Meselson, Stahl, and the Replication of DNA

A History of "The Most Beautiful Experiment in Biology"

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TO THE MEMORY OF

Mary Morgan Stahl

August 21, 1934–January 22, 1996

Her graceful spirit touched the lives of all who knew her,
even those who knew her too briefly

AND TO THE MEMORY OF

Harriet Vann Holmes

December 21, 1932–April 14, 2000

To the very end she kept her warmth, her humor, and
her deep interest in the lives of others

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Preface

In 1957 two young scientists at the California Institute of Technology performed an experiment that provided convincing evidence that DNA replicates in the manner predicted by the model of the double helix proposed four years earlier by James Watson and Francis Crick. Its timely appearance, after several years of controversy about whether the two strands of DNA could come apart without breaking, not only settled the issue as it was originally posed but persuaded many, beyond the immediate circle of enthusiastic supporters, that the double helix was more than an "ingenious speculation." Quickly known by the surnames of the two men who performed it, the Meselson-Stahl experiment became a classic model in the young field of molecular biology. It has been reproduced in schematic form in textbooks of molecular biology, biochemistry, and genetics for more than three decades. It is seen not only as a landmark but as possessing special qualities that lift it above the thousands of other experiments on which the modern biological sciences have been constructed. When Horace Judson discussed the Meselson-Stahl experiment with John Cairns, Cairns called it "the most beautiful experiment in biology."

The beauty of the Meselson-Stahl experiment is invariably connected with its simplicity. When reduced to its essential features, it is readily understood even by beginning students of the life sciences. Teachers look on it with fondness for the ease with which its message can be conveyed. Scientists throughout history have extolled the simplicity of nature and have admired theories and other discoveries that seem to reveal aspects of that simplicity. But simplicity in science is less a property of nature than a product of the human need to fit representations of nature within the limits of our cognitive capacities. When a simple relationship has been "revealed," it has, in fact, been

extracted from a matrix of complexity. This generalization applies to the Meselson-Stahl experiment with particular force. The experiment originated in complexity, was surrounded by complexity, and directed the way toward the discovery of future complexities. It was the product of a complex investigative pathway. Its beautiful result can be presented as simple only by ignoring the complexity of the reasoning that led to its design, of the instrument on which it was performed, of the prior knowledge on which it was built, and of the human environment in which it was conducted.

It is the central aim of this book to contrast the core simplicity of this beautiful experiment and with the many dimensions of complexity that made it possible.

Acknowledgments

The importance of the active participation of the two principal subjects of this book, Matt Meselson and Frank Stahl, is evident on every page. It is now more than a decade since I first showed up on their respective doorsteps to ask questions that required them to plumb memories of events already three decades old. Since then they have given generously of time and support, meeting with me singly and together, in Cambridge, Massachusetts, Eugene, Oregon, and Woods Hole. They have also read successive drafts and corrected my many small errors without seeking to sway the larger direction of my intentions. They must have wondered sometimes whether anything would come of their efforts, and I can only hope that the outcome will be a fair reward for their patience.

Gunther Stent received me warmly in Berkeley and answered my questions with refreshing candor and warm civility. A highlight of my work on this project was the afternoon it allowed me to spend in lively conversation with John Cairns at his country home in Charlbury, England. Both Stent and Cairns read more than one version of this manuscript and contributed in important ways to its improvement. James D. Watson received me with hospitality at Cold Spring Harbor, answered my questions, and made available to me pertinent documents from his personal files. Howard Schachman spoke with me in Berkeley.

Others who read the manuscript and made valuable suggestions were John W. Drake and Joseph S. Fruton. Charles A. Thomas, J. Herbert Taylor, and Robert L. Sinsheimer supplied helpful information by correspondence. The cogent recommendations of the anonymous reviewers helped to shape the final revisions.

William Summers, my colleague at Yale University, who has conducted experiments similar to those described in this book, helped

teach me how to read the ultraviolet absorption films produced in the Model E analytical centrifuge and explained many other technical matters to me. At the University of California at Fullerton, Bruce Weber arranged for me to observe a run of one of the few of the big machines still in operation.

As a historian with only undergraduate training in science, I have needed much help from those about whom I have written in this book. Despite their generous assistance, I am bound to have missed some of the deeper levels of the thought and analysis underlying the events described. If we are to give interpretations of the historical development of science that are truly revealing, rather than impositions of our own biases, historians of science must reach, as far as we can, to the levels at which our subjects thought and acted. But most of us will fall short of complete understanding of the complexity of modern scientific specialties, and we must hold ourselves responsible not to make judgments that are beyond our capacities.

I have also been greatly helped, in the practical production of a manuscript, by the skillful and devoted work of the staff of the Section of the History of Medicine. Joanna Gorman astutely managed my late transition from the pen to the personal computer and continues to rescue me from the pitfalls into which, from time to time, I still fall. She also prepared the final version of the manuscript. Patricia Johnson arranged the logistics of travel related to the project, acquired material from archives, and, through her efficient management of the life of the Section, protected as much of my time as possible for scholarship.

Judith Goodstein and her staff at the California Institute of Technology Archive greatly helped me to find and use documents of crucial importance to this story. The generous assistance of Denise Ogilvie, conservateur at the Service des Archives de l'Institut Pasteur, and Madeleine Brunerie enabled me to locate pertinent documents of Jacques Monod during a brief visit to Paris.

A grant from the American Philosophical Society in 1987 enabled me to begin this project. My relatively modest research costs in later years have been covered through a research fund supplied to my faculty position by Yale University.

During the last years of this project, my wife, Harriet, endured, bravely and with an undaunted spirit, a long illness. I was grateful that she was still here to share my pleasure in the completion of the manuscript, but saddened that she could not celebrate with me its publication.

Introduction

I

In April 1953, the American biologist James D. Watson and the British physicist Francis H. C. Crick proposed in a brief paper in *Nature* a "structure for the salt of deoxyribonucleic acid (D.N.A.)."[1] Soon known as the double helix, their structural model attracted immediate interest. Not only did the model decisively swing opinion to the view that DNA was the chemical basis of the classical gene; it suggested also how the DNA molecule might function in genetic replication. Coupled with the recently established doctrine that genes control life by directing the synthesis of proteins, the advent of the double helix set off intensive research on the manner in which the sequence of the base pairs in DNA determines the sequence of amino acids in protein. Besides defining the coding problem, this relationship brought into prominence the putative role of the other nucleic acid, RNA, as the intermediary between the DNA contained in cell nuclei and the proteins synthesized in the cytoplasm. Within a decade the discovery of transfer and messenger RNA had resolved the latter problem, and the genetic code had been cracked. As Gunther Stent has put it, the "brilliant wedding of structural and genetic considerations embodied in the DNA helix thus opened the era of molecular biology."[2]

Peter Medawar commented in 1968 that "the great thing about" Watson and Crick's discovery "was its completeness, its air of finality." Watson and Crick had not groped toward a partial answer but produced the right solution in one grand stroke. This was a perspective only attainable more than a decade after the discovery, however, when many later developments had both solidified the evidence for the basic features of the model and demonstrated its immense heuristic value for further research. Michael Morange has pointed out that

the very favorable reception accorded the double helix could not conceal how fragile it was during the years following its publication.[3]

The fragility of the double helix was due not only to the fact, acknowledged by Watson and Crick from the outset, that their general scheme was speculative,[4] that it rested mainly on their ability to build a physical model conforming to accepted atomic dimensions, bond lengths, and angles and was compatible with X-ray crystallographic pictures made by others. A more urgent problem arose through the difficulty of imagining how the two nucleotide strands wrapped many times around each other in the double helix could separate, as they were supposed by Watson and Crick to do in the process of duplication.

This replication problem, first clearly formulated by Max Delbrück in 1954, vexed the newly emerging field for the next three years. Some people—in particular, physicists who had moved into biology—tried to solve the problem theoretically with various topological schemes. Members of the phage group attempted to solve it experimentally by incorporating into the DNA of bacteriophage or bacteria radioactive isotopes whose distribution they hoped to trace into progeny DNA molecules. All of these efforts were ineffective. In 1957 Herbert Taylor showed by incorporating a radioactive tracer into germinating seedlings that in cell divisions the chromosomes divide semiconservatively, in conformity with the predictions of the Watson-Crick model. Taylor's evidence was impressive, but it did not reach directly to the replicative process at the molecular level. In 1956, Matthew Meselson and Franklin Stahl began to carry out an idea Meselson had earlier had to investigate the problem by incorporating a heavy isotope into the DNA molecules of a microorganism and tracing the distribution of these atoms into progeny DNA by separating molecules of different density in a centrifuge. In October 1957 they produced the experiment, published eight months later, that quickly appeared to settle the question whether DNA replicated in the manner predicted by the Watson-Crick model. This result played a central role in the transformation of the "fragile" double helix into the robust model seen afterward as the axis around which the new molecular biology revolved.

The Meselson-Stahl experiment has already taken its place as one of the mainstream events in the early history of molecular biology. In his broad survey of that history, Horace Judson included a lively account of the origins of this experiment, oriented around several stories Meselson related to him about dramatic moments that had punctuated

the investigation.[5] Michael Morange's shorter history of molecular biology also concludes the chapter on the discovery of the double helix with a summary of Meselson and Stahl's "demonstration of the semiconservative replication of DNA."[6] The Meselson-Stahl experiment has thus become a canonical part of the story of the Watson-Crick model of DNA, the event that conferred on the model that air of finality that Medawar attributed retrospectively to the initial announcement of the structure four years earlier.

II

The central aim of the present volume is to follow, in as full detail as the surviving documents and the memories of the participants permit, the investigative program that led Meselson and Stahl to perform the classic experiment referred to ever since as the Meselson-Stahl experiment. I have previously reconstructed in a similar manner extended portions of the investigative pathways of three other scientists: Antoine Lavoisier, Claude Bernard, and Hans Krebs. The conviction underlying all these studies has been that if we are to understand deeply how major scientific discoveries originate, we must probe the "fine structure" of the research that produces them down to the level of the daily interplay between thought and action. Synoptic accounts of discovery tend either to leave the impression that scientific investigations proceed methodically, by linear sequences of logical steps to definitive solutions, or that mysterious mental leaps carry creative scientists over the conceptual barriers that do not yield to logic. In order to include the steps later deemed essential to a discovery or a novel scientific achievement, a compressed history usually excludes, for lack of space, the moves that the scientist might have omitted had she known in advance the shortest route to the goal. It is only by following research trials in the richness of their fine structure that we can recognize both that each step of the way may be guided by fathomable reasoning and that the overall pathway is cluttered with unanticipated shifts in direction, goals, and tactics.

In his studies of the role of experimental systems in biological research, Hans-Jörg Rheinberger has sought to capture the subtle relation between the control that an experimentalist must maintain over the direction of an investigation and the openness that the system must retain for unanticipated developments. When pursuing an investigation, the investigator never knows in advance where it will come out.

As soon as an outcome is reached, however, the events preceding it begin to reorganize themselves in the minds of the participants and other observers as logical steps leading to an inevitable conclusion.[7]

The case of the Meselson-Stahl experiment is a prime illustration of the ubiquity of such mental reorganization. In the textbooks that have regularly recapitulated the major outlines of the experiment, it is often depicted as a straightforward exercise in the hypothetico-deductive logic by which science is presumed to advance. A proof was needed that DNA replicates semiconservatively, and through the elegant techniques devised by Meselson and Stahl that proof was duly provided. The experiment appeared so decisive that its result seemed, in retrospect, foreordained by the logic of the situation. In reconstructing the investigative pathway prior to the performance, I have tried to recover the uncertainty about whether Meselson and Stahl would reach their goal. Opportunities arose repeatedly that might have subverted their plan by diverting their attention to other problems. Their eventual success depended on a number of circumstances that they could not know in advance would arise. The successful experiment differed in fundamental ways from the one whose outlines they had in mind when they began. That it was successful depended on a series of fortuitous conditions, some of which did not become evident until after the experiment was received by the relevant scientific community as the confirmation of semiconservative replication.

There has been much interest recently, among historians of science, in what is termed "scientific practice." This history of the Meselson-Stahl experiment can be taken as an episode in the practice of modern experimental biology. The experiment that is the subject of this story is not, however, an actor in it but the passive denouement of many actions taken—most directly by the two young scientists who performed it, indirectly by a number of other scientists who framed the problem the experiment was designed to solve, and at a greater distance by many others who contributed to the repertoire of knowledge and techniques on which the central figures drew to attain their solution. The boundaries of such a story are not sharp and clear. The shape of the experiment was the outcome of multiple interactions, some intellectual, some methodological, some personal, and some institutional. Each of the intersections connects this story with other stories, and the question of how much of the connected stories to include is not easy to resolve.

I have chosen to structure the story in the form of a drama in several

acts, with two central characters and a larger cast of other individuals who enter it along the way. Several of the scientists who appear here in supporting roles were leading figures in the development that led to the formation of molecular biology. I have not attempted to summarize their own careers and achievements. Each of them has been treated extensively by other historians. Neither, however, have I limited the narrative to the narrow investigative pathway that the two leading actors followed to the performance of the Meselson-Stahl experiment. Just as scientists reorganize prior investigative moves so that they become logical precursors to the result, so historians are constrained, when we try to account for the origins of an experiment, a discovery, a field or a discipline, to select from the profusion of earlier events those which appear in some degree relevant to the culminating developments in our narratives. Some teleological shaping is inevitable. But we can come closer to the indeterminate conditions out of which other outcomes might have materialized, by allowing some flexibility in our identification of relevant prior events.

One of the circumstances relevant to understanding the course of Meselson and Stahl's investigative enterprise is that they pursued it at Caltech in close association with the phage group led there by Max Delbrück. The role of the phage group in the formation of molecular biology has been discussed at length, in the reminiscences of those who participated in it[8] and by historians. The prominence generally attributed to the group has recently been contested. Some historians have pointed out that Delbrück's scientific achievements have been magnified by the force of his personality. The style of his leadership created an ethos that made his laboratory at Caltech a mecca through which many of those involved in the emergence of the new molecular biology passed during the 1940s and 1950s. His influence was further enhanced by the popularity of the phage course that he taught at Cold Spring Harbor each summer during these years. I have portrayed Delbrück and his group at Caltech as Meselson and Stahl experienced them, but I have not attempted a reassessment of the place of the phage group in the larger events of its time.[9]

At Caltech Meselson became the last graduate student of the legendary Linus Pauling. There he learned the techniques of X-ray crystallography that Pauling had used to establish the structures of biologically significant molecules. A few years earlier Pauling had established the alpha-helix model of protein structure that inspired Watson and Crick in their efforts to solve the structure of DNA. Al-

though Pauling played no direct part in the investigation that led his last student to the Meselson-Stahl experiment, he did much to inspire the scientific style that Meselson carried into the project. Several biographies and other accounts of Pauling's life and work have recently appeared.[10] Meselson has himself drawn on his experience with Pauling to provide a vivid portrait of Pauling's personality and attributes as a mentor.[11]

The appearances of James Watson in the present story outline events that might serve as a potential first chapter for a sequel to the story so engagingly told by Watson in his personal memoir of the discovery of the double helix.[12] Judson and others have discussed Watson's activities during the decade in which the double helix dominated the emerging field of molecular biology, but a full treatment of his role awaits further scholarship.

This book is divided into three parts. Part 1 describes the replication problem that arose in the wake of the publication of the Watson-Crick model and various efforts to grapple with it during the following years. It introduces Matthew Meselson and Franklin Stahl, describes the idea Meselson had for resolving the problem, and summarizes their separate research activities while they awaited the opportunity to carry out together a plan to implement Meselson's idea. Part 2 follows their investigative program from the time they took it up in September 1956 until the publication of their paper "The Replication of DNA in *Escherichia coli,*" in June 1958. Part 3 treats the reception of the Meselson-Stahl experiment during the years following its publication, further investigations to which it gave rise, its representation in textbooks of molecular biology, biochemistry, and genetics, and some of the reasons for its reputation as a very beautiful experiment.

Interwoven with the story of the Meselson-Stahl experiment are two other stories that deal with problems not directly related to the problem of DNA replication. One was the effort of Jim Watson to solve the structure of RNA by the methods that had succeeded so well for DNA. The second was a quest by Meselson and Stahl themselves for a mechanism that would explain mutagenesis at a molecular level. I have interjected these subsidiary stories partly to show that imaginative investigators often entertain multiple research possibilities, and that it is not laid out in advance which ones they will pursue with auspicious success. A second reason for their inclusion is that all three projects were stimulated by the properties of the double helix. They

illustrate the radiating research problems that are created by discoveries with such widespread consequences.

I have also given, through a flashback, attention to an event that preceded the discovery of the double helix: the Hershey-Chase experiment, which convinced the group within which Watson's scientific career was formed that DNA is the hereditary material. This event too is connected through coincidental personal contacts with the main story, but I have included it because it and the Meselson-Stahl experiment stand out as the two eponymous experiments that loom largest on the early landscape of molecular biology. Comparisons between them provide perspective on judgments about experimental beauty, as well as on the attributes that raise a very few, out of the myriad of experiments performed in an investigative field, to canonical status.

The narrative of the investigation that Meselson and Stahl pursued for nearly two years is based on surviving correspondence, progress reports, the log records for the experiments performed on the analytical ultracentrifuges at Caltech, the original films that comprise the immediate results of these experiments, and extensive recorded conversations, conducted at intervals spread over more than a decade, with Matt Meselson and Frank Stahl. Full laboratory records of the experiments, if they were ever kept, have been lost. The remaining evidence nevertheless allows a relatively full reconstruction of the day-to-day experimental activity and reasoning of which the Meselson-Stahl experiment was the most dramatic (although far from the only significant) outcome. For the other events included in this book I have relied on published papers, some correspondence made available to me by James Watson from his personal files, and interviews with Watson, John Cairns, Howard Schachman, and Gunther Stent. Cairns, Stent, Jan Drake, Herbert Taylor, and Charles Thomas have supplied me with further recollections by correspondence.

My reliance on the memories of participants for some of the information used in the narrative requires commentary. Historians commonly regard such memories as unreliable. They are, however, indispensable for recovering the personal aspects of such an investigative venture that leave few traces in publications or surviving documents. There are often checks on recalled events. Memories fit or do not fit with the information contained in contemporary records. From such checks we can gain a sense of how far we can trust recollections for which there is no corroborating evidence. Some of the events in which

they participated, Meselson and Stahl remember very accurately and clearly. Others they remember vaguely or uncertainly. They have given much time and effort to work with me to reconstruct from their memories, and from the documents that can confront those memories, aspects of their collaboration not otherwise recorded. Where discrepancies have arisen, we have returned repeatedly to the evidence in our efforts to resolve them. Nevertheless, some gaps inevitably remain, and some of the memories remain problematic. In constructing the narrative I have had to apply judgments of plausibility in deciding how much reliance to place on individual recollections of particular events. In most cases I have made these judgments tacitly. In one crucial example related in Chapter 9, I have, however, made explicit the difficulties encountered in reconciling a vivid memory with the surviving records. This example illustrates the general problems that occur whenever we rely on the fertile but elusive traces of past events presented to us by the memories of living participants in those events.

The names of Matthew Meselson and Franklin Stahl are indelibly linked through the eponym "Meselson-Stahl experiment" by which their joint achievement is widely known. Does the order of their names reflect only the order of the alphabet, or their relative contributions to the outcome? On this question the two principals disagree. Meselson describes them as equal partners, whereas Stahl insists that the experiment belongs essentially to Meselson. If we view the events leading to the Meselson-Stahl experiment narrowly, it seems clear that Meselson provided the germinal ideas and performed the central operations from which the experiment emerged. But the collaboration in which the two young scientists engaged during the years covered in this story was multifaceted. In other aspects of their common venture Stahl took the lead.

I have tried to give equal attention to the parts both men played in this enterprise, but the surviving documentary evidence gives a systematic bias toward fuller description of Meselson's activities. The existence of the analytical ultracentrifuge log and films enables the reconstruction of nearly every experiment that he performed on those machines. Original records of the operations that Stahl performed to support the centrifuge runs and of the experiments he performed on other aspects of their collaboration have disappeared. I have been able to reconstruct only summary accounts of his activities from correspondence, progress reports, and the memories of the two partners. These

distorting factors should be kept in mind when we balance their respective roles in the events portrayed.

In addition to describing their parts in their common scientific venture, I have depicted Matt Meselson and Frank Stahl as two distinct persons at a formative time in their respective careers. To give their individuality some broad contours, I have included glimpses of events in their personal lives that occurred during the time of the narrative, but I have not attempted comprehensive biographical treatments. These are snapshots of two young men at a crucial juncture in their lives, with no pretense at a deeper analysis of the motivations or the earlier developments that brought them to the point at which they entered the stage on which the actions pertinent to the scientific achievement bearing their names took place.

For Meselson, as well as for James Watson and others among their contemporaries who were still single, the nonscientific events of their lives often revolved around meeting or establishing ties with women. I have not described any of their encounters with the "woman problem" (as they called it) in detail, but I do mention them repeatedly, in part as a reminder of how different from today the social circumstances of young men and young women in America often were in the 1950s, when they were much less likely to meet in the ordinary course of their daily activity, and how much of their attention was absorbed in the problem of finding one another.

Detailed narratives of events on a small scale, such as this history of the Meselson-Stahl experiment, ought also to illuminate more broadly the nature of similar events. The achievement of Meselson and Stahl was singular, but their experiences along the way resonate with those of other scientists who have engaged in laboratory work of this kind. Limitations of space preclude an extended examination here of the generalizable features of this particular investigative pathway, but one of the reviewers of this text for the Yale University Press expressed cogently some of the experiences common to his own that he has found illustrated in this story. They include

> the observation that the most informative experiments are frequently those which met most difficulties and had, in principle, less chance to be successful, the existence of periods of time in which all the experiments are working, whereas, previously, they were delayed by numerous, different, and frequently unexplainable problems. The psychology of scientists is also depicted . . . the

> useless experiments done only to reassure oneself, the difficulty for two researchers to participate fully [and equally in] a decisive breakthrough. It is perhaps the way science develops that is most acutely described; how the objectives are frequently changed, even if the previous research objectives reappear, . . . the important role of informal exchanges between scientists, the permanent, preeminent role of chance events. The coexistence in the same person of stable knowledge and interests and . . . moving goals and occupations.[13]

Aesthetic judgments are often more important to scientists than is sometimes recognized by those who view science as a coldly methodical activity. The special beauty of the Meselson-Stahl experiment sets it apart from many other research pathways[14] but serves also as an ideal to which scientists frequently aspire. In the last chapter I have mentioned the views of several scientists about what makes this experiment beautiful, but another reader of this text has expressed, better than I have been able to do, the value placed on such experiments by scientific communities:

> The experiment both confirmed a powerfully heuristic hypothesis (Watson-Crick structure/function model of DNA), and did so elegantly and with perceived simplicity and clear message. Such experiments are rare and when understood by the scientific community are celebrated as particularly noteworthy. [This book shows] us how a work of art, albeit in the form of a scientific experiment, came into being.[15]

CHAPTER ONE

The Replication Problem

I

One of the most famous sentences in the recent literature of science is the statement near the end of the brief article in *Nature* in which Francis Crick and James Watson announced, in April 1953, their proposed structure for deoxyribose nucleic acid:

> It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.[1]

Crick has since written that his enigmatic assertion had been "a compromise, reflecting a difference of opinion." He had thought that the paper should discuss the genetic implications, whereas "Jim was against it. He suffered from periodic fears that the structure might be wrong and that he had made an ass of himself."[2] In his popular narrative *The Double Helix,* Watson described the same difference of opinion but in a contrasting tone: "For awhile Francis wanted to expand our note to write at length about the biological implications. But finally he saw the point to a short remark and composed the sentence [quoted above]."[3] Privately Watson commented in 1990 that his reluctance about discussing the implications in the article had probably been "a reaction to . . . Francis talking too much." Francis "talks so much," Watson said, "that the hope is . . . [to] get him to do an understatement." Watson's preference for an understatement reflected also a desire to emulate the British style that he had come to admire during his time in Cambridge.[4]

Retrospective explanations by these two principals must be viewed with caution because the misunderstandings that arose between Watson and Crick subsequent to the publication of their historic paper

may affect the way in which each of them describes this incident. Yet these are not necessarily conflicting accounts of what happened, for each may have experienced their difference of opinion subjectively in the way he afterward remembered it.

That Watson really did harbor serious doubts about the validity of their structure for DNA, before and after he and Crick published their first paper in *Nature,* is clear from contemporary letters that he wrote from Cambridge to Max Delbrück at Caltech. On 12 March he described "our model," including rough diagrams of the way in which they envisioned the two complementary base pairs, thymine with adenine and cytosine with guanine, to be held together by hydrogen bonds (figure 1.1). Watson went on:

> The model has been derived almost entirely from stereochemical considerations with the only X-ray consideration being the spacing between the pair of bases *3.4A* which was originally found by Astbury. It tends to build itself with approximately 10 residues per turn in 34A. The screw is right-handed.
>
> The X-ray pattern approximately agrees with the model, but since the photographs available to us are poor and meager (we have no photographs of our own and like Pauling must use Astbury's photographs) this agreement in no way constitutes a proof of our model. We are certainly a long way from proving its correctness. To do this we must obtain collaboration from the group at King's College London who possess very excellent photographs. . . .
>
> In the next day or so Crick and I shall send a note to Nature proposing our structure as a possible model, at the same time emphasizing its provisional nature and the lack of proof in its favor. Even if wrong I believe it to be interesting since it provides a concrete example of a structure composed of complementary chains.[5]

As Watson's lively account of the events surrounding the elucidation of the structure in *The Double Helix* shows, he was not entirely candid in this letter to Delbrück about the nature of the X-ray evidence on which they had relied. If they had not yet secured the "collaboration" of the King's College group, they had already secured some critical information from X-ray photographs taken there. Maurice Wilkins had privately shown Watson a particularly revealing X-ray photograph of the "B" form of DNA made by Rosalind Franklin. Max Perutz then made available to them a report circulated privately to the Medical Research Council that included a discussion by Franklin of the crystalline forms. This information yielded for Crick the critical clue

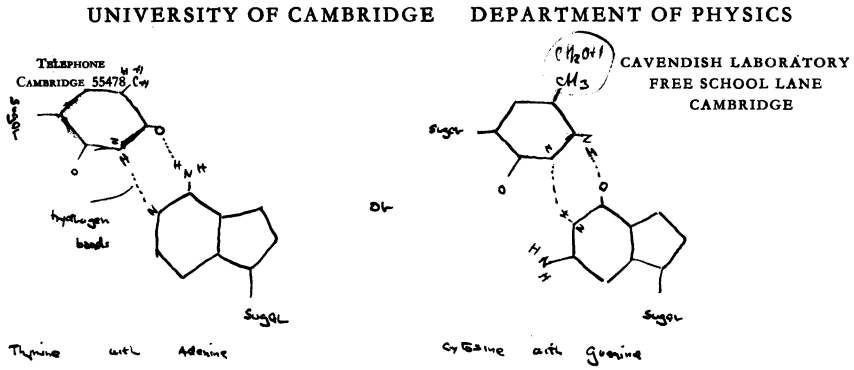

Fig. 1.1. Sketch of base pairs sent by James Watson to Max Delbrück

that the two strands in the double helix must run in opposite directions. Because Franklin was unaware that Watson and Crick had access to her data, Watson was apparently inhibited from acknowledging the way in which they had benefited from her work.[6] That circumstance aside, he was here only maintaining a caution appropriate to the boldness of their proposal, its potential importance, and the fact that the structure rested heavily on exercises in model-building that were not universally regarded as sufficient grounds for drawing such conclusions. In the letter to *Nature* Crick was nearly as cautious publicly as Watson was privately: "The previously published X-ray data on deoxyribo-nucleic acid are insufficient for a rigorous test of our structure. So far as we can tell, it is roughly compatible with the experimental data, but it must be regarded as unproven until it has been checked against more exact results."[7]

By the time Watson sent Delbrück a copy of the draft of the *Nature* article, on 22 March, he had already obtained additional support for one of the critical assumptions on which his and Crick's model had been built—the "Chargaff ratios," or equivalent quantities of the bases in DNA that were paired in the helical model. In the data of Erwin Chargaff on which they first relied, these quantities, measured on the DNA of the bacterium *Escherichia coli,* were approximately equal. The ratios for adenine-thymine ranged between 1.03 and 1.06, and those for guanine-cytosine varied from 0.85 to 0.93. Gerard Wyatt had published similar results for DNA obtained from insect viruses. Although Wyatt described both ratios as "constant and close to unity," his results were also less close for guanine-cytosine than for adenine-

thymine. By comparison with the variable ratios of adenine-guanine (0.76 to 1.75 in Chargaff's results) or thymine-cytosine (0.63 to 1.54), these were striking regularities.[8] Nevertheless, Watson worried that, although the ratios were "approaching one-to-one, they were not perfect," and Chargaff himself had not placed much stress on that aspect of his results. During the ten days between his two letters to Delbrück, Watson had visited Wyatt at the Institut Pasteur in Paris, where Wyatt had told him that "the more he refines the analysis of the bases, the closer he finds the 1 to 1 equivalence. This 1 to 1 ratio also holds for [the sum of cytosine and] 5 methyl-hydroxycytosine [found by Wyatt and Seymour Cohen to replace cytosine in phage DNA], which after more careful analysis comes to be equal to guanine." Wyatt's new data were the first that seemed to Watson to be "super-good" for their purposes.[9]

Despite this helpful development, Watson felt ambivalent about his situation: "I have," he wrote Delbrück, "a rather strange feeling about our DNA structure. If it is correct, we should obviously follow it up at a rapid rate. On the other hand it will at the same time be difficult to avoid the desire to forget completely about nucleic acid and to concentrate on other aspects of life."[10]

Max Delbrück had no doubt about the importance of the new DNA molecule. To Niels Bohr he wrote on April 14, "I think that Jim Watson has made a discovery that may rival that of Rutherford in 1911."[11] On the same day, in reply to Watson's letters, he wrote, "I understand things are going well for your DNA structure, and I am not surprised. The more I think of it, the more I become enamored of it myself." After conversations with several of his colleagues, Delbrück put down "certain considerations" that he wished to state "to see whether we are thinking along the same lines." The first two points were as follows:

> (1) In your model the DNA molecule consists of two threads each of which determines the other completely. One thinks of reproduction taking place by separation of the two threads, followed by the formation of a complementary thread by each one of them.
>
> (2) The most attractive feature of this model is that for each link to be added a correct choice of only one out of four has to be made. Moreover, the structure is such as to utilize the *specific* end of the link (the base) directly for steric fit purposes.[12]

Here Delbrück was not merely rephrasing what Watson and Crick had already written but succinctly drawing "genetic implications"

that they had so far refrained from discussing. In their *Nature* article they had written: "The sequence of bases on a single chain does not appear to be restricted in any way. However, if only specific pairs of bases can be formed, it follows that if the sequence of bases on one chain is given, then the sequence on the other chain is automatically determined."[13] In describing the model to Delbrück, Watson had only hinted that, if the idea of complementary bases "is right, then I suspect we may be making a slight dent into the manner in which DNA can reproduce itself."[14] That Delbrück so readily translated their statements about the structure into one about "reproduction taking place by the separation of the two threads, followed by the formation of a complementary thread by one of them" shows just how immediately the structure that Watson and Crick had proposed *did* suggest a possible copying mechanism.

The next point referred to particular implications for the separation and reproduction of the DNA threads in bacteriophage. True to his reputation for raising objections to any significant scientific assertion, however, Delbrück went on to bring up what he took to be a major dilemma arising from the relation between the proposed structure for DNA and its inferred biological function:

> If we understand your model correctly it implies that the two threads are wound around each other plectonemically (do you remember the terms plectonemic and paranemic from Huskins' CSH paper . . . ? They are very useful terms in this connection). For a DNA molecule of MW 3,000,000 there would be about 500 turns around each other. These would have to be untwiddled to separate the threads. A feasible way to do this would be to assume the existence of an *alternate equilibrium state,* in which the double thread is contracted. In contracting, it forms a superhelix (like chromosomes do), and at the same time the threads arrange themselves in a paranemic manner, i.e., such that for each turn of the superhelix the threads turn around each other in a compensating turn. In such a configuration the two threads can be pulled apart sideways without interlocking.[15]

The two terms to which Delbrück referred had been introduced by C. L. Huskins in a paper read at a conference at Cold Spring Harbor in 1941 that Delbrück had attended. Huskins was describing the various coiled structures that are formed during cell divisions by "chromonemata"—that is, the strands comprising the condensed chromosomes that appear during mitosis or meiosis. "A helix consisting of two

strands twisted about each other so that they cannot be separated without uncoiling is termed a 'plectonemic coil,' while two helixes which are not intertwined form a 'paranemic coil.' "[16]

Huskins found paired chromosomes or chromomenata in both plectonemic and paranemic coils. He also observed strands composed of "major" and "minor" coils, and others containing "reversals of direction."[17] In responding to Watson and Crick's helical structure for DNA, Delbrück evidently assumed that the properties of the morphologically visible strands of the hereditary material of cells might also be applicable at the molecular level. "In any event," he went on in his letter to Watson, "one must postulate that the DNA opens up in some manner, both for replication and for doing its business otherwise. In the structure you describe this opening up is opposed both by the two hydrogen bonds per nucleotide, and by the interlocking of the helices, and it becomes a very important consideration to find a way out of this dilemma, or to think of a modification of the structure that does not involve interlocking. One certainly has to assume that the DNA must go through a cyclic structural change."[18]

After relaying the opinion of his colleague Robert Sinsheimer that, because wheat contains methyl-cytosine in addition to cytosine, "one has to find a partner" for the former in order to avoid a "Waterloo for the whole idea," Delbrück predicted, "I have a feeling that if your structure is true, and if its suggestions concerning the nature of replication have any validity at all, then all hell will break loose, and theoretical biology will enter a most tumultuous phase."[19]

By the time Watson received Delbrück's letter, further developments in England had strengthened the case for the DNA structure that he and Crick had worked out. Both Maurice Wilkins and Rosalind Franklin at King's College had reacted favorably to the model. Franklin's response "amazed" and relieved Watson. Being under the misapprehension that she was stubbornly "antihelical," Watson had feared that she might find some reason to reject and cast doubt on his and Crick's handiwork. The two King's College investigators each requested permission to submit, simultaneously with Watson and Crick's note to *Nature,* papers describing their evidence from X-ray diagrams for the helical structure.[20] Watson and Crick were particularly impressed by Franklin's compelling evidence that the "phosphate groups lie on the outside of the structural unit, on a helix of diameter about 20A. The structural unit probably consists of two coaxial molecules which are not equally spaced along the fibre axis."

These characteristics, as well as the "repeat unit of 34A," fit harmoniously with the parameters of the model.[21] On 2 April, all three papers were submitted to *Nature*.[22] In mid-April Watson had another momentary qualm. Visiting Franklin at King's College, he found her attempting to measure the diameter of the DNA molecule. Franklin thought that the diameter differed from what Watson and Crick had assumed in their structure. Apparently, the discrepancy was quickly resolved. Watson remained nervous about the propensity of Crick and others to "talk too much" about their grand discovery, before other problems could be ironed out, but his confidence in its basic validity was becoming firm.[23] When he responded to Delbrück's suggestions on 25 April (the same day that the issue of *Nature* containing the papers appeared), his attitude toward the questions that Delbrück raised was therefore different from what it might have been when he had written Delbrück several weeks earlier. He opened his letter by quoting at length the passages from Franklin's paper that made, as she put it, "the existence of a helical structure highly probable." Turning then to the points Delbrück had made, Watson wrote:

> Thus I am inclined to believe that our structure has a good probability to be correct. However I'm not as yet ready to commit myself that it is right. Thus at present I'm more concerned with seeing whether it is correct than in following up its implications, though it is of course naturally impossible not to occasionally think about them. With regard to your specific points (1) we would also guess that reproduction takes place by separation of the two threads, followed by the formation of a complementary thread by each of them. (2) We are naturally worried about how the threads would untwiddle—the fact that rather frantic coiling does occur during mitosis is comforting but it is difficult to avoid considering the gigantic number of turns which must exist in a chromosome. As far as we know our helix can only be made in the right hand sense and so we cannot use this device for producing compensating coiling. At present we are basically without ideas on this subject. (3) We have to find a mechanism for breaking the two hydrogen bonds. This, I would guess occurs by a tautomeric shift in one of each pair of bases. This might result from a change in pH or possibly by chelation in the purine partner. . . . We are inclined to agree with you that the DNA must go through a cyclic structural change.[24]

Watson was able to dismiss Sinsheimer's view that another partner must be found for methyl-cytosine. From Wyatt in Paris he had

learned that "the amount of 5 methyl cytosine + cytosine = the amount of guanine." Both bases were, therefore, likely to pair with guanine. Since guanine "cannot distinguish between the two cytosines," he guessed that the methyl group must be nonfunctional and inquired whether Sinsheimer might be interested in doing an experiment to see whether 5-methyl cytosine is incorporated randomly into the DNA of *E. coli*.[25]

Watson's reaction to Delbrück's arguments displays a subtle blend of caution and self-assurance. The supporting evidence from King's College for the DNA model enabled him to move from his position of early March that "we are a long way from proving its correctness" to the assertion that "our structure has a great probability to be correct"; yet he could at the same time allow sufficient remaining uncertainty to justify avoiding a full discussion of the biological implications on which Delbrück had fastened his attention. Even while not committing himself to the correctness of the structure, he could invoke critical features of the structure as a defense against modifications of the model that Delbrück's compensating coiling would entail. Even while treating Delbrück's ideas with respect, he could imply that, at this point, to be "without ideas on the subject" might be better than to entertain Delbrück's idea that the two threads could be in such a configuration as to be pulled apart sideways without interlocking.

Nevertheless, Watson must have taken seriously an admonition from Max Delbrück that it was "very important . . . to find a way out of this dilemma." The dominant member of the phage group in which Watson had "grown up," Delbrück had been for him the "legendary figure" discussed in Erwin Schrödinger's *What Is Life?* After spending two summers in the presence of Delbrück at Cold Spring Harbor and one at Caltech, Watson had come to admire especially Delbrück's "insistence that the results [presented in the many seminars over which he presided] fit into some form of pretty hypothesis."[26] It was only in keeping with that style that Delbrück now insisted on considering how the structure of DNA could be fitted into a hypothesis explaining how it might function.

Meanwhile, Watson and Crick had decided, as Watson explained to Delbrück in a letter on 5 May, that it would be "useful" to write a second letter to *Nature,* "in view of the abrupt nature of our first note (it was completed before we knew the contents of the notes from King's)." They were at work on a long manuscript "of a crystallographic type in which we adequately describe the structure," but it

would not appear until early the following year, and in the meantime "it seems logical to emphasize the biological aspects of complementary structures and not to emphasize too strongly the exact details of the structure which may in detail be proved wrong."[27] The title of their second note, a copy of which Watson sent to Delbrück, was, in fact, "Genetical Implications of the Structure of Deoxyribonucleic Acid."[28]

Within ten days, therefore, Watson appears to have reversed the priorities he had expressed to Delbrück on 25 April in the statement that he was "more concerned with seeing whether [the structure] is correct than in following up the implications." In their text, Watson and Crick wrote that it had been the "qualitative support" given to their structure "by the X-ray evidence obtained by the workers at King's College" that made them "now feel sufficient confidence in its general correctness to discuss its genetic implications."[29] That evidence, however, must have been available to Watson on 25 April, when he wrote Delbrück still resisting temptations to take up these implications. Something else must have persuaded him now to acquiesce in the view that Crick had held from the start: that they should write at length on that subject. Perhaps it was in part that Delbrück's letters made him realize that, if they themselves did not soon do so, someone else might take the initiative from them. Years later Watson related that when he had been carrying out experiments on X-ray inactivated phage at Caltech in 1949, Delbrück, who had been "only mildly interested" in those results, had "told me that I was lucky that I had not found anything as exciting as [Renato] Dulbecco had, thereby being trapped into a rat race where people wanted you to solve everything immediately."[30] Now Watson was experiencing the converse of that comparison, and Delbrück himself was among those pressing him for solutions.

The second *Nature* paper, also written by Crick,[31] first reviewed, at somewhat greater length, the description of the structure of DNA outlined in the first note. Then it drew out the inferences that this structure held for "the essential operation required of a genetic material, that of exact self-duplication":

> The phosphate-sugar backbone of our model is completely regular, but any sequence of the pairs of bases can fit into the structure. It follows that in a long molecule many different permutations are possible, and it therefore seems likely that the precise sequence of the bases is the code which carries the genetical information. If the actual order of the bases on one of the pair of chains were given,

> one could write down the exact order of the bases on the other one, because of the specific pairing. . . . It is this feature which suggests how the . . . molecule might duplicate itself. . . . Our model for deoxyribonucleic acid is, in effect, a *pair* of templates, each of which is complementary to the other. We imagine that prior to duplication the hydrogen bonds are broken, and the two chains unwind and separate. Each chain then acts as a template for the formation on to itself of a new companion chain, so that eventually we shall have *two* pairs of chains, where we only had one before. Moreover, the sequence of the pairs of base will have been duplicated exactly.

Following a brief suggestion that this duplication could occur most simply if free nucleotides available in quantity in the cell joined up from time to time on single chains remaining in a helical configuration and were then polymerized, the paper approached the separation problem:

> Since the two chains in our model are intertwined, it is essential for them to untwist if they are to separate. As they make one complete turn around each other in 34A, there will be about 150 turns per million molecular weight, so that whatever the precise structure of the chromosome a considerable amount of coiling would be necessary. It is well known from microscopic observation that much coiling and uncoiling occurs during mitosis, and though this is on a much larger scale it probably reflects similar processes on a molecular level. Although it is difficult to see how these processes occur without everything getting tangled, we do not feel that this objection will be insuperable.[32]

While thus acknowledging implicitly the objection that Delbrück had conveyed to Watson, Crick made no concession to it. The question "what makes the pair of chains unwind and separate?" was, in his view, only one of many things that remained "to be discovered before the picture of genetic duplication can be described in detail." Although the general scheme proposed "must be regarded as speculative," Watson and Crick felt that their hypothesis, that "the template is the pattern of bases formed by one chain of the deoxyribonucleic acid and that the gene contains a complementary pair of such templates," might nevertheless "help to solve one of the fundamental biological problems."[33]

Since the beginning of the year, Watson had been negotiating with Delbrück to come to Caltech on a fellowship after he completed his

work in Cambridge. He had also raised the question whether funds from the fellowship might be used in advance to enable him to attend the Cold Spring Harbor Symposium on Viruses, scheduled for June. By late April Delbrück decided that the recently discovered structure of DNA was of such relevance to the discussions that would take place at the symposium that he arranged for Watson to be invited as a last-minute participant in the conference. He persuaded H. M. Weaver, the director for research of the National Foundation for Infantile Paralysis, which paid the expenses of all the invited participants, to cover Watson's round-trip transportation from England and his living expenses at the symposium.[34] On 1 May Delbrück wrote Watson:

> In further explanation of the official invitation . . . let me say that the reference to "your research" (about which you are supposed to have a manuscript ready *at the time of the meeting,* under penalty of not getting your trip paid), is to your *DNA structure,* and not your work with [Bill] Hayes [on bacterial genetics]. You are invited because I swore (and Pauling seconded my oath by a long distance phone call to Weaver) that the Watson-Crick DNA structure is of basic importance in connection with at least half a dozen of the principal papers to be given at the Symposium. I also suggested, that, since we would not be able to schedule a major paper by you, that you should be commissioned to draw up a memorandum about the structure and its implications for circulation among all participants *before* the meeting.

"Perhaps," he suggested, "it would be sufficient to mimeograph the three letters to *Nature* and to send these around, and let everybody draw his own conclusions."[35]

When Delbrück received from Watson a copy of the manuscript that Crick had written for the second note to *Nature,* he found his previous objection to the implications of the structure only reinforced. On 12 May he wrote back,

> Let me start out by stating what I feel about your structure. . . . I am willing to bet that the complementarity idea is correct, on the basis of the base analysis data and because of the implication regarding replication. Further, I am willing to bet that the plectonemic coiling of the chains in your structure is radically wrong, because
>
> (1) The difficulties of untangling the chains do seem, after all, insuperable to me.

(2) The X-ray data suggest only coiling but not specifically your kind of coiling.

I would suggest, therefore, that your second publication de-emphasize the mode of coiling.

Delbrück suggested further that the note be published in the Cold Spring Harbor Symposium volume rather than in *Nature,* "because the paper, as it stands, contains too much that is repeated from the first letter."[36] Watson's reply of 21 May hints that he was caught in an uncomfortable position between the divergent opinions of two powerful figures in his life—Crick, who regarded the objection to the unwinding of the chains as "not insuperable," and Delbrück, who thought just the opposite. More generally, he was now having deep pangs about the widespread publicity that the Watson-Crick model was attracting:

With regard to your comments on our note: (1) biologically we are unhappy about our plectonemic coiling but (2) we believe we should consider the X-ray evidence and stereochemical consideration first and then worry about the biological complications. If it is not a plectonemic helix, then we would favor a sheet like structure in which the two chains are complementary. As yet, however, we cannot think of a neat way to pack sheets in a way as to give the X-ray pattern, and so we strongly favor a helix. However we may be blind to something obvious.

The next paragraphs revealed Watson's anxieties:

Crick was very much in favor of sending in the second *Nature* note despite the repetition since he feels that most readers of *Nature* did not understand the first note. To preserve peace I have agreed to it and so it shall come out shortly since Gale (the editor of *Nature*) is very close to Bragg. It is all rather embarrassing to me since the Professor (Bragg) is frightfully keen about it and insists upon talking about it everywhere. Until we produced the model Bragg did not know what either DNA or genes were and his reaction to our original *Nature* note was "it's all Greek to me." After we had convinced him that DNA might be interesting, he then got out of control and I spend most of my time de-emphasizing it since I have not infrequent spells of seriously worrying about whether it is correct or whether it will turn out to be Watson's folly.

Bragg, however, remains cheerful as ever, and has even told the story to the press and so next Friday's "News Chronicle" carries a story on how the secret of life was discovered in Cambridge. This

> immediately led a reporter of "Time" to Bragg and I am dreadfully afraid that I shall see the story in gory print when I am in the States.

"I am now working very hard" on a manuscript for the Cold Spring Harbor Symposium, Watson reported. "It is a difficult paper to write since it would be much prettier if we could present a crystallographic proof or disproof of plectonemic coiling. I am assuming, however, that the deadline is June 1st and so we shall emphasize (1) two chains and (2) complementary pairing."[37]

His difficulty in writing this paper was hardly diminished by the fact that Watson was preparing to present it in precisely the setting habitually dominated by Max Delbrück. If he did not take sufficient account of Delbrück's "insuperable" objections to the plectonemic helix, he could expect to be subjected to the trenchant criticism that Delbrück characteristically delivered on such occasions. If, on the other hand, he conceded too much to Delbrück, it might become difficult for him to keep the peace with Crick.

When scientists write successive papers on the same ongoing or completed investigation, the resulting texts are commonly not independent productions but variations on a theme, orchestrated for particular occasions and audiences. The paper that Watson composed on the structure of DNA during the month of May incorporated much of what had already appeared in the two *Nature* articles, as well as information from the accompanying papers of Franklin and Wilkins. All of this was recast to adapt it to the forum he had to address. The opening paragraph was designed clearly to connect what he wished to report with the topic of the Cold Spring Harbor meeting:

> It would be superfluous at a Symposium on Viruses to introduce a paper on the structure of DNA with a discussion on its importance to the problem of virus reproduction. Instead we shall not only assume that DNA is important, but in addition that it is the carrier of the genetic specificity of the virus . . . and thus must possess in some sense the capacity for exact self-duplication. In this paper we shall describe a structure for DNA which suggests a mechanism for its self-duplication and allows us to propose, for the first time, a detailed hypothesis on the atomic level for the self-reproduction of genetic material.[38]

After this diplomatic nod Watson made little further mention of viruses. The first four sections of the paper—"Evidence for the Fibrous Nature of DNA," "Evidence for the Existence of Two Chemical Chains

in the Fiber," "Description of the Proposed Structure," and "Evidence in Favor of the Complementary Model"—repeated much of what Crick had written in the earlier papers. In places phrases extracted from the earlier pages were reorganized to shift the emphasis. As he had indicated in his letter to Delbrück, Watson amplified the aspects of the argument that stressed the two chains and complementary base pairs. He also provided more details concerning the evidence on which the structure was based, particularly that drawn from the X-ray fiber diagrams of Wilkins and of Franklin. Whereas Crick had written in the first *Nature* note that the structure rests mainly on "published experimental data and stereochemical arguments," acknowledging only "stimulation" from the "general nature of the unpublished results and ideas" of Wilkins and Franklin, Watson now offered the structure of DNA as one that he and Crick had proposed "to account for these findings."[39] The incompatibility of these two statements is self-evident. Both appear to reflect Watson and Crick's embarrassment over the way in which they had been given access to the "findings" for which their structure accounted. Now that the results and ideas of Franklin and of Wilkins were published, Watson and Crick could safely leave the impression that they based their structure for DNA on detailed evidence that had, in fact, become public knowledge only after they had constructed their model.

Section V, "Genetic Implications of the Complementary Model," expanded considerably on the corresponding discussion in the second *Nature* article. It was here that Watson labored to satisfy both Delbrück and Crick. Rather than follow Delbrück's advice to de-emphasize the method of coiling, he and Crick had evidently decided that they must meet his objection head on and fully defend their position. In two paragraphs the first subsection described a mechanism for DNA replication very much as the *Nature* paper had done. In place of the single paragraph in which Crick had brushed off objections to the unwinding of the strands as not insuperable, however, Watson devoted more than a quarter of the paper to a subsection titled "Difficulties of the Replication Scheme."[40]

Watson recognized three main objections. The first, that DNA contains 5-methyl cytosine in addition to cytosine, he could readily answer with the data of Gerard Wyatt showing that the sum of the amounts of cytosine and 5-methyl cytosine is equal to the amount of guanine. The second objection, that "our scheme . . . completely ignores the role of the . . . proteins known to be combined with DNA

in most living organisms," he deflected with the observation that "as yet nothing is known about the function of the protein." The third difficulty

> involves the necessity for the two complementary chains to unwind in order to serve as a template for a new chain. This is a very fundamental difficulty when the two chains are interlaced as in our model. The two main ways in which a pair of helices can be coiled together have been called plectonemic coiling and paranemic coiling. These terms have been used by cytologists to describe the coiling of chromosomes. . . . The type of coiling found in our model . . . is called plectonemic. Paranemic coiling is found when two separate helices are brought to lie side by side and then pushed together so that their axes roughly coincide. Though one may start with two regular helices the process of pushing them together necessarily distorts them. It is impossible to have paranemic coiling with two regular simple helices going around the same axis. This point can only be clearly grasped by studying the models.[41]

It was perhaps because of the difficulty of visualizing these complex spatial relations from verbal descriptions, or from the two-dimensional schematic diagram published in the *Nature* papers, that Watson decided to have built for him, in the Cambridge machine shop, a small wire model that he could carry with him to the symposium.[42]

Having rejected the bet Delbrück had made that plectonemic coiling "is radically wrong," Watson had now to confront the unwinding difficulty. "The difficulty is a topological one," he wrote, "and cannot be surmounted by simple manipulation. Apart from breaking the chains there are only two sorts of ways to separate two chains coiled plectonemically." That the two chains might be pulled apart in the axial direction he considered "highly unlikely." They must therefore "be directly untwisted." Addressing himself to the problem of how many turns must be made, and how is tangling avoided, Watson estimated a lower limit of one thousand turns, based on the molecular weight of isolated DNA fibers, and an upper limit of twenty thousand turns based on the total DNA in a virus. In higher organisms the number might be "1,000 fold higher."[43]

"The difficulty might be more simple to resolve," Watson acknowledged, "if successive parts of a chromosome coiled in opposite directions. The most obvious way would be to have both right and left handed DNA helices in sequence but this seems unlikely as we have

only been able to build our model in the right handed sense." Having thus tacitly eliminated Delbrück's suggestion that compensating coiling might alleviate the unwinding problem (as he had already explicitly done in his letter of 25 April to Delbrück), Watson turned to the danger of tangling. This problem would be considerably decreased if replication began at the ends as soon as the chains started to separate. The structure would remain rigid, and "the growing end of the pair of double stranded structures might facilitate the breaking of hydrogen bonds in the original unduplicated section and allow replication to proceed in a zipper-like fashion." He allowed also that one chain of a pair might "occasionally" break "under the strain of twisting." The accumulated twist would then be relieved by rotation of the second chain, after which the broken ends "might rejoin."[44] In spite of these tentative suggestions,

> the difficulty of untwisting is a formidable one, and it is therefore worthwhile re-examining why we postulate plectonemic coiling. . . . Our answer is that with paranemic coiling, the specific pairing of bases would not allow the successive residues of each helix to be in equivalent orientation with regard to the helical axis. This is a possibility we strongly oppose as it implies that a large number of stereochemical alternatives for the sugar-phosphate backbone are possible, an inference at variance to our finding, with stereochemical models . . . that the position of the sugar-phosphate group is rather restrictive and cannot be subject to the large variability necessary for paranemic coiling. Moreover, such a model would not lead to specific pairing of the bases, since this only follows if the glucosidic links are arranged regularly in space. We therefore believe that if a helical structure is present, the relationship between the helices will be plectonemic.

Elaborating a possible alternative that he also mentioned in his letter to Delbrück while working on the paper, Watson added:

> We should ask, however, whether there might not be another complementary structure which maintains the necessary regularity but which is not helical. One such structure can, in fact, be imagined. It would consist of a ribbon-like arrangement in which again the two chains are joined together by specific pairs of bases, located 3.4 Å above each other, but in which the sugar-phosphate backbone, instead of forming a helix, runs in a straight line at an angle approximately 30° off the line formed by the pair of bases. While this ribbon-like structure would give many of the features of the

> X-ray diagram of structure B [the crystalline form assumed by DNA at high humidity], we are unable to define precisely how it should give a strong equatorial reflexion at 20–24 A. We are thus not enthusiastic about this model though we should emphasize that it has not yet been disproved.[45]

Even though his text did not mention Delbrück, it is obvious in the light of the correspondence between them that Watson was composing a public answer to the private objections Delbrück had raised. Essentially his response was that he and Crick had not found the way out of the dilemma but that they had compelling reasons to remain in it rather than to choose the route that Delbrück offered. Delbrück wanted to have complementarity without plectonemic coiling. Watson and Crick were telling him that he could not have one without the other, because the plectonemic relation between the two polynucleotide strands was essential to the structure that defined complementary base pairs.

The answer to Delbrück's claim that "the X-ray data suggest only coiling but not specifically your kind of coiling" was subtler, because it could not be conveyed entirely in words. Delbrück had seen only summaries of the data and schematic drawings of the double helix. He had not had the experience that Watson and Crick had had constructing models to fit the data. Few scientists besides these two had such experience. Here they were saying to him, if you try it, you will see that you cannot construct *your* paranemic kind of coiling in a manner that is compatible with the data.

Why were Watson and Crick, who still acknowledged that their model had not been proved correct, so confident in it as to maintain that the "formidable" difficulties that their replication scheme faced were not insuperable? Here, they were, of course, not of one mind, even when they spoke publicly with one voice. Crick seems not to have felt the doubts that sporadically afflicted Watson. Watson's determination to stick with their solution rested probably as much on feeling and aesthetics as on the strength of the evidence supporting it. Years later, in his text *Molecular Biology of the Gene,* he wrote of the double helix: "Before the answer was known, there had always been the mild fear that it would turn out to be dull, and reveal nothing about how genes replicate and function. Fortunately, however, the answer was immensely exciting."[46] Both the fear and the excitement to which he alluded had been his own. Ever since reading Erwin Schrödinger's *What Is Life?* as an undergraduate at the University of Chi-

cago, he had been "polarized toward finding out the secret of the gene."[47] He had, therefore, a great deal of emotional investment in the outcome that he and Crick had together reached. The qualities that made the model exciting were, ironically, the same ones that made Watson sometimes feel that it might prove to be his folly. He conjured up his apprehension retrospectively, in 1990, in the elliptical comment, "You know, there was a beautiful model, but it wasn't correct."[48] The search for beauty is a powerful motivating force, in science as in life; but he was well aware that, in both realms, beauty is seductive.

Looking forward to the chance to see the United States after an absence of three years, Watson flew across the Atlantic on 2 June and came directly to Cold Spring Harbor, where the symposium opened on 5 June.[49] Two hundred and seventy-two scientists attended—the largest gathering ever in the series of symposia on quantitative biology that had been held annually since 1932. The meetings were held in the lecture hall of the laboratory.[50]

As he had planned, Delbrück circulated the copies of the three letters to *Nature* by Watson and Crick, Wilkins, and Franklin before the meeting began, so that the participants would be prepared for the discussion that he expected Watson's talk to evoke.[51] In his presentation Watson showed slides of Wilkins's and Franklin's X-ray diffraction pictures, as well as the previously published schematic drawings of the double helix and the polynucleotide chains and scale drawings of the base pairs, and he displayed the model he had brought with him. One of the younger participants in the meeting, François Jacob, has described the feeling of this dramatic moment: "With an air more bewildered than ever, his shirt fluttering, wide-eyed, his nose in the air, interrupting his discourse with brief exclamations underlining the importance of his subject, Jim explained the details of the structure." After he had finished describing the play with models, the crystallographic arguments, the physical and chemical characteristics of the molecule, and the genetic implications for replication and mutation, "for a moment the hall remained silent. There were a few questions. How, for example, can the two chains wrapped around each other separate during the replication of the double helix without breaking? But no criticism. No objections. There was in that structure such a simplicity, such a perfection and harmony, such beauty even; the biological advantages flowed from it with such rigor and such evidence, that one could not believe that it was not true."[52]

That the question about how the chains could separate did not lead to objections such as those Delbrück had raised privately suggests that Watson's thoughtful defense of his and Crick's position against Delbrück's must have preempted Delbrück from pressing the issue during the discussion. When Cy Levinthal congratulated him after his talk, Watson replied, in the English-style understatement he emulated then, that Crick's skill at X-ray crystallography had made it all easy.[53]

II

It was obvious to all who heard Watson's Cold Spring Harbor talk with such intense interest that if the postulated structure were confirmed it would bring radical changes to their understanding of the replication of viruses in particular and to genetics in general. Few were persuaded on the spot, however, that the structure was firmly established. In the papers that they had so far published or presented, Watson and Crick had outlined the general features of their structure and asserted its compatibility with the characteristics of the molecule that could be inferred from X-ray diagrams, but they had as yet not revealed the detailed "stereochemical arguments" on which they claimed to have based their model. The prevailing approach among those who had read the *Nature* articles or had heard Watson speak was probably to await with open minds for further information—unless, like the plant physiologist Barry Commoner, who, according to Watson's recollection, "hated the talk," they adamantly opposed Watson and Crick's strategy of ignoring the protein component of the gene.[54]

Many of the participants must also have puzzled over the conundrum of how the two strands of a coiled helix could separate. To judge from his later actions, Delbrück must have been persuaded to give up his idea that paranemic coiling or compensatory winding could solve the problem, but he was still dissatisfied with Watson and Crick's optimistic belief that the two strands could somehow untwist. Among those present who were stimulated to think about the problem was Robert Sinsheimer, a biophysicist at Iowa State College who had spent the previous year at Caltech studying the degradation of deoxyribonucleic acid to dinucleotides and mononucleotides. During the meeting Sinsheimer made the suggestion that, if DNA is a two-stranded helix as the Watson-Crick model asserted, then when it is degraded by the enzyme DNAse "there ought to be a lag in the disintegration of the

two-ply molecule as presumably more or less adjacent bands in the two chains would have to be broken before the chain length could decrease."[55]

Consulting with Paul Doty at Harvard University, Sinsheimer learned that Doty's data on the rate of DNAse degradation of DNA measured by light-scattering methods showed "just such a lag in the decline in average molecular weight," although his own data on the release of titratable acid showed no lag. This difference suggested that as individual bonds began splitting on each chain, some time would pass before the breaks would occur close enough together along both chains to cause the molecule to come apart. To Delbrück he wrote, "Score one for Watson and Crick." Pondering the unwinding problem, Sinsheimer thought that if "only one chain is important and the other may be discarded, then one might go further and assume that the latter chain is not really complete but is broken maybe every 30–50 nucleotides. . . . Such a state of affairs would of course greatly simplify the unraveling under some set of conditions that would release the H bonds." Sinsheimer saw no evidence against such an idea.[56] Delbrück undoubtedly did not like it, because the distinction it made between the status of the two chains violated the symmetry of the DNA structure; but he may not, at the moment, have had any better thoughts on the subject.

Soon after Watson returned to Cambridge, he received from Linus Pauling an invitation to attend a protein conference that Pauling had organized for September in Pasadena. Watson made arrangements to come to Caltech in time for the conference and to begin his research fellowship immediately afterward. The main task that he had to complete before leaving Cambridge was the longer paper on DNA on which he and Crick had begun to work in March, the paper that would give the coordinates and other structural details of the model. Because Crick was now busy finishing his thesis before his impending departure to the United States to take up a position at the Brooklyn Polytechnic University, the task of writing fell to Watson. He had it finished by early August. The Royal Society received it from Bragg on 24 August, for publication in the *Proceedings*. It would, therefore, not actually appear until the following spring.[57]

Although there was some overlap between the paper on the complementary structure of deoxyribonucleic acid and the three papers on the same subject that had preceded it, it was quite different in character. Not only did it concentrate on the structural details of the model,

with only brief reference to the biological implications; for the first time in print Watson and Crick made it clear that their model rested on "stereochemical arguments" and that they had arrived at it by actually constructing physical models in laboratory space. "It has seemed worthwhile," Watson wrote, "for us to build models of idealized polynucleotide chains to see if stereochemical considerations might tell us something about their arrangement in space. In doing so we have utilized interatomic distances and bond angles obtained from the simpler constituents of DNA and have only attempted to formulate structures in which configurational parameters assume accepted dimensions. We have only considered such structures as would fit the preliminary X-ray data of Wilkins, Franklin and their co-workers. Our search has so far yielded only one suitable structure."[58]

The paper indicated how the spacings of the reflections on the X-ray pictures imposed severe restrictions on the types of models that could be built and how the possibilities allowed by the X-ray data can be differentiated by building models. Although he did not mention all of the false starts and detours about which he later gave so entertaining an account in *The Double Helix,* Watson did describe the considerations that had led him initially to believe that the phosphate groups should be in the center. He explained how they came to realize that this approach would lead nowhere, gave up the attempt, and decided it was "most likely that the bases form the central core and that the regular sugar-phosphate backbone forms the circumference."[59]

Less conspicuously, the paper revealed also the strategic importance for Watson and Crick of a paper published in 1950 by Sven Furberg on the crystal structure of cytidine. Cytidine is the nucleoside composed of cytosine and a deoxyribose sugar molecule. Because there were no published reports of the structure of cytosine alone, Furberg's paper served as the only source of information on the dimensions of this base. Moreover, Furberg had concluded that, contrary to the suggestion by William Astbury that the rings of the sugar and of the base are parallel, "they are oriented in such a way that they are nearly perpendicular to each other. This would seem to be a point of considerable importance for the understanding of the structure of the nucleic acids." Furberg's prophecy was dramatically fulfilled when Watson and Crick adopted this perpendicular orientation of the two rings in the construction of the double helix.[60]

The paper provided scale drawings of the base pairs, projections of the spatial arrangements of the phosphate-sugar backbone, and pho-

tographs of the simplified wire model that Watson had carried to Cold Spring Harbor.[61] Short of being able to see and touch an actual physical model of the molecule, a reader of this lucidly written and carefully illustrated paper could come as close as possible to a full appreciation of the compelling stereochemical arguments, as well as the celebrated beauty of the resulting structure.

Here, too, Watson revealed clearly why for him and for Crick the complementarity of the base pairs was inseparable from the helical structure of their model. "We should note the reason why the two chains cannot be linked together by two purines or by two pyrimidines. It arises from our postulate that each of the sugar-phosphate backbone chains is in the form of a regular helix."[62] To be sure, Watson tacitly acknowledged in the discussion section that the same conclusion about base pairing *might* have been reached from the data of Chargaff and of Wyatt alone. "It is difficult to imagine a structural explanation for the equivalence of adenine with thymine and of guanine with cytosine which does not involve specific pairing."[63] Their resistance to considering alternative structures that might preserve base pairing while obviating the obstacles to replication posed by the double helix was logical, in that they had experimental evidence that the helical structure existed. But their lack of enthusiasm for alternatives was also psychologically reinforced by the history of their quest for the structure. It had been by building helices that they had come to recognize the special feature of their DNA model—its restrictions on base pairing—that imparted to it its exciting genetic implications.

By the time Watson reached Caltech in September, he had lost all interest in DNA. No longer doubting the correctness of the model—perhaps the experience of writing the detailed description of its structure had bolstered his confidence in the solidity of his and Crick's arguments—he felt that that problem was now solved. He probably saw no way to attack the unsolved problem of its replication. He had earlier intended to start working on phage during his fellowship, a highly reasonable plan, because Caltech under Delbrück's leadership had long been a mecca for phage research. Already in the spring of 1952, however, he had written Delbrück that he would "like to go on to the structure of RNA" when he returned to Pasadena. When he arrived in the fall of 1953 he found that Alexander Rich in the chemistry division had recently begun to take X-ray pictures of ribonucleic acid. At that point Watson became "totally fixated on RNA."[64]

In the ensuing collaboration, Rich continued to take the X-ray pic-

tures. Watson contributed a method to obtain RNA in fibers ordered in a crystalline or semicrystalline form that would yield distinct diffraction reflections. Adapting a technique that Maurice Wilkins had used with DNA, he drew RNA out into fibers more than a centimeter in length. When he and Rich saw that these fibers were, like those of DNA, birefringent, they quickly became excited, because this feature indicated to them that the nucleotide bases were probably, like the bases in DNA, perpendicular to the fiber axis.[65]

The X-ray pictures that Rich took with these fibers were less well resolved than those that Wilkins and Franklin had obtained with DNA; yet their pattern resembled the DNA patterns sufficiently to suggest to Watson something that looked "slightly like a double helix."[66] In November he reported to Crick by letter, "Naturally I've tried model building."[67] Not long afterward he wrote in the annual report of research in the Caltech Division of Biology that he and Rich "hoped to establish the three-dimensional shape of this compound [RNA] and, if possible, to find a relationship between its structure and function." X-ray diffraction patterns for all RNAs examined up to that time appeared similar enough to suggest that there was only one type of RNA structure. The pattern had some resemblance to that for DNA. They were attempting to build stereochemical models with "particular attention . . . to possible helical structures." Although the results had not been encouraging, they felt that "model building . . . may in the final analysis be the most profitable approach to a solution of the structure." Watson was clearly betting that the assumptions and strategies that had led him and Crick to their recent triumph with DNA could be transferred to the chemically similar RNA.[68]

Despite picking up this scent of a possible sequel to the DNA success, Watson was thoroughly unhappy in Pasadena. The dominant cause of his somber mood was the prospect that he would be called up for military service. Almost as soon as he arrived, he was notified that he had been reclassified 1-A. Appeals made on his behalf to defer him because of his importance to the work of the virus group at Caltech were turned down by his draft board, and he felt that the army might take him "at any moment."[69]

Watson was, in addition, disappointed with Pasadena itself. Compared to the enchantment of Cambridge, the suburban area around Caltech appeared sterile, and he disliked the smog. Worst of all, there "was no social life." Still as preoccupied with meeting pretty women as he appears from his self-portrait in *The Double Helix* to have been

during his three years in Europe, Watson quickly realized at Caltech that "there were no women there." For him that made it "a pretty bleak place."[70]

Most disheartening of all to Watson was that coming back to Delbrück's virology and biophysics section turned out to be a letdown. During the summers he had spent there he had been caught up in the excitement of the phage group, and like others, he had felt the enormous charm that Delbrück exerted on those whose work he liked. Having long anticipated his return to this setting, Watson arrived after three heady years at the Cavendish laboratory only to find that everything seemed different to him. Compared to people like Crick, John Kendrew, Max Perutz, and the others in Cambridge, those in the Biology Division at Caltech appeared to be good but dull workers. Enamored by the facility and wit with which the English used words, he found Pasadena "verbally boring." Over in the Chemistry Division the great Linus Pauling, whose methods Watson and Crick had applied to such advantage to build the double helix, seemed distant and aloof. Cambridge seemed to him still the center of his world, and he in far-off exile.[71]

Max Delbrück himself suddenly ceased to be Watson's hero. For years Watson had written Delbrück regularly about his scientific activities and plans, seeking advice and approval. Watson expected Delbrück, of all people, to appreciate fully the significance of the double helix and to pursue its implications for his own long-standing interest in the replication of bacteriophage. Instead, Delbrück was just at that time making a more radical shift in his research interests. Feeling that phage genetics might have become too fashionable for him, Delbrück gave up his own phage work and sought a different arena in which to probe his persistent belief that biological phenomena would eventually reveal deep paradoxes in the laws of physics. He now thought he might find such phenomena in the basic mechanisms through which living organisms react to their environments. Seeking the simplest system imaginable in which such reactions occur, he began a study of the phototropism of the single-celled fungus *Phycomyces*. While Watson was taking up the structure of RNA in Caltech's Kerckhoff Laboratory of Biology, Delbrück was studying there the relation between changes in the intensity of illumination and transient changes in the velocity of growth of sporangiophores on a slime mold.[72]

Watson thought that Delbrück's work on *Phycomyces* was boring. Instead of stimulating Delbrück to examine its implications for phage

genetics, the double helix had actually made it easier for him to leave genetics. Delbrück saw that the discovery of the structure of DNA would make genetics increasingly molecular. As one who disliked biochemistry and knew little about it, he did not wish to move in that direction. Watson now began to perceive Delbrück as someone who seemed to want to solve fundamental biological problems without learning the facts of biology. Unlike Francis Crick, another physicist who "switched over," Delbrück remained, in Watson's view, "always a physicist looking at biology rather than a molecular biologist." Consequently, Watson lost interest in what Delbrück thought. Given his current location, that was an awkward situation.[73]

Those in Delbrück's group who still were doing phage genetics did not seem to Watson to be studying the right problems. Work such as Jean Weigle's research on the induction of phage mutations by ultraviolet irradiation, Joe Bertani's work on the inheritance of P2 prophage in bacterial crosses, Robert DeMars's investigation of genetic recombination of UV irradiated phage T2, or George Streisinger's study of the genetics of T2 and T4 host ranges continued the classical methods of studying genetic crosses, identifying genetic markers, and measuring linkages between markers. To Watson it seemed that they were working as if the double helix did not exist. No one changed what he was doing because of it.[74]

Feeling intellectually isolated, and missing particularly the stimulation of daily conversations with Crick, Watson fluctuated from high optimism to discouragement over his progress with RNA. Late in the fall he believed that he was about to attain the correct structure. One of the obstacles that he still had to overcome, however, was that some chemists thought that, unlike DNA, the polynucleotide chains of RNA might be branched. Branching would play such havoc with the search for a structure that Watson hoped he could somehow rule out that possibility. Early in January he wrote Delbrück from Washington that he would like "to convince a chemist that RNA is an unbranched 3–5 chain, before sticking my neck out on a structure." By late January he had come to feel that he was still far from the solution. Nevertheless, having interested the physicist Richard Feynman—in his opinion "the best person in Caltech if not in the States"—in the problem, he no longer felt isolated: "Instead, so stimulated that I cannot sleep much."[75]

In early February Watson was full of enthusiasm for a new scheme that he had devised. By reading up on the literature about base ratios

in RNA he convinced himself that in all RNA, except for that of plant viruses, the ratios are complementary. Inferring that all RNA, whether single- or double-stranded, replicates as DNA does by forming complementary strands, he decided that the reason DNA has two strands is that one of them retains the code, while the other is transformed to RNA, which then crosses into the cytoplasm to make protein. He wrote to Crick on the thirteenth that he had persuaded Feynman of his scheme "and slightly Delbrück." Although the idea "is slightly mad, as it is cute I think it is correct." Three days after the idea came to him, Watson impulsively began to write a letter to *Nature*.[76]

Alex Rich was also caught up in the enthusiasm. He built a large helical model of RNA that contained twenty different trapezoidal holes into which, inspired by George Gamow's coding scheme, he believed the twenty amino acids of the proteins synthesized by RNA could fit. When Gamow drove to Pasadena to inspect the model, however, he found that the combination rules that he had formulated would not work with the model. He wrote Crick that Watson and Delbrück did "not believe in it very much" either.[77]

Delbrück left Caltech for Germany in March to spend three months at Göttingen. Watson recovered from his fantasy that he could solve all the mysteries of life and saw that there was much work to be done before he could dispatch another thunderbolt to *Nature*. In late March, Watson wrote Delbrück that he and Leslie Orgel, a member of Pauling's group, had been "giving RNA another serious going over—I believe with some success." They were "observing a very pretty reversible change in the RNA fibre length which occurs upon raising or lowering the relative humidity. This change in fibre length can be correlated with changes in the X-ray pattern in a nice way." The new evidence seemed to rule out the helical model that Alex Rich had constructed. New photographs that Rich had obtained now made them "suspicious that the structure may be much closer to DNA than we would have guessed. . . . The whole picture is now very queer and paradoxical and so I have great hopes that the solution will not be trivial."[78]

By May the solution to this paradoxical picture had not yet appeared. Watson and Rich decided to announce in *Nature,* not the grand scheme that Watson had started to write up in February, but the technical achievement of having drawn RNA into fibers enabling them to take the first X-ray diffraction photographs of RNA that showed distinctive patterns.[79] More interpretative was a paper titled

"Some Relations Between DNA and RNA" that they sent, via Linus Pauling, to the *Proceedings of the National Academy of Sciences*. In it they addressed themselves to the same questions that Watson had treated in his letter to Crick in February. In place of the unguarded exuberance with which Watson had proclaimed his answers to these questions to his scientific partner, however, was cautious recognition of a conglomeration of solved and unsolved problems. "About the functions of RNA," they began, "we possess little definite information. It has been implicated in protein synthesis, but only indirectly. The really interesting thing about both nucleic acids is that we know very little about how they function chemically in a cell."[80]

Pointing to the known similarities between the two polymeric compounds, they acknowledged that "Up to now we have had success in understanding only one of these two structures." Summarizing briefly the characteristics of the two-stranded helical structure of DNA, they went on:

> The most attractive feature of the two-stranded complementary helix is the fact that it suggests an answer to the question of how DNA can replicate itself exactly, a function it must possess if it is a genetic material. The complementary structure fits this requirement neatly if we make the assumption that one strand can serve as a template for the formation of its complement. We visualize, then, a mechanism involving initial separation of the two strands, with each of the separated strands serving as a template for its complement—the whole process occurring in zipper-like fashion. This method of replication is likely to be very exact, as the necessity for specific pairing is absolute, and misformed pairs will not fit into the structure.[81]

In view of the "formidable unresolved difficulties concerning the separation of the two strands, we can see that the mechanism that Watson could visualize was far from a definitive answer to the question of how DNA can replicate itself." It was a statement of confidence that such a mechanism eventually could be found. Watson could not describe it literally, but only through the metaphor of a zipper. Whatever the detailed mechanism might be, it must conform to the fundamental feature of the two-stranded complementary helix, because, as he recalled in 1990, "it would be very unlikely that anything better [than base-pairing] would be forthcoming."[82]

In the spring of 1954, Watson was not immediately concerned to

describe the mechanism in detail. Knowing the general principles on which it must sometime be built was a sufficient support for him as he fixed his attention on the way in which DNA may control, "either directly or indirectly, the synthesis of specific proteins." Enumerating several objections to the direct role, Watson wrote that it was more "plausible to suppose a connection between RNA and protein synthesis. Under such a scheme, DNA could control RNA, with RNA responsible for protein synthesis."[83] In spite of his proposing to Crick that one of the two DNA chains is transformed to RNA, Watson did not specify in the paper how DNA can "control" RNA. "We shall not be able to check a structural relationship between RNA and protein synthesis or between RNA and DNA," he wrote, "until we know the structure of RNA."[84]

At the time, RNA appeared to be more complex in several ways than DNA, including the possibility that its chains might be branched. "The analytical composition of the bases in RNA also appears more complex." The paper presented a table of the ratios of adenine, uracil (which could be considered the functional equivalent of the thymine of DNA), guanine, and cytosine found by several other analysts. The ratios of adenine to uracil and of guanine to cytosine were close enough to 1:1 in all except the RNAs from plant viruses to support the claim Watson had made in his letter to Crick that they *are* complementary. In the plant viruses, however, the distribution of the various bases appeared "fairly random." The possible explanation that there are two types of RNA conflicted, however, with Watson and Rich's diffraction photographs, which showed that "RNA of all sources produces the same X-ray pattern. A simple interpretation of the analytical data does not appear possible."[85] Undoubtedly this was a part of the picture that Watson had called "queer and paradoxical" in his letter to Delbrück.

The paper next compared an X-ray diffraction photograph that Rich and Watson had obtained from RNA with the two well-known photographs of DNA by Wilkins and by Franklin. Drawing attention to their similar features, Watson concluded, "The X-ray pattern therefore suggests a DNA-like structure for RNA. However, since the DNA model is based upon complementary base ratios which are not found in many RNA's, this suggestion has many difficulties. It is possible that non-complementary side chains may arise from a complementary main structure, but proof of this awaits more direct chemical evidence of branches in RNA."[86]

The suggestion that the noncomplementary overall base ratios of plant virus RNA might derive from side chains illustrates the fluidity of Watson's position as he grappled with the various difficulties he encountered in his search for the structure of RNA. Having failed to convince himself that the chains were unbranched, he now came to see the possibility of branches as a potential advantage, a means to resolve a paradox that had in the meantime arisen.

In model-building, too, Watson and Rich could only report efforts that fell short of solutions: "We have been able to construct single-chain helical models for RNA in which the free ribose hydroxyl group is satisfactorily hydrogen-bonded to a negatively charged phosphate group. However, we have not been able to form satisfactory intramolecular hydrogen bonds between the bases, which, in this model, remain free to form external hydrogen bonds." They ended their brief summary section with the prudent admission that "further chemical and crystallographic work is necessary before we can discover the relationship between the structure of RNA and the origin of protein specificity."[87]

On 1 June, Watson wrote Delbrück, "Our work on RNA is at a standstill. We need a cute idea or a much better X-ray photograph and neither possibility seems in the air." Noting that Gamow and others were doing much work on a "protein code," Watson commented, "I do not think the problem can be solved in this way and that we shall have to know RNA structure first. It is more prosaic this way but I'm afraid nevertheless true." After indicating his willingness to work with a student in the laboratory on bacterial genetics, he added, "I still feel that RNA is the most important problem for us to crack but it will probably come from inspiration and not from solid concentration."[88]

For now Watson had, in any case, to interrupt his work on RNA for two months, because he had agreed to be an instructor in the general physiology summer course at Woods Hole, beginning on 15 July. At the end of the first week in June he left Pasadena in his car for a cross-country dash with the radioactive phage stocks he had prepared to use in the course.[89]

It is facile to judge Jim Watson's unsuccessful search for the structure of RNA during his unhappy year at Caltech as a futile attempt to recapture the magic of what he and Crick had done the year before with DNA. It is easy to view his hope that a new idea as clever as complementary base pairs would come to him through inspiration rather than sustained concentration as a yearning for lightning to

strike twice. But Watson was not misguided to approach the problem in the way he did. For him their auspicious solution for the structure of DNA functioned as a paradigm, in the sense that Thomas S. Kuhn has used that term. According to Kuhn, scientists typically "solve puzzles by modeling them on previous puzzle-solutions."[90] At first the ways in which the problems are similar and the ways in which they differ are often not apparent. There was ample motive to take up the structure of RNA as a problem strongly resembling the one that had just yielded so beautiful a solution. Although he may have appeared to some observers more erratic on his own than when his enthusiasms had been controlled by his conversations with Crick, the two papers Watson published during this period show that he was circumspect enough to control in public the brash inspirations to which he gave free rein in his private correspondence. John Kendrew wrote Watson in June that Maurice Wilkins "is very kindly disposed towards yourself though he still thinks you are at times carried away by the impetuosity of extreme youth!"[91] Impetuous though Watson undoubtedly was, there are no grounds to say that, on his own, he lacked critical scientific judgment.

III

Writing to Watson in November 1953, Kendrew asked, "Have you reconciled Max to the DNA structure?"[92] Undoubtedly, Watson had not been able to overcome Delbrück's resistance to unwinding. At Pauling's protein conference in September Delbrück had made a five-dollar bet with Crick that the two strands would never separate.[93] He did not change his mind that winter, despite Watson's presence in his laboratory. At Göttingen in the spring Delbrück gave a seminar on the new genetics and the double helix, news of which had apparently not yet spread widely in Germany.[94] Perhaps it was that occasion that stimulated him to concentrate his attention on the problem of how DNA might replicate. At any rate, in mid-May he sent to the *Proceedings of the National Academy of Sciences* a paper titled "On the Replication of Deoxyribonucleic Acid (DNA)," which set forth a cogent theoretical analysis of the problem.

After summarizing the structure proposed by Watson and Crick and their conception of its replication in a "zipper-like fashion," Delbrück wrote:

> The principal difficulty of this mechanism lies in the fact that the two chains are wound around each other in a large number of turns and that, therefore, the daughter-duplexes generated by the process just outlined are wound around each other with an equally large number of turns. There are three ways of separating the daughter duplexes: (a) by slipping them past each other longitudinally; (b) by unwinding the two duplexes from each other; (c) by breaks and reunions.
>
> We reject the first two possibilities as too inelegant to be efficient and propose to analyze the third possibility.[95]

Before proceeding with Delbrück's analysis, we may note that he made no attempt to revive the idea that the two strands might form a paranemic coil. Watson's argument at Cold Spring Harbor must have reconciled him at least to the requirement that the two chains be wound *around* each other. It is also characteristic of Delbrück's style that inelegance and inefficiency were for him sufficient grounds to reject the possibility that either of the two mechanisms that did not require breaks and reunions could operate in nature.

Taking up the third possibility, Delbrück reasoned that

> If one tries to separate the two chains of a duplex by moving the two chains laterally in opposite directions, an interlock occurs for each turn of the helix, i.e., at each tenth link. Such an interlock can be resolved in two ways: (a) by breaking one of the chains, slipping the other chain through the gap, and rejoining the broken ends; (b) by breaking both chains at each half-turn and rejoining them crisscross.
>
> We reject both these mechanisms—the first one because it introduces an asymmetry between the two chains (only one of them being broken) which is contrary to the symmetry of the structure and the second one because it rejoins chains with opposite polarity, which is chemically not permissible. We conclude that it is not feasible to separate by breaks and rejoins the two chains of a single duplex. The situation is quite different, however, when one considers a duplex during the process of replication. Let us consider a duplex in which replication has proceeded synchronously along the two chains up to link n. We will call this point the "growth point." If we now break both the old chains between links n and $n + 1$, we may join the lower terminals of the breaks in a crisscross fashion, not to the upper terminals of the breaks but to the open ends of the *new* chains of equal polarity. The upper termi-

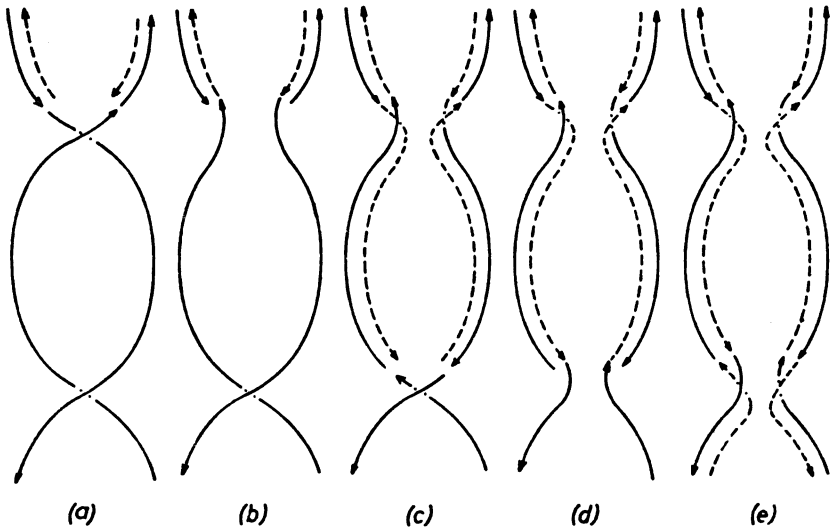

FIG. 3.—Resolution of an interlock in a replicating duplex by breaking both old chains at each half-turn of the helix and rejoining the lower terminals of the breaks to the open ends of equal polarity of the new chains. Lateral view. *a*, Location of first pair of breaks. *b*, Rejoining of lower terminals of breaks. *c*, Location of second pair of breaks. *d*, Rejoining of lower terminals.

Parental chains are represented by solid lines; new chains, by dashed lines. At the overlaps the lower chains are dotted.

Fig. 1.2. Replication mechanism proposed by Max Delbrück

nals of the breaks now become the open ends for the continuation of the replication process.[96]

Delbrück illustrated his conception of the situation by several diagrams, including the lateral view of the process shown in figure 1.2.

His abstract approach to the replication problem is evident in Delbrück's reasoning and in his diagrams. The structure of DNA is reduced to two linear strands—a "duplex." The polarities due to the directionality of the 3′–5′ linkages of the deoxyribose residues in the polynucleotide chains are reduced to arrows. The complementary base pairs are reduced to links, denoted n and $n + 1$. The style was indeed that of the physicist seeking the fundamental features of a biological mechanism that did not depend on detailed descriptions of the molecules involved.

Abstract though Delbrück's scheme appeared to be, it entailed a consequence that was potentially testable:

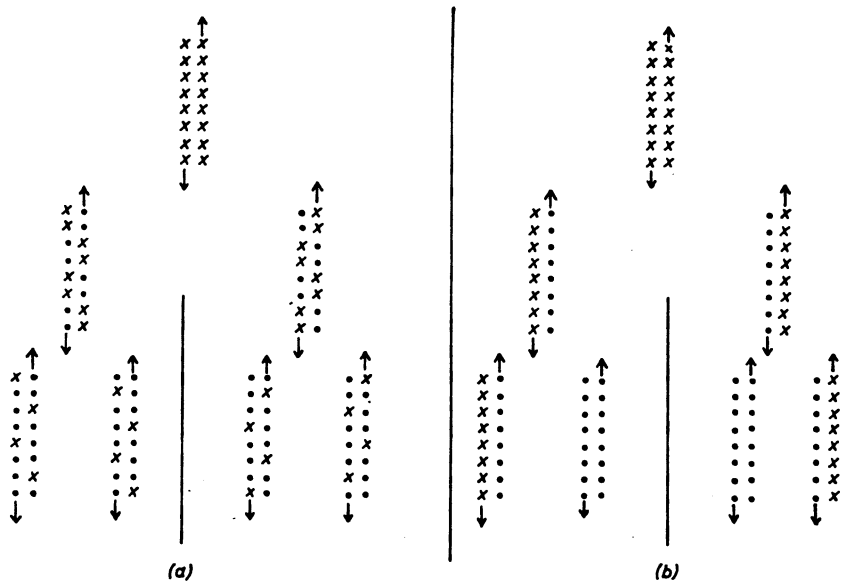

FIG. 6.—Distribution of labeled parental chains to daughter-duplexes in two successive cycles of replication. × = labeled parental chains; ● = unlabeled chain material assimilated from pool of precursors during replication. *a*, With breaks and rejoins as postulated in the theory here presented. *b*, Without breaks.

For simplicity of representation it is assumed that the breaks in *a* occur at exactly every second link and that the break points during the second replication are intermediate between those of the first replication.

Fig. 1.3. Distribution of labeled parental DNA chains according to replication mechanism of Delbrück (with breaks) and alternative (without breaks)

> It is an important implication of the proposed mechanism that the chains of the daughter-duplexes consist of alternating sections of parental and assimilated nucleotides, each section with an average length of five nucleotides. If a labeled duplex replicates repeatedly at the expense of an unlabeled pool, then, according to this model, the label will be statistically equally distributed to the daughter-duplexes at *each successive replication*. Without the breaks and reunions the distribution of label would occur only at the first replication. At each subsequent replication one daughter-duplex would receive all of the label, the other none.[97]

Delbrück illustrated these alternatives with the scheme shown in figure 1.3.

Delbrück did not indicate what kind of label might be attached experimentally to a DNA duplex to test these implications, but it is hardly coincidental that he referred in the sentence following the

quoted passage to experiments by Gunther Stent on "the mortality due to the decay of incorporated P^{32} of phage infective centers at various stages of the reproductive center." From the relation between the rate at which bacteriophage incorporating ^{32}P are killed and the inherent rate of the decay reaction $^{32}P \rightarrow {}^{32}S$, Stent had inferred in 1953 that the "cause of death" must be the disruption of the DNA molecule by the disintegration of a ^{32}P atom contained in its polynucleotide chain. That the "efficiency" of killing—that is, the ratio between the number of disintegrations and deaths—was only 1/12 or less Stent thought might be explained in part by the likelihood that only a fraction of the disintegrating ^{32}P atoms cause a break in the polynucleotide chain, and in part, as he had suggested at the Cold Spring Harbor Symposium, because "if DNA is an intertwined, interlocked double strand, as proposed by Watson and Crick, it is not inconceivable that the molecule could sustain loss of an occasional phosphate link without being broken."[98]

Stent had made another point relevant to Delbrück's concern:

> We do not know to what extent the atomic identity of a parental molecule is preserved when it is being duplicated: do all the original atoms remain together in one structure and do, consequently, the atoms of the duplicate consist entirely of newcomers or are the parental atoms distributed over both structures at the end of the replication act? Experiments on the P^{32} mortality during duplication offer a clear operational distinction between these alternatives: If the atoms of the parent structure remain together and the duplicate contains only material synthesized *de novo,* then mortality due to P^{32} atoms incorporated into [the] parent molecule must come to a stop as soon as the first duplicate is finished. If, on the other hand, the parental atoms are equi-distributed among the two daughter structures, then P^{32} mortality would continue after duplication with one half the ultimate rate of death of the original structure before duplication.
>
> The possible non-synchronism of duplication of different parts of the parental phage DNA unfortunately obscures the conclusions which might be drawn . . . concerning this question, the answer to which would be of capital importance to an understanding of the replication mechanism.[99]

Stent reported to Delbrück in March 1954 that his experiments were "going very slowly" but that he had "a theory now to account for the factor of 1/12 of the efficiency of P^{32} death": "The idea is based

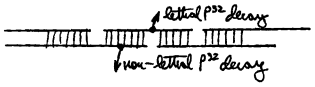

Fig. 1.4. Interrupted chains of Schachman and Dekker, drawn by Gunther Stent

on the interrupted chains of Schachman and Dekker and simply considered to be the probability that the P^{32} decay occurs in a nucleotide at a spot not sufficiently close on one chain to a spontaneous break on the sister strand that the 'point heat' generated by the decay overcomes the resistance of any hydrogen bonds which might be still in the way and causes a complete rupture of the double helix"[100] (figure 1.4).

The possibility that the polynucleotide chains of DNA molecules contain breaks was clearly pertinent to the replication question. Evidently Delbrück did not welcome this news, however, because he wrote to Stent somewhat later asking for an " 'unprejudiced' account of the interrupted DNA chains." Along with a long letter he sent a manuscript of his replication paper.[101]

Stent replied on 11 May, reporting that "Howard Schachman presented his ideas at the National Academy meeting a couple of weeks ago and, rightly or wrongly, they were greeted with general approval by Crick, Todd, and other hot shots, as just the sort of thing that *ought* to exist." Stent summarized the "pretty convincing" evidence, from titration data, heat degradation, and the action of DNAase, from which Schachman had concluded that the polynucleotide chains of purified DNA in solution are interrupted.[102]

Stent stressed that all of these data pertained only to solutions of purified DNA. "The only *in vivo* 'evidence' is the minimum P^{32} killing efficiency of 1/20 which I attribute speculatively to decay in apposition to spontaneous breaks, with the corollary that the DNA *can* support a large number of non-lethal breaks as those induced by radioactive decay." This was essentially the theory that Stent had outlined to Delbrück in his previous letter. "I wonder why you find the interrupted chains so unappealing?" he now added; "it would make the uncoiling problem much less formidable. As you guessed correctly, I was rather more excited by your ideas on replication than by the cofactor renaissance. The manuscript seems very ingenious to me, and I will write to you about it in more detail soon."[103]

It is not hard to discern why these interrupted chains did not ap-

peal to Delbrück. To envision polynucleotide strands of molecular weight 10^4 unwinding would be no less inelegant to him than to imagine the process extending over the entire molecule. His scheme assumed that breaks and reunions were integral to the process of replication and that they took place at every turn of the helix, corresponding to a molecular weight of about 650. Preexisting breaks at longer intervals along the chains were of no help to him.

Stent had further news concerning his own work that was not exactly favorable to Delbrück's scheme: "Right now, I'm snowed under with work, since I'm trying real hard to get an answer quickly to this distribution-of-atoms-during-duplication question. My preliminary idea at present is that they are *not* distributed, but that final experiment which was supposed to have clinched everything doesn't seem to want to come out right."[104]

Stent mailed his letter on 11 May, and Delbrück's paper on the replication of DNA was communicated to the *Proceedings of the National Academy of Sciences* on 18 May. It is not certain, therefore, that Delbrück read Stent's comments before sending off his manuscript. In any case he did not allow the idea of interrupted chains or Stent's preliminary idea that the atoms are not distributed during duplication to deflect him from proposing a mechanism that had no room for either phenomenon. In his paper he simply commented, "At present it does not seem possible to discuss the bearing of this implication [that is, of the distributions of atoms that would result from his mechanism] on the experiments of Stent. . . . These mortality experiments are complicated by the phenomena of multiplicity reactivation, i.e., an interaction between different duplexes, the nature of which is uncertain."[105] If Delbrück did have in mind Stent's latest view on distribution, then his remark is a little puzzling; these complications would involve recombination events and would be more likely therefore to contribute to a misleading appearance of distribution than to a misleading appearance of nondistribution. For Delbrück the formal elegance of his mechanism seems to have been an overriding consideration.

Watson was not persuaded by Delbrück's proposed mechanism. Rather, it is a prime example of what he had in mind when he remarked that Delbrück lacked "biological intuition."[106] We may note that predictions about the shape of a future solution involve multiple levels of judgment. In this case the problem itself was a product of the compelling nature of a solution that had been around for only a

Fig. 1.5. James Watson at Cold Spring Harbor, 1953. Photo courtesy of the Archives, Cold Spring Harbor Laboratory.

short while. Base pairs set the parameters within which one could now discuss replication, but the structure that held the base pairs provided the obstacle to understanding just how that replication could take place without everything getting tangled. Watson judged that the separation problem was solved in principle and that one need not worry yet about how it could be solved in specific detail. Delbrück judged this to be a pressing problem and sought to overcome what he

Fig. 1.6. Max Delbrück at Cold Spring Harbor, 1953. Photo courtesy of the Archives, Cold Spring Harbor Laboratory.

had formerly seen as the insuperable difficulty of unwinding a plectonemic coil by postulating a process of breaks and reunions for which he had no direct evidence.

Aesthetic criteria played a strong role in the judgments of both Watson and Delbrück. Just as Delbrück preferred his scheme because, even with all the breaks and reunions, it seemed to him more elegant and efficient than any unwinding scheme he could imagine, so Watson was content with a metaphorical zipper-like stand-in for a specific separation mechanism in part because the beauty of the double helix gave him confidence that eventually some satisfactory means to separate its strands would be discovered.

On the other hand, judgments of beauty and elegance in science are not independent of evaluations of the strength of the supporting evidence. The beauty of the double helix does not inhere only in the imposing structure of a physical model, or in schematic drawings that enable one to visualize it, but also in the sense of beauty that the scientist can discern in the harmonious fit between the many coordinates of the atoms of the molecule and the parameters set by X-ray patterns and base pair ratios. Even in the spare formality of Delbrück's replication scheme the elegance one can discern lies in large part in the fit between his diagrams and the requirement of the Watson-Crick model that the two polynucleotide chains run in opposite directions.

Even when connected to critical evidence, judgments involving beauty, elegance, or efficiency are inevitably also subjective. Delbrück's paper not only presented an elegant scheme but offered, in principle, a clear-cut, objective test that could decide between it and the alternative that he personally rejected. All that was required was the ingenuity to find out how one might label the strands of a DNA duplex in such a manner that one could actually trace the distribution of their "atoms" into daughter duplexes.