts* v. *Coe*, 140 F. 2d 470 (D.C. Cir. 1944); and Walton Hamilton, "Patents and Free Enterprise," TNEC Monograph No. 31, at 155–156 (1941).

[29] For a summary of TNEC testimony to this effect, see William B. Bennett, "The American Patent System," at 182–188 (1943). See also, Frank J. Kottke, "Electrical Technology and the Public Interest" (1944).

[30] For an analysis of the similarity of the inventive processes under individual and group research, see A. P. Usher, "A History of Mechanical Inventions," at 21–22 (1929).

are the market uncertainties which prevail in exploiting patented inventions unique. In fact, many patents are for improved means of manufacturing known products or for improved forms of such products.

There is, however, a more fundamental objection to the grant of monopoly powers specifically to aid in the exploitation of patented inventions. Where market prospects are uncertain, caution in the use of the Nation's resources serves a social purpose. And it cannot be demonstrated that society will benefit by according to patented inventions a generally preferred status in the use of these resources. In any event, where the only bar to entry in an industry is uncertainty of demand, rather than conditions of supply such as in the "public utilities," monopoly is not necessary to sustain production once undertaken.

In supporting the argument for monopoly to insure the exploitation of patented inventions, a great deal of stress has been laid on the costs which the pioneering firm will have to bear which its rivals will be spared, thus producing a constraint against initial market development. The problem differs according to the stage of exploitation.

During the pilot plant stage, the knowledge acquired takes such forms as records of tests and experiments, the production of models and samples, blueprints, plans for plant organization and layout, and other results of a similar nature. Such information is closely akin to patentable inventions in the sense that acquisition by competitors may be costless and accordingly requires protection to assure its supply. However, it is not usually difficult to keep such information secret. In fact, even where licenses are granted under a patent, it is often difficult to transmit to the licensee sufficient know-how to assure effective operation under the invention.

The second stage, which consists of the erection of production facilities, entails expenditures which any rival will have to duplicate. An extended market for such facilities may produce so-called external economies which will lower costs, but these conditions prevail in many industries other than those which operate under patent protection, and are unlikely to be sufficiently significant or progressive to justify the grant of monopoly powers for initial market development.

The third stage, commercialization, entails market development expenditures such as advertising, salesmen's salaries, transportation, and warehousing. It is said that the benefits of market development are shared by those who follow in the paths broken by the innovator. Per unit costs of sales are likely to be greater at an early stage than after market acceptance of a new product has been attained. Competitors, however, will not always benefit from the market development activities of their rivals, since such activities often attach trade to a single seller,[31] and may in fact create an obstacle to entry by competitors. The advantages which do fall to latecomers as a result of the general demand for a product created by the pioneering firm are not, moreover, confined to patent-protected industries, nor are they likely to be important enough to warrant the grant of monopoly powers for the mere task of initial market development.

[31] See Edward H. Chamberlin, "The Theory of Monopolistic Competition" (5th ed. 1940); and Joan Robinson, "The Economics of Imperfect Competition" (1933).

5. Patents are sometimes compared to tariffs and supported on the ground that they also safeguard infant industries. The analogy is not entirely apt. While tariffs are publicly administered, patent powers are privately exercised. Moreover, while tariffs have a clearly national orientation in the sense that they are designed to protect domestic production, patents which convey powers over domestic markets may be granted to foreign nationals who will then be free to supply such markets entirely through exports of foreign production. For these reasons, patents cannot effectively serve the public purpose of sheltering domestic industries.

B. SOME SUGGESTED STANDARDS

Over the years, many proposals have been advanced for reform of the patent system. In the chapters to follow, and in Economic Report No. 2, we shall examine some of these proposals and suggest a plan of our own. To provide a point of reference by which to fashion and appraise these measures of reform, two ideal standards are applied throughout the discussion. Certain of these thoughts will be evident from the preceding analysis; others will be more fully developed later.

1. *If a patent system is to work to best advantage socially, grants will be made only where they are required to secure the invention or its disclosure.* The free discretion to undertake industrial and commercial ventures, and to retain the fruits of those labors, are two of the most basic incentives upon which society relies under a private enterprise system to attain the best use of its resources. There is a presumption, under such a system, against any impairment of these incentives unless a clear showing can be made of social benefit. Patents operate both to limit entry in industry and commerce, and to deny to subsequent inventors the use of their own discoveries. In terms of the ideal suggested, no grants would therefore be made where the costs of the invention were nominal, or where the invention could be used competitively at a fair profit.

No patent system at present follows this ideal. All base the grant of patents on the technical achievement of the inventor, and not the need for monopoly to assure supply of the invention or its disclosure. Under our system the principal requirements for a patent are novelty in the invention, utility, and a degree of inventiveness exceeding that readily apparent to those skilled in the art.

In practical operation, the standards actually followed are likely to produce results not greatly different from those suggested as ideal, and they are far easier to administer. By confining patents to important technical contributions, the grants are likely to be made chiefly where costly experimentation has been undertaken which could not be supported without a means of safeguarding the commercial value of the results. The high rewards for inspired work, or for sheer good fortune, may perhaps be justified, as pointed out in the preceding chapter, as a means of overcoming the reluctance to undertake the hazards of inventive activity which are by their very nature unpredictable.[32]

Basing the patent on "inventive contribution" limits its application to the stimulation of invention and prevents its use broadly as a means of fostering production. This limitation appears proper. Investments made in the exploitation of inventions (new or old) do not have

[32] For further discussion, see ch. III.

the fugitive character of those made in the inventions themselves. Nor are the risks encountered in exploiting an invention likely to be as great as those in producing it, since costs and yields are subject to less uncertainty.

The grant of but a single patent for an invention appears unavoidable under any system. In any other circumstance, competition among the patentees would destroy the commercial value of the grant for the reasons cited in the preceding chapter. The grant of the patent to the first inventor has the further advantage of accelerating the perfection of the invention and its disclosure through commercial use or the application for a patent.[33]

2. *A second ideal in fashioning a patent system is to limit the powers conferred so as to confine the patentee's reward to the recovery of costs within the bounds of the social value of the invention, and to insure, insofar as compatible with the objectives sought, that production and sale under patented inventions are competitive.* In considering the costs which should properly be recoverable under a patent, account will have to be taken of the unsuccessful experiments which precede the final successful result. It is not true, as some have urged, that returns under patents should be kept high enough to meet the costs of all unsuccessful experiments, for to do so would impair the incentive to careful direction of inventive effort. But the costs of some failures are no doubt properly ascribable to the inventions actually patented.

Since under a patent the inventor depends for his return on commercial use of his invention, his reward is likely to be proportioned in some degree according to its social value.[34] The exact degree of correspondence may vary greatly, however, depending upon the limitations over output imposed by the patentee. The extent of these limitations will be conditioned by the degree of competition which prevails with other forms of technology, patented or unpatented.[35]

Two factors are counted upon under our patent system to limit the returns to inventors and to insure competitive use of the inventions: the freedom to invent and use substitutes, bolstered by the disclosure requirement; and the limited life of the grant. The purpose in conveying powers of exclusion under patents is to enable the inventor to reap the benefits of the specific invention covered by the grant, and not to provide effective control of the market; the "equivalents" covered are also determined according to technical, and not market, considerations. New inventions to provide effective market competition with the old are, in fact, encouraged through the disclosure

[33] Professor Machlup questions the theory that patent protection is exchanged for the disclosure of secrets. Senate Patent Study No. 15, supra note 14, at 52–53 and 76–77. While in his initial discussion he appears to be considering only one of the purposes of disclosure—to assure workable specifications at the expiration of the grant, he does later consider the usefulness of disclosure as a means of stimulating further research and avoiding the duplication of inventive effort. His rejection of the "disclosure" theory is founded on the judgment that "inventions probably are patented only when the inventor or user fears that others would soon find out his secret or independently come upon the same idea." It is not at all clear, however, that this fear can be equated with actual independent achievement or discovery. Professor Machlup's suggestion that comparable dissemination of technical knowledge could be achieved by special agencies in the absence of patents is meaningful only if it can be assumed that patents are rarely sought where there is any real likelihood that the invention would otherwise remain secret. This is an assumption of doubtful validity. It is the uncertainty of competition which confronts new inventors, and the added protection against this uncertainty provided by patents, that leads them to seek this safeguard. In these circumstances, the assumption would more probably have to be the opposite of that made by Machlup. In any event, the duration of the patent grant is not necessarily at issue here, as Machlup seems to suggest, since patents are designed to foster invention as well as disclosure.

[34] For an oft-quoted statement of this defense for patents, see Jeremy Bentham, "The Rationale of Reward," at 92 (1825).

[35] Professor Machlup challenges the view that any proportionality, or even approximate proportionality, can possibly be shown between the "rewards" of inventors and the "social usefulness" of inventions. Senate Patent Study No. 15, supra note 14, at p. 54. However, he bases this judgment on the timing of inventions in relation to the appearance or creation of public demand, largely subjective views of what is "trivial," and on a prediction that the socially most important inventions would not be allowed to be monopolistically exploited through patents. These considerations are, at most, limited in their applicability to the issue.

requirement. The results of inventive effort are, however, highly uncertain, and it is unlikely that close substitutes will always be found. Moreover, the concentration of patent control may impair the competitive effectiveness of new inventions.

Nor is limited duration of the patent grant a sensitive device for proportioning the returns under patents to the costs of the invention. These costs vary greatly from invention to invention, and they differ markedly in the rate at which they can be amortized irrespective of the skill and energy of exploitation. The period of the patent grant was initially based on considerations which now have little meaning. In the beginning, following the English pattern, we granted patents for a 14-year term. This term was selected by the English at a time when manufacture was in the handicraft stage and when "new inventions" were largely synonymous with wider dissemination of known skills. The aim was to secure the teaching of these skills, and patentees were protected against competition for the period during which they could train two new sets of apprentices. Little attention was given at that time to patents as a means of encouraging inventive effort. Later, as machine and chemical technology grew to importance, the emphasis shifted to fostering new inventions, and written disclosure requirements were added. In our own country, a 7-year renewal period was added in 1836; and in 1861 this was dropped and the period extended to 17 years, as a compromise with pressures for a 20-year term in lieu of the 7-year renewal.

There have been suggestions for varying the duration of patents, and even the monopoly powers conferred, according to whether the inventions are "major" or "minor." [36] Difficulties are likely to be encountered, however, if these distinctions are to be based on scientific and technical standards such as those now employed in Patent Office examinations. While there may be a rough correspondence between the social merit and technical excellence of inventions generally, and between their costs and scientific importance, these relationships are less likely to hold true for individual inventions. Administration of a "major-minor" patent system is therefore likely to prove troublesome, in terms of the ideals suggested above.[37]

It shall be the principal thesis of the remaining chapters of this report, and of Economic Report No. 2, that the most effective and practicable means of attaining the ideals of a sound patent system are to place limits on the concentration of patent control, and to outlaw certain types of restrictive provisions sometimes found in patent licenses and assignments. The positive suggestions for patent reform are presented in Economic Report No. 2. In the remaining chapters of this report, we shall examine the factors which influence the concentration of patent control, and consider the wisdom of general compulsory licensing of patented inventions.

[36] See, for example, the recommendations of the Science Advisory Board, reproduced in TNEC hearings, "Investigation of Concentration of Economic Power," pt. 3, at 1144 (1939).

[37] Professor Machlup applies the techniques of economic analysis to the problem of the socially ideal duration of patent protection in the now popular game of "model" construction. Senate Patent Study No. 15, supra note 14, at pp. 66–73. As might be expected of any "model," the assumptions made determine the conclusions reached. The "model" Machlup has chosen to illustrate the technique has, it seems to me, a pessimistic bias because he treats the "supply" of research workers on a short-run basis, without allowing time for the incentives of the patent system to produce an added supply. This bias is further evident in his assumptions, also questionable as I see it, that an increase in the amount of research activity will always increase the proportion of duplicate and substitute inventions and decrease the proportion of usable inventions, and that business firms always tend to budget their research activities as a fixed proportion of sales. It is also evident in the importance he attaches to the demand for patents as a "replacement demand." Professor Machlup's treatment of accelerated capital obsolescence as a social cost of the patent system is also questionable, since existing fixed equipment will continue to be used so long as "variable" costs of production can be met, beyond which point it would be socially disadvantageous to continue its use. Carried to its logical conclusion, his standard would appear to be a counsel against scientific advance.

CHAPTER III

CONCENTRATION OF PATENT CONTROL

The requirements of a sound patent system have greatly altered since the last basic modification was made in the patent statutes more than a century ago.[38] At that time new inventions were infrequent, and they made up only a small part of the technology in use. In those circumstances, disclosure requirements and limited duration of the patent may have been sufficient to protect the public interest.

The rise of the Nation to industrial maturity has brought a profound change in the role of patents. Increases in per capita income have made it socially worth while to devote a larger part of the Nation's resources to research yielding benefits only in the future, and have provided the means to put new discoveries to commercial use. As a result, through the years, the Nation has grown more dependent for the best use of its resources upon the enterprise of patentees holding a degree of monopoly power over new technology. To an important extent, the social effectiveness of the patent system now depends on diffusion of patent ownership and the competitive use of inventions which such diffusion will bring.

Discussion of this general problem, which is closely bound up with restrictive agreements among owners of competing patents, is deferred to Economic Report No. 2 dealing with patent abuse. However, since the concentration of patent control is often unrelated to abuse, the principal factors leading to such concentration are examined here. Three considerations have been important in patent concentration: (1) the desire to diminish the risks of inventive activity; (2) the desire to provide safeguards against competing inventions; and (3) the concentration of manufacturing control.

A. TO DIMINISH RISKS OF INVENTIVE ACTIVITY

The most fundamental cause of patent concentration is the extraordinarily hazardous nature of inventive work. In all business activity there are production and market factors which cannot be appraised on a predictable basis. Inventive projects are subject to an unusually high degree of such uncertainty. There is no clear way of estimating in advance the product of inventive activity, nor the probable cost or commercial value of any discoveries which may result. For this reason, there is no reliable guide to the amount of capital and labor which may profitably be devoted to such projects. In other fields, production and marketing experience ordinarily provide a basis for more accurate estimates of probable costs and returns, and a great many of the risks are predictable.

[38] Although the patent laws were codified and revised in 1952 (Public Law 593; 35 U.S.C. secs. 1–293), and a few minor substantive changes were made, the basic structure and philosophy of the 1836 statute was retained.

There are only two ways in which the risks of inventive effort may be diminished for a particular investor, business firm, or inventor: (1) efforts or investments may be distributed over a wide field so as to improve the chance of encountering a successful result; or (2) effort or investment devoted to a given field of research may be expanded, making possible more extensive use of specialized personnel, a larger body of experience and a larger number of tries, thus improving the chance of securing an outstanding result.[39]

Whichever tactic is employed to diminish uncertainty, those who use larger amounts of capital will in the long run have an advantage. These benefits of large-scale research are likely to lead to concentration of patent control, and the latter tactic is likely to result in consolidation of competing inventions. Small investors may be able, in some degree, to overcome this disability by joining with others in employing specialized research organizations to carry on experiments for them. But it is unlikely to be wholly overcome in this way, since outside research groups ordinarily lack intimate knowledge of manufacturing problems and market prospects.[40]

Several common errors of thinking must be avoided. Concentration of patent control is often ascribed to the superior financial resources of large firms. And some observers have expressed the view that larger firms are favored in the development of inventions because the funds to support inventive activity must come from the proceeds of previously successful inventions. There is some truth in these contentions, since there is a tendency for corporate earnings to be used preferentially within the firm's own operations. However, there is a common market for capital and labor from which productive resources are drawn into various employments on the basis of anticipated profits. Projects for experimental activity have access to this general supply of capital and labor on the same basis as do other enterprises, and larger firms enjoy at best only a limited advantage in this respect.

B. TO MONOPOLIZE COMPETING INVENTIONS

Patent concentration is also sometimes the result of deliberate efforts to acquire control over competing inventions without regard to the economies of large-scale research. Because of the monopoly powers conferred under patents, business firms always stand in danger of exclusion from the market by rival patentees. A comparable hazard exists also in patent-free industries, but it can more easily be overcome where entry is not impeded by the protection of a patent. The only effective countervailing measure against patents is to anticipate the inventions of competitors or to develop acceptable

[39] For a general discussion of this problem, see Knight, op. cit, supra note 23.

[40] For discussion of cooperative and contract research, including attention to the problems of smaller business concerns in connection therewith, see: OEEC, "The Organization of Applied Research in Europe, the United States, and Canada," 3 volumes (Paris 1954); Proceedings, President's Conference on Technical and Distribution Research for the Benefit of Small Business, Washington, Sept. 23-25, 1957; Office of Technical Services (John C. Green, Director), "Technical Research Activities of Cooperative Associations," Senate Patent Study No. 21 (1958), Herner, Meyer & Co., "Research and Development and the Use of Technical Information in Small and Medium Sized Manufacturing Firms," a report to the Office of Technical Services (Washington 1956); Herner, Meyer and Ramsey, "How Smaller Firms Solve Problems and Keep Abreast of Technical Developments," prepared for the Office of Technical Services (1957); Arnold, "Why Not Try Cooperative Research?" 32 Harv. Bus. Rev. 115-22 (1954). For additional references containing discussion of the subject, see Bureau of Labor Statistics (U.S. Department of Labor), "Productivity: a Bibliography" (Washington 1957); National Science Foundation, "A Selected Bibliography of Research and Development and Its Impact on the Economy" (1958).

substitutes. While this rivalry to perfect patentable inventions may result in patent concentration, it has also a tendency to disperse patent control.

A more prolific source of patent concentration is the desire to provide protection against existing rivalry in order to improve profits. This is an objective in which all the members of an industry may join. The existence of patents simplifies industrywide controls because patentees enjoy legally enforceable monopolies in limited fields, and the competition to be confronted is thus more readily defined and more easily brought under control. Concentration of patent control arising from these pressures is likely to take the form of agreements among individual patentees, rather than centralized ownership. However, where one firm in an industry begins with a strong patent position, it may be able to prolong and extend its control.

The pressure for such agreements has increased. Where capital is growing in volume, and increased efforts are being devoted to research, the competitive position of individual firms is more seriously in danger. There is greater likelihood that new firms will be organized to manufacture known products under existing methods of production. And it is more probable that new products and new processes and machines will appear to impair or overthrow the competitive position of existing firms. Moreover, the losses through such innovations are greater where there are investments in specialized facilities such as are required to employ modern technology. The growth of markets in a spatial sense, resulting from improved means of transportation and communication, has a similar effect by expanding the sources of new competition. These hazards of competition are probably the principal, although not the sole, cause of restrictive patent agreements.

Firms with established research, manufacturing, and marketing facilities are likely to be favored in the acquisition of new inventions. They are assured of control over the output of their own research. And, where they have related inventions of their own, they may be able to bid higher than others for new inventions independently conceived. Firms already operating a plant or sales organization may be able to exploit a new invention more economically than it can be separately done; and the possession of these facilities may afford assurance of prompt exploitation of new inventions.[41]

The larger firms in an industry have a stronger incentive to acquire patents for defensive purposes than do the smaller. This is true because of the greater size of their investments which would benefit from protection against competition. The greater the investment in specialized capital, the more is the potential loss through competing products or processes. Hence the larger the financial outlay which mere defensive protection will support. Nevertheless, the primary stimulus to the development and acquisition of new inventions lies in the competitive advantages which these inventions hold. It will therefore be to the interest of any firm in the industry, large or small, or of any possessor of free capital, to develop or acquire control of the more advantageous product forms or techniques of manufacture, within the limits of the commercial value of the invention.

[41] For an analysis of how these factors have worked out in a specific industry, see Kottke, op. cit. supra note 29.

C. AS AN OUTGROWTH OF CONCENTRATION OF MANUFACTURING CONTROL

Patent concentration may also be an incidental result of industrial concentration growing out of the production and distributive economies of large-scale manufacture.[42] We cannot here examine the many considerations which have given rise to industrial mergers and consolidations, or the growth in size of individual business firms. It is sufficient to note that even where such concentration is the result wholly of cost advantages in production or distribution, it may bring integration of patent ownership as thoroughgoing as that which stems from the factors earlier discussed. It is probable that industrial integration which is horizontal (at the same stage of manufacture or distribution) will cause a more significant degree of patent concentration than vertical consolidations. Moreover, the patent concentration which results from horizontal integration is more likely to involve competing inventions.

In some degree, the cost advantages of large-scale enterprise have been the result of advances in technology. Technological progress has thus indirectly promoted patent concentration. It is probable, however, that only a limited group of patented inventions have had this effect. And there are reasons to believe that the industrial concentration which we have actually experienced may have exceeded that which rests on this ground. There can be no certainty how far future scientific progress will promote further industrial concentration.

[42] For a discussion of patents and technology as a factor in corporate mergers and acquisitions, see Murray Friedman, "The Research and Development Factor in Mergers and Acquisitions," Senate Patent Study No. 16 (1958).

CHAPTER IV

GENERAL COMPULSORY LICENSING

Both the virtues and the faults of the patent system, it will be clear from the foregoing chapters, may be traced to the monopoly powers conferred under patents. Many have seen in general compulsory licensing of patented inventions a happy escape from this dilemma.[43] Under this plan patents would continue, but patented inventions would be made available to all producers at "reasonable" royalties. The objective would be to place the use of patented inventions beyond the discretion of patentees while preserving "fair" returns for the inventors. Thus, while patentees would lose power over manufacture and commerce under their inventions, they would retain "exclusive rights" to the fruits of their discoveries. And royalties would presumably be set so as to preserve the role of patents as a stimulus to invention and disclosure.

General compulsory licensing would clearly remedy certain of the deficiencies of the patent system. It would open the most advanced technology to all producers, and so would assure larger output at lower prices (at comparable royalty rates), and greater effectiveness and better balance in the use of productive resources. There would be less danger of inventions lying idle for want of rights under collateral patents, or because of the shortsightedness or inertia of patentees or deliberate nonuse founded on the desire to protect existing investments. Independent inventors would experience a wider demand for their discoveries. Patents would cease to serve as an instrument of industrial concentration, or as a basis for industry-wide controls over manufacture and commerce. And the opportunity would be diminished for monopoly through product differentiation resting wholly on physical composition.

In practical operation, however, a system of general compulsory licensing would be likely to impair the effectiveness of patents as a stimulus to invention and disclosure. The principal problems relate to (1) the assurance of returns within the life of the patent; (2) the rate of these returns; and (3) the enforcement of the patent. The chief hazard is that general compulsory licensing would dim the prospect of returns, upon which the stimulative influence of patents depends at the inventive stage.

A. ASSURANCE OF RETURNS

The effectiveness of patents as a stimulus to invention depends on the prospect of earnings during the period of the grant. Any delay in exploitation results in a loss of earnings which cannot later be recovered when the invention becomes available to competitors.

[43] President Roosevelt suggested this approach in his message to Congress of Apr. 29, 1938, which led to the establishment of the Temporary National Economic Committee. The TNEC in its final recommendations adopted this proposal. See S. Doc. 35, 77th Cong., 1st sess., at 18, 36 (1941).

Under general compulsory licensing, patentees would be deprived of certain inducements which are now operative to accelerate the exploitation of their inventions.

The competition induced by general compulsory licensing would probably speed the immediate use of clearly profitable inventions. However, at the time research is carried on there is no way of estimating the probable appeal of any discovery. Inventors are likely to overestimate the need for exclusive rights to assure prompt exploitation. For this reason, general compulsory licensing may have an unnecessarily retarding effect on invention.

These effects are likely to be most serious where patentees are dependent upon others for the exploitation of their inventions. Where only nonexclusive licenses may be offered, as under a system of general compulsory licensing, it will not be possible for the patentee to impose more than nominal minimum royalties. Accordingly, the patentee's income will be dependent upon actual commercial use of the invention by his licensees. An exclusive licensee may also withhold the use of an invention, but in these cases the patentee may successfully require the payment of substantial minimum royalties.

General compulsory licensing may also limit opportunities for the disposal of inventions through assignment. This represents the principal means of realizing at the time of patenting the full future value of an invention. With access to inventions assured at reasonable rates, and confronted with the necessity of issuing licenses to all competitors at royalties beyond their control, business firms will have little incentive to risk capital in the purchase of patents. The reduction of this market for patented inventions is of particular concern to independent inventors.

The effects of general compulsory licensing on firms which exploit their own inventions are less clear. Since there will be assured access to inventions developed by competitors, there will be less incentive to undertake the risks of invention. And where there are already investments in one form of technology, there may be reluctance to develop competing inventions which will immediately become available to rivals. On the other hand, even under general compulsory licensing the inventing firm is likely to reach the market first under a new invention. The monopoly profits which can be gained in this way, and the long-range benefits of a reputation for preeminence, provide a strong inducement to invention. And there will always remain some incentive to invent on the basis of anticipated royalties under general compulsory licensing. Where inventions can be used effectively in secrecy, or are likely to be profitable only for a short period, general compulsory licensing may result in nonpatenting.

B. RATE OF RETURNS

At present we rely on bargaining between patentee and licensee to determine royalties. This affords an opportunity to proportion royalties somewhat in correspondence with the commercial value of individual inventions. The incentive is thus sustained to supply all inventions which offer prospect of profitable use. The right to bargain privately for the use of inventions is important if for no reason other than the fact that inventors are likely to place a high value on their own capacities to secure favorable terms.

Under general compulsory licensing, patentees would be allowed to issue licenses on privately agreed terms. But applicants would have recourse to rate determination by the Government, and the rates so fixed would be likely to control all private negotiations. In any effort publicly to fix royalties for patents, only the broadest classes of inventions could be recognized, and the rates set would have to be highly arbitrary. Inventors would be uncertain of the treatment they might receive, and the prospect would therefore be diminished for the supply of all inventions whose costs could be recovered through commercial use.

These effects can be seen more clearly by considering the problems of rate determination under general compulsory licensing. Four principal standards have been suggested for this purpose: (1) recovery of the value of the invention to the licensee; (2) recovery of the cost of the invention to the patentee; (3) compensation for damages suffered by the patentee through the competition of licensees; and (4) "conventional" or "typical" rates for the class of invention involved.

The value standard has little meaning where licenses are to be available to all applicants. Since an invention may be used at the same time by a number of producers, and since the value of an invention to any one producer depends partly on the terms offered to competitors, this standard places no floor under royalties.

The cost standard is, in principle, the most satisfactory. However, as we pointed out in chapter I, this standard would be difficult to administer. Since each invention is unique, past experience would be of little use in determining the costs of new inventions, so that these costs would have to be separately calculated. Nor does past experience aid in estimating probable royalty incomes at alternative rates for a new invention; even early demands for a new invention may fail to reflect its full future value. Thus, the margin of error in such calculations would probably be extremely great.

The damage standard is applicable only where the patentee manufactures under the invention. Where the patentee has invested in manufacture, only royalties high enough to exclude licensees will prevent losses through competition. If compensation were to be granted for losses actually experienced, account would have to be taken of investments in specialized production and distribution facilities. This would greatly complicate royalty determination.

The fourth standard is the one most commonly suggested, and is probably the most expedient and practicable, at least for a short period. This is to base royalties on "typical" rates as shown by past experience. New inventions are not always easy, however, to fit into old categories. And under general compulsory licensing the number of categories, to be workable, would have to be limited. It is doubtful whether "typical" rates can be found in many fields.[44] But even if they can, they are unlikely to reflect cost and income relationships applicable to new inventions. If general compulsory licensing should be instituted, there would no longer be an independent source for such determinations. It is questionable, finally, how far royalties set in private bargaining can serve the purposes of general compulsory licensing. Rates privately set are ordinarily designed to maximize revenue, considering the manufacturing and distributive position of

[44] A survey by the author of royalty terms in a group of patent licenses vested by the Alien Property Custodian disclosed little in the way of a uniform pattern in the fields examined.

the patentee. Since the purpose of general compulsory licensing would be to secure wider use of patented inventions insofar as this could be done without impairing the future supply of inventions, the rates set would have to be at the lowest point which would permit the recovery of costs.

It is probable that general compulsory licensing would affect the returns under different inventions in different ways. Inferior inventions now used because of the unavailability (or limited use) of the better ones would be likely to suffer reduced income. Conversely, the superior inventions, almost without regard to how royalties were set, would be likely to benefit. And dependent inventions would in all cases tend to increase in value.

C. ENFORCEMENT OF THE PATENT

General compulsory licensing may make the enforcement of a patent more difficult and more costly. With so many properly licensed manufacturers, infringement may be more difficult to isolate. And it may grow more common, since where it is detected a license will be available to assure continued operation.[45] The burden of enforcing the patent will rest solely with the patentee where there is general compulsory licensing. Nonexclusive licensees have, individually, insufficient stake in the invention to bear the cost of enforcement, and they are legally in no position to take such action. Moreover, as licensing is extended, costs of negotiation, audit, and royalty collection are likely to increase relative to royalty income, and beyond a point may exceed that income. This is a likely result of the fact that the more licensees there are the smaller are the probable sales of any one. Costs of administering the licenses are not likely to decrease proportionately, and the net income of the patentee is therefore likely to decline. How far this can be taken care of in the royalties set will vary with the worth of the individual inventions.

D. A QUESTION OF PRINCIPLE

Apart from administrative difficulties, general compulsory licensing involves also an important question of principle. Two choices are open to safeguard the public interest in the use of patented inventions. One, represented by general compulsory licensing, is to impose conditions of price and service comparable to those now applied to the "public utilities." The other is to maintain competition in the use of patented inventions through measures especially suited to the conditions of limited monopoly which prevail where patented technology is important in an industry.

The public is concerned, as we pointed out in chapters I and II, to assure the use of superior technology and to secure output under that technology at as high a level as possible considering the need to maintain a continued supply of new technology. At present we rely chiefly on the freedom to invent and to use substitutes, and on certain applications of the antitrust laws, to perform this task. The competition so preserved in some degree induces the use of the best

[45] The Swan committee in England found that in many cases the opposite occurred. Licenses were often taken because it was cheaper to do so than to challenge patent validity, with the result that invalid patents often remained unchallenged. See "Second Interim Report, Board of Trade, Patents and Designs Acts" (April 1946).

technology, limits the returns to inventors, and encourages the supply of new inventions.

Under general compulsory licensing, governmental action would supplant competition in performing these tasks. The royalties set under such licensing would determine the technology used, govern the earnings of inventors, and condition the supply of new inventions. The assumption of these responsibilities by Government may require either regulation of entry into inventive activity, authority to extend the period of monopoly to assure a proper return to inventors, or some form of public subsidy. Without these added powers, rates could not be set with any assurance of their effects on the supply and use of inventions. The choice of general compulsory licensing amounts, therefore, to a decision to deal with the problem of patent abuse through strengthening the monopolies conferred and subjecting them to close public control.

Such regulation has been resorted to in the past principally where cost conditions have made competition either unenforcible or socially wasteful, and where the product or service involved has been regarded as vital in the public interest. Where decreasing-cost conditions prevail in an industry, there is a so-called natural tendency either toward monopoly or agreement among competitors. Efforts to maintain competition in such industries are likely to prove unsuccessful; and if successful, tend only to bring prices below costs and to cause unnecessary duplication of facilities. In these circumstances, there may be reluctance to enter the industry, or ruinous competition leading to agreement among competitors. Monopoly has therefore been publicly sanctioned in these industries as a means of assuring private investment sufficient to provide adequate service, and to prevent wasteful commitments of capital. And public controls have been imposed to assure adequate service at reasonable rates. An essential part of this scheme of control has been regulation of entry on the basis of "public convenience and necessity."

The limiting principle observed in the application of public utility controls reflects a distinction which makes a real difference in a democracy. It expresses the policy that competitive private enterprise should be relied upon to secure and regulate production wherever it can adequately serve social needs. By this standard, no clear justification exists for the general compulsory licensing of patented inventions.

In the case of inventions, effective monopoly is not inevitable. A successful invention stimulates a search for substitutes. To preserve this incentive it is necessary only to confer monopoly for individual inventions and their technical equivalents. Rivalry between competing inventions has not, in a general sense, exhibited a natural tendency toward monopoly, nor are there general dangers of social waste in competition among inventions which can be substituted for one another. Except in a limited group of cases, individual inventions are not of sufficient public importance to justify a policy of general availability apart from the production undertaken by the patentee.

In view of these facts, it appears that reliance has properly been placed on competition to secure the commercial use of superior technology and to limit the returns to inventors. However, neither the antitrust laws nor the patent statutes are in their present form

adequate for the purpose of maintaining such competition. A plan to make them so is presented in Economic Report No. 2. Accordingly, in anticipation of those proposals—

E. RECOMMENDATION NO. E–2

It is recommended that no provision for general compulsory licensing be incorporated in our patent system. The arguments against general compulsory licensing, recited in this report, do not apply to the limited compulsory licensing proposed in chapters XII and XIII of Economic Report No. 2. The sanctions there recommended apply principally where there have been violations of the suggested Code of Fair Patent Contract Provisions, and in all cases the patentee is in a position to avoid the application of this remedy. Where other remedies fail to provide proper use of patented inventions, there is greater justification for resort to compulsory licensing. And where it is applied only in a limited number of cases, individual determination of royalties is more feasible: there will be a previous record of experience in the cases in which compulsory licensing is imposed, and a continuing body of privately negotiated license terms to furnish comparisons. Finally, where compulsory licensing is imposed, as suggested, after prolonged nonuse of an invention, there is less danger that the reward to the inventor will be adversely affected.

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94TH CONGRESS
2d Session

SENATE

REPORT
No. 94-1058

PATENTS, TRADEMARKS, AND COPYRIGHTS

REPORT

OF THE

COMMITTEE ON THE JUDICIARY
UNITED STATES SENATE

MADE BY ITS

SUBCOMMITTEE ON PATENTS, TRADEMARKS, AND COPYRIGHTS

PURSUANT TO

S. RES. 72

NINETY-FOURTH CONGRESS

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(II)

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94TH CONGRESS 2d Session | SENATE | REPORT No. 94-1058

PATENTS, TRADEMARKS, AND COPYRIGHTS

AUGUST 2, 1976.—Ordered to be printed

Mr. MCCLELLAN, from the Committee on the Judiciary, submitted the following

REPORT

[Pursuant to S. Res. 72 (94th Cong., 1st sess.)]

INTRODUCTION

During the first session of the 94th Congress, the Subcommittee on Patents, Trademarks and Copyrights was authorized by the Committee on the Judiciary pursuant to section 13 of Senate Resolution 72 to "conduct a complete examination and review of the administration of the Patent Office and a complete examination and review of the statutes relating to patents, trademarks and copyrights", and to submit a report of its activities in connection therewith.

In carrying out its responsibilities under Senate Resolution 72, the Subcommittee studied and evaluated 15 measures referred to it by the Committee on the Judiciary. The purpose of these bills range from revising the patent, trademark and copyright laws to affording private relief from the patent statutes. The Subcommittee acted favorably upon legislation to provide for the general revision of the patent and copyright statutes and procedures, measures to extend the term of patent protection in certain cases, and legislation to implement the provisions of the Patent Cooperation Treaty. Several of these bills were approved by the Committee on the Judiciary and the Senate, and one was passed by the House of Representatives and signed into law by the President.

The Subcommittee also held hearings on legislation to provide for performance rights in sound recordings. In addition, the staff provided assistance to members of the Senate on matters relating to the subject matter of patents, trademarks, and copyrights.

LEGISLATION

1. Legislation reported by the Subcommittee, approved by the Committee on the Judiciary, passed by the Senate and the House of Representatives, and approved by the President

Public Law 94-131, (S. 24, Mr. McClellan), to carry into effect certain provisions of the Patent Cooperation Treaty, and for other purposes.

The purpose of this legislation is to implement the provisions of the Patent Cooperation Treaty signed by the United States June 19, 1970, and ratified by the Senate on October 30, 1973.

The purpose of the treaty is to reduce the duplication of effort involved in the filing and processing of patent applications for the same invention in different countries. When the treaty is in full force, it will enable patent applicants from the United States and those countries adhering to the document to enjoy the advantages available under the treaty.

The treaty offers several major advantages. One is to simplify the filing of patent applications on the same invention in different countries by providing, among other things, authorized filing procedures and a standardized application format. Another advantage is the longer period of time available to an applicant before he must decide whether to go to the expense of further prosecution of the application. An additional advantage is that the examining process is facilitated in those member countries which provide for the examination of patent applications.

Although the bill provides for the implementation of the treaty, it does not change any substantive requirements for securing a patent under the present United States patent statutes. The legislation merely adds to the current law new international procedures for obtaining a patent. Such procedures are optional and are not intended to replace the present domestic filing regulations. The bill further provides that the rights of priority and national treatment afforded applicants under the Paris Convention for the Protection of Industrial Property would be reduced.

The Subcommittee reported favorably S. 24 to the Committee on the Judiciary on April 28, 1975. The Committee on the Judiciary reported the measure favorably on June 19, 1975, and the Senate passed it on June 21, 1975. The House of Representatives passed the legislation on November 3, 1975, and the President approved it on November 14, 1975. A more complete statement of the Committee's views on S. 24 is contained in Senate Report 94–215 of the First Session of the 94th Congress.

II. Legislation reported by the subcommittee, approved by the Committee on the Judiciary and passed by the Senate, but no action taken by the House of Representatives

S. 719 (Mr. McClellan), granting a renewal of patent numbered 92,187 relating to the badge of the Sons of the American Legion.

The purpose of this measure is to extend the term of design patent numbered 92,187 granted to the Sons of the American Legion for protection of its emblem and insignia. The patent was first issued on May 8, 1934, for the statutory period of 14 years, and has been renewed by the Congress for two additional 14 year terms. The first extension was approved on June 27, 1949, and the second was granted on June 25, 1962. This measure would renew the patent for another 14 years from the date of its enactment into law. For over 50 years the Congress has been extending the statutory protection for symbols or badges of patriotic or religious associations. The primary purpose of such legislation is to enable these organizations to control the use of their identifying marks.

The Subcommittee reported favorably S. 719 to the Committee on the Judiciary on April 28, 1975. The Committee on the Judiciary reported the measure favorably on May 12, 1975, and the Senate passed it on May 13, 1975. A more complete statement of the Committee's views on S. 719 is contained in Senate Report 94–115 of the First Session of the 94th Congress.

S. 720 (Mr. McClellan), granting a renewal of patent numbered 54,296 relating to the badge of the Sons of the American Legion.

The purpose of this measure is to extend the term of design patent numbered 54,296 granted to the Sons of the American Legion for protection of its emblem and insignia. The patent was first issued on December 9, 1919, for the statutory period of 14 years, and has been renewed by the Congress for three additional 14 year terms. The first extension was approved on August 2, 1935, the second was granted on June 27, 1949, and the third on June 25, 1962. This measure would renew the patent for another 14 years from the date of its enactment into law. For over 50 years the Congress has been extending the statutory protection for symbols or badges of patriotic or religious associations. The primary purpose of such legislation is to enable these organizations to control the use of their identifying marks.

The Subcommittee reported favorably S. 720 to the Committee on the Judiciary on April 28, 1975. The Committee on the Judiciary reported the measure favorably on May 12, 1975, and the Senate passed it on May 13, 1975. A more complete statement of the Committee's views on S. 720 is contained in Senate Report 94–116 of the First Session of the 94th Congress.

S. 721 (Mr. McClellan), granting a renewal for patent numbered 55,398 relating to the badge of the Sons of the American Legion.

The purpose of this measure is to extend the term of design patent numbered 55,398 granted to the Sons of the American Legion for protection of its emblem and insignia. The patent was first issued on June 1, 1920, for the statutory period of 14 years, and has been renewed by the Congress for three additional 14 year terms. The first renewal was on August 2, 1935, the second was granted June 27, 1949, and the third on June 25, 1962. This measure would renew the patent for another 14 years from the date of its enactment into law. For over 50 years the Congress has been extending the statutory protection for symbols or badges of patriotic or religious associations. The primary purpose of such legislation is to enable these organizations to control the use of their identifying marks.

The Subcommittee reported favorably S. 721 to the Committee on the Judiciary on April 28, 1975. The Committee on the Judiciary reported the measure favorably on May 12, 1975, and the Senate passed it on May 13, 1975. A more complete statement of the Committee's views on S. 720 is contained in Senate Report 94–117 of the First Session of the 94th Congress.

III. Legislation reported by the Subcommittee, approved by the Committee on the Judiciary, but no action taken by the Senate

S. 22 (Mr. McClellan), for the general revision of the copyright law, Title 17 of the United States Code, and for other purposes.

Title I of this measure provides for the general revision of the copyright laws and procedures. Title II provides for the protection of ornamental designs of useful articles.

The Subcommittee reported favorably S. 22 to the Committee on the Judiciary on June 13, 1975. The Committee on the Judiciary reported it favorably on November 20, 1975. A more complete statement of the Committee's views on S. 22 is contained in Senate Report 94-473 of the First Session of the 94th Congress. This measure is is also discussed elsewhere in this report.

IV. Legislation reported by the Subcommittee, but no action taken by the Committee on the Judiciary

S. 2255 (Mr. McClellan for himself, Mr. Burdick, Mr. Philip A. Hart, and Mr. Hugh Scott), for the general revision of the patent laws, Title 35 of the United States Code, and for other purposes.

The Subcommittee reported favorably S. 2255 to the Committee on the Judiciary on August 4, 1975. A more detailed discussion of this measure is contained elsewhere in this report.

V. Legislation pending in the Subcommittee at the adjournment of the First Session of the 94th Congress

S. 23 (Mr. McClellan), for the general revision of the patent laws, Title 35 of the United States Code, and for other purposes.

Due to the favorable action taken on S. 2255, a measure to revise the patent laws, the Subcommittee postponed further consideration of S. 23.

S. 31 (Mr. McClellan) to amend the Act to provide for the registration and protection of trademarks used in commerce, to carry out the provisions of certain international conventions and for other purposes. This bill is known as the Unfair Competition Act.

S. 175 (Mr. Beall), for the relief of the estate of Albert W. Small.

The purpose of this legislation is to authorize and direct the Secretary to the Treasury to pay to the estate of Albert W. Small, out of the money in the Treasury not toherwise appropriated, the sum of $150,000 in full payment for all rights in respect to the cryptologic inventions of Albert W. Small which are now or at any time have been placed in security status by the War Department, the Department of Defense, or the Commissioner of Patents, including, but not limited to, all rights with respect to his inventions covered by patents 2,964,856 and 2,984,700 and by patent application serial no. 421,459.

S. 214 (Mr. Fong for himself and Mr. Buckley), for the modernization and general revision of the patent laws, Title 35 of the United States Code, and for other purposes.

Due to the favorable action taken on S. 2255, a measure to revise the patent laws and procedures, the Subcommittee postponed further consideration of S. 214.

S. 473 (Mr. Philip A. Hart), for the general reform and modernization of the patent laws, title 35 of the United States Code, and for other purposes.

Due to the favorable action taken on S. 2255, a bill to revise the patent statutes, the Subcommittee postponed further consideration of S. 473.

S. 1111 (Mr. Hugh Scott for himself, Mr. Baker, Mr. Bayh, Mr. Cranston, Mr. Hartke, Mr. Tunney, Mr. Williams, Mr. Inouye, and Mr. Javits), to amend the Copyright Act of 1909, and for other purposes.

The purpose of this legislation is to provide the copyright owner the exclusive right of public performance in sound recordings. The Sub-

committee held hearings on S. 1111, and a more detailed discussion of the measure is contained elsewhere in this report.

S. 1258 (Mr. Tunney), for the relief of Benjamin Baxter.

S. 1308 (Mr. Hugh Scott), for the general reform and modernization of the patent laws, Title 35 of the United States Code, and for other purposes.

Due to the favorable action taken on S. 2255, a bill to revise the patent laws, the Subcommittee postponed further consideration of S. 1308.

S. 2355 (Mr. Cannon for himself and Mr. Laxalt), to provide that four publications detailing the history of the Indian tribes of Nevada shall be subject to copyright by the Inter-Tribal Council of Nevada.

COPYRIGHT LAW REVISION

During the Second Session of the 93rd Congress S. 1361, the bill for a general revision of the copyright law, was passed by the Senate on September 9, 1974. No opportunity remained in the 93rd Congress for consideration of that bill by the House of Representatives prior to the adjournment of the Congress. A successor bill, S. 22, was introduced by Senator John L. McClellan in the 94th Congress on January 15, 1975. Other than for technical amendments and changes required by the enactment of P.L. 93–573, the bill is identical to that passed by the Senate in the 93rd Congress.

The Subcommittee reported S. 22 with an amendment in the nature of a substitute on June 13, 1975. The Subcommittee made several changes in the text of the bill adopted by the Senate in the previous Congress. The most important of these provides that the jukebox royalty shall be subject to periodic review by the proposed Copyright Royalty Tribunal, as are the other statutory royalty rates. When the bill was considered in the full Committee on the Judiciary, additional changes were made. Under both the existing copyright statute and the pending legislation, once a copyright owner of a musical work has permitted its use on a phonorecord, anyone else may also record the work upon notifying the copyright owner and paying a mechanical royalty fee. The statutory rate under the Copyright Act of 1909 is 2¢ which would have been increased to 3¢ under the bill passed by the Senate in the 93rd Congress and as approved by the Subcommittee in the 94th Congress. The Committee adopted an amendment to fix the statutory rate at 2½¢.

Another major change was the addition to S. 22 of what is now Section 118, to establish a statutory compulsory license for the benefit of public broadcasting. Under this section, as proposed by Senator Charles Mathias, it would not be an infringement of copyright for a public broadcasting entity to broadcast certain categories of copyrighted works upon compliance with the conditions of Section 118. These include the payment of reasonable royalty fees which would be established by the proposed Copyright Royalty Tribunal. The Committee also adopted an amendment by Senator Strom Thurmond to alter and delay the periods in which the statutory royalty rates could be reviewed by the Copyright Royalty Tribunal. The bill, as passed by the Senate in the 93rd Congress and approved by the Subcommittee in the 94th Congress, provided that the royalty rates shall be initially reviewed commencing 6 months after the effective date of the bill and at 5 year intervals thereafter. The Thurmond amendment

provides that the initial review shall occur 3 years after the effective date of the bill and the subsequent reviews shall take place at 10 year intervals.

PERFORMANCE ROYALTY

The Subcommittee on July 24, 1975, held a public hearing on S. 1111, to amend the Copyright Act of 1909 to establish a performance royalty in sound recordings. The same subject had previously been considered by the Subcommittee as part of the legislation for the general revision of the copyright law. A performance right in sound recordings was included in the copyright revision bill reported by the Committee on the Judiciary in the 93rd Congress, but was deleted on the Senate Floor. No performance right in recordings is contained in S. 22.

S. 1111 would require royalty payments to performing recording artists and the owners of the copyrights in such recordings by broadcasters, jukebox operators, background music services, and others who use recorded music for profit. The Subcommittee received testimony from the Chairman of the National Endowment of the Arts, the Register of Copyrights, representatives of the record industry, performers, labor, broadcasters, and jukebox operators. The views expressed by the various parties were unchanged from those reflected in the previous Subcommittee hearings on this subject. No further action was taken by the Subcommittee on this legislation.

PATENT LAW REVISION

Early in the 94th Congress, four major bills for the general revision of the patent law were introduced and referred to the Subcommittee. These are S. 23, introduced by Senator John L. McClellan, S. 214 introduced by Senator Hiram Fong, S. 473, introduced by Senator Philip Hart, and S. 1308, introduced by Senator Hugh Scott. Since the subject of patent law revision had been extensively studied by the Subcommittee in previous Congresses, the major Subcommittee effort in 1975 consisted of exploring the possibility of reporting a patent revision bill which could be generally supported by the members of the Subcommittee. The Subcommittee has been sharply divided on proposed patent legislation. For the purposes of markup, the Subcommittee utilized S. 23. At the completion of the Subcommittee markup process a clean bill, S. 2255, was introduced and reported favorably by a vote of 4 to 0 with Senator Hiram Fong not voting. No further action on this bill occurred during the First Session of the 94th Congress.

S. 2255, if enacted, would provide the most comprehensive revision of the American patent system since the Patent Act of 1836. Major provisions of the bill would require the patent applicant to make greater disclosure of relevant information to the Patent and Trademark Office; require persons dealing with the Office to act with candor and good faith; require the filing of a patentability brief; alter the terms of patents; strengthen the investigative powers of the Office; establish for the first time a form of opposition proceeding in the Office following the issuance of a patent; revise the patent fee schedule; clarify the relationship between the patent law and the State laws on trade secrets; and direct a study of the treatment of inventions made by employed inventors.

[COMMITTEE PRINT]

GENETIC ENGINEERING, HUMAN GENETICS, AND CELL BIOLOGY

EVOLUTION OF TECHNOLOGICAL ISSUES

DNA RECOMBINANT MOLECULE RESEARCH

(SUPPLEMENTAL REPORT II)

REPORT

PREPARED FOR THE

SUBCOMMITTEE ON SCIENCE, RESEARCH AND TECHNOLOGY

OF THE

COMMITTEE ON SCIENCE AND TECHNOLOGY

U.S. HOUSE OF REPRESENTATIVES

NINETY-FOURTH CONGRESS

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LETTER OF TRANSMITTAL

HOUSE OF REPRESENTATIVES,
COMMITTEE ON SCIENCE AND TECHNOLOGY,
Washington, D.C., December 18, 1976.

Hon. OLIN E. TEAGUE,
Chairman, Committee on Science and Technology, U.S. House of Representatives, Washington, D.C.

DEAR MR. CHAIRMAN: I am transmitting herewith a report dealing with the current circumstances surrounding research into genetic engineering, human genetics, and cell biology. This report was requested as a supplement to the studies performed in 1972 and 1974 entitled "Genetic Engineering: Evolution of a Technological Issue," including a first Supplemental Report of the same title.

This second supplemental report deals specifically with DNA recombinant molecule research, a field which is now receiving much public attention. The report is especially timely and of particular significance in view of the issues raised by the recent developments in this field, and I commend the report to you and all Members of the Committee. It is my hope that the Committee will consider holding hearings on this important area during the next Congress.

Sincerely,

JAMES W. SYMINGTON, *Chairman,*
Subcommittee on Science, Research and Technology.

LETTER OF TRANSMITTAL

House of Representatives,
Committee on Science and Technology,
Washington, D.C., December 13, 1976.

Hon. Olin E. Teague,
Chairman, General Law Science and Technology, U.S. House of Representatives, Washington, D.C.

Dear Mr. Chairman: I am transmitting herewith a report dealing with the current circumstances surrounding research into genetic engineering, human genetics, and cell biology. This report was requested as a supplement to the studies performed in 1972 and 1974 entitled "Genetic Engineering: Evolution of a Technologic Issue," including a first Supplemental Report of the same title.

This second supplemental report deals specifically with DNA recombinant molecule research, a note which is now receiving much public attention. The report is especially timely and of particular significance in view of the issues raised by the recent developments in this field, and I commend this report to you and all Members of the Committee. It is my hope that the Committee will consider holding hearings on this important area during the next Congress.

Sincerely,

Louis W. Sullivan, *Chairman,*
Subcommittee on Science, Research and Technology.

LETTER OF SUBMITTAL

THE LIBRARY OF CONGRESS,
CONGRESSIONAL RESEARCH SERVICE,
Washington, D.C., December 17, 1976

Hon. JAMES SYMINGTON,
Chairman, Subcommittee on Science, Research and Technology, Committee on Science and Technology, U.S. House of Representatives, Washington, D.C.

DEAR MR. SYMINGTON: I am pleased to transmit this report entitled "Genetic Engineering, Human Genetics, and Cell Biology: Evolution of Technological Issues-Supplemental Report II" prepared at your request.

The study examines the developments associated with the controversial subject of DNA recombinant molecule research, a rapidly advancing research field in molecular biology supportive of progress in plant and animal genetics. This research field has produced national and international interest as a case history study of the emerging problem of public participation in science policy and the legal, ethical, and moral implications of an expanded role of the public in planning and applying scientific research. The study is intended to supplement earlier committee reports on this subject by providing an analysis of activities, with emphasis on DNA recombinant molecule research, which have taken place since 1974.

The committee print was prepared by Dr. James M. McCullough, our Senior Specialist in Life Sciences, Science Policy Research Division, Congressional Research Service. Dr. McCullough consulted with a number of investigators during the preparation of this report. We would like to acknowledge at this time the very helpful advice and constructive criticism offered by Dr. Joshua Lederberg, Department of Genetics, Stanford Medical School; Dr. Bernard D. Davis, Bacterial Physiology Unit, Harvard University; Dr. Richard Trumbull, Executive Director, American Institute of Biological Sciences; Dr. Robert Acker, Executive Director, American Society For Microbiology, and Dr. Bernard Talbot, Office of the Director, National Institutes of Health, although the final responsibility rests with the author and the Congressional Research Service. Mr. Douglas Paynter, Information Resources Assistant, Library Services Division, Congressional Research Service, provided research assistance, and manuscript preparation was performed by Ms. Sandra Kay Al-Nazer and Ms. Jeannette E. Porter, Editorial Assistants, Science Policy Research Division. This study was coordinated with and reviewed by Mr. Philip B. Yeager, and Dr. Gail M. Pesyna, professional staff members of the Subcommittee on Science, Research, and Technology.

We appreciate this opportunity for the Congressional Research Service to cooperate in this study of a subject of such far reaching and serious social significance.

Sincerely,

LEON M. COLE,
Acting Director

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I. Introduction

A. Purpose

Nobel Laureate James Watson chose the topic of cloning and genetic engineering as the theme of his address to the House Science and Astronautics Committee [now the House Science and Technology Committee] in 1971.[1] His intention was to direct the committee's attention to the capabilities in molecular biology and genetics which those in the forefront of molecular biology research knew were near. Partly as a result of his remarks, the committee directed the preparation of a study which surveyed the status of this research.[2] The committee's first report confirmed the need for maintaining an awareness of the issues evolving in the technologies of genetic research. A second report [3] indicated the accelerating pace of these developments. One of these issues in genetics has now assumed a position of urgent importance throughout the world and is receiving the attention of numerous public policy making groups. Several policies of fundamental importance in the selection, management and application of this new technology are now considered of sufficient urgency that congressional attention seems necessary.

Biomedical research has entered a new era of public concern. The recipients of the results of modern medicine have been accustomed to accepting the benefits of developments in antibiotics, organ transplant, and new therapies and surgical techniques without question for some time. This acceptance of the "benefits" of research without full consideration of the costs has been called into question in increasing numbers of instances within the past decade. With the advent of organ transplantation techniques the realization arose, partially as a result of a sensitivity to the unique position of both the donor and recipient, of the associated moral, legal and ethical implications of such biomedical techniques. The growing awareness of the public to the risks associated with the development of new drugs focused attention on the use of experimental human subjects for evaluating such drugs. The refined techniques for examination and treatment of the developing fetus aroused concern, partially because of its close association with abortion as another public policy issue, and legislators acted to introduce control in this area of research.

Now, scientists have shown that they possess the tools to begin controlled manipulation of the very foundation of life itself. It is pos-

[1] Panel on Science and Technology. Twelfth Meeting, International Science Policy. Proceedings Before the Committee on Science and Astronautics. U.S. House of Representatives. 93d Congress, 1st session. January 26, 27, and 28, 1971: 336–366.

[2] U.S. Congress. House. Committee on Science and Astronautics. Subcommittee on Science, Research, and Development. Genetic Engineering: Evolution of a Technological Issue. [Washington, U.S. Govt. Print. Off.] 1972. 119 p. (92d Congress, 2d session)

[3] U.S. Congress. House. Committee on Science and Astronautics. Subcommittee on Science, Research, and Development. Genetic Engineering: Evolution of a Technological Issue. Supplemental Report I. [Washington, U.S. Govt. Print. Off.] December 1974. 215 p. (93d Congress, 2d session. House).

sible to determine accurately the sex of the developing fetus, to ascertain in utero whether the fetus possesses genetically induced abnormalities of many types, and to provide reasonably accurate guidance to prospective parents about the probabilities of bearing defective children. It is becoming obvious that these capabilities, supported by continuing research, are nearer to general application than had been anticipated only a few years ago.

It is the purpose of this report to provide a current perspective of one of these capabilities in genetics—the capability to effect "genetic engineering." The popular term "genetic engineering," while having many interpretations, is gradually being associated more specifically with man's capability to reconstruct the basic substances determining the heredity of an organism (the DNA). This type of research, known as *DNA recombinant molecule research*, offers the prospect of eventually being able to control or change the genetic information inherited by an organism. The developments in molecular biology or "genetic engineering" are of particular importance because of the rapidity with which these new capabilities are evolving and also because of potential risks being perceived by the public as associated with such research. The progress in medical genetics and related issues in cell fertilization and cell culture techniques as well as the status of fetal research provide a continuum in genetics research which produces related public policy issues. These issues will be examined in detail in a later committee report.

There has been vigorous "public" response to the new developments in genetics. In some instances, the response has been careful and conservative and based upon the best information available. In other instances, questions have been raised about the adequacy of societal involvement in the process of making decisions about the application of such new techniques in the conduct of research. The need for legislation to provide for more adequate public participation and to interpose regulations is growing as an issue of congressional concern.

Although "more public participation" is voiced as a major factor of concern in consideration of issues of the type discussed herein, it should be noted that this factor itself is difficult to define or to secure simply. Public participation has many meanings depending upon a particular situation or problem. It might mean representation as in the political sense; it may refer to specific public interest groups; it may refer to an "adequate representation" of informed, noninvolved (researchers not in the field of interest) individuals or individuals with unique capabilities; or groups representing other fields of expertise such as ethics or law. "Public participation" on scientific issues requires informed participation in order to be meaningful, and an associated implication is that such participation will be of a type that will receive attention. The problem then becomes one of determining when the public participation is adequate for a particular problem and whether the compromises decided upon are truly attentive to societal needs. "Public participation" is an issue that increasingly, as with legal and moral issues, will require careful evaluation. This is one of the reasons that the DNA recombinant issue is of such interest as a case history opportunity to explore participatory decision making at an

early stage of research. There are, of course, many other factors involved in the DNA issue which makes it important in terms of the establishment of new concepts of public policy determination.

This report will be directed at an analysis of developments in genetic engineering, and primarily DNA recombinant molecule research, since 1974 which appear to have a particular significance at this time in terms of issues of immediate potential interest to the Congress. It is impossible in any single paper to provide the detail on these subjects required by investigators in the field, nor would such detail be desirable for the use of congressional policy makers who have limited time to become familiar with issues of concern. Wherever possible, additional citations will be given for additional readings or for further information on summary statements of particular concern. It is hoped that this second supplemental report will be sufficiently detailed to provide the basis for any additional evaluations the committee may desire to initiate. The developments in all of the areas of genetics of potential interest are so rapid that it is almost impossible to insure absolute continuity and it will be necessary for the reader to maintain a sensitivity to these subjects so that new discussions may be fitted into a proper perspective. It is for this reason that this second supplemental report is limited primarily to the new knowledge in genetic engineering. However, comments to the committee about any of the topics in genetics are welcome at any time so that the committee members may be made aware of particular issues of concern which may not have been adequately addressed in this report. The reader also is invited to examine the 1972 and 1974 committee reports on subjects or citations to earlier reference material for recommended background information.[4]

B. BACKGROUND OF THE ISSUES

In the short interval between the publication of the earlier committee reports and this second supplemental report, the advances in genetic research have been remarkable. In some areas, the rate of progress has far exceeded the time estimates provided in the earlier reports. In other areas, while the estimates of potential application still indicate no immediate or near term application to human problems, the applications in plants and animals of agricultural or other commercial importance appear to be even closer.

As noted in the earlier reports, there is a full spectrum of related and overlapping scientific work leading from the fundamental work in molecular biology which lends increasing credence to the predictions of actual "genetic engineering" and to the almost routine use of complex diagnostic techniques in medical genetics.

Historically, and in the perspective of the formal study of man, the developments in genetics have proceeded in an uneven fashion. For example, as noted in a recent article, 1976 marks the tricentennial of the discovery of human sperm.[5] Most persons are at least vaguely familiar with the developments which led to Anton van Leeuwenhoek's

[4] Ibid.

[5] Brody, Jane E. 1976 Marks Tricentennial of the Discovery of Sperm. New York Times. December 1975: 29.

discovery of the microscope. Among his other observations, he reported to the Royal Society in London in 1677 the discovery of human sperm by a medical student who used this new scientific device. As reported in the 1972 committee report, the works of Gregor Mendel on fundamental principles of heredity were not accepted with a full understanding of their significance when reported in 1865. It was not until 1956 that a final accurate determination of the human chromosome number (46) was established and from this point on certain genetically determined diseases could be positively correlated with additions or deletions from this "normal" number.

The most recent discoveries in genetics have been of special interest because there has been an increased awareness of the social as well as the scientific significance of this area of research. The deepest of human emotions can be touched by the birth of a genetically defective child; the guilt of a parent furnished with the knowledge that the defect had been transmitted is particularly acute. The tremendously complex issues of abortion and "right-to-life" are now interwoven with the availability of techniques to detect prenatally a number of dangerous genetic diseases and modern medicine offers abortion of such defective fetuses as an alternative to a life of suffering for both parents and child. Arguments over race and IQ, biased and complex as they may be, are further indications of the implications to society of our increased understandings of the principles of genetics.

When it is realized that it took almost 100 years after the work of Mendel to get an accurate count of the number of chromosomes in man, it is truly amazing to contemplate the developments within the last decade and exciting to view the potential of the near future. At the same time this excitement must be tempered by consideration of several complex issues. The identification in 1953 of the precise molecular structure of DNA, the information bearing substance in the chromosome (which we now know carries the determining hereditary chemicals or genes) by Watson and Crick is one of the epic discoveries in man's scientific endeavor. From their work scientists have moved on to the accumulation of discrete units of knowledge about gene function and structure. There have been developments which are leading to a detailed understanding of gene control. The coding of the biochemical messages from the DNA to the cell's structural components is being deciphered. The biochemistry of the translation of the gene code information to function is being subjected to ever intensified analysis. Chemical start and stop signals are being identified and indeed even synthesized in an operational mode. The association of genetic errors with metabolic diseases and structural abnormalities has been established.

The matching of certain components of the chromosome (DNA or deoxyribonucleic acid) with function in 1961 by Dr. Marshal Nirenberg settled another important debate about the molecular biology of the gene. Years of research by hundreds of researchers can hardly be adequately summarized in a single document or even a series of reports no matter how voluminous. Nevertheless, as will be noted it is becoming increasingly essential that an effort be made to gain sufficient understanding to deal intelligently with these subjects.

The limitations of diet, drugs, or enzyme therapy to correct the effects of genetic defects have led to interest in the possibility of correcting the problem at the level of the gene. The problems with cancers which are suspected of being associated with gene control abnormalities have produced an interest in developing tools to study the molecule at the most basic level. The evidence suggesting that cancer viruses may become a part of normal cellular DNA has focused research attention on the systems of transfer of DNAs between cells. All of these efforts are intimately related to the research in genetic engineering.

Modern human genetics has been described as now providing social choices for our future where previously there were no choices. A significant political issue is to determine whether such choices should be made available and if so how the essential factors can be identified to provide reasonable assurance that the proper choicees are made (and by whom and under what circumstances and constraints).

Platt said:

> It is no longer enough to go on working in the labs just to build another brick in the temple of science, hoping it will fit into some great intellectual synthesis in 30 years. Nor is it enough to be politically concerned, working by circulating petitions or trying to influence the government in some 3 month crisis.
>
> Our urgent social problems now are more like war-time problems, such as anti-submarine warfare or the development of atomic energy. These are cases where we must get different experts and inventive minds together to make interdisciplinary operations-analysis and action-oriented designs and pilot studies, but where the time scale is that of a crash program, permitting, say, a few months or a year or two of study before we must come up with some much more effective solutions.[6]

While Platt was not referring only to research in genetics, nor even specifically to the precise problems to be discussed in this report, his concern is still appropriate. It can be interpreted to mean that *science policy* problems require the urgent analysis, not the science research needs. Indeed, in the context of genetic engineering and related genetics problems in some areas, there are those who have examined this problem and ask whether the rush to expand the fields of research should not be preceded by a more complete analysis of the public policy implications of such research. In this regard, Francoeur highlighted some of the observations made by others about new technological developments.[7] Perhaps there is a need for a mechanism to represent those advocating a selected legal moratorium on some research and application. This approach would be difficult of course. Which areas of research should be identified as "off-bounds"? What kinds of laws need to be formulated, passed, and policed universally without bias? What would really happen in terms of the prevention of harm or prolongation of the achievement of benefits? How could we move into the off-bounds research areas without new legal knowledge to deal with such unknowns? Would such actions drive research underground and out of sight of public policy examination and control?

There are historical precedents for this latter action and even today there is frequent discussion that national actions may simply result on

[6] Platt, John. The Scientific Urgencies of the Next Ten Years. Michigan Mental Health Research Bulletin. v. 4. 1970 : 12.

[7] Francoeur, Robert T. We Can—We Must : Reflections On the Technological Imperative. Theological Studies. v. 38. September 1972 : 428–439.

occasion in the transfer of research with potential commercial value into other nations where prohibitions do not exist. Could such actions result in the need for the establishment of a "deep freeze" information bank with some social judgment process determining when such information could be released for technological application? If so, who decides? What value judgments should be used? There are implications in his thesis which bear further examination, for to some, public control appears to offer a viable and effective solution to the new public policy issues produced by many technological innovations. Controls would establish a public recognition of the scientist's drive to inquire and produce new knowledge. The dissemination of new knowledge by modern communication methods promotes developments on an international level. With controls, there could be a continual testing and evaluation of the implications of the innovations before new steps take society beyond the point of no-return.

Lappé discusses some of these issues more specifically in terms of several of the arguments which evolved in genetics.[8] Crotty pursues the thesis of public involvement in the scientific decision making process.[9]

He asks the same question being asked in an increasing number of congressional discussions. To what extent are the "people" really sharing in decision making? Is there really a full exchange of information? Are scientists really willing to accept the intercedence of the public in the examination of the worth of their research? Crotty believes that in the field of genetic engineering policy analysis there is a need to differentiate between those developments which might have a genuine and easily identified therapeutic use as contrasted with the research for which there is no immediate therapeutic development. It is his opinion that much of the difficulty in this particular issue arises from the problem of evaluating the worth of the non-therapeutic research.

These few introductory comments are intended to serve as an outline of the questioning which has been associated with the various issues discussed within this report. The issues are complex. The rate of progress is rapid. If developments in this area are not to be treated as was the case in the nuclear energy issue, until after the appearance of the technology and the investments in the program, then the issues must be confronted very soon. It is essential that the true significance of the research, particularly in genetic engineering, be fully appreciated, so that the necessary attention may be focused on policy determination. Oliver Smithies, Professor of Genetics and Medical Genetics at the University of Wisconsin, put this new work in these terms:

> In my opinion, the ability to clone DNA fragments from higher organisms represents one of the most significant advances of 20th century biology. The procedures combine the ability to purify genetic material to homogeneity with the ability to replicate the material in virtually unlimited quantities.[10]

[8] Lappe, Marc. Moral Obligations and the Fallacies of Genetic Control. Theological Studies. v. 33. September 1972: 411–427.

[9] Crotty, Nicholas. The Technological Imperative: Reflection on Reflections. Theological Studies. v. 33. September 1972: 440–449.

[10] Smithies, Oliver. Letter to Dr. DeWitt Stetten, Jr. Deputy Director for Science. National Institutes of Health. [Letter written in response to a request for evaluation of proposed guidelines for DNA recombinant molecule research.] November 26, 1976.

II. Developments in Genetic Engineering

A. A Summary of the Status of DNA Recombinant Molecule Research

1. *Introduction.*—DNA recombinant molecule research is quite diverse and dependent upon a relatively high level of technological capability at the research stage. (The practice of the technology, once protocols are established, requires a lower level of ability. Some commentators have suggested that even undergraduate students could complete the work.) The work is conducted beyond the range of normal visibility, and with the exception of the studies with electron microscopic techniques, dependent upon delicate tests, analysis, and determination of biochemical functions. The investigator tries to isolate and purify extremely small quantities of very complex molecules and is required to utilize exquisite techniques to test the models hypothesized and ascertain the validity of his conceptions.

When an investigator reports the isolation of a particular gene fragment, he is usually dependent upon his experimental methodology to confirm or deny his interpretations. Occasionally, growth or the failure to grow can be utilized as evidence. That is, if a particular molecular fragment is isolated, the determination of the functions produced by this fragment are frequently the first proof that the fragment is indeed present in the system under study. Further proof is obtained by carefully induced reactions involving immunological tests, other biochemical tests or analyses which have evolved for the purpose of characterizing the chemical nature of a molecule, the utilization of theory to construct possible molecular structures, and often the use of other chemical-physical processes including electron microscopy, to support his experimental hypotheses.

This discussion is an oversimplification of the various cross-checking and replication experiments which the thorough scientist conducts to confirm or deny the validity of his results. The important point for purposes of this report is to understand that the geneticist or biochemist/molecular biologist is working on a scale of size frequently demanding the use of techniques to acquire indirect evidence of experimental results. These results must then be evaluated with various other methodologies to support and confirm the interpretation. This type of work is tedious and definitely demanding of a high degree of care and precision to avoid inadvertent contamination and to produce quality data.

An entirely new vocabulary has evolved with this new research. A system of code names for variants of various microorganisms, fragments of microorganisms, viruses of various types, and terminology for the precise enzymes used for synthesis and cutting of large molecules, makes the task of understanding the significance of the scientific reports on developments extremely difficult for the non-specialist. Such

a new language is common to all of the highly specialized fields of endeavor. In space, electronics warfare, psychology and business, the specialist develops and uses a language which permits communication quickly and accurately with his colleagues. It is the new language which is used to describe the research in DNA recombinant molecule research, as well as the complexity of the biochemical reactions involved, which often obscures the significance of these developments from the concerned lay person. Nevertheless, to the credit of the biochemists, geneticists, molecular biologists, microbiologists and others who are conducting this research, a very real effort has been made, from the very beginning of the search for guidelines to control research, to explain to the non-scientific public, the nature and great importance of this new field of investigation.

However, it should be recognized that the scientists who conduct this research are under intense pressure to carry out their chosen tasks. They are research investigators as well as concerned individuals. Their immersion in their work often makes them unaware of the difficulty that lay persons have in understanding the complexities of their work. As an example, several of these investigators, while at a public meeting, had just spent some time discussing the various problems associated with the certification of a newly developed vector. A precise transcript of their discussion would be almost totally unintelligible to the casual observer and yet these scientists had been discussing the research on the very issue of risk about which so much public concern has been expressed. There was little obvious awareness, during the intensity of the discussion, that the lay members of the committee and the observing public were "at sea" with regard to the technical details of the biological processes being examined. This same scientific group, moments later, expressed amusement at the unintelligible "jargon" which lawyers used to discuss patent problems of law associated with these new DNA recombinant developments.

It is obvious that a high degree of public visibility must be given to DNA recombinant molecule work if there is to be informed citizen participation in the determination of policies on this research. This committee report has as one of its objectives, an attempt to provide one more source of information to assist national policy makers to understand the critical nature of the work as well as to provide sufficient information to evaluate the risk/benefit analyses which are being discussed. If this objective is to be met, through the efforts of concerned researchers, the news media, this committee report, or any other medium, it will be necessary for the non-scientist to have at least an introductory understanding of the research. This understanding, as with all new knowledge, requires a careful consideration of the meanings of the terms being used to describe the research for, as with the language of law and politics, misinterpretations easily develop if the meaning of descriptive terms is not understood fully.

2. *Some Terminology of DNA Recombinant Molecule Research:*

(*a*) *DNA:* The acronym DNA has evolved quite naturally from the precise chemical terminology for the molecules which constitute the inheritable material in the typical cell; this substance is known as deoxyribonucleic acid—DNA. The research of interest in this section is associated with manipulations of this basic molecule which contains the genes that regulate the characteristics and life functions of the

cell, and ultimately the entire organism in the case of a multicellular organism. The discovery of DNA, its chemical nature, and the significance of this molecule in genetics is discussed in more detail within several papers included in the appendix of this report as well as within previous committee reports on the evolution of developments in genetic engineering.[1]

(*b*) *Recombinant Research:* The term "recombinant" refers to the fact that investigators have developed techniques to "recombine" fragments of DNA into new molecules. That is, it is now possible to chemically cut the DNA molecule apart and then to recombine various fragments or portions with some precision, into a new molecule—hence, the term recombinant molecule.

(*c*) *Host Cell and Biological Containment:* The term host is not new in ordinary vocabulary and in the biological science it has a similar connotation. In the case of DNA recombinant work, the term host is usually used to refer to the cell into which the recombinant molecule is introduced in order to find out if the new molecule can be reproduced or will function. The host cell may be one of the small microscopically sized bacteria or it may be another cell, or in certain types of research it may even be possible to use a totally synthetic environment, the essential chemicals in the right proportions within a test tube. It is more common to find that the host is a microorganism and at least in these early stages of recombinant work, a host has been selected for which a great deal of genetic information is already available.

The selection of the host cell for replicating (cloning or reproducing) the recombinant molecule is quite frequently a relatively "safe" variant of the bacterium known as *Escherichia coli or E. coli.* The "normal" strain of *E. coli* is a microorganism that is a common inhabitant of the human intestine; as an inhabitant of this environment the normal bacteria are found in enormously large numbers and perform a number of vital functions within the intestine. It is possible, however, for *E. coli* to produce serious disease in the human being if the blood stream is invaded or if other untoward events contribute to some instability in the normal floral composition of the intestine. Illnesses such as nausea and diarrhea, are quite common results of an upset in the normal intestinal activity of *E. coli.* The K–12 strain of *E. coli* used in the DNA recombinant experiments does not have this degree of pathogenicity—the pathogenic strains such as those which can produce blood infections are biochemically distinct from K–12. It is important to understand that while the DNA recombinant molecule researcher uses *E coli* as a primary host cell for testing or multiplying the recombinant molecule which has been constructed, it is a laboratory variant of *E. coli* which is the test vehicle; a variant not commonly found in a human intestine. There are many strains of *E. coli* and some variation of strains occur normally within the intestine as a result of environmental changes induced by the use of drugs, changes in diet, or other disturbances in human activity.

It is also important to understand that the investigators using this host cell are concentrating their efforts to develop other forms of *E. coli* which have been deliberately modified to "disable" the cell still further. This is usually done by inducing mutations (by a number of

[1] U.S. Congress. House. Committee on Science and Astronautics. Supplemental Report I. op. cit.

special techniques in microbiology) which provide a cell that has very special requirements for growth and reproduction. The logic of this approach is to produce an organism which meets the needs of the laboratory investigator for a cell which will provide the environment for the multiplication or testing of his newly created recombinant molecule and yet is a host cell which could not survive in a natural environment because of its new and fastidious growth requirements. In other words, the development of such mutants is intended to insure that inadvertent escape of such a host cell containing a recombinant molecule would result either in an inability to reproduce or more likely the death of the cell. This concept is referred to as *biological containment.*

(d) *Recombinant Vectors:* While it is possible, under some chemical conditions, to introduce mixed fragments of DNA directly into a host cell, the preferred method is to incorporate the fragments of DNA into another DNA containing structure which can enter the cell with a higher degree of efficiency and with the assurance that the specific desired recombinant is indeed being incorporated. For this reason, the DNA recombinant molecule researchers have concentrated on using "vectors" to transport the DNA fragments. Again, familiarity with *E. coli* has enabled the investigator to use extranuclear DNA containing structures called plasmids which are found in bacteria. These plasmids have the capacity to be self replicating within the cytoplasm of the cell, contain DNA similar to the more typical DNA of the bacteria, but have the advantage of being smaller units susceptible to ready manipulation. As a result, attention has been concentrated on gaining knowledge about these plasmids so that these structures can be extracted from the bacteria, cut and manipulated to include new fragments of DNA. The newly constructed plasmid then can be introduced into the host cell, again usually *E. coli*, and replication of the plasmid occurs simultaneously with reproduction of the cell. After a period of reproduction of bacterial cells (perhaps a division every 20 minutes) the researcher will now have available for further test and evaluation, a sufficient quantity of the recombinant molecule to permit biochemical analysis and measurement. If the new molecule is present, then the introduced DNA fragment can be identified. Since a major objective of DNA molecular biology research is to find a technique to identify the function of specific fragments (genes) of the total DNA molecule of an organism, this recombinant technique can simplify this difficult task. By careful manipulation of the total DNA molecule of an organism, each fragment can be correlated with function, and it is hoped that eventually the location of each gene/function can be constructed for each chromosome. Because of the commonality of the biochemical nature of all DNA, regardless of the species source, it is now believed that there should be no reason why mammalian chromosomes (including man's) could not be examined fragment by fragment within recombinant molecules multiplied in bacteria or some other host cell. There are some functions which may not be expressed within the capacity of a bacterial host cell and for this reason, other host cells will eventually be included.

The American Society of Biological Chemists held a symposium on plasmids in 1975.[2] Attempts are being made to gain an understanding of the biological functioning of plasmids from various bacterial strains. This information is critically needed now because of the accelerating emphasis on the use of plasmids as vectors for transferring recombinant DNA molecules into bacterial cells for cloning. The plasmids provide a variety of traits and are found in numerous species. An important characteristic is the plasmid's physical separation from the chromosome as a genetic structure in the bacterial cell and its genetic stability. The availability of a wide variety of plasmids permits the study by both biochemical and physical methods (e.g. electron microscopy) of the relative structure-function relationships among plasmid elements from different bacteria.

Plasmids are known to mediate such properties as antibiotic resistance, pathogenicity for plants and animals, and ability to degrade and utilize many natural and synthetic organic substrates. Some plasmids are potential vectors for transfer of genes between bacteria in different genera. These plasmids are said to be able to cross species' barriers naturally.[3] Much less is known about the function of plasmids in higher plants and animals that could be used for effective implants of genes. This area of research will require much more work before the "genetic engineering" of higher organisms can be attempted as with bacteria.

A virus is essentially a unit of DNA (or RNA—ribonucleic acid, with a chemical structure very similar to DNA) with a protein coat. For this reason, the value of viruses as vectors for carrying introduced fragments of DNA from other species is also under examination.[4] Bacteriophages in particular are in common use. The DNA "phages", or viruses which "infect' bacteria, are relatively small units of DNA and thus the possibility of working with small fragments of DNA increases the sensitivity of the genetic/biochemical analysis which is conducted. Since viruses multiply within the bacterial host and eventually cause "lysing" or death of the host cell, the researcher can readily determine the success of his experiment by observing the growth and development of his bacterial colonies. Further, by careful selection and isolation, the identification of the functions transported by the recombinant molecule, or the hybrid phage, is analogous to the use of plasmids as vecters.

(*e*) *Molecular Cloning:* A clone is a population of cells derived by asexual reproduction from a single cell. The process of securing an increased quantity of the recombinant molecule by replication in a host cell is referred to as molecular cloning. [Cloning has other biological applications as noted elsewhere.] As discussed by Hamer and Thomas, this process is an important tool for purifying and increasing

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[2] Plasmids. Symposium of the American Society of Biological Chemists. 59th Annual Meeting of the Federation of American Societies for Experimental Biology. Federation Proceedings. v. 35. July 1976 : 2024–2043.

[3] Saunders, J. R. Aspects of Plasmid Behavior. Report on a NATO Advanced Study Institute On the Biology Of Bacterial Plasmids. Kavouri, Athens. July 5–16, 1976. Nature. v. 262. August 12, 1976 : 536.

[4] Campbell, Allan M. How Viruses Insert Their DNA Into the DNA Of the Host Cell. Scientific American, v. 235. December 1976 : 102–113.

the quantity of specific fragments of DNA. The use of new restriction enzymes is under continuing evaluation in order to increase the versatility of the technique.[5]

A recombinant molecule (via phage or plasmid vector) is incorporated into a small number of *E. coli* cells. These hybrid plasmids are replicated by the usual biological processes during the growth and division of the bacterial cell. This precise duplication (cloning) of the recombinant molecule (the new plasmid) results in a "doubling" of the number of cells as well as plasmids each time a cell reproduces. Further doubling and redoubling results in a logarithmic increase in numbers of bacterial cells until the naturally self limiting growth of cells on a single culture plate slows the growth. If desired, the culture of cells containing the recombinant molecule (plasmid) could be redistributed on new growth media and an almost unlimited quantity of cells with the new recombinant molecules could be produced. For industrial purposes, this would be the logical technique. Indeed, in the production of vaccines, this is essentially the process by which large numbers of cells (or viruses) are cultured. Since there is insufficient knowledge at this time to understand all of the potential effects of recombinant molecules in the host cell, particularly in combination and in new relative positions to other genes on the vector (plasmid or phage), the researchers have suggested that for most of these experiments there should be a limitation placed upon the total volume of cells which can be cultured for purposes of limiting the availability (and providing some safety constraints) of the new recombinant molecule [the guidelines set an upper limit of 10 liters with recombinant DNA known to make harmful products].

It can readily be understood, once this concept is grasped, how some valuable product, such as insulin, could be produced by cloning within the bacterial (or other) cell. Fragmentation and processing of the cell contents would permit concentration of the desired new product, and an important substance could be made available. This "biosynthetic" technique could, in many instances, not only provide increased quantities of essential substances but might also provide these substances in a cost effective process. In fact, some of the needed medicinals probably could not be synthesized in any other way at this time.

(*f*) *Prokaryote-Eukaryote Research*: One of the objectives to be determined in DNA recombinant work, as well as a further examination of the universality of DNA, is whether DNA from a major group of "primitive" cell types, the prokaryotic cell [such as bacteria or other cell types without an organized nucleus with a nuclear membrane surrounding the chromosomes] can be exchanged with the DNA of eukaryotes, those cells with a highly organized nucleus [all of the higher organisms including man]. Such research would involve the isolation of DNA fragments from eukaryotic cells and transfer of these fragments via vectors (plasmids) to the host bacterial cell and then to determine whether the eukaryotic fragment is replicated in the new cell host and, of even greater importance, to determine

[5] Hamer, Dean H. and Charles A. Thomas, Jr. Molecular Cloning of DNA Fragments Produced by Rstriction Endonucleases SalI and BamI. Proceedings of the National Academy of Sciences. v. 73. May 1976: 1537–1541. (See also: Marx, Jean L. Molecular Cloning: Powerful Tool For Studying Genes. Science. v. 191. March 19, 1976: 1160–1162).

if the function regulated by the eukaryotic fragment is performed (such as the synthesis of an enzyme). Struhl isolated a segment of DNA from the eukaryote *Saccharomyces cerevisiae* (baker's yeast) and constructed a recombinant hybrid using bacteriophage lambda DNA as a vector. When this hybrid was incorporated into a strain of *E. coli* biochemical evidence was obtained that the yeast gene was functional within the bacterium.[6] The interpretation of the results of this experiment is that the transcription necessary for the biochemical synthesis observed was most likely initiated from the segment of yeast (eukaryotic) DNA which had been inserted into the recombinant molecule. This is a significant report of research also as it relates to the arguments concerning the question of evolution of genes from prokaryotes to eukaryotes or vice versa. It is related to studies of the question of the safety of this kind of research because of the arguments that the current DNA recombinant molecule research is creating cell hybrids which could not occur in nature. There is no full agreement that natural exchanges between such groups actually do not occur but one way of testing this theory is to continue research of this type.

The risk/benefit analysis of the new recombinant work does include a consideration of the possible acceleration of evolutionary change in various organisms. Opponents indicate that the usual environmental selection processes are being circumvented as a result of the artificial recombination efforts. For this reason, interest has been increased in the acquisition of more knowledge concerning the possible natural exchange of genetic units between diverse organisms. In a recent report,[7] the results of a study indicate that trans-species infection might be possible through viral infection. These investigators demonstrated the presence of similar viral genes in both the pig and the rat. Since viruses are known to have the capability to pick up genes from a host and incorporate these host genes in the viral DNA, it has been speculated that natural interspecies viral infection may be a system of gene transfer in evolution. Bacterial viruses (phages) are actually used in recombinant work. In the case of natural exchange via viruses, however, the processes of selection may require millions of years while in recombinant work, only the manpower of the laboratory limits the rate at which such recombinants can be produced. It should be kept in mind, however, that the possibilities for "exchange" in nature occur in the entire vast arena of biological contact. Selection processes while acting over a longer period do result in the formation of "new" recombinants. Some of the work thus far has shown that recombinant DNA is "maladaptive" and fails to survive in nature.

Dr. Terry Rabbits reported at a genetic engineering meeting in Glasgow that he had inserted a specific mammalian gene into bacteria. (His work follows within weeks the announcement of three similar claims from American and European laboratories.) The gene for globin, the major protein in red blood cells was inserted into bacteria.

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[6] Struhl, Kevin *et al.* Functional Genetic Expression of Eukaryotic DNA in *Escherichia coli*. Proceedings of the National Academy of Sciences. v. 73. May 1976: 1471–1475.

[7] Benveniste. Raoul L. and George J. Todaro. Evolution of Type C. Viral Genes: Preservation of Ancestral Murine Type C Viral Sequences in Pig Cellular DNA. Proceedings of the National Academy of Sciences. v. 72. October 1975: 4090–4094.

The gene was obtained by using a unique technique, part of other developments in biochemistry—he did not dissect out the globin regulating gene by restriction enzyme techniques. Instead a reverse transcriptase enzyme in pure form was used to make a DNA copy of the RNA messenger for this gene—thus getting a "pure" gene which could then be inserted.[8]

DNA recombinant molecule research requires the skills of the microbiologist, biochemist, geneticist, and virologist. A significant discovery which opened this research to rapid development was the isolation and purification of a series of bacterial enzymes. These enzymes, known as restriction enzymes, provide the means to "cut" DNA molecules into fragments by reactions at specific chemical sites within the DNA molecule. The site of cutting can be determined by the enzyme selected to produce the cleavage. Other enzymes, called ligases, can be used to recombine or "anneal" the cut DNA molecule and bind the new fragment into the vector which also has been subjected to a similar biochemical reaction. Then the new fragment, now incorporated in the recombinant molecule can be cloned as described earlier.

(*g*) *Gene Synthesis*: Interesting variations for securing DNA are becoming available. Recently, Dr. Harr Gobind Khorana and his research team completed nine years of research on the total synthesis of a gene. This synthetic gene has been demonstrated to be functional by transferring the gene into a cell and observing the biochemical evidence of activity. Earlier work on the gene had been completed by 1973 but final synthesis had to await the resolution of the information on the sequence of chemicals necessary to control the initiation and cessation of activity of the synthetic gene. This type of work is very laborious and much more time consuming than the recombinant work which utilizes genes already present in an organism. However, the potential for combining the totally synthetic gene with recombinant techniques may be viewed as a part of the overall development of the capability to control genetic activities. At the very least, the ability to synthesize precisely a gene, thus knowing the exact sequence of elements within the molecule, adds to the available technologies for probing the functions of genes. Some investigators in DNA recombinant work see the synthetic route of inquiry as a desirable approach for determining the structure-function relationships of genes.[9] The synthesis of a precisely identified gene which might be introduced into an organism is seen as being a lesser degree of potential risk than the potential risk from cutting the same gene out of a living organism and transferring or cloning this gene. In fact, Dr. Ramamoorthy Balagage, one of the team members in this historic synthesis, reportedly noted that this gene synthesis poses no risk because it is a single gene already present in a living system.[10]

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[8] Szekely, Maria. Two Approaches to Gene Synthesis. Nature. v. 263. September 23, 1976: 277–278 and Genetic Engineers Put Animal Genes into Bacteria. New Scientist. March 25, 1976: 659.

[9] Marians, K. J. et al. Cloned Synthetic lac Operator DNA Is Biologically Active. Nature. v. 263. October 28, 1976: 744–748 and Heynecker, Herbert L. et al. Synthetic lac Operator DNA Is Functional In Vivo. Nature. v. 263. October 28, 1976: 748–752.

[10] Synthetic Gene Reported Functional in Living Cell. Medical Tribune. v. 17. October 6, 1976: 1, 4. See also: Maugh, Thomas H. II. The Artificial Gene: It's Synthesized and it Works in Cells. Science. v. 194. October 1, 1976: 44.

3. *Other Research:* The emphasis at this time, particularly in the development of guidelines for the "regulation" of recombinant molecule research has been on DNA, although the guidelines do provide for RNA-DNA experiments. A reasonable question to ask is whether there is eventually going to be greater concern about RNA research. There is some evidence that the overlaps in this work may already be near. As noted earlier, the gene for globin recombinant work was obtained by using a reverse transcriptase to produce the DNA regulating gene from purified messenger RNA. In other areas, virologists have known for some time that RNA viruses may be concealed after incorporation within the DNA of a cell. As noted by McBride, there is some suspicion that even RNA segments which normally replicate via RNA may be transcribed into an infectious DNA copy.[11]

According to McBride, the evidence seems to indicate that some RNA's may transcribe the DNA by a means other than normal reverse transcriptase enzyme systems. A number of disease causing viruses such as measles and influenza may have this capacity. It is possible that such RNA produced DNA's may not be recognized in the DNA form and an infectious RNA virus might be transmitted inadvertently. McBride refers to experiments by Dr. Edward Skolnick of the National Cancer Institute which seem to indicate that mouse cell DNA when introduced into the cells of other species resulted in the appearance of RNA viruses. Apparently the mouse cell DNA was harboring an RNA in DNA form. This type of research suggests the presence of a continuum which exists not only between RNA and DNA but also possibly between other genetic fragments which might be exchanged between organisms in nature. Some opponents of DNA recombinant research might conjecture that recombinant work with DNA of poorly defined characteristics could involve a risk of a latent DNA concealed RNA of a dangerous RNA virus disease.

An important problem to be solved if genetic disease is to be examined at the molecular level is physical identification of the location of specific genes as correlated with their function. An unusual technique of value on this problem was initiated when human and plant cells were fused and grown in culture. The research is considered of interest as a part of an overall investigation to determine whether human cells do contain functional units which may have evolved from similar bacterial units. This research also is of importance as it relates to the identification of the functions of various human genes. HeLa cells, cultured human cells of a standard line evolved from cancer tissue, were merged with hybrid tobacco plant cells.[12] Using new techniques, the cells were induced to merge together; only the nucleus of the HeLa cells apparently merged with the intact plant cell. As with other cell hybrids from different species, eventually some of the chromosomes of one of the species are lost during cell division. This is considered an advantage in the research protocol since it is

[11] McBride, Gail. Do RNA Viruses Lurk 'Underground' in DNA Form: The Journal of the American Medical Association. v. 235. June 21, 1976: 2695–2698.

[12] Jones, C. Weldon *et al.* Interkingdom Fusion Between Human (HeLa) Cells and Tobacco Hybrid (GGGL) Protoplasts. Science. v. 193. July 30. 1976: 401–403. See also: Sherrill, Robert. Human, Plant Cells Grow Together for First Time. The New York Times. August 3, 1976: 33M; and Plant/Animal Hybrids Create New Era in Biology. New Scientist. July 29, 1976: 211.

hoped that the residual chromosome material will function and thus provide information about the residual fragment. Receptive fusions, with different residual chromosomes thus could permit the gradual mapping of additional chromosomes and perhaps eventual specific gene function or chromosome fractions.

Since the human and tobacco genomes are so different, the genes of human chromosomes can be identified on the residual human chromosomes by biochemical analysis to find the characteristic proteins and enzymes in the plant protoplasm. Similar experiments have been completed in Hungary and Great Britain. It is believed that this research will contribute to an understanding of gene control differences which may exist in plants, as well as animal kingdom cell types, and possibly contribute to the development of hybrid cells of importance in food production.

Other cell fusions can be used for gene mapping. For example, fusion of mouse cells with human cells and observation of losses of chromosomes and associated function may permit residual genomes to be identified as to function. Other cross taxonomic kingdom cell research has been completed between hen's red blood cells and yeast (in England) and carrot cells with HeLa cells in Hungary. There are still many technical difficulties which must be mastered before long term cell replication appears feasible. As with other cell fusion research, it is anticipated that one outcome of this type of research will be a loss of most or all of one set of chromosomes which have been added in the fusion of the two cells. It is anticipated that it will be the animal chromosomes which will eventually disappear. Even if the chromosomes of one of the cell types is lost, thus, permitting study of remaining functions, there is still inadequate information about cytoplasmic factors to be certain that no risk is involved in such experiments. The fusion of plant and animal cells into new hybrids marks an unusual accomplishment in cell research. Although not recombinant DNA research, this basic work in cell physiology is of interest as it permits an analysis of the survivability of DNA from organisms of major cell type differences.

Among other major problems of interest in modern cell physiology and genetics, is the determination of the control systems which turn on and off genetic activity—that is activity relative to synthesis within the cells. As noted earlier in discussions of Khorana's work, it was the task of constructing the "switching" system in the synthetic gene which was an important step toward final synthesis of an operating gene. Gurdon and his group (as well as investigators at the University of Indiana) have been experimenting with whole cell systems in attempts to gain more information about these control systems.[13] In this latest research, the English investigators injected human HeLa nuclei into frog (*Xenopus*) oocytes (egg cells) and noted that the subsequently formed RNA synthesized HeLa proteins. This work provides a good model for studying control processes within living cells. Gurdon is the same investigator, then at Oxford University, who cloned adult frogs by transferring the nuclei from skin cells to enucleated eggs (see

[13] Gurdon, J. B. *et al.* Injected Nuclei in Frog Oocytes Provide a Living Cell System for the Study of Transcriptional Control. Nature. v. 260. March 11, 1976 : 116–120.

the previous committee report for further discussions on this earlier research).[14] One hypothesis is that there is some "substance" in the cytoplasm of the egg which "turns on" the chromosomes in the introduced nucleus and induces renewed synthesis of proteins which had been "switched off." It is the identification of these regulator "substances" that is of interest in this research. Research on this same problem was reported by Dr. Ann Brothers in which a tentative identification has been made of a protein regulator synthesized during egg development.[15]

Another important application of recombinant techniques is to use specific viral genomes to aid in the genetic analysis of animal tumor viruses. Miller and Fried[16] indicated their success in beginning the task of locating the DNA regions coding for differences in parent virus strain. Using the standard technique of cutting with restriction enzymes and constructing hybrid viruses, these investigators were able to demonstrate that the hybrid viruses did contain fragments from each of the parent viruses. The follow-on work will be directed at cutting viral DNA in different locations and thus permitting a more precise location of a specific gene as related to a function. Since these are cancer inducing viruses, the work has important implications for the study of cancer induction. Large numbers of the genomes are needed; the technique of cloning associated with DNA recombinant research will permit the manufacture of the needed quantities. However, this is one type of work, that is the use of cancer inducing viruses, which is of particular concern to opponents of DNA recombinant molecule research.

In recognition of the serious concern about the use of viral-DNA recombinant experiments, the NIH has proposed to conduct a risk assessment experiment under the safest conditions available. In essence, the experiment will involve the use of a known rodent cancer virus. The recombinant molecule will then be tested in animal experiments to determine whether the hypothesized survival occurs and whether transmission of cancer takes place. This experiment was proposed in order to collect data to support the theoretical calculations regarding the risks of such experiments. While the expected results would be negative, the experiment is being carefully planned to insure no risk to human beings in the event that the anticipated hypothesis is not supported.[17]

B. THE DNA RECOMBINANT MOLECULE ISSUE

As noted earlier, the basic molecular structure in the cell which determines the nature of life is becoming accessible to controlled manipulation. The events which have led to this capability have occurred, not because of some unexpected or explosive breakthrough, but because of the slow incremental increase in knowledge which is characteristic of most basic scientific research. The issue seems to have

[14] U.S. House. Science and Astronautics Committee. Supplemental Report I. op. cit.
[15] Brothers, Ann Janice. Stable Nuclear Activation Dependent On a Protein Synthesized During Oogenesis. Nature, v. 260, March 11, 1976 : 112–115.
[16] Miller, Lois K. and Mike Fried. Construction of Infectious Polyoma Hybrid Genomes in Vitro. Nature. v. 259. February 19, 1976 : 598–601.
[17] Colin, Victor. Risk Seen in Genetics Experiment. The Washington Post, September 18, 1976. D1, D3.

evolved suddenly only to those who have not been aware of the developments in this field. These developments in the life sciences are of particular importance as a public policy issue for a number of reasons. However, some preliminary background information is useful at this point in order to place this problem in perspective.

DNA recombinant molecule research deals with the recombination in cell free systems of segments of deoxyribonucleic acid (DNA), the material that determines the hereditary characteristics of all cells. The research has evolved from the efforts of many scientists carrying out investigations in molecular biology and related work in genetics and cell physiology.

Often referred to as "genetic engineering," the ability to modify the genetic material within a cell with some reasonable assurance of outcome results from a number of events. One of the most significant discoveries was the identification and biochemical isolation of a series of enzymes (restriction enzymes) which actually can be used as precision tools for the cutting of the genetic material and the introduction of new genetic material into the original DNA. At the same time, enzymes have been isolated which permit the annealing or joining together of the cut strands after new genetic material is introduced. In other words, the biochemical tools are now available to permit the excision of segments of the genetic material from one organism and the insertion of this new and foreign genetic material into another organism (see appendix 2, for an article by Stanley Cohen which discusses these discoveries in more detail).

Although the bulk of the basic research associated with the development of this technique has been completed with microorganisms (and most frequently with *Escherichia coli* [*E. coli*]), there is hope for the eventual insertion of any animal gene into plants or any plant gene into animals. For example, it has been demonstrated that genes from yeast, a eukaryote (an organism higher on the evolutionary scale than bacteria which are prokaryotes) can successfully survive when inserted into bacteria. The biochemical function of the yeast genes may be expressed in the bacterial activity. Other examples will be cited later and some of the exquisite techniques actually involve intermediate vectors such as modified viruses for transferring genes from one cell to another in a precise fashion. Whatever the specific technique or organism involved, the procedure is exciting from a basic research standpoint because it can function as a powerful tool for the elucidation of the genetic structure and gene function of many organisms and because it also offers the possibility of "installing" valuable new functions within organisms which lack such functions. As in all aspects of man's activities, however, the benefits cannot be achieved without consideration of potential risk.

When the capability to cut and recombine genes with reasonable reliability became available, a number of scientists recommended that this type of research be examined to determine whether control over the research should be instituted because of potential risks to health. As a result of these early recommendations and subsequent efforts by a large number of scientists, guidelines for the conduct of DNA recombinant research were developed. The effort to develop these guidelines is an interesting case history study of this unique field of research also discussed in more detail later within this paper.

The DNA recombinant molecule research issue is of public policy interest for a number of reasons. First of all, the potential benefits which have been postulated appear to be enormous. The technique offers the promise of the diagnosis of genetic disease in many forms, the capability to create new and more efficient forms of plant life, and the opportunity to manufacture many valuable biochemical substances by cost effective methods. Potential applications to problems of food and nutrition, waste disposal, medicine, and industry are abundant. In contrast, the unknown dangers of producing some combination of genetic characteristics in an organism which might inadvertently escape into the environment and produce human cancer or other novel infection, increase antibiotic resistance in pathogenic organisms, permit the survival of pathogens in environments not normally amenable to survival, or upset natural evolutionary processes, and similar dangers all have been cited in opposition to continuation of this research.

From a public policy perspective, the attention given to this area of research by the research scientists themselves was a unique experience. DNA recombinant molecule research also has focused attention on a broader science policy issue that has been evolving for more than a decade. This is the issue of how to evaluate the effect on society of the results of new research. The task of integrating the contrasting perspectives in an examination of scientific issues of national importance is assuming great significance. In the case of the DNA issue, the research is moving so fast that it is difficult to maintain an awareness of the status of development. The rewards and thus incentives for success in research in this area are extremely high for commercial developers and researchers alike. The risks in some instances can be partially defined but in most cases are highly speculative. Since most of the research is being supported by Federal funds, there is a considerable political challenge to maintain an awareness sufficient to exercise control over policy. At the same time, there has always been considerable resistance, from the basic research community, against any infringement upon the historic rights of academic freedom and the search for basic knowledge.

C. CHRONOLOGY OF RECENT DEVELOPMENTS ASSOCIATED WITH THE GUIDELINES

1. *Background.*—It was during the 1973 Gordon Conference on Nucleic Acids (held June 11–15, 1973, New Hampton, New Hampshire) that a group of scientists indicated publicly their concern about the potential hazards from the rapidly expanding research with DNA recombinant molecules. Following these expressions of concern to the National Academy of Sciences, an international meeting sponsored by an Academy committee was held at Asilomar, California on February 24–27, 1975. At the same time, the Director of the National Institutes of Health had appointed a special advisory committee on DNA recombinant research. During the period of planning for this meeting, the British government, through its medical council, also initiated a review program to develop recommendations with regard to the conduct of DNA recombinant research in England. These initial developments are discussed in more detail in the supplemental committee report cited earlier.[18]

[18] U.S. Congress, House, Committee on Science and Technology, 1974 Report, op. cit.

2. *The Asilomar Conference.*—The Asilomar Conference on Recombinant DNA Molecules in February 1975 was sponsored by the National Academy of Sciences with financial support from the National Cancer Institute and the National Science Foundation. Attendance was limited to invitation only. There were 155 participants, 83 from the United States representing research, governmental, and industrial institutions, 51 representatives from foreign nations, and 21 lay and news media representatives. The names of the attendees are provided in appendix 3.[19]

The conference proceedings were not published although tape recordings of the sessions were collected for further research purposes. Five subjects were placed upon the formal agenda for discussion. These were: Ecology of plasmids and enteric bacteria; molecular biology of prokaryote plasmids and their use for molecular cloning; synthetic recombinants involving animal virus DNAs; synthetic recombinants involving eukaryote DNAs; and ethical and legal concerns arising from work on synthetic recombinant DNAs.[20] A summary statement of the guidelines developed from this conference is provided in appendix 4.

These guidelines had a particular importance for they were accepted generally by the research community and served as the foundation for the work of the more formal group established by the Director of the National Institutes of Health to develop guidelines to govern NIH-sponsored research in this area. Of further significance with regard to these guidelines is that they were developed as a result of the initiative of the research community and were accepted on a voluntary basis because of a concern for potential hazards which were hypothesized for this research. Although there were strong feelings at this conference about the imposition of "regulations," there also was a very strong feeling about the social obligations of the investigators to provide a maximum of protection against any possible untoward event. From this debate, the Asilomar guidelines evolved.

3. *The NIH Recombinant DNA Molecule Program Advisory Committee.*—On October 7, 1974, an NIH Recombinant DNA Molecule Program Advisory Committee was established to provide advice to the Director of NIH (and the Secretary of HEW and the Assistant Secretary for Health). The committee was asked to consider a program for developing procedures to minimize potential dangers and to develop guidelines to be followed by investigators in this field of research. Thus, both safety requirements and research protocols are areas of responsibility.

The first meeting of the DNA Recombinant Molecule Advisory committee was held in San Francisco immediately after the Asilomar Conference in 1975. The NIH committee recognized the value of the work of the participants at the Asilomar conference and recommended interim adoption of the Asilomar guidelines until the NIH committee could develop more detailed guidelines. In examining the research work since 1974 and the efforts to get approval of certain types of

[19] U.S. Department of Health, Education, and Welfare. Public Health Service. National Institutes of Health. Recombinant DNA Research. v. 1. Documents Relating to NIH Guidelines for Research Involving Recombinant DNA Molecules. February 1975–June 1976. August 1976. p. 46.

[20] Ibid.

vectors and hosts for DNA recombinant work, it is important to note that the researchers were passing through a stage of evolving guidelines. These changing requirements induced frustration on the part of some investigators for it meant that while the requirements of existing guidelines were being satisfied, approval of biological research systems often was being considered in an atmosphere of debate on new qualification requirements. This "ad hoc" approach became more critical as the members of the NIH DNA committee became more sensitive to the legal and social implications of their task. (See appendix 5 for a list of the committee members as of April 1976. Dr. Leroy Walters, Director of the Kennedy Institute, Center for Bioethics, recently accepted appointment as a member).

The second meeting of the NIH DNA Recombinant committee, on May 12–13, 1975, dealt with the task of developing more specific recommendations as an evolution from the Asilomar guidelines. This task was initiated by a subcommittee chaired by Dr. David Hogness, Stanford University and produced a proposal which was referred to during subsequent discussions as the "Hogness" paper. Emphasis in the "Hogness" paper was placed upon more detailed descriptions of the concept of biological containment and also was directed toward the specification of the criteria to be used in selecting physical containment facilities for the conduct of experiments with a higher degree of risk.

The third meeting of the NIH committee was held in Woods Hole, Massachusetts in July 1975. At this meeting, the "Hogness" paper was revised and a significant level of controversy about the guidelines began to emerge.

As anticipated, the debate was polarized around the issues of the degree of biological and physical containment being proposed for certain types of research. Some critics believed that the guidelines were too strict and would seriously handicap or even prevent desirable research while others believed that the Woods Hole version was too lax and might induce an unsuspecting or poorly qualified researcher to conduct research under conditions which would inadequately insure safety in the event of an accident.[21]

For example, a group of 48 scientists who attended the Cold Spring Harbor bacteriophage meeting sent a letter to Dr. Dewitt Stetten, Chairman of the DNA committee, in which they expressed their concern about the Woods Hole guidelines. In their letter, they specifically listed examples of containment which were believed to provide an inadequate degree of safety. The petitioners, including Dr. Richard N. Goldstein of Harvard Medical School, also expressed their belief that the NIH committee should include broader representation from other fields of expertise and specifically should include scientists not directly involved in cloning experiments.[22]

Because of the rather significant controversy generated by the Woods Hole guidelines, Dr. Stetten decided to circulate the Woods Hole draft also within the scientific community in order to secure a wider peer review. The detailed comments which he received indicated

[21] Wade, Nicholas. Recombinant DNA: NIH Group Stirs Storm by Drafting Laxer Rules, Science v. 190. November 21, 1975: 767–769.
[22] DNA Committee Has Its Critics. Nature v. 257. October 23, 1975: 637.

a need for further significant revision. Accordingly, Dr. Elizabeth M. Kutter, Evergreen State College, Olympia, Washington, was asked to chair another subcommittee and prepare a revised version of the guidelines. The "Kutter" version was considered at a fourth public meeting of the NIH DNA committee in La Jolla, California on December 4–5, 1975. At this meeting, a side-by-side comparison was made of the "Hogness", "Woods Hole" and "Kutter" versions of the guidelines in which each section was compared (similar to a legislative bill analysis) and differences were examined by the committee members. The laborious and often argumentative discussion of these three versions resulted in the preparation of a revised document which was then presented to the Director of the National Institutes of Health (Dr. Donald S. Fredrickson) for his consideration and approval. The "La Jolla" document, now referred to as the "NIH Proposed Guidelines For Research Involving Recombinant DNA Molecules", represented the results of long hours of vigorous debate not only during committee meetings but involving long telephone conferences among committee members, interface during the public meetings between committee members and researchers attending as observers, examination of letters of comment from various groups, contributions by interested foreign nation representatives, an increasing acknowledgement of the need for public participation in the resolution of those points affecting the prohibition of certain types of research and the establishment of safety procedures, and for the approval of vector and host cell systems.

Following a public meeting on the guidelines held by the Director of NIH, the DNA Recombinant Molecule committee was asked by the Director to consider the new comments received and to recommend any further change to the guidelines. At a meeting held April 1–2, 1976, the DNA committee reviewed the comments received by the Director and provided him with a rationale for acceptance or rejection of proposals for change. At the same meeting, a viral vector developed by Dr. Philip Leder was approved.

At their most recent public meeting on September 13–14, 1976, the Recombinant DNA Molecule Program Advisory Committee continued their examination of the published guidelines with the intention of providing further change as necessary. This meeting also provided an opportunity for the committee to consider the research needs for a highly secure research facility, proposals for a program to construct and distribute cloned segments of mammalian DNA, NIH patent policies on developments in DNA recombinant molecule research, experiments to assess the biohazards which had been postulated for DNA recombinant molecules and requests for certification for a mutant host for cloning and a viral vector.

A mutuant strain of *E. coli* host with two specific plasmids developed by Dr. Roy Curtiss, University of Alabama, was approved for use in DNA recombinant research. A second viral vector developed by Dr. Philip Leder (NIH) as well as vectors developed by F. Blattner and others at the University of Wisconsin were approved contingent upon the completion of several additional tests. Thus additional formal steps of compliance with guidelines have been taken. Copies of the minutes of all meetings held by the Advisory committee

are available from Dr. William Gartland, Executive Secretary, Recombinant DNA Molecule Program Advisory Committee, NIGMS, NIH, PHS, Room 4A52, Bldg. #31, Bethesda, Md. 20014.

4. *NIH Advisory Committee Actions on the DNA Recombinant Guidelines.*—When the DNA Recombinant Advisory committee had completed their deliberations at La Jolla, the proposed guidelines were forwarded to the Director of NIH for his consideration and possible adoption. Despite the fact that all meetings of the DNA Recombinant Advisory committee had been public, Dr. Fredrickson decided that further public scrutiny of the proposed guidelines would be appropriate prior to adoption. The Director convened a public meeting of his NIH Advisory Committee (a special Advisory Committee to the Director, see appendix 6) for the purpose of discussing the guidelines and to invite public comment. This meeting was held on February 9–10, 1976. The Director broadened the participation in his Advisory Committee meeting to add additional scientific and lay representatives including former members and individuals knowledgeable in the fields of ethics and socioeconomics as well as biological research. The transcript of that meeting and the list of invited participants have been published.[23]

After review of the comments submitted during and following this meeting, the Director asked his DNA Recombinant Advisory committee to evaluate a number of the comments for possible incorporation into the proposed guidelines and to justify the exclusion of recommendations considered inappropriate. Since a great deal of concern had been expressed at his Advisory Committee meeting about the imposition of the guidelines on non-NIH investigators, the Director also held an interagency meeting with representatives of other Federal agencies to discuss the proposed DNA guidelines. The concern expressed about the problem of gaining compliance with the guidelines by private researchers also led the Director to hold a meeting with selected industry representatives. The list of the invited participants at this industry meeting is provided in appendix 7. Finally, the Director personally provided special briefings to selected House and Senate committee staff members on the actions being contemplated for dissemination of the guidelines.

The guidelines were then published in the Federal Register on July 7, 1976 after final consideration of all of the comments received (see appendix 8). A number of policy considerations were taken into account prior to publication. In his preface, the Director noted that he had been particularly concerned with the process of implementing the guidelines. He stated that the guidelines are not regulations and thus do not have the same force as law except that control could be exercised through the funding process controlled by NIH. He expressed his belief that administration should remain as flexible as possible since frequent adjustments in requirements were anticipated.

In publishing the guidelines in the Register, the Director invited further comments thus leaving the door open to further public debate on the applicability of any particular specification.

[23] U.S. Department of Health, Education, and Welfare. Recombinant DNA Research, v. 1. op. cit., pp. 140–349.

The Director of NIH has attempted to determine a method of resolving the applicability of the guidelines to investigators not funded with NIH money. For example, the National Science Foundation, the Energy Research and Development Administration and the Department of Agriculture all appeared to have potential interests in DNA recombinant molecule research. As noted, the Director of NIH held meetings with the Federal agencies which might be involved and it was decided to attempt to secure voluntary compliance from these Federal agencies and from industry. By September 22, 1976, the National Science Foundation, the Energy Research and Development Administration and the Department of Defense had indicated that they would comply in research funded by their agencies.[24] The Department of Defense indicated that although no research of this type was currently being funded, the Department would comply if such research was initiated. Although the Department of Agriculture had not indicated that they would comply, the absence of this agreement was noted as being due to the administrative review process as it might affect various research programs and not any basic disagreement with the intent of the guidelines. The Director of NIH indicated that he anticipated that the USDA also would indicate compliance with the guidelines in the near future.

At the Senate hearings held in September,[25] the President of the Pharmaceutical Manufacturers Association indicated that the drug industry endorsed the spirit and intent of the guidelines and that with some minor modifications should and would accept the guidelines. At this same hearing, the subcommittee chairman introduced into the record a copy of a letter to the President of the United States in which he and Senator Jacob K. Javits indicated their concern with the issue of DNA recombinant research.

D. GUIDELINES FOR RECOMBINANT DNA RESEARCH

1. *Introduction.*—The earlier committee reports, particularly Supplement I [26], provide additional background information concerning the unique actions of the research scientists who directed public attention to the new developments in DNA Recombinant research. As a result of these actions and the work discussed in this report, most of the public attention on the DNA recombinant molecule issue has been focused on the guidelines. The general public interest in the recombinant research itself has been somewhat more superficial even though it is believed, in the opinion of many observers, to be one of the greatest achievements in modern science; even more significant perhaps than the development of nuclear power. However, the guidelines have received the publicity because they are the first effort to control this research and, no matter whether the interest is to delay or prohibit such research or to accelerate developments, it has been quite natural that the debate in this area of genetic research should become polarized

[24] U.S. Senate, Labor and Public Welfare Committee. Subcommittee on Health. Hearings on the Guidelines for DNA Recombinant Molecule Research. Testimony by Dr. Donald Fredericksson. September 22, 1976. Unpublished.

[25] Ibid. Statement of C. Joseph Stetler, President of the Pharmaceutical Manufacturers Association.

[26] U.S. Congress. Committee on Science and Astronautics. 1974 Report—Supplement I. op. cit.

around the DNA recombinant molecule guidelines. The debates about the content of the guidelines have pitted friendly rivals against each other in the research field; aroused communities to a fever pitch about the control of research within universities; resulted in the fear that this important area of research might be driven to other lands if restrictions become too prohibitive; produced concern within the minds of environmentalists about a potential new source of pollution in the biosphere; and engaged the attention of ethicists, lawyers, theologians, and practically every other public interest group which can be identified. Since this is not the first effort by a Federal agency to control research in some way, an initial reaction might be to ask why so much furor has evolved over the proposals. The answer to this question involves a number of factors.

First of all, the proposals known as the Recombinant DNA Research Guidelines are guidelines and not Federal regulations being promulgated with the force of law. Second, these proposals for regulation are unique in that they were stimulated by the very research scientists who are conducting the research. Third, the "enforcement" procedure proposed in the guidelines will depend upon the approval by the peer review hierarchy which has evolved within the National Institutes of Health for review and approval of research funded under the usual contracts and grants procedures (since the National Institutes of Health has been funding the bulk of the government research in this area, control of the money also provides control over the research). Fourth, there is concern that commercial firms may not choose to comply with the guidelines and, since there is no prospective procedure for licensing, inspection, fines or other penalties for noncompliance, the guidelines may not really be effective with industry.

Other factors which make the guidelines of interest depend upon the perspective from which they are viewed. Some researchers consider the guidelines as an unnecessarily restrictive control over independent research; others are concerned that foreign nations may develop less retrictive guidelines or none at all and the benefits of the research will be lost to American industry. Others think that the guidelines should never have been written since they imply an approval of a type of research which is viewed as too dangerous to be conducted at all.[27] Those who are interested in a continuing participation of the public in the development of policies of such significance question the manner in which the guidelines were developed by researchers who are involved in the research, the limited analysis of risks and benefits, and whether the guidelines detract from consideration of alternatives to DNA research.[28]

The guidelines are an extremely interesting series of requirements for they reveal much of the status of the research and introduce new concepts regarding safety systems for research with potentially dangerous organisms. For these reasons alone, aside from the public policy implication of the guidelines, some time should be taken to examine the objectives established at this point. It should be kept in mind that although the guidelines have been published and are now being

[27] Chargoff, Erwin. On the Dangers of Genetic Meddling, Science, vol. 192, June 4, 1976: 938, 940.

[28] Simring, Francine Robinson. Recombinant DNA Risks and Benefits. Science, vol. 192. June 4, 1976: 940.

utilized, the NIH committees have a continuing task of evaluation and modification as experience dictates. Further, as will be discussed later, the Director has published a Draft Environmental Impact Statement which provides another route of participation by all interested parties for input and modification of the guidelines.

2. *Summary Comments On The Guidelines.*—The Department of Health, Education, and Welfare Guidelines For the Conduct of Recombinant DNA Research were formally published in the Federal Register on July 7, 1976.[29] These guidelines, the results of the efforts of the many individuals described in an earlier section of this report, were published with a preamble from the Director of NIH which indicated:

> On Wednesday, June 23, 1976, the Director, National Institutes of Health, with the concurrence of the Secretary of Health, Education, and Welfare, and the Assistant Secretary for Health, issued guidelines that will govern the conduct of NIH supported research on recombinant DNA molecules. The NIH is also undertaking an environmental impact assessment of these guidelines for recombinant DNA research in accordance with the National Environmental Policy Act of 1969.
>
> . . . The NIH recognizes a special obligation to disseminate information on these guidelines as widely as possible. . . . Accordingly, the Guidelines will be sent to all of the approximately 25,000 NIH grantees and contractors. The Guidelines will be sent to medical and scientific journals, and editors of these journals will be asked to request that investigators include a description of the physical and biological containment procedures used in any recombinant research they report on. International health and scientific organizations will also receive copies of the guidelines for their review.
>
> . . . It must be clearly understood by the reader that the material that follows is not proposed rulemaking in the technical sense, but is a document on which early public comment and participation is invited.[30]

The guidelines provide a summary of the chronology of the work conducted to prepare them as well as a summary of the science policy considerations and the considerations within NIH for further implementation of the guidelines outside the NIH.

There are three major provisions within the guidelines. They are quite comprehensive and are included as appendix 4 for further information.

The guidelines develop and expand the concepts proposed at the Asilomar Conference for the establishment of physical and biological containment criteria graded as to degree of safety dependent upon the risk assessed for a particular type of experiment.

(*a*) *Physical Containment:* Physical containment laboratories are described in four degrees of safety code numbered P1, P2, P3, and P4.

P1 facilities are described as minimal facilities involving laboratories with no special engineering design. This is the type of laboratory commonly used for microbiological work with no or only minimal hazard.[31] (It is of interest to recall, however, that a great deal of work with important pathogens had been performed in the past at levels now defined as P1–P2 levels of containment.)

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[29] U.S. Department of Health, Education, and Welfare. National Institutes of Health. Recombinant DNA Research Guidelines. Federal Register. vol. 41. July 7, 1976: 27902–27943.

[30] Ibid., p. 27002.

[31] Ibid., p. 27912.

The P2 level of confinement is similar to the P1 laboratory with the added requirements for an autoclave (a device for steam sterilizing culture media, glassware, etc.) within the building and the laboratory may have a biological safety cabinet depending upon the experimental work. Access to the laboratory may be somewhat more restricted than with the P1 laboratory. The guidelines prescribe the laboratory practices which should be followed as a minimum with such experiments as are authorized to be conducted in P2 facilities.[32]

P3 laboratories are described as providing a moderate level of safety. These laboratories must have special engineering design features and physical containment facilities. The laboratory is separated from general public access with controlled access facilities such as air-locks, separate corridors or other design features as necessary. Biological safety cabinets must be provided within the controlled laboratory area and an autoclave also must be available within the building and preferably within the controlled access laboratory. Ventilation systems or air flow control must be designed to prohibit recirculation of exhaust air without treatment and a positive air pressure is maintained within the laboratory with all exhaust going outside the building. Again, minimum laboratory practices are described as are the types of DNA recombinant experiments which can be conducted within such a laboratory.[33]

P4 facilities are intended to provide the highest degree of safety possible within available biohazard technologies. These facilities are designed to permit work designed to contain microorganisms that are extremely hazardous to man or may cause serious epidemic disease. The laboratory is either a separate building or a tightly controlled area within a building which is completely isolated from other areas within the building. Again, special safety cabinets must be used, engineering design features are developed to prevent the escape of microorganisms to the environment, air flow is controlled, personnel access and cleanliness is tightly controlled, and other safety features are prescribed. Operational procedures for work within such laboratories are described.[34]

(*b*) *Biological Containment:* The principle of biological containment is unique in these guidelines and a great deal of time is devoted to describing this idea. Basically, the idea of containment evolved from the work with *Escherichia coli* which suggested that it would be possible to "construct" a variant of this bacterium which would be so fastidious in its growth requirements that the probability of its surviving outside of the precisely controlled laboratory culture conditions would be very slight.

The levels of biological containment are designated EK1 through EK3 (the acronym EK derives from the K–12 variant of *Escherichia coli* used in many experiments) with the highest level of biological containment being an EK3 variant. The knowledge already gained from working with some variants of these microorganisms and with plasmid vectors of a particular strain supported this idea of a "weakened" strain suitable for experimental work. Furthermore, knowledge

[32] Ibid., p. 27913.
[33] Ibid., p. 27913.
[34] Ibid., pp. 27913, 27914.

had been acquired about the survivability outside the laboratory of *E. coli* host with plasmid or bacteriophage variants which also had certain propagation restrictions so that the combination of the restricted growth characteristics of the host cell (*E. coli*) and the plasmid or phage vector produced a degree of safety described as being suitable for use with the permissible experiments. Specific data on the survival probabilities permitted for various host vector systems are described (the testing of proposed host-vector systems is being continuously monitored and changes to the guidelines are already evolving).[35] The availability of a suitable mutant of *E. coli* (or an alternative organism) is absolutely essential to the concept of biological containment. Despite the fact that many are opposed to the use of this microorganism, it is the organism which has played the major role in DNA recombinant work thus far and is not likely to be either supplanted or prohibited without a great deal more discussion. Thus, Dr. Roy Curtiss' (University of Alabama) development of a mutant of *E. coli* and NIH Committee approval of this weakened mutant is a significant achievement.[36]

What he did was to manipulate the test strain until he had a mutant variety which is dependent upon an external source of an amino acid needed to construct its cell wall, made it sensitive to temperatures, reduced its capabilities to incorporate DNA within its chromosomes, and reduced its ability to exchange genetic material with other bacteria. This mutant is believed to have a very low probability of survival under non-laboratory conditions. Each time Curtiss thought he had solved the problem, the microorganism demonstrated an ability to use alternative mechanisms for development. Further selective mutation finally permitted Curtiss to demonstrate to the NIH–DNA Recombinant Committee that the mutant form was satisfactory for use in the "EK2" experiments permitted by the guidelines. Similar effort is expended in attempts to construct weakened plasmids or phages (viruses).

It is desirable in considering biological containment to insure that the combined host-vector does not survive, that is, that the vector does not transmit the required growth characteristics in some way to the host, or that the vector cannot survive if it should escape in the host even though the host might not survive. For this reason vectors are either selected for their specificity of host or vector mutations may be selected to provide the desired characteristics of limited infectivity. A complication of this construction of safe biological host-vector system is that the host and the vector must still be able to grow and reproduce under conditions which assure a reasonably high degree of productivity within the bounds of the experimental control. If the mutants selected are so weakened that reasonable productivity during cloning cannot be accomplished then one of the advantages of the DNA recombinant system is eliminated. Thus, the skills of the microbiologist or virologist must be devoted to the solution of several simultaneous problems.

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[35] Ibid., 27914–27917.

[36] Leeper, E. M. Self Destructing *E. coli* Developed at Alabama, Bioscience v. 26, April 1976 : 243.

Alternatives which might alleviate some of the difficulty in using biological containment as a safety factor would be to develop host-vector systems that do not rely on bacteria, some strains of which are pathogenic. Unfortunately, *E. coli* is the organism about which the largest quantity of information is currently available. The development of a similar data base on another microorganism might mean a significant delay of research. Work is proceeding on *Bacillus subtilis* as a potential alternative host cell.

The guidelines then list the various combinations of physical and biological containment which are required as a minimum for the conduct of various combinations of permissible experiments such as those involving DNA from plants, birds, cold blooded vertebrates, primates, and others. In certain instances, the host-vector systems are not yet available to permit some of these experiments to be conducted.[37]

Table I is a summary of the combinations of physical and biological containment required for various experiments.

TABLE I.—*Guidelines in detail*

The guidelines define four levels of physical containment, designated, in order of increasing stringency, P1 to P4, and three levels of biological containment, EK1 to EK3, and assign experiments to them on the basis of potential risk. The following is a summary of containment levels specified for various sources of DNA:

(*a*) Shotgun experiments using *E. coli* as the host:	
Non-embryonic primate tissue	P3+EK3 or P4+EK2.
Embryonic primate tissue or germ line cells	P3+EK2.
Other mammals	P3+EK2.
Birds	P3+EK2.
Cold blooded vertebrates:	
Nonembryonic	P2+EK2.
Embryonic or germ line	P2+EK1.
If vertebrate produces a toxin	P3+EK2.
Other cold blooded animals and lower eukaryotes.	P2+EK1.
If class 2 pathogen,[1] produces a toxin, or carries a pathogen.	P3+EK2.
Plants	P2+EK1.
Prokaryotes that exchange genes with *E. coli*:	
Class 1 agents (nonpathogens)	P1+EK1.
Low risk pathogens (for example, enterobacteria).	P2+EK1.
Moderate risk pathogens (for example, *S. typhi*).	P2+EK2.
Higher risk pathogens	Banned.
Prokaryotes that do not exchange genes with *E. coli*:	
Class 1 agents	P2+EK2 or P3+EK1.
Class 2 agents (moderate risk pathogens)	P2+EK2.
Higher pathogens	Banned.

In all above cases, if DNA is at least 99 percent pure before cloning and contains no harmful genes, either physical or biological containment levels can be reduced one step.

[1] Classes for pathogenic agents as defined by the Center for Disease Control.

[37] Ibid., pp. 27917–27920.

TABLE I.—*Guidelines in detail*—Continued

(*b*) Cloning plasmid, bacteriophage and other virus genes in *E. coli*:	
Animal viruses	P4+EK2 or P3+EK3.
If clones free from harmful regions	P3+EK2.
Plant viruses	P3+EK1 or P2+EK2.
99 percent pure organelle DNA, Primates	P3+EK1 or P2+EK2.
Other eukaryotes	P2+EK1.
Impure organelle DNA: shotgun conditions apply.	
Plasmid or phage DNA from hosts that exchange genes with *E. coli*:	
If plasmid or phage genome does not contain harmful genes or if DNA segment 99 percent pure and characterised.	P1+EK1.
Otherwise, shotgun conditions apply.	
Plasmids with phage from hosts which do not exchange genes with *E. coli*.	
Shotgun conditions apply, unless minimal risk that recombinant will increase pathogenicity or ecological potential of the host, then.	P2+EK2 or P3+EK1.
NB. cDNA's synthesised *in vitro* from cellular or viral RNA's are included in above categories.	
(*c*) Animal virus vectors:	
Defective polyoma virus:	
DNA from nonpathogen	P3.
DNA from Class 2 agent	P4.
If cloned recombinant contains no harmful genes and host range of polyoma unaltered, reduce to.	P3.
Defective SV40+DNA from nonpathogens	P4.
If inserted DNA is 99 percent pure segment of prokaryotic DNA lacking toxigenic genes, or a segment of eukaryotic DNA whose function has been established and which has previously been cloned in a prokaryotic host-vector system, and if infectivity of SV40 in human cells unaltered.	P3.
Defective SV40 lacking substantial section of the late region+DNA from nonpathogens, if no helper used and no virus particles produced.	P3.
Defective SV40+DNA from nonpathogen can be used to transform established lines of nonpermissive cells under P3 provided no infection particles produced. Rescue of SV40 from such cells requires.	P4.
(*d*) Plant host-vector systems:	
P2 conditions can be approximated by insect-free greenhouses, sterilization of plant pots, soil and runoff water, and use of standard microbiological practice.	
P3 conditions require use of growth chambers under negative pressure and routine fumigation for insect control.	
Otherwise, similar conditions to those prescribed for animal systems apply.	

NOTE.—Norman, Colin. Genetic Manipulation: Guidelines Issued. Nature. v. 262. July 1, 1976: 3.

The guidelines explicitly prohibit certain types of experiments:

(*i*) Cloning of recombinant DNAs derived from the pathogenic organisms in Classes 3, 4, and 5 of "Classification of Etiologic Agents on the Basis of Hazard" (see appendix 9) or oncogenic viruses classified by NCI as moderate risk, or cells known to be infected with such agents, regardless of the host-vector systems used.

(*ii*) Deliberate formation of recombinant DNAs containing genes for the biosynthesis of potent toxins (e.g, botulinum or diptheria toxins; venoms from insects, snakes, etc.).

(*iii*) Deliberate creation from plant pathogens of recombinant DNAs that are likely to increase virulence or host range.

(*iv*) Deliberate release into the environment of any organism containing a recombinant DNA molecule.

(*v*) Transfer of a drug resistance trait to microorganisms that are not known to acquire it naturally if such acquisition could compromise the use of a drug to control disease agents in human or veterinary medicine or agriculture.

In addition, at this time large-scale experiments (e.g., more than ten liters of culture) with recombinant DNAs known to make harmful products are not to be carried out. [Approval of larger scale experiments of obvious societal benefit may be possible if approved by the DNA Molecule Program Advisory Committee of NIH.] [38]

The guidelines also list the responsibilities of the individual investigator and the institution involved in a particular experiment. Additional responsibilities are assigned to the NIH Initial Review Groups to include requirements to insure evaluations of proposals involving DNA recombinant research. The responsibilities of the DNA Recombinant Molecule Program Advisory Committee are described (including responsibilities for approving proposed new host-vector systems), and the responsibilities of all NIH staff include special criteria to insure adequate review for safety of DNA recombinant molecule research.[39]

E. THE DNA RECOMBINANT MOLECULAR ENVIRONMENTAL IMPACT STATEMENT

During the considerations of the guidelines, the Director of NIH was urged to promulgate an Environmental Impact Statement. Subsequent to the issuance of the guidelines, the Director determined that it would be advantageous to the public and in compliance with the National Environmental Policy Act (NEPA) of 1969 to issue such a statement. The Draft Environmental Impact Statement was issued in the Federal Register on September 9, 1976 [40] (see appendix 10). This statement provides a description of the recombinant DNA research; events leading to the development of the guidelines, a description of the issues associated with DNA recombinant research, a discussion of the guidelines and other proposed action; and an assessment of the possible environmental impact of such guidelines. The issuance of the Draft Environmental Impact Statement *after* the publication

[38] Ibid., pp. 27914–27915.
[39] Ibid., pp. 27920–27921.
[40] Recombinant DNA Research Guidelines. Draft Environmental Impact Statement. Federal Register. vol. 41. September 9, 1976.: 38426–38483.

action on the guidelines has been criticized because the NEPA is intended to secure public reaction before the actions contemplated are actually implemented. In the Draft Environmental Statement, the Director justifies this unusual action by pointing out that it was his position that the public interest would be best served by immediate issuance of the guidelines. His opinion was that the likelihood of the escape of potentially dangerous organisms was greater in the absence of guidelines and that prompt issuance of guidelines was necessary to gain cooperation of scientists not controlled by NIH funds as well as that of researchers in other nations.

The possibility that NEPA procedures, particularly the Environmental Impact Statement, would be the appropriate procedure for assessing biological technologies, and more specifically the DNA recombinant issue was considered earlier by Parenteau and Catz.[41]

These authors point out:

> At present, no mechanism exists for systematically disseminating information on this important research effort to the public; public debate of these issues [biomedical technologies] requires finding some such mechanism.
>
> . . . One solution to the information gap problem lies in requiring Federal agencies responsible for funding these research programs to prepare and disseminate detailed statements explaining the nature of the work and the costs and benefits that are likely to result.
>
> . . . As we stand on the verge of such breakthroughs (genetic, invitro fertilization, etc.) in biological research, it becomes necessary to examine the degree to which society can and should control that research.
>
> . . . It would seem that biological technologies, with their great potential for direct impact of mankind's physical, intellectual, and psychological characteristics fall squarely within the policy declarations of NEPA.
>
> . . . Where a technology is rapidly taking shape and will be ready for application within a short time, NIH ought to make a serious effort to explain, in as great detail as data will permit, the environmental effects of its application.
>
> . . . The need for relying on NEPA procedures in this area is underscored, however, by the alternative of leaving the process entirely in the hands of the scientific community without public participation or scrutiny. That alternative is unacceptable.[42]

This discussion, encouraging the use of the Environmental Impact Statement (EIS) for assessing biomedical technologies, succinctly summarizes the larger issue of public participation in the decision making process for technologies having obvious societal impacts. Apparently, the Director of NIH reached the same conclusion about the use of an EIS, although the timing of the publication may not have been fully acceptable.

F. RISKS AND BENEFITS OF DNA RECOMBINANT MOLECULE RESEARCH

1. *Benefits.*—The benefits postulated most frequently, if the research with DNA recombinant molecules is successful, can be classified in three broad categories.

First, and of fundamental importance to all genetics research, the technique is considered important as a fine tool for the examination and identification of gene function. The number of genes per chromosome for the higher organisms is so large that, with procedures other

[41] Parenteau, Patrick A. and Robert S. Catz. Public Assessment of Biological Technologies: Can NEPA Answer the Challenge? Georgetown Law Journal. vol. 64. February 1975: 679–695.

[42] Ibid., pp. 680, 682, 684, 695.

than recombinant molecule research, it has been almost impossible to do more than correlate function with a particular chromosome. It has (except in a few rare instances) been very difficult to construct maps of the human chromosome to ascertain the point (gene) which regulates a particular biochemical activity. The deciphering of the meaning of duplicate gene sequences on a chromosome, the location of activation or repression sections (or stop and start sections of chromosomes), the determination of interactions of adjacent genes, the effect of relocation or displacement of normally adjacent sections, and many other positional factors are of the utmost interest. As pointed out by Lane, the raw materials for experiments to gain information on the control of gene expression might be provided by cloning DNA recombinant molecules.[43]

It will only be possible to correct by genetic engineering a particular gene controlled deficiency when knowledge of the gene or combination of genes, or positional relationships of genes within chromosome pairs or even between pairs of chromosomes, is known. Current information is far from sufficient to accomplish this objective. DNA recombinant research is identified as an important method for carefully isolating many of these individual factors and then relating these factors to function. Even with this research technique, the task will be laborious and detailed for the DNA of a mammalian cell adds up to be the equivalent of several million genes. It is the knowledge that the task will require a great deal of time and effort which adds to the sense of urgency about continuing research.

The attempts to determine this type of information have been initiated primarily with microorganisms and viruses because these contain some of the simplest organized chromosome structure, that is small numbers of genes or information units. Work on the exchange of DNA between species, genera, and even different kingdoms, has been pursued in order to test the thesis of the common nature of DNA to all living organisms. An alternative but closely allied technique is direct transfer of DNA by cell fusion or other procedures for incorporation of DNA fragments.

In order to have confidence in the information being derived from recombinant research, the investigator must be sure that the genes introduced into the host system are the structures of interest and that these genes actually are producing the function being observed. For this reason, the techniques for assuring a reasonable supply of purified segments of DNA are important. Cloning facilitates the collection of this material.

The research with recombinant molecules as well as with cell fusion and other methods for introducing exotic DNA into cells also provides an opportunity to explore some of the interactions involving extra nuclear structures such as the plasmids in bacteria and the cytoplasmic activities of interest in the cells of higher organisms. There is considerable interest in all of the mechanisms of gene translation, the actions of messenger RNA, and protein production. Much of this activity occurs outside the nucleus and therefore is of interest in the total study of genetic function.

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[43] Lane, Charles. Rabbit Hemoglobin From Frog Eggs. Scientific American. v. 235. August 1976: 71.

On an even more fundamental level, recombinant research adds to the knowledge concerning the evolution of different species. These investigations permit exploration of theories concerning the genetic mechanisms of natural selection and provide an opportunity to test some of the theories concerning mutation and selection at the molecular level. It is apparent already that there are many sections of chromosomes of distantly related species based on current classical taxonomic methods, which are very similar if not precisely identical.

A second classification of benefits from recombinant research falls into the more easily identifiable area of potential therapeutic benefits. These are the benefits most frequently identified by the lay person as being directly related to this research. Although there is considerable doubt at this point as to whether such an achievement is really possible, the brightest vision is the dream of being able to insert the correct gene to replace or override the influence of a defective gene or combination of genes which is producing a serious structural or metabolic defect. It is hoped that some day the recombinant techniques will produce the knowledge to permit the isolation of a defective gene controlling a particular defect and permit the introduction and incorporation of a correct gene. Thus, the gene therapy would be permanent and no drug or other lifetime care would be required. If defects can be detected during early development, and provided our knowledge of growth and development at the earliest stages is adequate, such "genetic engineering" techniques would enable mankind to prevent the suffering and sorrow now borne by the thousands of children with genetically induced birth defects.

If the answers to the questions about the disruptive activities associated with cancer can be secured as a result of contributions from recombinant research, then the diseases may possibly be attacked at the most fundamental level. In some instances, the association of viruses with cancer leads to the suspicion that viral transport of DNA and other incorporation of new or foreign DNA may induce cancer. In other instances, the basic assumption is that, in some way, the control system of the cell may be disrupted, thus leading to the uncontrolled growth known as cancer. Another theory suggests that genomes (genes) with the potential for initiating malignant activity may be resident in the cells of cancer prone individuals and exposure to appropriate environmental stresses induces tumorigenic or malignant activity. Investigations at the molecular level should aid in evaluating many of these hypotheses and ultimately may permit genetic intervention to prohibit the start of the cancer cycle.

A final example in this group, but not the last which could be discussed in a more comprehensive report, is that these research techniques offer the opportunity to biosynthesize an enormous variety of proteins of extremely great value in therapeutic medicine. Enzymes, blood components, and a host of other important human proteins seem to be the promise at the end of this research (see the paper by Lederberg in appendix 11 for further discussion on this point).

The third broad category of benefits relates to the opportunities hypothesized for the improvement of plant and animal species, not only in agriculture but in other important applications.

It has been estimated, for example, that it may be possible some day to produce more plants with the genetic capability to convert atmospheric nitrogen into the nitrate form necessary for plant synthesis of protein. This capability now exists in some plants as a result of symbiotic relationships between certain plants and bacteria. It has been speculated, and indeed this speculation may be near fruition, that it may be possible to induce genetically this nitrogen fixation capability in plants, such as corn, where such a capability does not now exist. The implications, in terms of reduced energy demands for the production of artificial fertilizers containing nitrogen, are indeed important in today's energy deficient environment and are also relevant to the need for increased production of food.

The opportunity to improve the efficiency of biosynthetic production of enzymes and other chemicals of industrial importance by genetically engineering improved characteristics in microorganisms used in fermentation and other processes appears to be an obviously important commercial opportunity. Processes involving the production of alcohol from grain, or modification of metabolic routes to provide such capabilities for other plant products, stretch the imagination in terms of potential bioenergy conversion systems.

The mechanisms of photosynthesis, while already one of the more efficient processes in nature, if significantly improved in efficiency might help to alleviate food shortages. Indeed, the potential exists to permit the construction of specific organisms with unusual characteristics for improvements in the photosynthetic process and also changes in metabolic functions related to the synthesis of all of the essential amino acids within one plant food source.

Only the imagination of the investigator seems to limit the potential applications in agriculture and industry. At the same time, an acceleration in the improvement of characteristics of agriculturally important animals is being hypothesized.

The use of microorganisms to aid in the conversion of wastes into useful products or to "clean-up" hazardous spills of chemicals is being examined. If the characteristics of an oil consuming microorganism could be improved, perhaps such an organism could be used to convert fuels into innocuous breakdown products and thus the pollution danger to water and land ecosystems from such spills could be significantly reduced. In other problems, sludges or industrial wastes might be treated with specially constructed microorganisms to permit conversion either to useful products, even with some side benefits in the form of useful energy, or at least a chemical reduction to products which could be safely returned to the environment.

While it is true, that many of these benefits could be obtained through normal genetic hybridization procedures, the scope of modification and the rate at which such modifications could be accelerated is said to be orders of magnitude greater if the recombinant work can be developed to the point where such capabilities can be applied. In most instances, excluding a few near term developments of potential commercial value with microorganisms, a great deal of work must be done at the basic research level to determine whether many of these potential benefits are actually feasible. Much of the information made

available from traditional hybridization experiments can be utilized. However, the DNA recombinations being produced or contemplated will result in many rearrangements and gene combinations which do not occur at all naturally or, if they have occurred, do so with such a low order of frequency that it is almost impossible to detect such unusual variants.

2. *Risks.*—The discussions of risks almost invariably take the form of concern about catastrophic epidemics or the creation of new and uncontrollable harmful organisms. For purposes of systematizing these discussions, the risk estimates may also be classified into three general categories.

At the basic research level, opponents enter a philosophical level of debate and challenge the ability of investigators to ever quantify the benefits or the risks in a fashion to permit evaluation and intelligent decision making. The fear has been expressed that DNA recombinant research may somehow adversely affect the diversity of natural gene pools. (See the papers by George Wald, Marc Ptashne and Robert Sinsheimer in appendixes 12 and 13.)

There are frequent and detailed analogies drawn between the dilemmas confronted in the current nuclear power debates and the basic research proposals in the field of DNA recombinant research. Statements, occasionally in the form of demands, have been made that a full moratorium on all DNA recombinant research should be instituted until all of the social, legal, and moral implications of this research have been thoroughly examined. Chargaff, for example, discussed the "awesome irreversibility of what is being contemplated." [44] He continued his discussion by expressing concern about the fact that there is no way of really knowing what is happening in changing the orientation of genes within new organisms and that we might be producing an irreversible attack on the biosphere. Haring asks whether mankind is to be allowed to try, by direct genetic manipulation, to improve the human species beyond the requirements for therapy? He questions whether man can be trusted to approach such important research frontiers in the right spirit. He expresses the fear that the altruistic aims of DNA recombinant molecular research may fall under the heartless rules of the marketplace.[45]

In general, many of these objectives would have to be countered by proving the negative, an impossible task. The issues are very important as they expose basic concerns about the ethics of science generally. As pointed out by Sinsheimer, risks must be assessed in terms of probability calculations which are virtually impossible to measure.[46] It was this general issue of ethics in science and the problem of resolving philosophical conflicts between science and non-scientists that was the topic of a conference held in June 1976 at the very time that the Director of the National Institutes of Health was requiring a continuing examination of public reactions to proposals for guidelines to control DNA recombinant research.[47] The coincidence between this

[44] Chargaff, Erwin. On the dangers of genetic meddling. Science. vol. 192. June 4, 1976: 938, 940.

[45] Haring, Bernard. Ethics of Manipulation. New York. Seabury Press. 1975: 159–211.

[46] Sinsheimer, Robert. Troubled Dawn For Genetic Engineering. New Scientist. October 16. 1975: 148–151.

[47] Steinfels, Peter. Biomedical Research and the Public. A Report From the Airlie House Conference. Hastings Report. June 1976: 21–25.

increasing expression of concern about ethical issues in science and the controversy over the ability to carry out basic manipulations of basic life processes is most remarkable. It provides an ideal opportunity to introduce the evolving methodologies of ethicists in an examination of the most important developments of life sciences from the perspective of public participation in the science policy making process. The DNA recombinant molecule issue does indeed provide a unique opportunity to study a case history during its evolution rather than after the fact.

While it is more difficult to criticize the value of DNA recombinant work from the perspective of potential therapeutic applications, even here there are strong opposing opinions. Part of this concern is directed toward the fact that much of the research involves the use of *E. coli*, a microorganism which is a common inhabitant of the human intestine. Since this is an organism already adapted to the human environment, the concern is that accidents might result in easy entry and infection of human beings.[48]

If the host with the recombinant molecule carried all or part of an oncogenic virus, for example, or now had an unexpected resistance to drug therapy, or could produce some new and unexpected toxin, then human beings might be exposed to a disease which could reach epidemic proportions. The arguments about probabilities of escape, probabilities of survival if escape does occur, and probabilities that such an escaped host would indeed be pathogenic are described as impossible to calculate and therefore meaningless in terms of evaluating potential risk. The position is that the opportunity for risk exists and therefore the research should not be conducted. For example, the Boston Area Recombinant DNA Group has presented a recommendation that a safer host be developed and *E. coli* be abandoned within two years for use in this research. The counterargument is that delay would occur until the required information about alternate hosts was made available. Another concern is about the need for haste to continue this research. What difference does it really make if it takes five years longer to develop a process or technique if, in waiting, a higher degree of safety is assured. The proposal is made that the risk at this point is too great to justify hurried continuation in the face of so many unknowns.

Those opposed to DNA recombinant research also suggest that the successes in drug therapy, improvements in diagnosis, the new knowledge of dietary therapy, and the evolution of a greater understanding and control of environmental factors may provide just as much of an opportunity to cope with genetically induced disease without gambling on the poorly defined risks associated with recombinant research. The dangers of producing some uncontrollable combination of genes with unknown pathogenic characteristics is considered by some individuals to be too great at this time.

With regard to the third group of benefits, opponents point to the great successes already achieved in the more classic types of plant and animal hybridization experiments.

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[48] Anderson, E. S. Viability of and Transfer of a Plasmid From *E. coli* in the Human Intestine. Nature, v. 255, June 5, 1975 : 502–504.

Some of the potential dangers of using recombinant techniques in plant hybridization are discussed in more detail by Doy. He indicated that genetic engineering with plants cells should be discussed as thoroughly as the present discussions are beginning with animal cells. Specifically, he noted:

> The possibilities of this field are going to attract a lot of workers because of the science, but also because of the possibility of grants, fame, and fortune and realistically, I think in some quarters, because of the possibility of creating agents of biological warfare. I find among many scientists, and plant biologists in particular, either a lack of understanding or a reluctance to acknowledge the possibilities of accidental disaster or deliberate evil. Scientists working with transgenosis in animal systems and viruses have recently clearly recognized the possible dangers . . . I shall not reiterate the arguments, but I would urge that plant biologists participate in the proposed discussions [on DNA guidelines]. The potential dangers of the human and animal work appeal to the emotions and therefore have an immediate impact, especially in the media. To my knowledge the analogous possibilities in plant biology have not been discussed. I do not think that ideas can be suppressed, nor do I think that possibilities for understanding and good should be foregone because of possibilities for evil which might then go on in secret [Note: the plant sciences are represented on the NIH DNA Recombinant Molecule Advisory Committee].[49]

The use of in-vitro fertilization techniques with reimplantation in host mothers is viewed as a safer method for improving the production of animals of agricultural importance which has not yet been fully exploited. While acknowledging the possible value of securing improved scavengers or organisms capable of currently unavailable bioenergy conversions or waste processing, the counterargument is that too little is known about ecosystem interactions to be able to predict the potential effects of such organisms if released into the environment. Experiences with other accidentally introduced organisms (such as American chestnut blight) which have proved catastrophic are cited as supporting this fear. Again, however, the ability to select naturally occurring hybrids suggests that there is no need to rush into the unknown dangers of recombinant research.[50]

During a symposium at the University of California, Berkeley, April 1976, a number of the unusual events which might ensue following supposedly beneficial genetic engineering were discussed. Dr. Ananda Chakrabarty, a microbiologist at General Electric Laboratories, Schenectady, New York, reportedly pointed out that while it had been possible to manipulate *E. coli* to produce a strain which can convert cellulose into assimilable sugars and fatty acids, this might not be as valuable a metabolic capability as first perceived. For example, while it might appear that the ability to convert cellulose (such as wood) into soluble products would be a valuable capability in the human gut, as is now the case with ruminating animals, the establishment of such organisms in human beings might result in the production of fatty acids and sugars faster than the intestine could absorb them and lead to dietary problems, and possibly even harmful toxins. Chakrabarty also described the GE lab's success in constructing

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[49] Doy, Colin H. Asexual Approaches, Including Transgenosis and Somatic Cell Hybridization to the Modification of Plant Genotypes and Phenotypes. In: Genetic Improvement of Seed Protectins. Proceedings of a Workshop. National Academy of Sciences. Washington 1976: 341–357.

[50] Canadian Scientist Isolates Pollutant-Gobbling Bacteria. InterCom. vol. 4. August 1976: 5.

a bacterium which could metabolize crude oil. He indicated, however, that it might be possible for pathogens in the environment to capture these new gene combinations and permit the pathogen to multiply in a crude oil spill to the point where an epidemic of disease might be possible. These examples are illustrative of the type of concerns being expressed by many researchers about the need for total ecological information before such research results in the release of genetically engineered organisms into an environment.[51]

3. *General Comments.*—Other comments which emerge in the risk/benefit debate associated with the justification of the continuation of DNA recombinant research examine more specific as well as broader issues on general research and development. There are questions as to the wisdom of diverting research funds at this time to an expansion of recombinant research when other areas of lower risk require funding. There are assertions of the increasing need for a fuller social participation in decision making for research which will ultimately impact on all of society.

Others have been quoted as saying that scientific investigation must never be permanently halted in the face of hazard—only ignorance, not knowledge, is the real danger to mankind.[52] McDougall points out that genetic engineering has been going on for many years.[53] He suggests that the real concern stems from the suspicion that there will be an abuse of power and that there has been undue emphasis on potential hazards.

Davis has asked opponents of the research on recombinant molecules to consider that *E. coli* is already exposed to free human DNA which has been released from broken cells in the gut and that natural recombination may very well have been going on continuously.[54] Under these conditions, one would expect that random recombinations between free DNA and bacterial DNA would have occurred given the number of opportunities available and the time period of association of the two organisms. Thus, there probably already has been some testing of these combinations by natural selection and, if this is true, then experimental recombinants would probably not produce any new unusual combinations. His second point is that since natural evolution tends to emphasize selection of the combination providing a competitive advantage, deliberate recombinants would have a lower probability of survival. He concludes by asking whether the risk of working with recombinant molecules is really so much greater than the historical risk of dealing with many of the known pathogens to warrant prohibition or severe restrictions on recombinant research.

There is a general recognition by both sides of the controversy that the success of either biological or physical containment control systems imposed for research on recombinant molecule will be dependent to a high degree on compliance with any guidelines and on the capability of the investigator. Investigators involved in the development of these techniques at this time tend to be the elite among the total scien-

[51] Genetic Engineering: Two-edged Sword. Chemical Week. May 12, 1976: 65–66.
[52] McWethy, Jack. Science's Newest Magic, A Blessing or a Curse. U.S. News and World Report. vol. 81. July 12, 1976: 34–35.
[53] McDougall, Kenneth J. Genetic Engineering: Hazard or Blessing? Intellect, vol. 104. April 1976: 528–530.
[54] Davis, Bernard D. Evolution, Epidemiology, and Recombinant DNA. Science. vol. 193. August 6, 1976: 442.

tific (and semiscientific) community which may eventually enter this field. While not discussed intensively in the debates over this research, there appears to be in the background of many of the discussions, a concern that "sloppy" technique or a casual approach to research may increase the risk to a higher degree than has been estimated on the basis of research accomplished thus far. There is no question that accidents will occur.

Recent instances confirm that the biohazards of controlling dangerous microbiological research exist even under the best of conditions and even when the danger is evident. For example, a research worker at the Microbiological Research Establishment, Porton Down, Salisbury, England was reported to have been infected with viral hemorrhagic fever as a result of accidental penetration of the protective gloves being used in the highest level of biological security for such experimentation. This accident occurred at a laboratory reported as providing facilities unrivaled in Western Europe for safe handling of the most dangerous viruses known.[55] (Similar exposures have been reported in a rare accident during research work with Lassa Fever, another dangerous disease.) In the case of viral hemorrhagic fever, no known cure is available. Yet, such research must continue if the vaccines are to be developed. This is not to say that such risks must be assumed for dangerous work with recombinant DNA research, it simply illustrates that viruses develop normally in nature and can be coped with under existing experimental situations albeit with some degree of risk. This is, however, the type of situation envisioned by some critics as a potential hazard in working with recombinant molecules involving the transfer of genes with unknown biological activity.

Studies have been made to determine the extent of accidental infection even within such highly secure and tightly controlled facilities as the former biological warfare research laboratory at Ft. Detrick, Maryland. These studies have shown that while the incidence of infection leading to either morbidity or mortality has been relatively low, it has occurred frequently enough to demonstrate that the best of systems is not one hundred percent fail-safe. In these instances, a large proportion of the infections were the result of human failure to comply with safety requirements. None of the infections resulted in epidemics in the surrounding communities.

Irwin and Stoner have indicated that there is a need for continuous evaluation of laboratory procedures to insure that all safety conditions are being followed.[56] They propose a need for a continuous review of the biohazard control literature to aid in identifying weaknesses in control systems; consultation with special authorities on biohazard control; the need for an independent active surveillance program involving engineers, microbiologists, and other specialists; the need for regular on-site inspections to check physical conditions; the availability of safety cabinets; special instrumentation of safety cabinets to insure appropriate operation at all times; regular evaluation of labora-

[55] Lawrence, Eleanor, Porton Lab Will Study Fever Virus. Nature, v. 255, May 15, 1975: 185. (See: Morbidity and Mortality Weekly Report, Center for Disease Control, Atlanta, U.S. Department of Health, Education and Welfare, Public Health Service, v. 25, December 23, 1975: 378, 383 for a report of the accident with African hemorrhagic fever).

[56] Irwin, John and Gerald D. Stoner. A Facet of the Biohazard Control Program: Agent Registration, Risk Assessment and Computerization of Data. American Journal of Public Health. v. 66. April 1976: 372–374.

tory researchers and technicians to determine the adequacy of practices; and the use of written reports of evaluation to insure a legal record of investigations. As may be appreciated, such a description hints strongly that legislation and government regulation may be required which might lead to inspection and certification of laboratories in a fashion now being proposed for certification of clinical laboratories. The Center for Disease Control, Atlanta, already has some responsibilities in this area. Legislators have suggested publicly that legislation may be required to insure public safety, particularly for commercial recombinant research where compliance with the NIH guidelines is only voluntary. A key question about such legislation is whether it would be flexible enough so that it does not impose an unacceptable degree of restriction on all research, academic and industrial.

Dr. Roy Curtiss III, Professor of Microbiology at the Univerity of Alabama and the designer of the first host-plasmid variant of *E. coli* to be approved by the NIH DNA Recombinant Advisory Committee as EK2 has provided a detailed analysis of the potential hazards associated with DNA recombinant work. As a trained microbiologist, who obviously is supportive of the DNA recombinant work, he is quite frank about the need to provide a high degree of assurance for the safety of such work. Perhaps it is his realization that inexperience and careless personnel can so easily lead to accidents that prompts his attention to this problem. In a recent review, he summarized the potential biohazards and identified the need for personnel training, the types of facilities required, and the requirements for emergency or accident contingency plans. He also provides information on the probabilities for escape and survival of recombinant molecules and the need for additional information before deliberate introduction into the environment in any form is accomplished. As he points out in his analysis, even the best of guidelines and safety procedures will be meaningless if there is noncompliance with recommended procedures. He notes that it is his belief that any release of DNA in one country would essentially mean release throughout the world (assuming survival). He suggests the need for some international authority to regulate beneficial uses of recombinant molecules.[57]

The NIH DNA Recombinant Molecule Advisory Committee has not ignored many of these well justified expressions of concern. As a part of continuous revision of the guidelines, several tasks are of immediate concern.

The NIH has a special task to provide continuing information about the conditions necessary to ensure safety of the physical facilities described in the guidelines for experiments of varying degree of risk.

The DNA Recombinant Molecule Advisory Committee is meeting regularly to consider comments from all sources to determine the need for revision of the guidelines as new information is made available. The development of weakened hosts and vectors is being closely monitored and the test protocols for approval of such hosts and vectors is in a dynamic state of development with the best available information being used to ensure that all potential hazards are being considered.

[57] Curtiss, Roy III. Genetic Manipulation of Microorganisms: Potential Risks and Benefits, Annual Review of Microbiology. v. 30. 1976: 507–533.

Because so much of the information about both risk and benefit is very speculative, there is a continuing feeling of uncertainty which can only be resolved by regular reevaluation. To this end, the Director of the National Institutes of Health has indicated every intention to provide for public participation and contribution to all of the processes leading to the guidelines under his control.

As noted by a number of investigators, and a point which was addressed specifically by the American Society for Microbiology in its considerations of the DNA recombinant research issue, the task of coping with the fears raised by speculation about the potential of an epidemic from some recombinant molecule will require greater participation by epidemiologists. There is a great deal of experience from the laboratory study of extremely virulent pathogens. Microbiologists and virologists have learned to work with a high degree of safety with such organisms. Epidemiologists have a familiarity with the factors determining the spread of disease. Thus, there are data available, both from history and from theoretical risk models, to support a more precise examination of this concern and perhaps clarify the actual extent of the risk.

III. Congressional and Federal Agency Reactions Related to DNA Recombinant Research

A. House Committee on Science and Technology

The House Committee on Science and Technology, Subcommittee on Science, Research, and Technology has been evaluating the impending developments in the various genetic technologies for a number of years. The committee's interest became formalized in 1971 during an annual conference on research and development. As a result, a program of monitoring the developments to follow the progress of DNA research was initiated. Although no formal hearings have been held specifically on DNA recombinant research to date, the committee has published two separate reports on the progress of this technology so that the Members might be kept aware of the issues. These reports have served as useful reference documents not only for the committee members but also for other Members of both Houses. This report has been prepared to provide the committee and other Members with a summary analysis of the current status of the work in DNA recombinant work specifically so that the need for further action can be determined.

B. Senate Committee on Labor and Public Welfare

The Subcommittee on Health, Senate Committee on Labor and Public Welfare held two hearings during the 94th Congress which were focused directly on the DNA recombinant molecule issue. The first hearing was held immediately following the Asilomar conference. Questions emphasized in this hearing and considered by witnesses as being of primary interest included:

What is the nature of this research which so disturbed the investigators that they felt compelled to stop it for a time?

Is there a safety threat to the general population?

What are the implications of the research for society as a whole?

How could nonscientists participate in the process; even if that were desirable, what should be done now in terms of public policy in this area?

Was it proper for scientists alone to decide to stop and then resume the research?

What are the potential dangers of Federal intervention?[1]

These questions were not answered fully during this brief hearing and it was announced that the issue would be the subject of a continuing dialogue.

A second hearing was held by the subcommittee on September 21, 1976. These hearings were much more comprehensive with the theme

[1] U.S. Congress. Senate. Committee on Labor and Public Welfare. Subcommittee on Health. Genetic Engineering. 1975. Examination of the Relationship of a Free Society and its Scientific Community. 94th Congress, 1st session. April 22, 1975. Washington, U.S. Govt. Print. Off. 1975. 35 p.

being the NIH Guidelines on Recombinant DNA Research. Witnesses included representatives from the DHEW, the EPA, the Pharmaceutical Manufacturers Association, and the Environmental Defense Fund. The General Electric Company was invited to send a representative because of their known involvement in the DNA research but refused the invitation. Researchers testified from several of the major universities (Dr. David Baltimore, MIT; Dr. Norton Zinder, Rockefeller University; Dr. Robert Sinsheimer, Cal Tech; and Dr. Halsted Holman, Stanford). These witnesses represented the contrasting range of views concerning the acceptability of the guidelines and the need for the research. The views expressed by some of these witnesses have already been cited in other sections of this report with the exception of the statement by Dr. Wilson K. Talley, Assistant Administrator for Research and Development. His comments are of interest for they indicate the concerns which led to the establishment of a Federal interagency coordination committee on DNA to determine the applicability of the guidelines to all Federal agencies. During his testimony, Dr. Talley said:

> Because the NIH guidelines only apply to research conducted or sponsored by NIH, universal protection against the potential hazards of this research can only be accomplished if the guidelines are extended to cover recombinant research performed by other Federal agencies and the private sector. I strongly support the extension of the coverage of the guidelines to all recombinant DNA research performed in the U.S. To this end, EPA will actively participate on the interagency committee on DNA research which has been established by the President.[2]

[Note: While Dr. Talley, has referred to this interagency committee as being established by the President, the formation is not quite that formal. The committee is one formed by the Secretary of HEW with the President's approval and is chaired by the Director of the National Institutes of Health. Senators Kennedy and Javits had forwarded a letter to the President on July 19, 1976 in which they had expressed their concern about the need for implementation of the NIH guidelines at all levels of responsibility. In their letter, the Senators urged the President to explore all executive means for extending the guidelines and if legislation was considered necessary, to make proposals to the Congress. The interagency committee is one of the mechanisms adopted by the Secretary of HEW to explore the problem of implementing the guidelines among all Federal agencies.]

Again the Subcommittee on Health indicated that this topic was considered to be of sufficient concern to warrant further evaluation and as indicated by the Chairman, he would consider legislative action in the event that industry does not voluntarily comply with the guidelines.

C. NATIONAL SCIENCE FOUNDATION

The National Science Foundation is funding a very unusual project which eventually may be viewed as a model method for studying evolving social problems. Under the Directorate for Science Education of the NSF, there is a special project on Ethical and Human Values in Science and Technology. As one part of this program, the Massa-

[2] U.S. Congress. Senate. Committee on Labor and Public Welfare. Hearings, September 21, 1976. op. cit.

chusetts Institute of Technology has accepted a task, funded by NSF, to prepare an oral and documentary history of all activities associated with the DNA recombinant molecule issue. Personal interviews are being taped with all individuals who have significant contributions to make in the debate. The proceedings of the various conferences and meetings in this country, and wherever possible in other nations, are being recorded. An archive of official documents, articles, and other printed material pertinent to any aspect of the controversy is being constructed to supplement the taped interviews. This project, under the direction of Dr. Charles Weiner, Department of History, MIT, is being identified with increasing interest and enthusiasm by researchers around the country. The project materials will be available to historians or other researchers desiring to study the evolution of this issue and for this reason will be a unique record of an exceedingly complex social policy issue.

D. OTHER FEDERAL ACTIVITIES

The Director of the National Institutes of Health has been holding interagency meetings with other executive agencies to determine the best course of action to follow with regard to adherence of these agencies with the NIH guidelines. As indicated earlier, most of these agencies have indicated their intention to comply. Total agreement has not been reached on this problem however, and the interagency meetings are continuing in an attempt to resolve this problem.

This interagency committee also is examining legislation to determine whether there is authority already in existence to permit regulation of all DNA recombinant research—whether Federal, State or local government, university, or private. The laws under which the FDA, OSHA, EPA, the Center for Disease Control and others operate are being studied to ascertain whether these agencies, collectively or individually, already have the responsibility to permit regulation if necessary. There are many difficulties involved, such as the need for additional State-Federal agreements for OSHA regulation of universities, and if it appears necessary, one of the tasks of the interagency committee is to recommend such additional legislation as might be necessary.

Among other ideas tentatively explored has been the potential need for a Biohazards Commission of some type to oversee DNA recombinant research as well as possibly other biological hazardous experimentation. In the Office of Technology Assessment, the Advisory Panel on Decision Making on R&D Policies and Priorities, has initiated a case study of the manner in which decisions are made regarding the funding of research and development. Dr. Robert F. Rushmer, Professor of Bioengineering and Social Management of Technology, University of Washington, a member of this panel, has initiated an analysis of the DNA recombinant molecule issue as a prototype for developing mechanisms for presenting points and counterpoints about evolving technologies.[3] It is his intention to develop this analysis into a case study for presentation to OTA.

[3] Letter to the Advisory Committee on Recombinant DNA Molecule Program, September 3, 1976.

As an example of the type of legislative action related to problems in genetics which was initiated during the 94th Congress, one bill is of particular interest. S. 2515, introduced by Senator Kennedy for himself and Senators Javits and Schweiker, contained a provision of direct relevance to the DNA recombinant issue. The primary purpose of the bill was to amend the Public Health Service Act to establish a President's Commission For the Protection of Human Subjects involved in biomedical and behavior research. Section 483 of the bill would have required the Commission also to:

". . . conduct an investigation and study of past, present and projected research in the modification of any living organism or virus by the inspection of recombinant DNA molecules. The Commission shall consider the ethical, social, and legal implications of such research, and evaluate the potential hazards posed by such research both to research personnel, the human subjects of such research, and to the public at large. The Commission shall, if appropriate, develop guidelines on how such research should be carried out in order to protect human health.

The legislation passed the Senate but not the House.

IV. Non-Federal Reaction to DNA Recombinant Research and the Guidelines

A. Introduction

The debate concerning the NIH guidelines and the issue of DNA recombinant research is not limited to the Federal hierarchy alone nor to those institutions participating in the Federal decision-making process. This is a truly national debate, indeed, it is even international in scope.

As may be noted in the selected examples in the following paragraphs, the issue has rapidly expanded down to the level of local government. There are active discussions going on ranging in size and intensity from small student/faculty discussion groups up to the level of serious consideration at the State level of the need for controls through legislation or other regulation. A few of the more prominent instances have been selected and summarized in order to convey the extent to which this issue occupies attention throughout the Nation and the World.

B. University of Michigan

University of Michigan faculty members attended the Asilomar Conference and have assisted on the NIH Recombinant Molecule Advisory Committee. The University, following the suggestions of several faculty members, initiated a parallel local study and discussion of the research on recombinant DNA in early 1975. The University committee has utilized the same process of evaluation being followed at the Federal level. The committee members represent university programs in health and human values, law and psychiatry, philosophy, medicine, genetics, history, biochemistry, physics and mental health, English, literature, social work and social psychology. Deans of the Schools of the University were consulted and the news media was contacted to insure public awareness. The faculty was informed of the deliberations, university opponents of the research programs were offered opportunities to discuss their views, critics from other universities or institutions were invited to submit their views, the literature was examined—both scientific and ethical literature—and the occupational and safety aspects of the issue were considered.

The University of Michigan report on a "Policy for the Molecular Genetics and Oncology Program" essentially adopted the NIH guidelines with the recommendation that the research be allowed to continue. It was recommended that: the NIH guidelines should be the code of practice for all work on the campus regardless of the source of funds; only research up to and including work at the P3 level of containment should be permitted (P4 work would have to be completed outside the University campus unless separate and specific ap-

proval was provided by an appropriate University decision-making authority); the University should establish a Biological Research Review Committee to maintain continuous surveillance of activities associated with such research; the Review Committee should set up a procedure for reporting accidents and maintaining records of such events; appropriate training for all personnel be instituted; procedures for continuous monitoring be established; and that the University Senate Assembly Committee on Research Policies regularly review all practices to determine whether any new policies or changes needed to be instituted.

The University committee also considered the potential liabilities which might be associated with formal approval of research which might involve injury. The legal liabilities were considered by the University counsel from the standpoint of negligence and strict liability, workmen's compensation, nuisance statutes, State occupational health and safety legislation, Federal statutes, immunity against claims, and insurance requirements. The University committee determined on the basis of this legal analysis that there were no exceptional legal inhibitions to be anticipated with the possible exception of the need for strict adherence to safety regulations and included in their recommendation that DNA recombinant research be permitted to continue.

Nevertheless, there was not unanimity in the committee's decision. A dissension was filed by Dr. Shaw Livermore, Jr. of the University's Department of History. Dr. Livermore's disagreement was not with regard to the considerations given to the containment and other safety considerations. Like several other objections which have been voiced nationally, he said:

> I do not believe that the University of Michigan should encourage research in DNA recombinant technology . . . I believe that the limitations of our social capacities for directing such a capability to fulfilling human purposes will bring with it a train of awesome and possibly disastrous consequences . . . Neither do I share a generalized fear of science and technology . . . What I am intent upon is the particular nature of DNA recombinant research . . . The claims of free inquiry and individual initiative are among the most zealously guarded in a free society and they should remain so . . . I do not sense that we are presently at such a crisis [. . . all temporarily-safe means to relieve human distress are justifiable] or are so powerless, that we must suspend judgment to grasp at each prospect of temporary alleviation.[1]

After the publication of the University committee's report, a formal critique of the report was prepared by a group of faculty members and presented to the Regents of the University on April 15, 1976. The committee responded to the critique in a detailed comment which left the impression that the criticisms were for the most part unfounded. The arguments and counterarguments were similar to the objections and counterobjections being voiced about the National Institutes of Health guidelines. As at Harvard University, examination of the DNA research issue was coupled with the need to upgrade university facilities to provide appropriate containment and security to meet the requirements of the guidelines.

It should not be surmised from the preceding summary that the only considerations on this topic in Michigan were at the University

[1] Statement of Dissent, Shaw Livermore, Jr. Report of the University Committee to Recommend Policy for the Molecular Genetics and Oncology Program. (Committee B). The University of Michigan. March 1976.

level. The Washtenaw County Democratic Party provided a copy of a resolution they initiated which recommended that DNA recombinant molecule research be restricted by law to a limited number of facilities equipped to prevent inadvertent escape of test organisms until further data on the magnitude of the risk are available. Three institutions in Washtenaw County, Michigan were identified as carrying out DNA recombinant work: The University of Michigan, Eastern Michigan University and the Parke-Davis Research Laboratories. In their letter to the Chairman of the Science and Technology Committee, the suggestion was made that other researchers could make arrangements to conduct research at these limited number of facilities until such time as more information on the risks could be developed.[2]

C. HARVARD UNIVERSITY-CAMBRIDGE

Perhaps the most highly publicized disagreement regarding the conduct of DNA recombinant research occurred at Cambridge, Massachusetts. In this university setting, the Cambridge City Council challenged the right of Harvard University to conduct potentially dangerous research within the City. As in the case at the University of Michigan, Harvard University needed to upgrade some of its laboratory space in order to meet the more demanding requirements specified in the NIH guidelines. The controversy about the research drew the attention of proponents and opponents of DNA recombinant research from all over the Nation.

One of the reasons that the Harvard controversy received so much high level attention is that Harvard and MIT are already among the relatively few institutions having researchers highly capable of conducting such research. The issue had also been discussed during a public symposium at Massachusetts Institute of Technology and earlier events, not only in research in molecular biology but also in the social impact of medical genetics, had made members of the faculties of these universities particularly sensitive to the public policy implications of their research.

The issues discussed at the public hearings held by the Cambridge City Council were no different from those summarized within this report or discussed at other symposia. However, here the problem was immediate and local. Harvard and MIT have members of their faculty who present both opposition and support of the research. The City Council position was one of concern about the potential risk to the public. The result of the hearings was to establish a temporary moratorium on the conduct of the "higher risk" types of such research. In the meantime, Harvard University is completing the planned renovation of the laboratories which led to the focus of attention on this issue.

D. NEW YORK STATE

The first State level action on the DNA research issue has been initiated by the State Attorney General's Office in New York. Hearings were held in October 1976 to consider the need for action to control DNA recombinant research. The options considered during the

[2] Washtenaw County Democratic Party letter to the Chairman, Committee on Science and Technology. May 26, 1976.

October 21 hearings ranged from witnesses calling for a complete moratorium to a requirement for adherence to the NIH guidelines as suitably modified to meet any additional State regulations. The State hearing provided another forum for a discussion of the main grounds of debate which had been covered by essentially the same witnesses at the University of Michigan, the Harvard-Cambridge hearings, and during the various stages of development of the NIH guidelines. There has evolved a well identified core of proponents and objectors in this area and public hearings tend to provide an opportunity for further discussion of the same issues. No definite action has been taken as yet but it is significant that a State judicial body has now entered the national arena of debate on this issue.[3]

E. SAN DIEGO, CALIF., CITY COUNCIL

The San Diego City Department of Environmental Quality has been holding a series of semi-formal meetings for the past several months to examine the different points of view regarding the conduct of DNA recombinant molecule research at the University of California San Diego campus. These meetings are not being held in response to any particular public pressure but to insure that the city government and the university officials have examined the issue sufficiently to avoid such conflict as has evolved in other localities. It is anticipated that after one or two additional meetings the informal hearing group, a so-called "Quality of Life Group" will prepare a report for the Mayor of San Diego and the City Council which will provide some perspective for the local government to determine whether any action is needed. Since the City has no jurisdiction over university activities, any formal disagreements or representations for change or control will probably have to flow through the State government to university officials. It is unlikely that serious misunderstandings will occur since the University is represented on the working group by Dr. Clifford Grobstein, Vice Chancellor for University Relations and William Davis, staff member from the City Council's Department of Environmental Quality participates in the public meetings. At this time (December 1976) it is anticipated that it will probably be February 1977 before the report to the Mayor will be available.

F. INDUSTRY RESEARCH

Perhaps the area of primary concern regarding DNA recombinant research is that segment of the industrial research community which is already conducting such research. As practical applications of the technique come near, there will certainly be an expansion of effort in the non-Federal sector, including primarily commercial research efforts.

The Director of the National Institutes of Health was aware during the early stages of guideline development that one of the critical factors in the success of a voluntary compliance with the guidelines

[3] Wade, Nicholas. Recombinant DNA: New York State Ponders Action to Control Research. Science. v. 194. November 12, 1976: 905–706.

would be industry acceptance. It was for this reason that he held a meeting with some 30 industrial representatives (see appendix 7) to determine their reactions to the proposed guidelines. During this meeting, it was evident that some research was already underway. General Electric, for example, had been reporting on its work with waste converting microorganisms primarily for purposes of developing bioconversion energy systems. Miles Laboratories indicated an interest in biosynthesis of enzymes. In general, the industries seemed to be somewhat hesitant to commit themselves with regard to the guidelines since it was believed that the guidelines might eventually assume the status of regulatory law and this would place an entirely different perspective on their views about the details in the guidelines. There is no comprehensive compilation of the extent and nature of DNA work which is being conducted in industry either in this country or throughout the world, although it appears that at least seven companies are doing some recombinant work. These are, in addition to Lilly, GE, and Miles, Abbott Laboratories, W. R. Grace & Co., Merck, and Upjohn.[4] It is obvious that knowledge of the precise nature of any research being conducted would have great value in the competitive industries and just as with other proprietary work, there evidently is concern about maintaining industrial security. However, it is this very tendency for secrecy which produces a counter concern that potentially risky research might be attempted if no control or guidance is exercised.

Although Pharmaceutical Manufacturers Association President, Joseph Stetler implied during congressional hearings that the drug industry endorsed the guidelines and probably would not object to some monitoring,[5] it does not appear that this spirit is general through all industries. (Stelter added Upjohn to the known list of other companies presently conducting DNA recombinant research.) Stetler indicated during his testimony that the only problems he anticipated had to do with the protection of trade secrets and the provision restricting volumes to ten liters. This latter provision would not be acceptable in any commercial applications.

PMA also indicated their support for the use of normal patent application procedures to protect developments which emerge during DNA recombinant research.

More recently, a news report was interpreted by some individuals as meaning that there was more resistance to the guidelines on the part of drug and chemical executives than might be inferred from the earlier testimony of Mr. Stetler. The Department of Commerce held a meeting with representatives of 17 companies to discuss the compliance procedures needed in order that commercial development might proceed safely in this area of research. During this meeting, the representatives of these industries apparently indicated that there would be a number of changes required before the guidelines would be acceptable as regulations. According to reports available, the industrial representatives would accept a system which would require them to register to conduct such research but would not force them to

[4] Industry Wary About Genetic Guidelines. Chemical and Engineering News. June 7, 1976: 7.

[5] U.S. Congress, Senate, Committee on Labor and Public Welfare, Subcommittee on Health. Hearings. September 21, 1976. op. cit.

comply with the guidelines, even though the implication was that there would be voluntary compliance.[6] In general, however, there is no specific information to indicate that any basic changes in industry attitude have occurred. Again, a primary concern seemed to be the need to protect trade secrets until patent rights had been established.

G. GENERAL

The listing of the preceding specific examples of State or local government examination of the DNA recombinant molecule issue or industry reactions should by no means be interpreted to mean that these are the only discussions which are occurring. The Biological Safety Committee at Yale University, New Haven Connecticut has attempted, through public discussions which have included the city government, to keep their community apprised of activities at that university. In fact, Dr. Frank H. Ruddle, Chairman of the Yale Biological Safety Committee has already made a proposal to the NIH with regard to the possibility of establishing a national repository for DNA material which would provide some support to all investigators and thus prevent unnecessary duplication of effort. Such a national repository for DNA material would be similar in concept to the American Type Culture collection. Princeton University has completed a study recommending approval for research on recombinant DNA.

Other individuals and groups have expressed concern or support for this area of research from all over the Nation and from many diverse sections of our society.

The New York Academy of Sciences has sponsored one major symposium which included a discussion of this issue. The National Academy of Sciences has endorsed the guidelines. The Environmental Defense Fund and the Natural Resources Defense Council have petitioned the Department of Health, Education, and Welfare to apply the guidelines to all investigators regardless of source of funding. The petition, incidentally, cites as legal justification for HEW action of this sort the authority of NIH to regulate the spread of communicable diseases. The Federation of American Scientists has polled its membership to determine opinions regarding the research.

The American Association for the Advancement of Sciences, as a part of its expanding role in increasing public understanding of public policy issues will probably continue to play an important role in providing a public forum for the discussion of this issue. The American Institute of Biological Sciences regularly provides discussions on this subject for its membership. The American Society for Microbiology established an ad hoc committee to study the NIH guidelines. Their recommendations essentially endorsed the guidelines with several recommendations to strengthen containment criteria and to protect susceptible researchers. The ASM committee also indicated a need for increased ASM responsibilities in the area of education for DNA recombinant molecule researchers. The National Academy of Sciences is planning a special workshop in their Academy Forum Series (March 1977) to consider research on recombinant DNA.

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[6] Cohn, Victor. Drug Industry Seeks to Alter U.S. Rules on Genetic Studies. The Washington Post. November 20, 1976: A3.

A special congressional staff briefing on the need for legislation to control recombinant DNA research was held on December 14, 1976 under the sponsorship of the Environmental Study Conference [an informal congressional group supported by Members of both Houses] and the Scientists' Institute for Public Information.

Although the proliferation of interest in this issue has not been totally unexpected, there is some concern about the potential for the evolution of ordinances or regulations on a local basis. Since the research transcends local boundaries, there is a strong interest in the development of standard guidelines. In the discussions held thus far, the NIH guidelines have occupied a central focus of attention. There probably would be no objection by NIH if State or local regulations evolved which utilized these guidelines as the core for any locally enforced regulations. The evolution of a maze of regulations would, on the other hand, contribute to great confusion as to requirements and undoubtedly interfere with effective control over research which crosses not only State but international boundaries. Evidence for this same interest in other Nations is available not only from the statements made by foreign participants at U.S. meetings but also in the debates which are producing regulations in these other Nations.

V. International Reactions to the DNA Recombinant Molecule Research Issue

A. Introduction

A number of nations have already taken formal action to regulate or consider regulation of DNA recombinant research. The U.S. Department of Health, Education, and Welfare is making a direct effort to maintain open lines of communication with these nations so that their views regarding the NIH guidelines may be considered as well as to determine any new data which might require evaluation in the United States. This cooperation was evidenced from the first Asilomar meeting on and including the meetings of the NIH DNA Advisory Committee meetings which have been attended by foreign representatives, principally the United Kingdom, West Germany, and the U.S.S.R.

B. United Kingdom

Toward the end of 1971, the British Association for the Advancement of Science expanded its efforts to make the public aware of the developments and consequences of science. In this objective at least, the BAAS was attempting, in the same way as the American Association for the Advancement of Science, to be more responsive to the need for greater interaction between society and the scientific community. Among the several areas of long range interest selected for special study by a working group of the BAAS was a thorough examination of the scientific, social, ethical and legal issues associated with advances in genetics and biology.[1] By the end of 1974, the working group had completed a series of papers on topics in this subject area and a report had been published in the form of a book.[2] The efforts of the working group are of interest not only because of the perspectives about the evolving issues in genetics which are presented but also because this group attempted to provide for an examination of these issues by a broad spectrum of representatives of different segments of society: the press, the Parliament, many fields of medicine and biomedical research, law, and sociology. This working group effort provided a natural background for the more intense examination of the DNA recombinant molecule issue which began to evolve during this period.

In another related action within the United Kingdom, a working party was set up by the Secretary of State for Social Services to

[1] Social Concern and Biological Advances. Report of a Study Group. British Association Publication 7412. British Association For the Advancement of Science. London. September 1974. 16 p.

[2] Jones, Alun and Walter F. Bodmer. Our Future Inheritance: Choice or Chance? A Study by a British Association Working Party. Oxford University Press. 1974. 141 p.

determine whether there was a need for taking special measures to control laboratory studies with pathogens. This action was initiated following an accidental release of smallpox virus from a laboratory in London. The time span of this study overlapped the DNA recombinant issue. Therefore, their report included a recommendation that a "Dangerous Pathogens Advisory Group" be constituted to provide advice on control measures for DNA recombinant research.[3]

The first comprehensive assessment of DNA recombinant molecule research was initiated following the publication in the journal *Nature* of the request by Paul Berg and others for a moratorium on certain forms of this research. Upon review of this statement, the Advisory Board to the Research Councils established another Working Party:

> To assess the potential benefits and potential hazards of techniques which allow the experimental manipulation of the genetic composition of micro-organism; and to report to the Advisory Board for the Research Council.[4]

The "Ashby" Report provided a number of recommendations which focused on the need for safety in handling and work with DNA recombinant molecules. A central theme in this report, as in many reports in other nations, dealt with the potential danger of accidental dissemination of DNA recombinants with unpredictable and potentially dangerous characteristics. The general reaction to the report appeared to be quite favorable. For example, Bernard Dixon reported:

> Lord Ashby's report is notable, therefore, in examining a potential hazard of unique seriousness—and one which has been brought into the arena of public debate by a group of scientists anxious about the repercussions of their own work. It is also unprecedented in the clarity and simplicity of its prose. The committee felt, quite rightly, that the subject should be made accessible to people not familiar with increasingly opaque jargon of microbial genetics. One cannot but applaud the motives of both the researchers and the Ashby panel in stimulating public awareness and discussion in this way.[5]

Dixon was not entirely satisfied with the report, however, and pointed out that the Ashby report identified research indicating that the K–12 *E. coli* could serve in the human intestine [6] but at the same time suggested that the likelihood of such an event was extremely remote. The Ashby report was criticized further by Dixon for not calling for a complete stop to all research until the necessary safety systems had been developed.

The next phase of the British examination of this issue was completed by a "Working Party" assigned the task to:

> (a) draft a central code of practice and to make recommendations for the establishment of a central advisory service for laboratories using the techniques available for such genetic manipulation, and for the provision of necessary training facilities;
>
> (b) to consider the practical aspects of applying in appropriate cases the controls advocated by the Working Party on the Laboratory Use of Dangerous Pathogens.[7]

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[3] Department of Health and Social Security. Report of the Working Party on the Laboratory Use of Dangerous Pathogens. [Sir George Godber, Chairman. London. Her Majesty's Stationery Office. May 1975. 40 p.

[4] Secretary of State for Education and Science. Report of the Working Party on the Experimental Manipulation of the Genetic Composition of Micro-Organisms. [Lord Ashby Chairman]. January 1975. London. Her Majesty's Stationery Office. 23 p.

[5] Dixon, Bernard. Not Good Enough. New Scientist. January 23, 1975. 186.

[6] Anderson, E. S. op. cit.

[7] Secretary of State for Education and Service. Report of the Working Party on the Practice of Genetic Manipulation. [Professor Sir Robert William, Chairman]. August 1976. London. Her Majesty's Stationery Office. 31 p.

A summary of the recommendations provided within this report was prepared by the editors of *Nature*:

> The working party divides experiments into four categories (depending on their hazards) and provides a code of practice to cover each category . . . Researchers will submit details of their experiments to a Genetic Manipulation Advisory Group (GMAG) which will vet and categorize the work. They can then decide voluntarily whether or not to abide by the advice of the GMAG and to follow the code of practice.
>
> But at the same time, details of the experiments will have to be submitted to the Health and Safety Commission (HSC) which has turned its eye specifically to all forms of genetic manipulation of microorganisms, including those which preceded the advent of the new technology for recombinant DNA. The HSC will, through its inspectors, police the work using the existing (and very wide ranging) Health and Safety at Work Act, which it administers. The great advantage of this Act is that it applies to all employers, in industry, public laboratories and universities. This has allowed the working party to avoid the problem being faced in the United States, where guidelines control only research sponsored by the National Institutes of Health (NIH) and leave industrial and defense-related work largely untouched.[8]

The British Health and Safety Commission did not take long to promulgate a proposed document for regulations for "Compulsory Notification of Proposed Experiments in the Genetic Manipulation of Micro-organisms.[9]

Although the request for comments on this document had a closing date of November 1, 1976, this date was extended to permit additional comments to be submitted. Reports in the literature indicate that the scientific community is quite disturbed by the stringency of the proposals in the HSC draft regulations and by the sweeping scope of the research encompassed by the regulations.

As the HSC regulations are under evaluation and consideration for revision prior to promulgation, the British Genetic Manipulation Advisory Group has initiated its examination of the problem. Sir Gordon Wolstenholme, Chairman of the Group has already met with the Director of the U.S. National Institutes of Health to consider the practicality of the guidelines which are evolving.[10]

Britain's Institute of Biology had already endorsed the guidelines developed at the Asilomar Conference. This organization as well as the British Society for General Microbiology, the Association of University Teachers, and the Association of Scientific, Technical, and Managerial Staffs are all directly affected by the proposals of the Health and Safety Commission.

C. CANADA

The Medical Research Council of Canada established an ad hoc committee:

> to make recommendations to the Council regarding the safeguards to be required in MRC supported research on recombinant DNA molecules and certain animal viruses and cells.[11]

[8] Genetic Guidelines: Handle With Care. Nature. V. 263. September 2, 1976: 1. See also: Lawrence, Eleanor. Genetic Manipulation: Guidelines Out. Nature. v. 263. September 2, 1976: 4–5.

[9] Health and Safety Commission. Consultative Document. Compulsory Notification of Proposed Experiments in the Genetic Manipulation of Micro-Organisms. London. August 1976. 6 p.

[10] Britain and U.S. Discuss Genetic Engineering. New Scientist. November 18, 1976: 372.

[11] Draft Report to the Medical Research Council From Its Ad Hoc Committee on Guidelines for Handling Recombinant DNA Molecules and Certain Animal Viruses and Cells. March 1976. 72 p.

The Committee submitted its report to the Canadian MRC and a copy was provided to the Director of the U.S. National Institutes of Health for his comments. The report provides recommendations for mechanisms and procedures for monitoring of MRC supported research. As in the U.S. guidelines, it was suggested that the proposed MRC guidelines also be adopted for non-MRC funded research. Safety procedures and containment levels are described for varying degrees of hazardous work with viruses, cells, and recombinant DNA molecules.

D. AUSTRALIA

There is no formal government policy in this area; nor is there likely to be. The number of Australian scientists likely to do work in this field is strictly limited and well known to the scientific community.

The Australian Academy of Sciences has convened a "Standing Committee on Recombinant DNA Molecules." On behalf of the committee, Professor G. L. Ada of the Australian National University has prepared a report, titled "Guidelines for Both Physical and Biological Containment Procedures for Work Involving Recombinant Nucleic Acid Molecules."

Basically the document sets up and describes five "risk" categories and prescribes appropriate "containment measures" to be followed in each case. These categories are as follows: (*a*) minimal risk experiments; (*b*) low risk experiments; (*c*) moderate risk experiments; (*d*) high risk experiments; and (*e*) experiments to be deferred.

A final category includes:

> Technically feasible experiments which present such serious dangers that their performance should not be undertaken at this time with currently available vector-host systems and presently available containment capability. These include the cloning of recombinant nucleic acids from highly pathogenic organisms (i.e. class 3 and 4 aetiological agents as classified by HEW), nucleic acids containing toxin genes and large scale experiments (more than ten liters of culture) using recombinant nucleic acids that are able to make products potentially harmful to man, animals or plants.

High risk experiments are described as those in which:

> The Potential for Ecological Disruption or Pathogenicity of of the Modified Organism Could be Severe, and Thereby Pose a Serious Biohazard Both Within and Outside the Laboratory.

Containment procedures for "high risk experiments" include "isolation from other areas by air locks and a negative pressure environment, clothing changes and showers for entering personnel and laboratories fitted with treatment systems to inactivate or remove biological agents that may be contaminants in exhaust air and liquid and solid wastes. The handling of agents should be confined to biological safety cabinets from which the exhaust air is incinerated." Containment procedures also prescribe use of "rigorously tested vectors and hosts whose growth can be confined to the laboratory."

Risk descriptions and containment levels for other categories are appropriately scaled down from high risk category.

The Standing Committee of the Academy requests scientists working on or proposing work in this area to study guidelines and then fill in a questionnaire. The committee will assess the degree of hazard in

submitted proposals and will recommend appropriate containment procedures. The Department of Health expects to be able to monitor proposed studies through the need for financing of proposed projects, the vast majority of which comes from government sources in one form or another.[12]

E. U.S.S.R.

There is no evidence available at this time that there are any restrictions on DNA recombinant research in the Soviet Union. This nation has had representatives in attendance at meetings in the United States, for example, at the Asilomar Conference which developed the initial guidelines, and at the public meeting of the NIH DNA Recombinant Advisory Committee. Some indication of the Soviet attitude about this research can be found in a recent paper prepared by I.T. Frolov. In addition to discussing the usual examples cited with regard to the benefits and risks of this research, including "a big danger in the case of their use for military purposes as well as in the hands of various kinds of ill-intentioned persons" Frolov notes: ". . . voices are being raised with increasing frequency concerning the need for democratic (sic) control over scientific research in fields abutting on the vial interests and man and mankind." [13] It has also been learned informally that the Soviets have requested a culture of the viral vector being proposed for approval in DNA recombinant research at the U.S. National Institutes of Health.

In another report, Academician Vladimir Engelhardt who attended the Asilomar Conference is quoted as saying:

> Soviet biologists . . . believe the ethical side of the problem has probably been exaggerated. At the moment, molecular biologists are happy if they can transfer just one gene. . . . The possibility of manipulating the huge number of separate genes that would be necessary if one was meddling with man's characteristics, is such a complex problem that it clearly lies in the distant future . . . when such genetic engineering becomes possible, society will be mature enough to overcome the possible dangers.[14]

F. FRANCE

The principal site of controversy over recombinant DNA work in this country has been at the Pasteur Institute. Genetic experiments of this type had been temporarily halted awaiting the guidelines from Asilomar. Following the publication of these guidelines, the French government formed two committees: one to examine the ethics of the research, the other to develop safety limits to control the research. At the time of this report, no definitive guidelines had been made available to the U.S. government, but the controversy at the Pasteur Institute is very similar to the debates occurring at Harvard, University of Michigan and other campuses in the United States.

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[12] Source. Informal Document Provided by the Office of the Executive Secretary, NIH Recombinant Molecule Advisory Group, HEW, March 1976.

[13] Frolov, I.T. Research on Man, Genetic Engineering. Voprosy Filosofii. no. 7, 1975: 83–95. no. 8, 1975: 121–138. (U.S. Joint Publications Research Service. JPRS 66307. December 5, 1975.)

[14] A Unique Plan for Soviet Molecular Biology. New Scientist. January 8, 1976: 53.

G. OTHER NATIONS AND INTERNATIONAL ORGANIZATIONS

Committees to examine the DNA recombinant research problem and develop national positions regarding this research have been established in Sweden, (Swedish Medical Research Council); Japan, the Netherlands (Royal Academy of Science Advisory Committee), and West Germany. While other nations have entered into discussions at international conferences on genetics and cell physiology, there is at present no indication that procedures as detailed as those described for the United States, the United Kingdom, or Canada have been completed.

The European Science Foundation has recommended adoption of the guidelines proposed by the United Kingdom. Apparently, the ESF prefers the British approach because of the greater emphasis on physical containment rather than biological containment and the fact that the British approach would apply to all laboratories and not just government funded research. One important factor considered by ESF in its evaluations was the need for all nations to establish essentially similar control levels in order to prevent the movement of research from one country to another in search of the least stringent conditions.[15]

At the 16th General Assembly of the International Council of Scientific Unions meeting in Washington, D.C. in October 1976, the Council approved the formation of a Committee on Genetic Experimentation to monitor, assist, and advise on recombinant DNA research.[16]

The European Molecular Biology Organization has established a standing committee on Recombinant DNA to provide advice and assistance to any members engaged in genetic engineering research. Although the EMBO standing committee has no regulatory or legislative responsibilities, it is prepared to provide help on scientific and technical aspects of recombinant research. EMBO also has noted that a collection of bacteria, plasmids, and bacteriophages best suited for recombinant work should be established within Europe or elsewhere within the framework of EMBO. The EMBO advisory committee on DNA recombinant research also has advised the Director of NIH of their full support of the need to carry out experiments specifically designed to provide information to permit assessment of the hazards being postulated for this type of research. EMBO has been represented at several of the meetings held by NIH and at Asilomar and exchanges communications with the Director of NIH with regard to the guidelines which are evolving in the United States.

The World Health Organization has been urged to coordinate recombinant DNA studies. In the September WHO Chronicle, however, the position of WHO was stated as follows:

> While WHO has a clear duty to act as a worldwide coordinator and promoter of international collaboration in this field [Safety of research on DNA recombinants], it should not itself set up guidelines but should ensure that Member States are kept fully informed of guidelines promulgated within countries chiefly with such research.

[15] Kenward, Michael. Europe Urged to Adopt UK's Genetic Rules. Science and Government Report. v. VI. December 1, 1976: 3–4.
[16] ICSU Acts on DNA, Taiwan, Space Issues. Chemical and Engineering News. October 25, 1976: 8.

. . . In view of the potential benefits of research on DNA recombinants, it is suggested that an expert group should meet within the next 12–15 months for a detailed examination of certain promising technical areas.

. . . The potential benefits of research on DNA recombinants in relation to agriculture are emphasized. The nutritional implications are enormous, and the possibility of obtaining new energy sources from plants should also be borne in mind.[17]

In summary, the DNA recombinant issue is receiving world wide examination in actions ranging from the specific recommendations to utilize the resources of the Occupational Safety and Health legislation in the United Kingdom to control all research wherever performed to an attitude of little or no immediate concern about the issue at this time. In all instances, it appears that lines of communication have been established among the various governmental groups and the efforts of the U.S. National Institutes of Health are receiving careful and regular scrutiny.

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[17] Towards More Effective Biomedical Research. WHO Chronicle. v. 30. September 1976: 377.

VI. Concluding Remarks

A. General

In her introductory remarks in a recent paper, Barbara Gardner provides a good summary of the DNA recombinant research dilemma:

> There is a growing realization in modern society that science and technology alone cannot solve the problems of contemporary life. Indeed, technology has in some cases given rise to problems . . . The rapid developments in the field of genetic research present perhaps the foremost area for social concern about the possible application of basic research. Future discoveries and refinements of current procedures will force society to confront squarely and resolve the question of the role of science and technology in modern life. The necessity for political, legal and ethical decisions will arise in genetics more than in other areas of scientific research because of the far reaching impact genetics has on humanity. Genetic research involves the fundamental elements of what it means to be human and alive. The imminent technological capability to alter or manipulate human nature and the human organism is the central concern . . .
>
> . . . A leading commentator has postulated that there are four types of perception with regard to scientific research [citation given in the Gardner article]. When the consequences of any line of research are unknown, the possible outcome may be viewed with extreme optimism, moderate optimism, moderate pessimism, or radical pessimism. The extreme optimist sees the pursuit of scientific research as an intrinsic good which even the greatest possible dangers should not deter. The moderate optimist believes that more benefit than harm generally results from scientific research and therefore that research should proceed when the consequences are unknown. The moderate pessimist asserts that, based upon historical evidence, harm is as likely to result from research as benefit. Finally, the radical pessimist holds that despite the benefits scientific research has produced, its products are intrinsically harmful to modern society.
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> . . . In no other field of scientific research will the perception that society ultimately adopts prove as important as in genetic research.[1]

As is evident in any examination of the debates on the DNA recombinant issue, there *is* a spectrum of perceptions present. One significant aspect of the debate is the fact that these various perceptions are being vocalized early in the research stage and thus the debate can be effectively engaged before full blown technology emerges. It is in the action-reaction part of the issue where there is a particular concern.

For example, in a recent commentary on public issues over the past 20 years, the *New Scientist* noted:

> Cell biology, in the form of recombinant DNA research, is another controversial public concern, currently the subject for *unprecedented* [emphasis added] moves in Britain to establish legal constraints on scientific work.[2]

The implications of this comment vis-a-vis an unprecedented constraint over scientific work is evident also in the remarks of Dr. Stanley N. Cohen when he testified before the Senate Subcommittee on Health. Dr. Cohen pointed out:

> While it is essential for the public to be assured that experiments seeking basic knowledge are carried out safely, I believe that it would be contrary to the

[1] Gardner, Barbara Jeremiah. The Potential for Genetic Engineering: A Proposal for International Legal Control. Virginia Journal of International Law, v. 16. Winter 1976: 1–2.

[2] Twenty Years On. New Scientist. November 25, 1976: 427.

public interest if the initiative of the scientific community in raising issues of experimental safety should lead to a decision by the public *to direct* [emphasis added] the scientific course of such investigations.[3]

Dr. Richard Roblin voiced a similar concern:

. . . I hope that this move toward self-regulation on the part of the scientific community will be given a chance to demonstrate its effectiveness before other forms of social control are applied.[4]

In contrast with this concern about certain basic scientific rights of free inquiry, Sinsheimer believes that we may be at a point in scientific achievement beyond which we should not proceed. He perceives long range philosophical issues in the DNA recombinant debate which he believes have not been adequately addressed.[5]

Dr. Susan Wright (University of Michigan), an outspoken critic of the process by which the NIH guidelines evolved, recently summarized her concern about reaching public policy decisions on difficult issues generally:

Advocates of the present policy [on DNA recombinant research] maintain that the public has participated in its formation. Let it be clear that expression of views to decision makers is a quite different matter from participation in decisions. Through the mechanism of a technical committee, decision-making power has been concentrated in the hands of front-rank researchers, all of whom are committed to biological research in general and many, to recombinant research in particular. There has been no representation from those most immediately at risk—technicians and maintenance personnel, for example; no representation from public interest and environmental organizations; no representation from the public at large.

It is questionable whether self-regulation of this type can be relied upon as a means of making public policy . . . Scientists must recognize that in a democratic society, they do not have special rights to self-government for an activity which carries serious implications for the whole society. . . . Unfortunately, procedures for making policy decision on hazardous areas of science and technology have not yet been developed.

Accountable commissions at the local and national levels established to formulate policy for all work that poses biological hazards might afford one path. Such bodies would require access to the widest possible range of technical perspectives from both advocates and critics. But their memberships should reflect the fact that their decisions would be on matters of public policy.[6]

Whether one agrees with the NIH guidelines or not, there is evidence that there was a deliberate effort to provide for participation by the public at large and by public interest groups. The persistence of this concern by the advocates of a need for even more public participation indicates that further efforts may need to be made. (For examples of the spread of participation thus far, see the several lists of participants in the appendices.)

It is difficult to resolve this complex issue into a minimum of factors for easy evaluation. Fundamentally, however, there appear to be several basic issues. One, there is a strong criticism that the decision to continue the research was made essentially on the basis of a determination that the research could be conducted at an "acceptable" level of

[3] U.S. Congress. Senate. Genetic Engineering. 1975. Hearings. op. cit. p. 10–11.
[4] Roblin, Richard. Ethical and Social Aspects of Experimental Gene Manipulation. Federation Proceedings, v. 34. May 1975: 1424.
[5] U.S. Congress. Senate. Recombinant DNA Research and the NIH Guidelines. September 21, 1976. op. cit. (See also Appendix 13 for an editorial by Sinscheimer on this theme.)
[6] Wright, Susan. Doubts Over Genetic Engineering Controls. New Scientist. December 2, 1976: 520–521.

safety rather than examining the issue from the perspective of whether the research should be conducted at all. In this respect, the DNA recombinant molecule issue is being likened to the nuclear energy problem. Some would prefer that the research had never continued to the technology. Two, there is an even more fundamental question which many wish would receive more attention. This is the issue of society interacting with science and the determination of the basic social responsibilities for the decision making process. The scientist is beginning to acknowledge the right of society to participate in the evaluation of the scope and rate of investment of resources in research but still wants to retain certain basic rights of freedom of inquiry. There is a nucleus of resistance to total scientific freedom as the ability to tamper with the most fundamental processes of life challenges the ability of society to perceive the implications of this capability. Perhaps this is fundamentally a fear reaction. The ethicists are finding this aspect of the issue a fertile field for investigation. Third, if the research is to continue, there is concern being implied that the investigator is not to be trusted.

This is the basis of the evolution of guidelines and the gradual emergence of stronger criteria such as monitoring, licensing, inspection, education, and training of investigators in this field. The British approach, through their Occupational Health and Safety Act, presumes a need for such regulation. Accidents recorded in history support the need for control, particularly as the research becomes more widespread and involves individuals without as high a level of competence or experience as the early cautious investigators. Related to this need is the fact that this research is not limited geographically or by national scientific capability. Experience in other fields of research have demonstrated that reasonably standard controls, if established, will be required, otherwise the research effort will move to the area of least resistance. In fact, Gardner emphasized this point specifically:

> Genetic research has reached a crucial stage in its development. International society is now challenged to assert reasonable and carefully considered control over the direction of man's evolution. Such control is essential in order to prevent an irrational reaction to unexpected future events or an uninformed public perception of scientific manipulation of human evolution.[7]

In a very thought provoking lecture, Dr. Arthur Kornberg considered this new social evaluation of biomedical research which is occurring and which has lent strength to the current controversies confronting the DNA recombinant molecule research. He summarized his concern in one sentence when he said: "Strong social, economic and political pressures now threaten acquisition of basic knowledge." Kornberg certainly does not challenge, in his article, the serious evaluation of the commitment of resources to basic research, but he asks that the impact be carefully considered in terms of the rewards which may be lost if basic research is actively inhibited.[8]

[7] Gardner, Barbara Jeremiah, op. cit. p. 428.
[8] Kornberg, Arthur. Research, The Lifeline of Medicine. The New England Journal of Medicine, v. 294, May 27, 1976: 1212–1216.

Perutz pointed out in a review article:

> Molecular biology is sometimes said to be of little medical significance because it has not cured anyone yet. A hundred years ago the same might have been said of histology. At that time cellular anatomy and pathology began to improve our understanding of many diseases; today, molecular anatomy and pathology give us much deeper insights . . .
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> What has molecular biology contributed to this work [studies of proteolytic enzymes and their inhibitors, haemoglobin diseases, etc.]? It has supplied the basic concepts of microbial genetics, mutagenesis, repair and feed-back control; it has supplied the techniques of transferring genetic material from one strain of bacteria to another. . . . These concepts and techniques were developed by scientists who set out to interpret fundamental biological processes in physical and chemical terms.
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> . . . Although we know more now than when we started, molecular biology is still too young a science for it to be clear exactly where it will pay off, whence we may do best if we spread our efforts over a wide field.
>
> . . . There is a unity of life at the molecular level which implies that anything found to be trne in *E. coli* may also hold in man. . . .
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> . . . In the future, the most important contribution of molecular biology to medical practice may well be genetic engineering, but early hopes that eukaryotic genes could be transcribed and translated in prokaryotes have not yet materialized [note, this has now been accomplished]. Instead, workers may try to see if cultures of animal viruses carrying human genes could be used for the manufacture of therapeutically important human proteins.[9]

The guidelines are out and the limitations on certain types of DNA recombinant research are now proscribed more specifically. The continuation of DNA recombinant research and the rapid progress in exploring new areas of research with this tool are evidenced in the many papers cited within this report and in the selected bibliography. In fact, the interest is so intense now that a new journal, "Gene," will be devoted to publication of research in this area. In her report of the Biochemical Society's 9th Harden Conference "The Role of Recombinant DNA in Molecular Biology," September 20–24, 1976, Eleanor Lawrence provides ample illustration of how the researchers have continued their efforts to solve the mysteries of DNA regulated activities.[10] She identifies research from all over the world. West Germany, Switzerland, the Netherlands, England, the United States, and Scotland, for example, all had scientists in attendance who reported on their efforts involving plasmid and viral vectors and the intricate techniques of recombinant DNA molecular research. This is not to say that the practical benefits are immediate nor that here has been any change in the status of firm knowledge about the risks.

B. MOVING ON

It is just as difficult to identify majority opinions regarding the nearness of application of genetic engineering techniques in human beings as it is to secure a resolution of the public policy issues concerning the risks of the experiments. In an editorial in Lancet, it was noted that:

> . . . Application of gene cloning to "genetic engineering"—in the sense of deliberate manipulation of the genetic constitution of an organism with a view to altering its characteristics—is a very distant prospect.

[9] Perutz, M.F. Fundamental Research in Molecular Biology: Relevance to Medicine. Nature, v. 262. August 5, 1976: 449–453.

[10] Lawrence, Eleanor. Nuts and Bolts of Genetic Engineering. Nature, v. 263. October 28, 1976: 726–727.

> Before any serious steps can be taken in this direction, at least three major problems must be resolved. Firstly, the gene or genes to be cloned have to be isolated from the parent organism in pure form. It is no accident that all the successful experiments to date have involved the gene coding for rabbit globin. . . . No other mammalian gene, or its corresponding messenger R.N.A. template, has yet been isolated with comparable purity. . . . Secondly, a suitable vector must be found to carry the gene from donor to recipient species, since native D.N.A. does not readily gain access to an intact cell. . . . Thirdly, there are the fundamental questions of whether a gene inserted into the cells of a given organism will function at all and, if so, whether its expression will be subject to normal controls at a cellular level. . . . At present this whole area is a closed book. . . .[11]

The Medical Tribune is more optimistic:

> Clearly, it is now possible to make any double-stranded DNA once its purified RNA has been prepared. It should then be relatively simple with the use of available techniques to synthesize large quantities of particular genes. The ultimate direction taken by these advances in molecular biology remains uncertain.[12]

However, as noted in the earlier discussions on benefits, potential applications are much closer in other areas such as biosynthesis of pharmaceuticals and the construction of "scavenger" bacteria. In these instances, the technology for producing the "genetically engineered" organisms is not the immediate obstacle. It is concern that insufficient information is available to predict that there will be no adverse environmental hazards which seems to have temporarily slowed progress in this area.

The NIH guidelines (as well as the regulations/guidelines of other nations) are a fact. These guidelines are obviously a dynamic compromise between those who would hold up all DNA recombinant research until all of the pertinent public policy or safety questions are answered and those who would like to continue to enjoy the freedom to exercise their own prerogatives about the nature and direction of their work. Since the Director of the National Institutes of Health has clearly indicated that the NIH guidelines are subject to revision, there still exists a continuing opportunity for inputs into the process of evaluating these standards.

Several questions still seem to be relevant to this continuing evaluation. The guidelines are voluntary. The British approach suggests that alternative methods might be utilized to insure enforcement. In the United States as in the British Isles, the Occupational Safety and Health Act requires the conduct of work under safe conditions. Further, some laboratories are already subject to inspection and certification by the Center for Disease Control and proposals to expand clinical laboratories legislation will project this authority into other laboratories.

Although the NIH guidelines provide for a system of peer review extending from responsibilities of the individual investigator through his university and to the NIH, there is really no central control over all DNA recombinant research. The publication of a Draft Environmental Impact Statement to secure public reaction to the NIH guidelines provides an opportunity for ideas to be considered concerning the need for national biohazards control or some other licensing or registration system to be considered. Proposals for registration and

[11] Gene Cloning: One Milestone on a Very Long Road. The Lancet. April 24, 1976: 893.
[12] Advances in Molecular Biology. The Medical Tribune and Medical News. February 4, 1976: 11.

certification of all laboratories and personnel undertaking DNA recombinant research have been discussed.

As noted by the testimony of Dr. Talley from the Environmental Protection Agency, there is little information available from the standpoint of potential ecosystem hazard. This aspect of the DNA recombinant issue could profitably be examined in more detail and the necessary programs to acquire the needed information properly implemented. The current plans of the National Institutes of Health to begin an assessment of the hazards to acquire data to validate (or invalidate) the probability calculations of risk are being supported on a much smaller scale of investment than the investments to continue the DNA recombinant research. The original charge to the DNA recombinant molecule committee was to:

> Evaluate . . . the potential biological and ecological hazards of DNA recombinants of various types, for developing procedures which will minimize the spread of such molecules within the human and other populations, and for devising guidelines to be followed by investigators working with potentially hazardous recombinants.[13]

The last charge seems to have received the highest priority. Critics of the pace of reactivation of DNA recombinant research efforts have said that the first two charges should have been thoroughly developed before the guidelines were approved. As a matter of fact, however, since adherence to any guidelines at this point is voluntary (except as governed by the peer review process during NIH funding), the Asilomar guidelines were actually the first step toward lifting the moratorium on certain types of research and the NIH guidelines simply are more specific and in some instances more restrictive as they apply to NIH funded research.

It is difficult to determine the best course among the many actions being proposed. The majority opinion seems to be to get on with the work. Grobstein has said:

> Questions dictated by anxiety about the future are often vague and difficult both to phrase and to answer. They are, nonetheless, dangerous to ignore. . . . both the risks and the benefits are hard to quantitate, and neither may bear equally on all groups. Discussion of what can be done to reduce uncertainty may not yield universal assurance but it can lessen purely imagined fears. Such fears, otherwise, may come to dominate public reaction and become major determinants in new policy decisions.
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> It is important, therefore, to broaden and transform the restricted context of the Asilomar conference and the resulting NIH guidelines. The approach should now be dominated not by fears but by fundamental and positive objectives: (i) to continue expansion of the understanding of genetic phenomena; (ii) to minimize foreseeable hazard, whether to health, essential human relations, or biotic environment; (iii) to consider the priorities to be assigned to realization of positive social benefits from growing genetic engineering capability; (iv) to give "due process" to deeply held values, whose accommodations may require time and special attention; and (v) to provide opportunity for "informed consent" or other reaction from the several publics that may otherwise see themselves involuntarily placed at risk.[14]

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[13] U.S. Department of Health, Education, and Welfare. Public Health Service. National Institutes of Health. NIH Public Advisory Groups: Authority, Structure, Functions, Members. July 1, 1976: 4.

[14] Grobstein, Clifford. Recombinant DNA Research: Beyond the NIH Guidelines. Science, v. 194. December 10, 1976: 1133–1135.