Introduction

This book was written for scientists of all kinds. It is unapologetically historical. But, you say, the world of biology is rocketing ahead at a pace undreamed of even a decade ago. The advancing technological age in biology that began roughly 35 years ago with the “recombinant DNA revolution” now presents a daily mountain of new information. So why be so misguided in the midst of this whirlwind of the new as to turn out a history? And why a history of RNA?

Consider this: How in the next couple of decades are newcomers to biology going to learn, and how and what are established scientists going to teach them? Already, virtually all college-age students have had exposure, often since grade school, to the mantra “DNA makes RNA makes protein.” In this computer age, the notion that biology is an information science and that DNA is the library seems a congenial concept to most who are inclined toward an analytical/scientific career. Perhaps the sensible and necessary course to properly prepare declared biology students and analytically trained “transfers” (mathematicians, physicists, engineers) is first to serve up a predigested catechism of settled conclusions achieved in the 20th century by “wet” laboratory experiments. With this concise biological “periodic table” under command, the newcomer then can be efficiently prepared to deal with the rapidly advancing technology both for doing experiments and for collecting and analyzing to a useful purpose the enormous quantity of data that emerges from today’s genomic, proteomic, and computationally enhanced microscopic investigations.

It is by no means my intent to deflect teachers/scientists (mostly young, under 40 years of age) who must carry out the indispensable task of getting students ready to enter today’s biology world. Rather, my aim in writing this
book is to provide a supplement in historical form—both to the younger generation of scientists and teachers and through them to incoming students—that describes how we first learned some of the molecular fundamentals of biology in the days of the “hands-on wet laboratory.”

One can legitimately argue whether a 2011 biology student “needs” to know any pre-1990 history. I am not prepared to defend vigorously the affirmative in this debate. But I will argue that many may choose to know how we came to know all that we did in the era before commercial kits and genomic sequencing took hold. Many of today’s major questions (e.g., about how messenger RNAs [mRNAs] are formed and about how gene control is exercised in eukaryotes) are the same questions that were pursued in 1962–1980. More detailed answers to these questions are arriving today at breathtaking speed, but fundamentally informative and important answers came between 1962 and the early 1980s. How these still-central questions first arose, and how early experiments were structured and answers obtained, it seems to me, ought to be at least available in usable form for teachers and, most of all, the curious students of today.

I have been privileged to listen in on a number of “after hours” (read “faculty club cocktail hour”) discussions among physicists. Both elders and youngsters in that community seem able to discuss where ideas, questions, and answers came from, easily back to Maxwell and his equations. Biological science, specifically the role of RNA in current and past life on this planet, also has a history worth knowing, I believe.

This history begins with the following questions: How did macromolecules finally become recognized as the necessary starting place for first learning about biology and now teaching biology? And why was RNA the latecomer in this overall picture?

The bold discovery by James Watson and Francis Crick of the structure of DNA, often told, and well told, by the protagonists themselves, is frequently recited as the “start” of molecular biology. And if one watershed discovery is to be chosen as the “beginning,” that discovery is it. But there was a preceding half-century struggle of genetics and physical biochemistry that prepared at first a small group of scientists to grasp what the Watson-Crick structure both predicted and demanded but did not answer. For the discovery of the DNA structure and following discoveries to occur, biology/biochemistry had to take on macromolecules. The reign of organic chemistry (and recalcitrant organic chemists) as the main route to understanding life had to be at least momentarily sidestepped so that large molecules, poorly understood and comparatively difficult to study, could become the major research focus. How molecular biology involving macromolecules emerged from these early 20th-century battles is fascinating history.
The double helix discovery instantly revealed, through what Crick in his book *What Mad Pursuit* called “such a beautiful structure” (p. 60), how the molecule worked in inheritance. But the Watson-Crick revelation also lit the fuse that led to uncovering the centrality of RNA to life. The miracle years of 1955–1961—just 50 years ago—finally saw RNA recognized to be not monolithic but a collection of different types of molecules with specific functions. Courtesy of the insight of François Jacob and Jacques Monod, biological specificity among different cells, formally a completely opaque problem, could now at least provisionally be explained by controlling the synthesis of specific mRNAs.

The establishment of RNA function—first by discovering how genetic information is transferred into a readable form and then by proving the intimate roles of RNA in translation—led shortly to deciphering the universal genetic code, the first breakthrough toward which Marshall Nirenberg carried out in 1961. But all of these heady achievements were accomplished (largely) with bacteria and their viruses.

As biologists took these ideas to eukaryotic cells, first with cultured human cells, RNA remained the major focus. Throughout the 1960s and 1970s, a new world of macromolecular genetics was unearthed through studies of eukaryotic RNA. Unknown at the time, storage of information in the DNA of eukaryotes was very different from that of bacteria. Simply copying DNA into RNA did not suffice for genetic function. Primary RNA transcripts required molecular carpentry of various kinds—generically termed RNA processing—to produce functional RNAs. This era culminated in 1977 with the discovery of pre-mRNA splicing to produce functional mRNA. Both the complicated machinery for digging out the primary transcript as well as the processing to make a specific mRNA opened our eyes to additional points at which regulation of mRNA might occur. All of this was well established before facile genomic sequencing confirmed these conclusions.

Soon thereafter (1979–1981), a second bombshell burst. Chemical catalysis can be performed by pure RNAs, most often held in the proper tertiary structure inside cells by protein scaffolds. These major new concepts largely dealing with making and controlling functional RNAs also preceded the era of rapid DNA sequencing.

The young student of today or their youngish mentors can hardly be blamed for knowing very few details of this era, which ended before they were born (in case of students) or before they had finished their first decade or had begun their college years (in the case of young professors). The intellectual sweep of these many achievements before the early 1980s would, of course, be available by reading a selected sample of the hundreds of original papers from 1960 to 1980. But a relatively abbreviated historical discussion
told from the point of view of a long-interested RNA biochemist has been unavailable. This is what compelled me to assemble the material in this book. I note here that I began working with the RNA of poliovirus in the late 1950s in the laboratory of Harry Eagle at the National Institutes of Health. This was followed by a year (1960–1961) with François Jacob at L’Institut Pasteur at the time when the concept and proof of mRNA were just being described (although I had absolutely nothing to do with these landmark experiments). However, my own laboratory work was, and still is, directed by these early very fortuitous training experiences and perhaps will help the reader to forgive the personal voice that appears in various spots throughout the book.

Chapter 1 presents early discoveries that were not fitted into an understandable fabric of cell function for decades. For example, more than 100 years ago, organic chemists were able to identify all of the nucleobases, even placing uracil only in “yeast” nucleic acid (aka RNA) and thymine only in “nuclein,” later “thymus” nucleic acid (aka DNA). However, only in 1920 was deoxyribose finally identified as the sugar in DNA.

The peptide bond was described and accepted as the most probable link among amino acids by 1902. But a long disputatious history of the molecular nature of proteins followed, literally until after World War II. How could scientists of 1950 begin to think of cells making proteins by uniting amino acids in the correct order (step by step and therefore uncovering RNA functions) until after 1951, which brought Linus Pauling’s models of the α-helix and Fred Sanger’s sequencing of the first chain of insulin?

The monumental accomplishments of George Beadle and Edward Tatum in showing that genes were responsible for the function of individual proteins (enzymes) and the discovery of DNA as the genetic material by Oswald Avery, Colin MacLeod, and Maclyn McCarty are stories that preceded Watson and Crick and are known by many at least in outline. But a recitation of exactly what experiments these heroes performed does not trip lightly off the tongue of the majority of today’s biologists, young or old.

Therefore, in diplomatic language, after “frank discussions” with my editors, and with the support of many colleagues who have read early versions of the book, Chapter 1 presents some of this history of the centrality of macromolecules, with my hope that, at the very least, it will be entertaining.

Chapter 2 needs no such defense. If we were going to have a history of RNA, it was obligatory to recount the signal achievements of the 1950s–1960s that finally brought RNA out of the shadows. On reflection, viruses with only RNA as a genome were obvious candidates to first catch attention for the genetic/biochemical importance of RNA. This proved to be the case,
with TMV (tobacco mosaic virus) and the RNA formed after T-even (T2, T4) bacteriophage infection of *Escherichia coli* leading the way.

Although the gene/protein connection was made in the 1940s, it took in vitro protein synthesis by rat liver extracts, largely carried out by Paul Zamecnik and colleagues, to begin to truly connect proteins and RNA in 1953–1958. These years saw the discovery of transfer RNA (tRNA) and established a role for ribosomes (and presumably their RNA) in making proteins. Given these advances, it remains something of a puzzle as to why it took so many remarkably gifted scientists so long after the Watson-Crick structure (≏7 years) to hit intellectual and molecular pay dirt with the idea of and discovery of mRNA. This is one of the most intriguing stories in the history of molecular biology. The secret lay in closer attention to the genetics of gene regulation that explained switches in the proteins that the cell made. Making mRNA in a controlled fashion in the test tube was then accomplished with bacterial systems in the late 1960s and early 1970s. Discussion of all these accomplishments constitutes Chapter 2.

Chapter 3 guides the reader stepwise through achievements that unlocked the universal genetic code. Virtually all biology students and many from other disciplines will know the conclusions of this era. The aim, however, is to put some experimental meat on the bones of the catechism symbolized by “DNA makes RNA makes protein.” The clarity of these conclusions led Gunther Stent, a physicist turned biologist, to title a 1968 paper in *Science* “That Was the Molecular Biology That Was,” in which he seemed to argue it was all over but the shouting.

The stunning achievements on bacterial gene functions were the logical takeoff point for beginning to work toward understanding how eukaryotic cells controlled their genes and performed such tricks as differentiation. Chapter 4 picks up this problem that began, however, with several years of inability to define mRNA in eukaryotic cells. Kinetic studies following incorporation of labeled RNA precursors into properly separated classes of RNA in cultured animal cells and in animal cells infected with DNA viruses finally wrestled this problem to the ground. Processing of preribosomal RNA (pre-rRNA) was uncovered by 1962–1963 and processing of pre-tRNA by 1968, but RNA processing to make mRNA was not completely understood until the final details of splicing of adenovirus pre-mRNA into mRNA were discovered in 1977. This ≏15-year period (1962–1977) is recounted in detail in Chapter 4. Also described in this chapter are the initial discoveries of the biochemistry of the three eukaryotic RNA polymerases and the original illustration of the complexity of nuclear factors required to initiate RNA synthesis correctly in cultured human cells and cell-free systems.
Between the discovery of RNA splicing in 1977 and the early 1980s, additional astonishing discoveries occurred. The capacity of RNA to perform enzymatic functions was recognized. Also, the involvement of previously unknown small ribonucleoprotein particles (in particular, their RNA) in carrying out splicing to make mRNA was discovered. These topics are also introduced in their appropriate historical frame in Chapter 4.

Finally, complementary DNA (cDNA) cloning and pulse-labeled nuclear RNA allowed the measurement of the rate of synthesis of individual genes, which clinched the previously widely assumed, but not yet proven, primary control of gene expression at the level of transcription.

The end of Chapter 4 marks a dividing point in the book. A reasonably comprehensive historical accounting of important events in which RNA is the chief actor ends.

Chapter 5 is an attempt to provide a useful summary of important events in work on RNA after the early 1980s. Because the regulation of mRNA is the central event in all biological specificity, a discussion of the arcane array of proteins that control regulated transcription of chromatin is the first order of business. The positively required factors for the initiation and manufacture of an mRNA from pre-mRNA had first to be understood. This allowed more recent proofs of the wide variety of negative-acting proteins and protein complexes in preventing initiation and of the details of differential pre-mRNA processing, also a regulated process.

The most recent stunning advances in regulation of mRNA translation efficiency and lifetime have come from discoveries of yet more and different RNA molecules, both short and long noncoding RNAs. How these were uncovered and initial insight into how they function are products of research in the last ~15 years, and new discoveries and insights into noncoding RNAs continue with each new journal issue. A running summary, necessarily incomplete, of all this experimental activity brings up the rear of Chapter 5. No attempt is made (even if it could have been) to be comprehensive in the material of Chapter 5. Rather, important areas are included with discussion of some key discoveries, and up-to-date references are provided. The shelf life of all of these new findings makes discussions about them admittedly problematic. But no attempt to describe a history of RNA could fail to include a digest of this recent material.

Chapter 6 is brief and highlights, first, a research area that looks back on 3 billion plus years to how RNA likely had an indispensable role in initiating life on the planet. Organic chemical and geochemical advances are being made that may enlighten us about events in the Archaean era. This is possibly the most difficult of all areas in biology, but it no longer seems the impossible field that it did a couple of decades ago.
Perhaps of equal difficulty is the tangled problem of the origin of cells. Challenges to the conventional wisdom of prokaryote → eukaryote evolution began with Carl Woese’s discovery of archaea more than 30 years ago and remains a fascinating, unsettled area today despite hundreds of genomic sequences of microorganisms. One of the most challenging unsolved problems in this area also centers on RNA. How and when did splicing of RNA arise—before or after cells arose? If we had an unambiguous answer to this question, might we not also better trace how the three cellular kingdoms arose and persisted? The evolution of cells is intimately tied to the idea of an initial RNA world, a hypothetical but increasingly probable time in the evolution of life. Given this likely history and considering the many functions of RNA in the cells of today, shouldn’t RNA share a wedge of the spotlight with DNA?
A sizeable number of colleagues read all or portions of this book at various times during its preparation. Most believed, as I did, that a book stressing the history of those phases of molecular biology centered on RNA was a sound and different idea and should produce a useful, even a needed, book. Early discussions with Shai Shaham, Paul Nurse, Sid Strickland, and Jan Breslow helped particularly in shaping the content of what was finally included. My gratitude to each of them.

As the project developed, I received positive encouragement, advice, suggestions, and corrections from a larger group. That list includes David Allis, Jan Breslow, Linda Chaput, Gene Cordes, Bob Darnell, Ford Doolittle, Jeff Friedman, Magda Konarska, Leon Levintow, Peter Model, Tom Muir, Paul Nurse, Lennart Philipson, Bob Roeder, Marjorie Russel, Shai Shaham, Sid Strickland, Jon Warner, and Mike Young.

To all of those friends and colleagues I offer my sincerest gratitude. For the remaining errors and especially for the omitted or neglected references (despite \( \sim 1000 \) included references), the responsibility remains with me.

Initial discussions with John Inglis, the Executive Director of Cold Spring Harbor Laboratory Press, were extremely encouraging and helpful in solidifying the purpose of what is presented. The Cold Spring Harbor Laboratory Press has a staff exceptionally gifted in publishing scientific works, and I am eternally grateful to all of them: in particular, Inez Sialiano, Project Manager, and Rena Steuer, Production Editor, who among many other wise contributions arranged to make figures taken from older articles readable. I especially thank Maria Smit, the Developmental Editor. I’ve had considerable experience in biology textbook writing and publishing but have never had anything approaching the skillful and thoughtful editorial help I’ve received on this book. Lois Cousseau, my assistant for more than 30 years,
merits very special thanks. Nothing I’ve written in all this time, all beginning in longhand, would have ever appeared without Lois’s cheerfulness, patience, and extraordinary competence. Even the most heartfelt thanks seem insufficient.

Finally, this labor of love was supported with my wife Kristin’s unflagging confidence and belief that I could do it.
Index

Page references followed by f denote figures.

<table>
<thead>
<tr>
<th>A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abelson, John, 202, 207</td>
</tr>
<tr>
<td>Abrams, Richard, 171–172</td>
</tr>
<tr>
<td>Adaptor hypothesis, 102</td>
</tr>
<tr>
<td>Adenine, 31</td>
</tr>
<tr>
<td>Adenosine triphosphate (ATP), 31, 70</td>
</tr>
<tr>
<td>Alanine, 12</td>
</tr>
<tr>
<td>Albert Einstein College of Medicine, 163</td>
</tr>
<tr>
<td>Alexander, Hattie, 49</td>
</tr>
<tr>
<td>Allfrey, Vincent, 265</td>
</tr>
<tr>
<td>Allfrey-Mirsky laboratories, 157</td>
</tr>
<tr>
<td>Allis, David, 266</td>
</tr>
<tr>
<td>Alloway, J. Lionel, 42–43</td>
</tr>
<tr>
<td>Alpher, Ralph, 101–102</td>
</tr>
<tr>
<td>Altman, Sidney, 202, 204, 352</td>
</tr>
<tr>
<td>α-Amanitin, 208, 210, 218</td>
</tr>
<tr>
<td>Ambros, Victor, 312</td>
</tr>
<tr>
<td>Ames, Bruce, 86</td>
</tr>
<tr>
<td>Amino acids, 12–14, 73–75, 108–109, 353</td>
</tr>
<tr>
<td>Ancient Earth, Ancient Skies: The Age of Earth and its Cosmic Surroundings, 366</td>
</tr>
<tr>
<td>Anfinsen, Christian, 72</td>
</tr>
<tr>
<td>AraC gene, 124</td>
</tr>
<tr>
<td>Archaean Earth. See RNA and the beginning of life</td>
</tr>
<tr>
<td>Acritarchs, 367</td>
</tr>
<tr>
<td>Argonaute family, 321</td>
</tr>
<tr>
<td>Asparagine, 12</td>
</tr>
<tr>
<td>Astbury, William T., 24</td>
</tr>
<tr>
<td>Astrachan, Lazarus, 64, 66, 76, 91, 152</td>
</tr>
<tr>
<td>ATP (adenosine triphosphate), 31, 70</td>
</tr>
<tr>
<td>Atwood, Kim, 163</td>
</tr>
<tr>
<td>Austrian, Robert, 42, 43</td>
</tr>
<tr>
<td>Avery, Oswald, 4, 41–42, 43, 44–45, 47</td>
</tr>
<tr>
<td>Avery, Roy, 45</td>
</tr>
<tr>
<td>Ayala, Francisco, 381</td>
</tr>
<tr>
<td>B</td>
</tr>
<tr>
<td>Bachenheimer, Steve, 189</td>
</tr>
<tr>
<td>Bacterial conjugation, 40</td>
</tr>
<tr>
<td>Bacteriophages, 64–66, 81–83</td>
</tr>
<tr>
<td>Baltimore, David, 175, 176</td>
</tr>
<tr>
<td>Banerjee, Amiya, 180</td>
</tr>
<tr>
<td>Barnett, Leslie, 109</td>
</tr>
<tr>
<td>Barrell, Bart, 370</td>
</tr>
<tr>
<td>Bartel, David, 321, 358</td>
</tr>
<tr>
<td>Bateson, William, 34</td>
</tr>
<tr>
<td>Baulcombe, David, 317</td>
</tr>
<tr>
<td>Bawden, F.C., 61</td>
</tr>
<tr>
<td>Beadle, George, 4, 38, 39–40, 58</td>
</tr>
<tr>
<td>Beaumont, William, 12</td>
</tr>
<tr>
<td>Belozersky, Andrei, 76</td>
</tr>
<tr>
<td>Benjamin, Tom, 170</td>
</tr>
<tr>
<td>Benner, Steve, 354</td>
</tr>
<tr>
<td>Benzer, Seymour, 109, 130</td>
</tr>
<tr>
<td>Berg, Paul, 74</td>
</tr>
<tr>
<td>Berget, Susan, 192</td>
</tr>
</tbody>
</table>
Bernal, J.D., 24, 25
Bernhardt, Deborah, 168
Berzelius, Jöns Jacob, 11, 22
Bird, Adrian, 289
Boveri, Theodor, 33
Boyer, Herb, 41
Brachet, Jean, 9, 10, 67
Bragg, Lawrence, 19–20
Brawerman, George, 172
Brenner, Sydney
C. elegans work, 311, 314
genetic code work, 102, 104, 109, 113–114
mRNA existence contributions, 89–90, 91
Bridges, Calvin, 35
Britten, Roy J., 168
Broker, Tom, 192, 194, 196
Bronson, H.R., 26
Brown, Carolyn, 325
Brown, Daniel M., 58
Brown, Don, 163, 211
Browne, Janet, 370
Brownlee, George, 370
Büchner, Eduard, 22
Buick, Roger, 368
Burdon, Roy, 168
Burley, Stephen, 258
Busch, Harris, 201

C

Caenorhabditis elegans
injected dsRNA triggering of mRNA suppression, 314, 316
lin4 and lin14 and RNA:RNA regulation, 312–314
number of miRNAs in, 318
programmed cell death discoveries, 311–312
Cairns, John, 41
Calcitonin/CGRP, 303–304
CAP protein, 126–127, 129
Carboxy-terminal domain (CTD), 274–275
Carlson, E.A., 35
Carothers, Wallace, 21
Carrel, Alexis, 143–144, 148
Caspersson, Torbjörn, 9, 37, 67
Catabolite repression and the CAP protein, 126–127, 129
Cavendish laboratory, 20
Cech, Tom, 202, 205, 352, 382
Cellulose, 21
Chambon, Pierre, 197
Chang, Howard, 327
Chargaff, Erwin, 48–49, 76
Chase, Martha, 50
Chibnall, Albert Charles, 28
Chow, Louise, 192, 194
Chromatin immunoprecipitation (ChIP), 267–268
Chromatin-modifying factors, 285–288
Chromosomes
early chemical analysis, 37–38
fly genetics work in Morgan’s lab, 34–37
heredity role discovery, 33–34, 35
recognition of a role in heredity, 31–32
Chymotrypsin, 23
Ci (cubitus interruptus) proteins, 283
Cinnabar, 38–39
Claude, Albert, 67, 69
CLIP (cross-link immunoprecipitation), 268
Cohen, Stanley, 41, 58
Cohesin, 274
Cold Spring Harbor Symposium, 95, 104, 196
Corey, Robert B., 9, 25, 58
Correns, Carl, 33
Cox, Ronald, 218
Crane-Robinson, Colyn, 265
Crick, Francis, 2, 3
genetic code work, 104, 109, 118
mRNA existence contributions, 89–90
paper on the adaptor hypothesis, 102
papers on RNA, 352
pre-double-helix work, 13, 49, 51
structure of DNA and, 57
theory of the adaptor, 75
Cross-link immunoprecipitation (CLIP), 268
Crowfoot, Dorothy, 24
CTD (carboxy-terminal domain), 274–275
Cubitus interruptus (Ci) proteins, 283
Cyclic AMP (cAMP), 126
Cyclol theory, 24–25
Cytosine, 30

D
Dalrymple, G. Brent, 366
Darnell, James
  adenovirus-infected cell experiments, 189
  cultured animal cell work, 151–152
  poly(A) discovery and work, 172, 173, 180, 184
  polyribosomes experiments, 158, 160–162
  recovery of long RNA molecules in HeLa cells, 153
  UV transcription mapping use, 190–192
  work with Eagle, 149
Darnell, Robert, 304
Darwin, Charles, 365
Davern, Rick, 90
Davidson, Norman, 193, 194
Davis, Ron, 193
Dawson, Martin, 42–43
DBD (DNA-binding domain), 244
Delbrück, Max, 45, 50, 151
DeMars, Robert, 109
Deoxyribose, 31, 44
de Vries, Hugo, 33
Dicer complex, 319
Dickerson, Richard E., 18, 23
Dintzis, Howard, 120–122, 158
DNA
  C-value paradox, 138–139
  definition of promoter sequences, 127, 128f, 129
  discovery by Miescher, 30
  DNA-binding domain, 244
  growing base of knowledge in 1950s, 57–58
  introns and exons in sequences, 199–200
  lack of appreciation of the length of, 41
  methylation as an epigenetic state, 290–291
mRNA manufacture control and, 246, 258, 260, 283, 285
nucleic acid bases discovery, 30–32
obstacles to acceptance of as the active agent, 47–49
phage school’s acceptance of, 50–51
purification of deoxyribonuclease, 46
sequence in related discoveries, 29–30
structure discovery, 57
DNA, The Secret of Life, 50
DNA-binding domain (DBD), 244
Doolittle, Ford, 372
Doty, Paul, 92, 153
Double Helix, The, 49
Double helix discovery, 2–3
Dounce, Alexander, 72
DRB and transcriptional elongation, 275–277
d-Ribose, 31
Drosha, 319
Drosophila melanogaster
  ChIP assays information, 268, 269
  Ci transcription factor, 283
  C value, 139
  Dscam, 295–296
  experiments showing rRNA was copied from ribosomal DNA, 163–164
  eye color studies, 38–39
  gene regulation studies using, 245–248
  genetics studies in Morgan’s lab, 34–37
  Groucho repressor protein, 285–286
  heat shock genes transcription, 277–282
  number of miRNAs in, 318
  piwi gene, 322
  Polycomb group, 287
  pri mutations, 332
  R-loop studies using, 193–194
  sex determination in, 303, 304f
  TFIID complex, 255–256
dsRNA triggering of mRNA suppression, 314, 316
Dujon, Bernard, 382
Dubbecco, Renato, 150–151, 170
du Vigneaud, Vincent, 15

E
Eagle, Harry, 4, 147–150, 163
Eagle’s Medium, 148–150
Earle, Wilton R., 144–145, 148
Eddy, Bernice, 170
Edman protein degradation technique, 28
Edmonds, Mary, 171–172
Eighth Day of Creation, The, 49, 91
EJC (exon junction complexes), 306, 309
Enders, John F., 146
Endosymbiosis, 378–379
Englesberg, Ellis, 124
Enhanceosomes, 248–249, 250f
Enzymology, 21–23
Ephrussi, Boris, 38, 58
Epigenetics and transcriptional control
DNA methylation as an epigenetic state, 290–291
H3K4me3 directed to TSSs, 292, 294–295
Polycomb and heterochromatin repression as modifications, 291–292, 293–294f
term meaning, 288–290
E. coli, 40–41
Eukaryotic RNA
colinerarity and, 200
C-value paradox, 138–139
differential poly(A) and splicing, 197–199
eukaryotic/bacterial divide, 200–201
exploration of an mRNA function in eukaryotes, 138
first continuous cultured animal cell line, 144–145
first continuous growing human cell culture, 145–146
genes in pieces concept, 196–197
hnRNA-to-mRNA processing evidence search, 168–169
introns and exons in DNA sequences, 199–200
investigation of transfer of nuclear RNA to the cytoplasm, 139–142
m7 “cap” and poly(A) tails on long hnRNAs
argument against processing to make ovalbumin mRNA, 182–183
connection between HeLa cell mRNA and hnRNA, 180
potential globin mRNA precursor, 181–182
use of both ends of hnRNA, 180–181
m7GpppN “cap,” 178, 179f, 180
methylation in mRNA, 177–178
molecular steps in information transfer, 142
poly(A) tail
added to hnRNA in the cell nucleus, 173–174, 175f
discovery of, 171–172
on hnRNAs, 180
identification as part of polysomal mRNA, 172–173
splicing and, 197–199
use in mRNA purification, 175–176
polyribosomes and animal cell mRNA
discovery
HeLa cell mRNA size and base composition determination, 160–162
identification of HeLa cell mRNA, 160
polyribosomes revealed through reticulocyte extracts, 158–159
question of ribosomal density on mRNA, 157–158
processing of large nuclear RNA into mRNA
adenovirus-specific nuclear RNA and mRNA properties, 183–185
discovery of RNA–RNA splicing, 192–193
mapping sites of origin of adenovirus mRNAs, 185–186
mapping the primary transcript precisely, 186
nascent chain transcript mapping, 186–190
R loops, 193–196
UV transcription mapping, 190–192
processing of tRNA precursors to tRNA, 166, 168
proof that human cell cultures could be made, 143–144
relating specific sequences in mRNA and hnRNA, 169–170, 171f
reproducible growth of mammalian cells and viruses
cloning of mammalian cells by Puck, 150
development of Eagle’s Medium, 148–150
quantitative animal virology work by Dulbecco, 150–151
RNA chemistry after discovery of splicing
RNA-directed RNA cleavage, 202–204
self-splicing RNA, 204–207
spliceosome for testing snRNPs, 201–202, 203f
splicing of pre-tRNA, 207
RNA polymerases and GTFs
adenovirus as the first in vitro Pol II template, 212–214
GTFs complexity recognition, 214–216
identification of three enzymes, 208–210
Pol III template, 211–212
RNA initiation using Pol II and Pol III, 210–211
search for mRNA in cultured animal cells
efforts to study animal RNA, 152
long RNA molecules in HeLa cells and, 153–155
nature of briefly labeled RNA, 157
RNA processing recognition through ribosomal precursor RNA, 155–157
separation of pre-rRNA from hnRNA by nuclear fractionation, 163–166, 167f
transcriptional control in eukaryotes
basic questions about, 216
hormone-dependent increases of specific mRNAs, 218–221
run-on transcription assays and, 217–218
virus production in primary cultured animal cells, 146–147
Evans, Ron, 189, 212
Exon junction complexes (EJCs), 306, 309

F
Ferat, Jean-Luc, 383
Feulgen, Robert, 67
Fire, Andrew, 314, 316
Fischer, Emil, 14–15, 18–19, 31
Flavell, Richard, 196
Flemming, Walther, 33
Flint, Sarah Jane, 185
Focused promoters, 241–242
Formation of Colloids, The, 20
Fox, George, 370
Fraenkel-Conrat, Heinz, 62, 64, 108, 152
Fraser, Nigel, 189
Fritz-Laylin, L.K., 374
Fruton, Joseph, 19

G
β-Galactosidase, 77–81, 83–86
Gall, Joe, 204
Gallimore, Phil, 185
Gamow, George, 101–102
Garen, Alan, 89, 114
Garen, Susan, 89
Gelinas, Rich, 192
Gemmatata obscuriglobus, 380
Gene expression in mammalian cells. See Eukaryotic RNA
General transcription factors. See GTFs (general transcription factors) and RNA polymerases
Genetic code
chromosomes’ role in heredity discovery, 33–34, 35
Genetic code (continued)
colinerarity of genes and proteins problem, 130
definition of promoter sequences in DNA, 127, 128f, 129
everal chemical analysis of chromosomes, 37–38
first identification of a genetic disease, 103
first use of word gene, 34
fly genetics work in Morgan’s lab, 34–37
hemoglobin studies results, 103–104, 105f
history of ideas regarding, 101–102
Mendel’s discoveries and, 32–33
polyribonucleotides used to designate codons, 110–112
protein synthesis direction work by Dintzis, 118, 120, 121f, 122
protein synthesis work by Nirenberg decision to remain at NIH, 104, 106
discovery that nucleotides encode amino acids, 108–109
techniques used to develop a system, 106–108
regulated RNA polymerase action requirement, 124–125
RNA polymerase composition, 127, 128f, 129
RNA polymerase discovery, 122–124
search for more positive-acting transcriptional proteins
catabolite repression and the CAP protein, 126–127, 129
cell-free gene regulation and, 126–127
start and stop signals
start codon AUG and initiator tRNA, 115
termination signals and nonsense codons, 113–115
universality of the code, 115–116
sum of knowledge by end of 1960s, 130–132
synthesis of ordered RNA templates by Khorana, 112–113, 114t
triplet code proof, 109–110
tRNA reading of the mRNA code process of information transfer, 118, 120f
tRNA’s anticodon loop, 116, 117f
“wobble” hypothesis, 118, 119f
Geological record and early cellular life acritarchs, 367
geochemistry and early cellular life, 368
global samples dating, 366
microfossils interpreted as bacteria or archaea, 366–367
present-day geographic distribution of life and, 365–366
Georgiev, Georgii, 152, 157, 166
Germ plasma theory, 33
Gey, George and Margaret, 145, 147
Gierer, Alfred, 62, 152, 159
Gilbert, Walter, 125, 127, 199
Glycine, 12
Goldberg, Seth, 190
Gortner, Ross, 18
Gottschling, Dan, 289
Graham, Thomas, 18
Granboulan, Nicole, 166
Grewal, Shiv, 288
Griffith, Fred, 41
Gros, François, 91, 92
Groucho/TLE repression, 285–286
Grunstein, Michael, 265
GTFs (general transcription factors) and RNA polymerases adenovirus as the first in vitro Pol II template, 212–214
GTFs complexity recognition, 214–216
identification of three enzymes, 208–210
Pol III template, 211–212
RNA initiation using Pol II and Pol III, 210–211
Guanine, 31
Guo, Su, 314
Gurdon, John, 163, 249

H

H3K27me3, 325
H3K4me3/H3K36me3, 272, 281, 292, 294–295
H3K9me3/H3K27me3, 274, 292
Hackett, Perry, 190
Hall, Ben, 76, 92, 153
Hamilton, Andrew, 317
Hammarsten, Einar, 37, 38, 47
Harris, Henry, 140–141, 155
Harrison, Ross, 143
Hayes, William, 40
Heat shock proteins and factors, 245
Hebbes, Tim, 265
Hedghog pathway, 283
HeLa cells, 145–146, 147, 153–155, 160–162, 180
Helix-loop-helix (HLH) family, 283, 284f
Hemoglobin, 17, 20
Heppel, Leon, 108
Herpes simplex virus, 169–170, 171f
Hershey, Al, 50
Hertwig, Oscar, 33
Heterogeneous nuclear RNA (hnRNA)
DRB and transcriptional elongation and, 275–276
hnRNA-to-mRNA processing evidence search, 168–169
lncRNAs and, 324
m7 “cap” and poly(A) tails on long hnRNAs
argument against processing to make ovalbumin mRNA, 182–183
connection between HeLa cell mRNA and hnRNA, 180
potential globin mRNA precursor, 181–182
use of both ends of hnRNA, 180–181
Poly(A) tail added to in the cell nucleus, 173–174, 175f
separation of pre-rRNA from hnRNA, 163–166, 167f
Hfq (host factor for Qβ), 364
HIF (hypoxia-induced factor), 246
Histone demethylases, 271–272
Histones
acetylation
active transcription and H3K4 and H3K36, 272
connection to active transcription, 268–269, 270f
enhancers and chromatin loops, 273–274
histone demethylases, 271–272
histone modifications at enhancers, 272–273
histone-remodeling complexes and NFRs, 269, 271
trimethylation of H3K9 and H3K27, 274
chromatin formation and histone acetylation role in transcriptional control, 265–266
nucleosome, histone tails, and the solenoid, 263, 264
nucleosome blocking of transcription, 264–265
modifying enzymes and complexes, 266–267
History of biology
double helix discovery, 2–3
early discovery work on RNA, 3
genetic code work (see Genetic code)
purpose of learning about, 2
History of macromolecules before RNA
birth of enzymology
cell-free fermentation by Büchner, 22
naming of catalysts and enzymes, 21–22
protein crystals and, 22–23
discoveries leading to RNA, 10–11
DNA (see DNA)
focus on proteins
discovery of amino acids as part of proteins, 12–14
discovery of breakdown of proteins in stomach enzymes, 12
essential amino acids identified, 13
first use of term, 11–12
peptide linkage work by Fischer, 14–15
synthesis of peptides, 15–16
Genetics
chromosomes’ role in heredity
discovery, 33–34, 35
History of macromolecules before RNA (continued)
early chemical analysis of chromosomes, 37–38
first use of word gene, 34
fly genetics work in Morgan’s lab, 34–37
Mendel’s discoveries and, 32–33
individual genes connection to individual proteins
enzymes/gene connection in bread mold, 39–40
eye color studies in Drosophila, 38–39
gene transfer discovery using E. coli, 40–41
lack of appreciation of the length of DNA, 41
mindset hindering recognition of RNA, 9–10
phage school’s acceptance of DNA, 50–51
primary protein structure experiments by Sanger, 27–29
protein chemistry early advances
acceptance of large polymeric molecules, 20–21
chain length and molecular weight estimates, 17
colloid chemistry, 18–19
physical evidence of long chain structure, 19–20
reticence to accept a long chain structure, 18–19
ultracentrifuge and Svedberg, 20
transforming principle
characterization of pneumococcal extracts, 42–44
identification of transformation, 41–42
obstacles to acceptance of DNA as the active agent, 46–47
purification of deoxyribonuclease, 46
researchers’ awareness of importance of their discovery, 44–46
support of DNA as genetic material by Chargaff, 47–49
X-ray analysis of proteins, peptides, and amino acids
 α-helix and β-pleated sheets work by Pauling and Lorey, 25–26, 27f
cyclol theory by Wrinch, 24–25
fiber studies, 24
X-ray-diffraction pictures of crystallized globular protein, 24
HLH (helix-loop-helix) family, 283, 284f
hnRNA. See Heterogeneous nuclear RNA
Hoagland, Mahlon, 73
Hofmeister, Franz, 15, 19
Holley, Robert, 73, 116, 370
Holoenzyme, 127
Holtzman, Eric, 163
Hoppe-Seyler, Felix, 30
Horvitz, Robert, 312, 314, 322
HOTAIR (Hox antisense inhibitory RNA), 327–329, 330f
Hotchkiss, Rollin, 49, 92
Hox genes, 248, 327–329
Hoyrup, M., 19
HP1 repression, 287–288
Hsu, Ming-Ta, 196
Hurwitz, Jerard (Jerry), 123
Hypoxia-induced factor (HIF), 246

I
i+ gene, 84–86, 87
Id proteins, 283, 284f
Ingram, Vernon, 75, 103–104, 116
Inosinic acid, 31
Insulin, 27
Introns, 199–200, 382–386
Itano, Harvey, 103

J
Jacob, François, 3, 4
gene control studies, 77, 79
genetic code work, 124, 131
gene transfer work, 40, 41
mRNA hypothesis, 10, 86, 89, 352
negative gene regulation work, 83
Jacob-Monod hypothesis of mRNA
acceptance of mRNA’s existence and role, 95–96
consideration of an mRNA product, 87–89
enzyme induction and lac operon, 79–81
evidence for mRNA found by a Caltech group, 90–93, 94f
gene control studies using lactose, 77–79
molecular hybridization technique used to prove mRNA, 93, 95
negative gene regulation, 83–86
proposal of the existence of mRNA, 89–90, 352
proposed existence of a messenger, 77
protein synthesis machinery investigation, 86–87
temperate bacteriophages and the lysogenic state, 81–83
Jelinek, Warren, 189
Johannsen, Wilhelm Ludwig, 34
Journal of Experimental Medicine, The (JEM), 45, 46
Joyce, Gerald, 358
Judson, Horace Freeland, 45, 49, 91

K
Kadonaga, Jim, 241
Kates, Joe, 172, 173
Keller, Elizabeth, 73
Kelley, Dawn, 177
Kemphues, Ken, 314
Keller, Elizabeth, 73
Khorana, H. Gobind, 112–113
Khoury, George, 196
Kleinschmidt, A.K., 41
Klessig, Dan, 192
Knight, C. Arthur, 62
Knopf, Paul, 158
Kohne, David, 168
Köle reuter, Joseph, 32
Koonin, Eugene, 381, 383, 385
Kornberg, Arthur, 110–112, 123
Kornberg, Roger, 257, 260
Kossel, Albrecht, 30–31
Kunitz, Moses, 44, 46

L
lac genes, 83, 84, 87
Lacks, Henrietta, 145
lac operon, 127–129
Lactose, 77–81
Langmuir, Irving, 24–25
Last universal common ancestor (LUCA), 371
Latent transcription factors, 254
Lateral gene transfer, 372–373
Lavi, Uri, 181
λ Bacteriophage, 82–83
Leder, Philip, 196
Lederberg, Esther, 82
Lederberg, Joshua, 40, 41, 47, 79
Lerman, Leonard, 109
Lerner, Michael, 201
Levene, Phoebs, 31, 46, 48
Levinthal, Cyrus, 104
Lewis, Edward B., 248
Likely, Gwendolyn, 144
lin4 and lin14, 312–314, 321
Lindberg, Uno, 170
Linnaeus, Carl, 32
Lipmann, Fritz, 70
Lis, John, 277, 280
Long-noncoding RNAs (IncRNAs)
conclusions, 332–333
from defined transcription units, 326–329, 330f
Flo11 and transcriptional regulation, 331
hnRNA and, 324
misnaming of noncoding RNAs, 332
p53-dependent repression, 329
RNA profiling, 325–326
transcription increased by, 329
Xist, 324–325
LUCA (last universal common ancestor), 371
Luria, Salvador E., 51, 109
Luse, Don, 212
Lwoff, André, 77, 82
Lyell, Charles, 365
Lyon, Mary, 324
Lysogenic state, 82–83

M
m1GpppN “cap,” 177–178, 179f, 180–183
Maaløe, Ole, 89
MacLeod, Colin, 4, 43, 45
Macromolecule term invention, 21
Magasanik, Boris, 126
Maizel, Jake, 196
Maniatis, Tom, 248
Marcaud, L., 166
Marcus, Philip, 150
Margulis, Lynn, 378
Markham, Roy, 64
Marmur, Julius, 92
Martin, William, 381, 383, 385
Martin-Koonin model, 381–386
Matthaei, Heinrich, 106, 158
Mattick, John, 326
Maturase, 380, 382
Maxam, Allan, 127, 199
Mayr, Ernst, 371
McCarty, Maclyn, 4, 43–44, 45, 46, 47, 49
McKnight, Stan, 181–182, 218, 219
Mechanism of Mendelian Heredity, The, 35
Mediator coactivator complex, 257–258, 259f, 274
Mello, Craig, 314, 316
Mendel, Gregor, 32–33
Mendel’s Legacy, 35
Merrifield, Bruce, 15–16
Meselson, Matthew, 90
Michel, François, 382, 383
Miescher, Friedrich, 29, 30
Miller, Stanley, 353
miR150, 323
miRNAs
encoding by genomic sequences
location and numbers of sequences, 317–318
mRNA sites as targets for small RNAs, 321–322
Piwi-interacting RNA, 322
pri-miRNA and pre-miRNA processing, 318–321
specific actions of small RNAs in mammals, 322–324
siRNAs studies involving C. elegans and injected dsRNA triggering of mRNA suppression, 314, 316
let7 and small RNA inhibition of mRNA function, 314, 315f
lin4 and lin14 and RNA:RNA regulation, 312–314
programmed cell death discoveries, 311–312
unstable nature
bacterial mRNA turnover, 309
eukaryotic mRNA turnover, 310–311
Mirsky, Alfred E., 25, 43–44, 46–47
Missense codons, 114
Miura, Kin-ichiro, 178
Mizutani, Satoshi, 175
MMTV (mouse mammary tumor virus), 218
Monod, Jacques, 3
gene control studies, 77, 79
genetic code work, 124, 131
gene transfer work, 40
mRNA hypothesis, 10, 86, 89, 352
negative gene regulation work, 83
Montmorillonite, 369
Moore, Claire, 192
Morgan, Thomas Hunt, 34, 38
Moss, Bernard, 178
Mouse L cells, 144–145
Mouse mammary tumor virus (MMTV), 218
Mowshowitz, Deborah Bernhardt, 168
mRNA manufacture control ChIP assays, 267–268
differential processing of pre-mRNA

cell-specific splicing factors, 303–306, 307–308f
major and minor splice site sequences and spliceosomes, 299
molecular recognition mechanisms in mRNA processing, 296–297
poly(A) addition complexes and site choice, 297–299
quantities of genes involved, 295–296
RNA-binding proteins’ roles, 306, 309
sequences that enhance and silence splicing, 300
spliceosome and its actions, 300–302
splice sites and splicing machinery recognition, 299
epigenetics and transcriptional control
DNA methylation as an epigenetic state, 290–291
H3K4me3 directed to TSSs, 292, 294–295
Polycomb and heterochromatin repression as modifications, 291–292, 293–294f
term meaning, 288–290
histone acetylation
active transcription and H3K4 and H3K36, 272
connection to active transcription, 268–269, 270f
enhancers and chromatin loops, 273–274
histone demethylases, 271–272
histone modifications at enhancers, 272–273
histone-remodeling complexes and NFRs, 269, 271
trimethylation of H3K9 and H3K27, 274
histone-modifying enzymes and complexes, 266–267
histones and chromatin formation
histone acetylation role in transcriptional control, 265–266
nucleosome, histone tails, and the solenoid, 263, 264
nucleosome blocking of transcription, 264–265
lncRNAs
conclusions, 332–333
from defined transcription units, 326–329, 330f
Flo11 and transcriptional regulation, 331
hnRNA and, 324
misnaming of noncoding RNAs, 332
p53-dependent repression, 329
RNA profiling, 325–326
transcription increased by, 329
Xist, 324–325
miRNA encoding by genomic sequences
location and numbers of sequences, 317–318
mRNA sites as targets for small RNAs, 321–322
Piwi-interacting RNA, 322
pri-miRNA and pre-mRNA processing, 318–321
specific actions of small RNAs in mammals, 322–324
miRNAs and siRNAs studies involving C. elegans
injected dsRNA triggering of mRNA suppression, 314, 316
let7 and small RNA inhibition of mRNA function, 314, 315f
lin4 and lin14 and RNA:RNA regulation, 312–314
programmed cell death discoveries, 311–312
mRNAs’ unstable nature
bacterial mRNA turnover, 309
eukaryotic mRNA turnover, 310–311
processing decisions discoveries, 236
recent progress in eukaryotic gene expression, 333–334
regulated transcriptional events after initiation
DRB and transcriptional elongation, 275–277
locating transcription start sites, 281–282
paused polymerases and elongation step, 277–280
phosphorylation of Pol II CTD, 274–275
short promoter-proximal transcripts, 280–281
regulation discoveries, 236–237
siRNAs in plants, 317
summary of regulation of gene expression, 234t
technological advances contributions, 238–239
transcriptional activators and initiation
mRNA manufacture control (continued)
activator proteins’ functional
domains, 244–245
cell signaling: external signaling
proteins, 252, 253f, 254
cell signaling: latent transcription
factors, 254
cell signaling: steroid receptor
superfamily, 251, 252f
developmental and cell-specific
functions, 246–248
DNA damage and p53 activation,
246
enhanceosomes, 248–249, 250f
Mediator coactivator complex,
257–258, 259f, 274
numbers and function, 243–244
response to environmental stress,
245–246
in stem cells, 249
TBP–DNA–TFIIB structure, 258,
260
TFIID and TAFs, 255–257
yeast structure determination
through crystallography,
260–263
transcriptional initiation regulation of
pre-mRNA
enhancers and discovery of transcrip-
tional activator proteins,
242–243
locating promoters, 239–242
transcription blocking in eukaryotic
cells
direct-acting repressor proteins,
282–283, 284f
inhibition of the action of a
DNA-bound activator, 283, 285
transcriptional inhibition by
chromatin-modifying factors,
285–288
transcription field discoveries,
235–236
Mulder, Gerrit Jan, 11
Müller, Hermann, 35, 37
Muller, H.J., 35
Müller-Hill, Benno, 125
My Life in Science, 91

N
Nakajima, N., 255
National Institutes of Health (NIH),
104, 112
Neurospora crassa, 39–40
Nevins, Joe, 190
NFRs (nucleosome-free regions), 269,
271
NICD (Notch intracellular domain), 244
Nieman, Carl, 25
NIH (National Institutes of Health), 104,
112
Nirenberg, Marshall, 3, 104, 106,
112, 158
NMD (nonsense-mediated decay), 309
Nobel: The Man and His Prizes, 47
Noll, Hans, 159
Noller, Henry, 359
Nomura, Masayasu, 76, 92
Nonsense codons, 114
Nonsense-mediated decay (NMD), 309
Northrop, John, 23, 44, 60
Notch intracellular domain (NICD), 244
Nuclear receptors (NRs), 251
Nucleic acid bases discovery, 30–32
Nuclein, 30–31
Nucleosome-free regions (NFRs), 269,
271
Nucleosomes, 263, 264–265
Nüsslein-Volhard, Christiane (Jani), 246

O
Ochoa, Severo, 110–112
Orgel, Leslie, 89, 352, 356, 358
Ørom, Ulf, 329
Osborne, Thomas, 17

P
P1 RNase, 204
p53 activation, 246
Pace, Norman, 203–204
Painter, Theophilus S., 35
PalaMa experiment, 83–86, 87, 106
Palade, George, 68
Palmiter, Richard, 218, 219
Pardee, Arthur, 83–84, 87
Pastan, Ira, 126
Index 411

Pauling, Linus, 4, 9, 25–26, 27f, 58, 103
Payne, Ferdandus, 34
Penicillin, 148–150
Penman, Sheldon, 160, 163
Penman-Holtzman nuclear fractionation technique, 163–166, 167f
Penny, David, 385
Pentose nucleic acid (PNA), 10
Pepsin, 23, 60
Peptides, 12, 14–16, 24–26, 27f
Peptidyl synthesis by rRNA, 359–361
Perry, Robert, 152, 155, 163, 177
*Phaseolus vulgaris*, 3
Philipson, Lennart, 183–185
Phosphate, 31
Pirie, N.W., 61
*Pisum sativum*, 32
Piwi-interacting RNAs (piRNAs), 322
Planctomycetes, 380
Plasmids, 41
PNA (pentose nucleic acid), 10
Poliovirus vaccine, 146–147
Poly(A) tail (polyadenylic acid) added to hnRNA in the cell nucleus, 173–174, 175f
addition complexes and site choice, 297–299
differential poly(A) and splicing, 197–199
discovery of, 171–172
on hnRNAs, 180
identification as part of polysomal mRNA, 172–173
splicing and, 197–199
use in mRNA purification, 175–176
Polycumb repression, 287, 291–292, 293–294f, 325
Polynucleotide phosphorylase, 111–112, 113
Pontecorvo, Guido, 200–201
Poole, Anthony, 385
Porter, Keith, 68
Positive-acting transcriptional proteins, 124–125
*Present at the Flood*, 23
pri mutations, 332
*Principles of Geology*, 365
Prophage, 82
Protein synthesis and RNA
  cell fractionation, 67–68
  cell-free extracts and, 69–70
  Crick’s theory of the “adaptor,” 75
cytoplasmic RNA related to protein synthesis, 67
directional work, 118, 120, 121f, 122
discovery that nucleotides encode amino acids, 108–109
observation by electron microscope, 68
ribosomes named and accepted as the site of protein synthesis, 70, 71f
search for the missing piece of mRNA, 75–76
techniques used to develop a system, 106–108
template hypothesis, 71–72
tRNA and amino acid–activating enzymes discovery, 73–75
Protoeurkaryote, 381
Ptashne, Mark, 125
Puck, Theodore, 150
Pyrimidines, 30

R
Rajewsky, Klaus, 324
Reannealing, 92
Reddy, Ramachandra, 201
Reichard, Peter, 47
Reverse transcriptase, 176
Ribozymes, 358
Rich, Alexander, 158
Riley, Monica, 87
RISC (RNA-induced silencing complex), 320–321
Ritossa, Ferruccio M., 163
R loops, 193–196
RNA and the beginning of life
  archaean–α-proteobacterial union
  precursors to introns, 382–386
  proposal bases, 381–382
  central roles of RNA in macromolecular synthesis, 352
development of a precellular state, 386
eukaryotic cells origin
  endosymbiosis, 378–379
RNA and the beginning of life (continued)
possible evolutionary pathways to an eukaryote, 379–381
first informational molecule, 351–352
geological record and early cellular life, 368
acritarchs, 367
geochemistry and early cellular life, 368
geological samples dating, 366
microfossils interpreted as bacteria or archaea, 366–367
present-day geographic distribution of life and, 365–366
prebiotic chemistry
amino acids, 353
nucleotides, 353–356
present-day RNA machines and an RNA world
peptidyl synthesis performed by rRNA, 359–361
pre-rRNA processing and snoRNAs, 361, 362f
RNase P1, 361, 363
signal recognition particle, 363
small RNAs and, 364–365
telomerase, 363–364
primacy of RNA, 387–388
protocell research, 368–369
self-replication of RNA, 356–359
three kingdoms of life proposal by Woese, 369–371
whole-genome sequencing and origin of cellular kingdoms
archaeal–eukaryotic similarity, 374, 376–378
lateral gene transfer, 372–373
protein sequence comparisons and evolutionary history, 373–374, 375f
RNA as the connector of genes and proteins
growing base of knowledge of DNA in 1950s, 57–58
Jacob-Monod hypothesis of mRNA acceptance of mRNA’s existence and role, 95–96
consideration of an mRNA product, 87–89
enzyme induction and lac operon, 79–81
evidence for mRNA found by a Caltech group, 90–93, 94f
gene control studies using lactose, 77–79
molecular hybridization technique used to prove mRNA, 93, 95
negative gene regulation, 83–86
proposal of the existence of mRNA, 89–90
proposed existence of a messenger, 77
protein synthesis machinery investigation, 86–87
temperate bacteriophages and the lysogenic state, 81–83
research leading to hypothesis of an RNA role in gene regulation, 58–60
RNA’s role in protein synthesis
cell fractionation, 67–68
cell-free extracts and, 69–70
Crick’s theory of the “adaptor,” 75
cytoplasmic RNA related to protein synthesis, 67
observation by electron microscope, 68
ribosomes named and accepted as the site of protein synthesis, 70, 71f
search for the missing piece of mRNA, 75–76
template hypothesis, 71–72
tRNA and amino acid–activating enzymes discovery, 73–75
RNA viruses
bacteriophage infection and, 64–66
determination of the base composition of RNA, 66
importance of timing in research discoveries, 64
proof of the genetic role of TMV RNA, 62–64
TMV studies, 60–62
viruses’ genetic capacity understanding, 60
state of understanding of RNA in early 1950s, 58
RNA-induced silencing complex (RISC), 320–321
RNA polymerases
composition, 127, 128f, 129
discovery, 122–124
GTFs and
adenovirus as the first in vitro Pol II template, 212–214
GTFs complexity recognition, 214–216
identification of three enzymes, 208–210
Pol III template, 211–212
RNA initiation using Pol II and Pol III, 210–211
regulated action requirement
lac and λ repressor proteins purification, 125
positive-acting transcriptional proteins and, 124–125
Robbins, Frederick, 146
Roberts, Richard, 70, 197
The Rockefeller Institute, 67, 68, 92, 157, 196
Rodríguez-Trelles, Francisco, 381
Roeder, Robert G., 208, 211, 212, 214, 255, 264
Roizman, Bernard, 169
Rose, William C., 13
Rothen, Alexandre, 44
Rubber, 21
Rutter, W.F. “Bill,” 208
Ruvkun, Gary, 312, 314
S
Salditt-Georgieff, Marianne, 180
Salk, Jonas, 146
Sandford, Katherine, 144
Sanger, Fred, 4, 9, 27–29, 58, 199
Sarabhai, Anand, 130
Sauerbier, Walter, 190
Schaffner, Walter, 242
Scherer, William, 147
Scherr, Klaus, 152, 153, 160, 166
Schimke, Bob, 182, 197
Schleiden, Matthias, 33
Schleif, Robert, 124
Schramm, Gerhard, 62, 152
Schultz, Jack, 38
Schwann, Theodor, 12, 33
Sebé-Pedró, A., 374
Second messengers, 254
Seed sequences, 321
Segall, Jackie, 212
Sevag, M.G., 43
Sharp, Phil, 185, 192, 194, 196, 197
Shatkin, Aaron, 178, 180
Short inhibitory RNA (siRNA), 317
Short RNAs, 280–281
Shubin, Neil, 365
Sickle cell anemia, 103
Siekevitz, Philip, 68, 69
Sigma (σ) factor, 127
Signal receptor domains, 244
Signal recognition protein (SRP), 363
Singer, Maxine, 108
siRNA (short inhibitory RNA) and miRNAs studies involving
C. elegans
injected dsRNA triggering of mRNA suppression, 314, 316
let7 and small RNA inhibition of mRNA function, 314, 315f
lin4 and lin14 and RNA:RNA regulation, 312–314
programmed cell death discoveries, 311–312
in plants, 317
Smadel, Joseph, 109
Sm proteins, 364, 385
snRNAs, 300–302
snRNPs, 201
SOCS1 (suppressor of cytokine signaling 1), 323
Soeiro, Ruy, 164
Sørenson, S.P.L., 19, 20
Spiegelman, Sol, 76, 92, 163
Spirin, Alexander, 76
Spliceosomes
- actions of, 300–302
- impact of discovery of, 382–386
- mRNA manufacture control and, 297–299
- for testing snRNPs, 201–202, 203f
SRP (signal recognition protein), 363
Stahl, Frank, 90
Stanley, Wendell, 58
Start and stop signals
- start codon AUG and initiator tRNA, 115
- termination signals and nonsense codons, 113–115
- universality of the code, 115–116
Statue Within, The, 83, 89
Staudinger, Hermann, 21
Steinberg, Daniel, 72
Steitz, Joan, 201, 299
Stem cells and transcriptional activators, 249
Stent, Gunther, 5, 131
Steroid receptor superfamily, 251, 252f
Stevens, Audrey, 123
Stewart, Sarah, 170
St. Martin, Alexis, 12
Stretton, Tony, 130
Stromatolites, 366
"Studies on the Chemical Nature of the Substance Inducing Transformation of Pneumococcal Types," 45
Sturtevant, Alfred, 35
Sulston, John, 311
Summons, Roger, 368
Sumner, James B., 22, 60
Suppression/suppressor strains, 114
Suppressor of cytokine signaling 1 (SOCS1), 323
Sutherland, Earl, 126
Sutherland, John, 354, 387
Sutton, Walter S., 33, 34
SV40 virus, 169–170, 171f
Svedberg, Theodor (The), 20
Syverton, Jerome, 147
Szostak, Jack, 358, 369
T
TAD (transcription activation domain), 244
TAFs (TBP-associated factors), 255
Tarrió, Rosa, 381
Tata, J.R., 218
Tatum, Edward L., 4, 39–40, 58
Taylor, Harriet, 49
TBP-associated factors (TAFs), 255
Telomerase, 363–364
Temin, Howard, 175, 176
Temperate bacteriophages, 82
Tetrahymena thermophila, 204–207, 266,
356–358, 382
Tetrano nucleotide hypothesis, 31
TFIID and TAFs, 255–257, 258, 260
Thompson, E.O.P., 28
Thorne, Alan, 265
Three kingdoms of life proposal by Woese, 369–371
Thymine, 30, 31
Thymus nucleic acid, 31
Tiktaalik, 365
Tissières, Alfred, 91, 106
Tjian, Robert, 255
TLE repression, 285–286
Tobacco mosaic virus (TMV) and RNA, 58–59, 60–64, 108
Todd, Alexander R., 58
Tomkins, Gordon, 106
Tonegawa, Susumu, 170
Transcription
- activators and initiation
- activator proteins’ functional domains, 244–245
- cell signaling: external signaling proteins, 252, 253f, 254
- cell signaling: latent transcription factors, 254
- cell signaling: steroid receptor superfamily, 251, 252f
- developmental and cell-specific functions, 246–248
- DNA damage and p53 activation, 246
enchesosomes, 248–249, 250f
Mediator coactivator complex, 257–258, 259f
numbers and function, 243–244
response to environmental stress, 245–246
in stem cells, 249
TBP–DNA–TFIIB structure, 258, 260
TFIID and TAFs, 255–257
yeast structure determination through crystallography, 260–263
blocking in eukaryotic cells
direct-acting repressor proteins, 282–283, 284f
inhibition of the action of a DNA-bound activator, 283, 285
transcriptional inhibition by chromatin-modifying factors, 285–288
field discoveries, 235–236
initiation regulation of pre-mRNA enhancers and discovery of transcriptional activator proteins, 242–243
locating promoters, 239–242
Transcription activation domain (TAD), 244
Transcription start site (TSS), 235, 281–282, 292, 294–295
Transesterification, 205
Transforming principle
characterization of pneumococcal extracts, 42–44
identification of transformation, 41–42
obstacles to acceptance of DNA as the active agent, 46–47
purification of deoxyribonuclease, 46
researchers’ awareness of importance of their discovery, 44–46
support of DNA as genetic material by Chargaff, 47–49
Transforming Principle, The, 47
tRNA
amino acid–activating enzymes
discovery and, 73–75
processing of tRNA precursors to tRNA, 166, 168
reading of the mRNA code
process of information transfer, 118, 120f
tRNA’s anticodon loop, 116, 117f
“wobble” hypothesis, 118, 119f
splicing of pre-tRNA, 207
start codon AUG and initiator, 115
Trypsin, 23
Tschermak-Seysenegg, Erich, 33
TSS (transcription start site), 235, 281–282, 294–295
Tuppy, Hans, 28
Turner, Chris, 265
Turnip yellow mosaic (TYM), 64
U
Unfolded protein complexes, 245
Uracil, 31
Urease, 22, 60
UV transcription mapping, 190–192
V
Vermillion, 38–39
Verrucomicrobia, 380
Vinograd, Jerome, 90
Vogt, Marguerite, 151
Volkin, Elliot, 64, 66, 76, 91, 152
von Ehrenstein, Gunter, 116
W
Waddington, C.H., 289
Wagner, Ed, 169
Warner, Jonathan, 158, 163
Watson, James D., 2
mRNA existence contributions, 89
pre-double-helix work, 13, 49, 50
structure of DNA and, 57
Weber, Jeffrey, 189
Wecker, Eberhard, 153
Wei, Cha-Mer, 178
Index

Weil, Tony, 212
Weiss, Sam, 123
Weissman, August, 33
Weissman, Sherman, 370
Weller, Thomas, 146
Westphal, Heiner, 196
White, Ray, 193
Widnell, C.C., 218
Wieschaus, Eric, 246
Wild, Martha, 204
Wilkins, Maurice, 51
Willard, Huntington, 325
Williams, Robley, 62
Willstätter, Richard, 23
Wilson, Edmund B., 31–32, 34
Wilson, Michael, 189
Witkowski, J.A., 144
“Wobble” hypothesis, 118, 119f
Woese, Carl, 7, 352, 369–371, 377, 381, 386
Wollman, Elie, 40, 79, 82, 83
Wrinch, Dorothy, 24–25

X
X-Inactivation center (Xic), 325
X-Inactivation RNA (Xist), 324–325
X-Ray sensitivity of cells, 150

Y
Yanofsky, Charles, 130
Yeast nucleic acid, 31
Young, Richard, 257

Z
z+ gene, 84–86, 87
Zamecnik, Paul, 5, 69, 73
Zaug, Arthur, 205
Ziff, Ed, 189, 212
Zymase, 22