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Total Quality

Many art aficionados would love to own a masterpiece, but only a select few have the means to privately enjoy such treasures. Cost simply prohibits most people from being able to afford them.

And yet, reproductions make these paintings widely accessible to millions of people. Through facsimiles—schools, libraries, museums, and individual collectors can procure images of the world's best artwork at a reasonable cost. Everyone benefits.

Fine art reproductions are manufactured in different ways. Expert artists trained in specific art movements, genres, and styles re-create desired masterpieces by hand. But, this technique is time consuming and expensive. And the reproductions are never an exact match. Still, many prefer these copies over other types, such as prints that have a more artificial appearance.

Recent innovations in camera, scanner, software, and ink technologies have overcome most of the problems, however. *Giclée* (a French term pronounced zhee-CLAY) reproductions have made fine art far more available.[1] In this process, a high-resolution printer transfers a digital image onto a canvas or fine art paper. Many connoisseurs are attracted to these prints because the digital image captures every nuance of the original including the most subtle details of lighting, shadowing, and texture.

The resolution exceeds that of traditional lithographs. And, giclée re-creations are relatively inexpensive even in small quantities. Such advantages have helped make these prints well-established fixtures in the fine art community.

A reproduction is only valuable, however, when it's virtually indistinguishable from the original. This requirement makes quality control steps an instrumental part of the manufacturing process—whether a piece is reproduced by an expert artist or sophisticated technology. Before a museum accepts a giclée re-creation, it must go through a rigorous quality assurance process.

After a digital image captures the masterpiece, the reproduction undergoes a proofing procedure to ensure that all aspects of the image (color, detail, brightness, contrast, brush strokes, texture, etc.) correspond exactly to the original. Then, a museum curator further evaluates the giclée. If unacceptable, it is sent back for additional changes until he is satisfied with the reproduction's quality.

This painstaking attention to every imaginable detail mirrors the strict biochemical requirements faced by the cell's machinery that manufactures proteins. For these biomolecules to be usable, they must be exact replicas—high-fidelity copies—of the information housed in the gene sequences of DNA (see chapter 2, p. 48). The cell's protein-manufacturing processes are well-designed to accomplish this task.

Still, from time to time, mistakes happen. And, as is the case for any good manufacturing process, biochemical quality control systems are in place to identify and rectify production errors. Quality assurance checks are also part of other key processes in the cell, like DNA replication, for example.

Avoiding Costly Mistakes

Manufacturing processes often rely on assembly lines to move production units from station to station. Workers, robots, and machinery carefully perform high-precision tasks transforming unrecognizable starting materials and components, one step at a time, into a finished product. Each stage is an engineering marvel that likely took years of research, careful planning, design, and construction to effectively implement.

Some of the most critical and sophisticated steps are not those that directly result in the final product but those that check the quality. These tasks

deliberately remove defective products from the production sequence and ensure that no substandard finished product reaches the consumer's hands.

Quality assurance procedures that simply evaluate and reject inferior products at the end of the production line may keep defective items from reaching consumers, but they are costly, inefficient, and of limited value. The best quality control measures intervene throughout the manufacturing process, particularly when mistakes are most likely to occur or are the most costly.

Defective products can then be removed near the point in the manufacturing sequence where the problem occurs and that saves time and resources. Without such intervention, defective units would be carried through to the assembly line's end only to be discarded.

Effective and efficient quality control procedures don't just happen. Rather, they require careful planning and a detailed understanding of the manufacturing process, the product, and the way the consumer will use it. In other words, quality control procedures reflect intelligence and ingenuity and indicate a deliberate, well-designed process.

Scientists compare many of the cell's activities to manufacturing processes. These comparisons provide an important conceptual handle that helps researchers understand the cell's operating systems.

An astounding chemical logic undergirds these complex, well-orchestrated processes. Biochemists have discovered that, just like manufacturing operations designed by human engineers, key cellular processes incorporate a number of quality control checks. Many of them play a central role in cell survival and the cell's ability to propagate from generation to generation.[2] These quality assurance procedures occur at critical junctures in the cell's systems and display remarkable chemical elegance and exquisite fine-tuning.

Describing all the cell's quality control operations is beyond the scope of this book. Therefore, this discussion is limited to some of the quality control procedures associated with the production of one of the cell's most important biochemical products, proteins.

Only the Best

The capacity of the cell's biochemical machinery to make proteins with a high degree of fidelity is critical. Protein ensembles play a role in every cell function and take part in every cell structure (see chapter 2, p. 42).

Wide-scale production of defective proteins would disrupt essential cell activities and result in a distorted cellular architecture.

The problems related to defective protein production extend beyond global disruption of cellular activities. Molecular biologist and physician Michael Denton points out that frequent mistakes in protein production will cause the cell to self-destruct.[3]

The threat of autodestruction stems from the circular nature of protein synthesis. Proteins constitute many components of the cell's protein manufacturing machinery. In other words, the cell uses proteins to make proteins (see chapter 5, p. 101). So, if the protein manufacturing machinery were assembled with defective parts, the cell would fail to accurately manufacture proteins. Such a manufacturing failure would cause protein production systems to become increasingly error-prone with each successive round of protein synthesis. Protein manufacturing systems made up of defective components would be more likely to produce defective proteins. This chain reaction would cascade out of control and quite quickly lead to the cell's self-destruction.

Effective quality assurance procedures must be in place for protein production or life would not be possible.

Manufacturing Instructions

At most production facilities, official documents that contain the manufacturing instructions are housed in a central office where they're formally maintained. The cell does the same. It stores DNA—the master directions for protein production—inside its nucleus. The nucleotide sequence of genes found along the DNA strands specifies the amino acid sequence of proteins, just like manufacturing plans describe the order of production steps for any manufacturing process (see chapter 2, p. 50).

When the time comes to produce a particular protein, the cell's machinery copies these instructions and takes them to the production floor. This reproduction operation results in the assembly of another type of polynucleotide, messenger RNA (mRNA).[4]

A Biochemical Assembly Line

The cell's protein-manufacturing machinery consists of three main components: messenger RNA (mRNA), transfer RNA (tRNA), and ribosomes.

All interact to form an assembly line that generates the polypeptides that constitute proteins.

Messenger RNA

After the manufacturing instructions for protein synthesis have been copied from the DNA (transcription), reviewed, and processed, the newly produced mRNA carries them from the cell's nucleus to the cytoplasm. Once there, the mRNA issues instructions to subcellular particles, the ribosomes, to produce the polypeptides that fold and interact to form proteins[5] (see chapter 2, p. 50). Ribosomes bind and manage the interactions between mRNA and tRNA.[6]

Transfer RNA

Like mRNA, transfer RNA (tRNA) consists of a single RNA strand. Unlike mRNA, tRNA adopts a precise three-dimensional structure critical for its role in protein synthesis.[7] As the single tRNA strand folds to form its three-dimensional shape, four segments of the tRNA strand pair. This union gives tRNA a cloverleaf shape in two dimensions. Bending the clover leaf and twisting the paired regions produces an overall L-shaped architecture. (See figure 10.1.)

Transfer RNAs bind amino acids and carry them to the ribosome.[8] This delivery makes amino acids—the starting materials for protein production—available to the protein synthetic machinery. Each of the twenty amino acids used by the cell to form proteins has at least one corresponding tRNA molecule. An activating enzyme (aminoacyl-tRNA synthetase) links each amino acid to its specific tRNA carrier.

Each tRNA and amino acid partnership has a corresponding activating enzyme specific to that pair. The amino acid binds to one end of the tRNA "L". The other end of the tRNA, the anticodon, "reads" the manufacturing instructions found in mRNA. This anticodon consists of a three-nucleotide sequence that pairs with a codon, a complementary three-nucleotide sequence in mRNA.

The four nucleotides of mRNA, and ultimately DNA, specify the twenty amino acids found in proteins by using groupings of three nucleotides to code for each amino acid.[9] There are sixty-four different codons that correspond to the twenty amino acids involved in protein synthesis. Some of
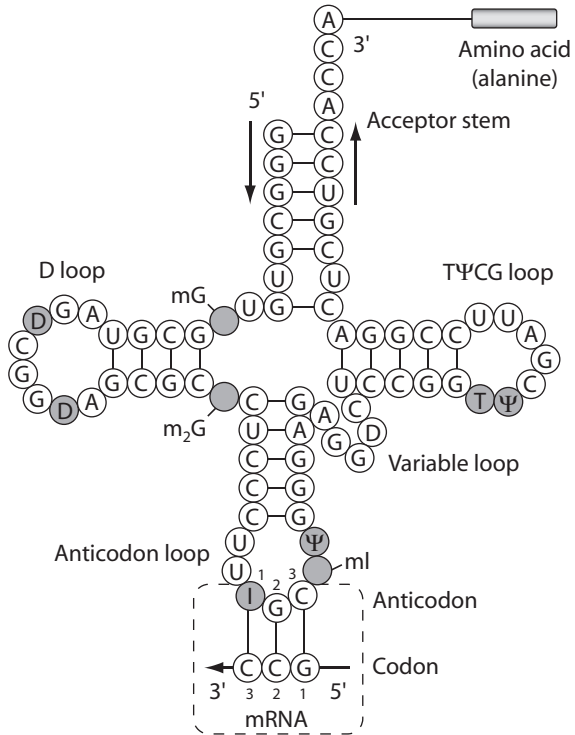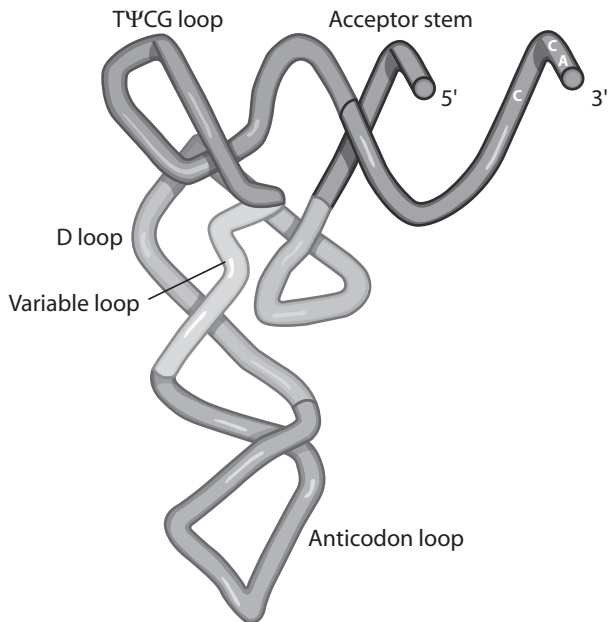
the sixty-four codons are redundant. That is, they code for the same amino acid. The genetic code (see chapter 9, p. 171) is the set of rules the cell uses to relate nucleotide triplets in mRNA to amino acids in proteins.

Each tRNA's anticodon matches a codon in mRNA. Because each tRNA binds a single and specific amino acid, the codon–anticodon pairs serve as the cellular hardware that implements the manufacturing instructions for protein production.

Ribosomes

These subcellular entities play a central role in protein production by binding and managing interactions between mRNA and tRNA. The chemical reactions that form the bonds that join amino acids together in polypeptide chains are catalyzed or assisted by ribosomes.

Proteins and RNA molecules, called ribosomal RNA (rRNA, see chapter 5, p. 102), form a functional ribosome when two subunits of different sizes combine. In prokaryotes, the large subunit contains two rRNA molecules and about thirty different protein molecules. The small subunit consists of a single rRNA molecule and about twenty proteins. In eukaryotes, the large subunit is formed by three rRNA molecules that combine with around fifty distinct proteins. The small subunit consists of a single rRNA molecule and over thirty different proteins. The rRNAs act as scaffolding that organizes a myriad of ribosomal proteins.

Ribosomes are abundant inside the cell. (A typical bacterium possesses about twenty thousand. They generally comprise one-fourth the total bacterial mass.) These dynamic structures readily self-assemble when mRNA and all of its components are present and disassemble once protein production is complete.

The Manufacturing Process

The ribosome, mRNA, and tRNA molecules work cooperatively to produce proteins. Using an assembly-line process, protein manufacturing machinery forms the polypeptide chains (that constitute proteins) one

Figure 10.1. tRNA Structure
The single tRNA strand folds to form its three-dimensional shape when four segments of tRNA pair. This pairing produces a cloverleaf shape in two dimensions. Bending the clover leaf and twisting the paired regions yields an upside-down L-shaped architecture.

amino acid at a time. This protein synthetic apparatus joins together three to five amino acids per second. Ribosomes, in conjunction with mRNA and tRNAs, assemble the cell's smallest proteins, about one hundred to two hundred amino acids in length, in less than one minute.

When protein synthesis begins, the ribosome complex assembles around mRNA. The rRNAs bind to mRNA and properly position it in the ribosome. This process establishes the proper reading frame (see chapter 8, p. 155). The tRNA–amino acid complex that corresponds to the first amino acid position in the polypeptide chain binds to a site in the ribosome called the P (product) site. The tRNA–amino acid complex corresponding to the second amino acid in the polypeptide chain binds to an adjacent site, the A (accepter) site. The protein synthetic machinery uses the mRNA codon–tRNA anticodon pairing interactions to properly position the tRNA–amino acid adducts. (See figure 10.2.)
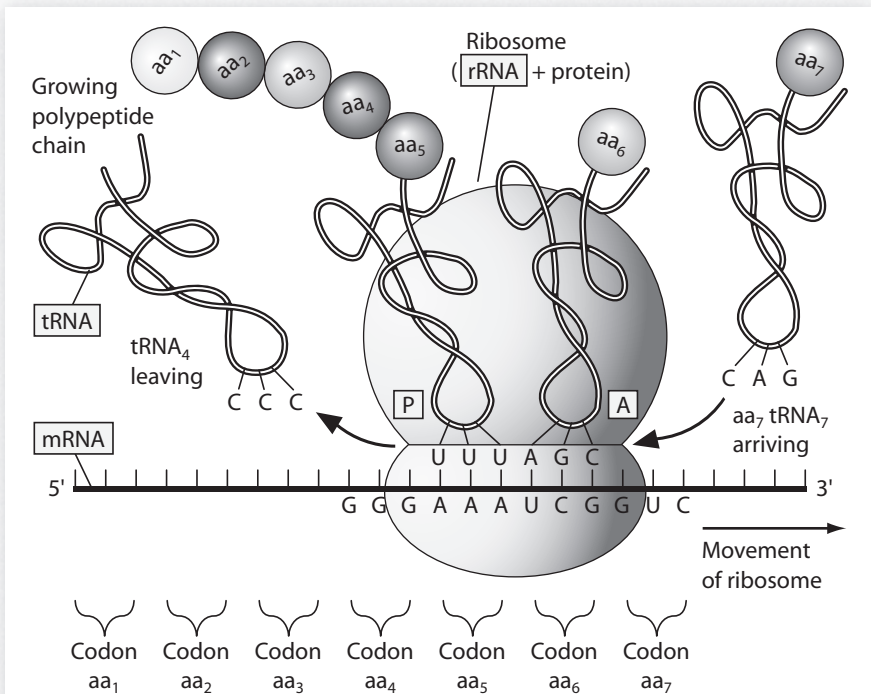
Figure 10.2. Protein Synthesis at the Ribosome
The mechanism of protein synthesis involves the binding of tRNA–amino acid adducts to the A site and the subsequent transfer of the amino acid to the growing polypeptide chain in the P site.

Once positioned in the P and A sites, a region of rRNA in the large subunit (referred to as peptidyl transferase) forms a chemical bond between the first and second amino acids in the polypeptide chain. When this occurs, the amino acid in the P site dissociates from its tRNA. The tRNA in the P site leaves the ribosomes and becomes available to bind another amino acid.

The tRNA in the A site, which has the growing polypeptide chain attached to it, translocates to the P site. And, the tRNA–amino acid complex for the third position in the polypeptide chain enters the A site. Then bond formation, tRNA dissociation, and transfer from A to P site repeats. This entire process occurs over and over again until all the information in the mRNA is read and the entire polypeptide is synthesized. For each step in this assembly-line process, the ribosome complex advances along the mRNA length—one codon at a time.

Quality Control Procedures

As with any well-designed production process, the cell's protein synthetic machinery employs quality assurance protocols. Checkpoints occur at several critical junctures during protein manufacture, including (1) tRNA and rRNA production, (2) mRNA production, (3) amino acid attachment to tRNA, (4) the movement of tRNA to the ribosome, and (5) the positioning of tRNA at the ribosome's A site.

Maintaining the Protein Production Machinery

Biochemists refer to tRNA and rRNA as stable RNAs because these molecules, once produced by the cell's machinery, persist for a long period of time under normal growth conditions. In contrast, mRNA has a high turnover rate (see chapter 6, p. 119).

The biosynthesis of tRNAs and rRNAs is highly accurate. Still, from time to time errors creep into the production process. If left unchecked, defective tRNAs and rRNAs will create havoc for the cell because these molecules are key cogs in the biochemical machinery that manufactures proteins. In any production process, if the machinery that makes the product doesn't work properly, the product either can't be produced or won't be assembled correctly. The stability of these biomolecules further exacerbates the potential

damage effected by defective tRNAs and rRNAs because, even if they're flawed, these molecules will persist in the cell. (In contrast, when flawed proteins are accidentally made, the cell's machinery eliminates them.)

In recent years biochemists have discovered the strict quality control governing the production of tRNAs and rRNAs in all cell types.[10] When improperly made, the protein poly(A) polymerase adds several adenine nucleotides to the defective RNAs to form what biochemists call a poly (A) tail (see chapter 5, p. 102). The addition of this poly (A) tail (polyadenylation) flags the faulty RNAs for destruction.[11] Studies on the bacterium *E. coli* show that when mistakes occur in the biosynthesis of tRNA and rRNA, cooperative activity between the proteins RNAase R and PNPase destroys the defective molecules.[12]

If these three enzymes—poly(A) polymerase, RNAase R, PNPase—are inoperable, cell death inevitably occurs. In the process, defective tRNA molecules and rRNA fragments accumulate in the cell and the number of functional ribosomes decreases. Presumably, the defective rRNA molecules disrupt the assembly of working ribosomes.

Placing a quality assurance check at the point of rRNA and tRNA production makes perfect sense. This foresight ensures that the cell's manufacturing machinery is in proper working order before protein production even begins. If this quality control is not in place, the cell's manufacturing floor becomes cluttered with inoperable manufacturing equipment to its detriment.

Recent work indicates that rRNA and tRNA quality control procedures are operable in eukaryotic organisms as well.[13] Just like in the bacterium *E. coli*, flawed tRNA and rRNA molecules are targeted for breakdown by polyadenylation. (In contrast, in eukaryotes the poly (A) tail stabilizes mRNA and directs the splicing operations.) These latest studies suggest that this quality control operation may be a universal feature in the living realm.

Operating at Peak Efficiency

Quality control checkpoints have been discovered at critical junctures in mRNA production, export from the nucleus, and translation at ribosomes.[14] An elegant rationale places quality assurance procedures at these points in protein biosynthesis as well. Before the assembly process even begins, these safeguards generate manufacturing efficiency by ensuring that the protein production machinery will use the correct instructions.

Biochemists recently discovered that RNA polymerases (chapter 5, p. 101)—the protein complexes that synthesize mRNA by copying the information stored in the gene sequences of DNA—use a proofreading mechanism to ensure that mRNA has been accurately transcribed.[15] Messenger RNA, like DNA, is a polynucleotide (see chapter 2, p. 50). Unlike DNA, which consists of two paired polynucleotide strands, mRNA is a single strand. Its nucleobase composition is similar but not identical to DNA. One of the most important differences between DNA and RNA is the use of uridine (U) in place of thymidine (T) in the RNA chains.

RNA polymerases produce mRNA by using a gene's nucleotide sequence, located along the sense strand of the DNA double helix, as a template (see chapter 8, p. 157).[16] RNA polymerases step along the DNA strand and add nucleotides to the mRNA strand one at a time. The nucleotide sequence of the gene dictates each of the nucleotides added to the growing mRNA chain. RNA polymerases rely on the same pairing rules that align the two DNA strands to specify the nucleotide sequence of mRNA.

When the side chain of the DNA template is a C, RNA polymerase adds a G to the growing mRNA strand. If the DNA side chain is a G, RNA polymerase uses a C (because G and C always pair with each other). When the DNA side chain is a T, RNA polymerase incorporates an A into the mRNA chain, and if the RNA polymerase encounters an A, it slots in a U (instead of a T; see figure 10.3).

As mRNA moves along the DNA sense strand adding nucleotides to the mRNA molecule, it constantly checks its work to make sure the correct nucleotide has been added. If an error occurs and the wrong nucleotide becomes incorporated into the mRNA strand, the RNA polymerase removes the incorrect nucleotide, backs up, and repeats the combination step. Biochemists refer to this activity as proofreading. This quality control operation ensures that mRNAs are accurately produced.

In eukaryotes, newly formed mRNA undergoes several processing steps before it leaves the nucleus and makes its way to a ribosome[17] (see chapter 5, p. 102). This processing includes adding a 7-methylguanine "cap" to one end of the mRNA and a poly A "tail" to the other end. Introns (noncoding intervening sequences within a gene) are removed and the remaining exons (the regions of a gene that contain information to make proteins) are spliced together. Biochemists have discovered that if the cell's machinery makes errors in processing mRNA, so-called discard pathways remove flawed mRNA molecules.[18]

Once processed, mRNA migrates from the cell's nucleus through nuclear pores to the cytoplasm where translation occurs. Another quality assurance checkpoint prevents improperly spliced mRNA from exiting the cell nucleus.[19] This quality control step is accomplished through binding and debinding of proteins to mRNA. When properly spliced, certain proteins that are part of the splicing procedure dissociate from mRNA. If errors occur in splicing, however, these proteins remain attached.

After splicing is completed, other proteins bind to the fully processed mRNA. If not properly spliced, these proteins can't bind to the defective mRNA. When it is associated with the wrong proteins, mRNA isn't granted passage through the nuclear pore, which is how imperfectly processed mRNA is prevented from reaching the ribosome.

Certain types of errors in mRNA production escape detection by the quality control operations in the nucleus. Messenger RNA molecules produced without a stop codon or with a premature stop codon occasionally make their way to the ribosome (see chapter 9, p. 173). Once there, these defective mRNA molecules stall protein production, jamming the ribosome machinery.[20] Several distinct biochemical safeguards are in place to destroy faulty mRNA molecules that clog the ribosomes.[21]

Exact Amino Acid Attachments

A quality control checkpoint also occurs at the step that attaches amino acids to their corresponding tRNA molecules.[22] This energy intensive attachment process, called charging, is highly selective. The error rate for the enzymes that carry out this reaction, aminoacyl-tRNA synthetase (activating enzymes) is about 1 in 3,000.

Activating enzymes achieve this low error rate by correctly binding the appropriate tRNA molecules and amino acids before catalyzing the reaction that joins these two biomolecules together. Proper tRNA binding is readily accomplished because of the chemical differences among the individual tRNAs. The binding of the correct amino acid by activating enzymes, however, is quite remarkable and involves careful biochemical fine-tuning.

The activating enzyme isoleucyl-tRNA synthetase best illustrates the mechanism for selecting the correct amino acid and the fine-tuning

Figure 10.3. RNA Polymerase Production of mRNA
RNA polymerases produce mRNA by using a gene's nucleotide sequence as a template. RNA polymerases step along the DNA strand and add nucleotides to the mRNA strand one at a time.

associated with this quality control step. The enzyme is able to effectively discriminate between the amino acids isoleucine and valine. Both have nearly identical chemical and physical properties. Based on the thermo-dynamics consideration alone, the binding differences between these two amino acids should allow only a 1 in 40 error rate, not a 1 in 3,000. This difference in expected error rate means another mechanism must be at work.

All activating enzymes perform proofreading and editing steps that recognize and delete mischarged amino acids from tRNAs. Activating enzymes proofread and edit through chemical fine-tuning that involves the "just-right" binding to the enzyme's active site (chapter 2, p. 45). Amino acids that are too large can't be accommodated. Those too small become translocated to the enzyme's editing site once the bond between the amino acid and tRNA forms. In the editing site, the enzyme removes the mis-charged amino acid from the tRNA and starts all over again.

New work indicates that translocation from the catalytic site to the editing site heavily depends on structural fine-tuning of the activating enzyme.[23] Changing a single amino acid in isoleucyl-tRNA synthetase compromises the enzyme's capacity to edit mischarged tRNAs by disrupt-ing the translocation step.

The proofreading and editing steps are critical. If not executed properly in bacteria, cell growth is inhibited.[24] Faulty proofreading and editing of aminoacyl-tRNA synthetases have been implicated in neurodegenerative diseases.[25]

Separating the Good from the Bad

Recent studies have identified a quality control checkpoint associated with the transport of tRNA–amino acid complexes to the ribosomes.[26] Once charged with an amino acid, tRNAs require a protein, elongation factor Tu (EF-Tu), to escort and position them in the ribosome A site.[27] For some time, biochemists regarded EF-Tu as a passive carrier that in-discriminately bound tRNA–amino acids adducts. These scientists now understand that EF-Tu actively distinguishes properly charged tRNAs from mischarged and uncharged tRNAs.

Biochemists from the University of Colorado at Boulder identified the mechanism EF-Tu employs to discriminate the 20 correctly charged tRNA–amino acid adducts from 380 incorrectly charged ones.[28] The interaction

between EF-Tu and properly charged tRNAs is "just right" with binding affinities occurring over a narrow range. Mischarged tRNAs bind to EF-Tu either too weakly or too strongly.

When bound too tight, the mischarged tRNA cannot be released at the ribosome, and if too loose, EF-Tu cannot transport the mischarged tRNA to the ribosome. This finely tuned quality-control system prevents incorrect amino acids from incorporating into polypeptide chains by catching any errors that escape detection by the activating enzyme's editing mechanism.

Less Accuracy Results in Lethal Errors

Collectively, the quality assurance procedures associated with activating enzymes and EF-Tu yield an error rate for protein synthesis on the order of 1 in 10,000 or 100 ppm (parts per million). If the protein manufacturing machinery did not operate with this accuracy, life would not be possible.

The accuracy of protein synthesis can be calculated. The equation $P = (1-E)^n$ expresses the probability for producing a polypeptide chain without error.[29] In this equation P represents the probability for producing an error-free polypeptide, E the error frequency, and n the number of amino acids in the polypeptide chain. An error rate of 1 in 100 is intolerable for the cell. At this frequency, the protein machinery has essentially no chance of producing an error-free polypeptide chain 1,000 amino acids in length and only a 36 percent probability of producing one 300 amino acids long.

An error rate of 1 in 1,000 permits 300-amino-acid-long polypeptide chains to form with an 85 percent error-free probability, but still 1,000-amino-acid-long polypeptide chains would experience only a 37 percent chance of being assembled correctly. At a 1 in 10,000 error rate, polypeptide chains of 1,000 amino acids have a greater than 90 percent chance of correct assembly. Given all this, an error rate of 1 in 10,000 is the minimum protein production efficiency for life to be possible.

An error rate of 1 in 100,000 yields a 99 percent probability of error-free polypeptide assembly for chain lengths 1,000 amino acids long. If this is the case, then why doesn't the protein production machinery include additional quality control steps to push the process accuracy closer to 1 in 100,000?

An error rate of this magnitude would slow down the protein production rate to the point that it becomes harmful to the cell. The error rate of 1 in 10,000

is "just right" to allow for high-fidelity protein synthesis at a rate fast enough to allow cellular chemistry to operate. The design of the protein manufacturing machinery recognizes the trade-offs between accuracy and production time, as does any well-designed production process (see chapter 13, p. 248).

Quality Control in the Endoplasmic Reticulum

A complex system of membrane channels and sacs (see chapter 2, p. 40), the endoplasmic reticulum (ER) is made up of two regions. In the *rough endoplasmic reticulum* ribosomes are associated with the outer surface of the ER membrane. The proteins made by these ribosomes are deposited into the *lumen* (central cavity) of the ER for further biochemical processing. The proteins transported into the lumen will eventually make their way into lysosomes and peroxisomes, become incorporated into the plasma membrane, or be secreted out of the cell.

The processing of proteins in the lumen (posttranslational modification) is quite extensive.[30] Posttranslational modifications include (1) formation and reshuffling of disulfide bonds (these bonds form between the side chains of cysteine amino acid residues within a protein, stabilizing its three dimensional structure), (2) folding proteins into three-dimensional structures, (3) addition and processing of carbohydrate units to form oligosaccharide attachments (see chapter 8, p. 146), (4) cleavage of the protein chains, and (5) assembly of protein complexes. A number of enzymes associated with the ER lumen mediate these posttranslational operations.

Once posttranslation modifications are successfully executed, the fully mature proteins make their way to their final destination.

Error Prone

The complexity and intricacy of the posttranslational modifications that take place within the ER make these processes susceptible to errors. It's not uncommon for proteins in the ER lumen to wind up misfolded or to be improperly assembled because of unbalanced subunit production.

Quality control activities ensure that proteins are properly produced and processed by the rough ER.[31] In fact, many scientists consider the quality assurance procedures of the ER to be the quintessential biochemical quality control systems.[32]

Biochemists have discovered that proteins in the ER lumen experience primary and secondary quality control checks. Primary quality control operations monitor general aspects of protein folding. Secondary quality control activities oversee posttranslational processing unique to specific proteins.

One of the most remarkable features of the ER quality assurance systems is the ability to discriminate between misfolded proteins and partially folded proteins that appear misfolded but are well on their way to adopting their intended three-dimensional architectures. If the quality control operations cannot efficiently make this distinction, it is devastating to the cell. In fact, some diseases have been linked to faulty quality control activities in the ER.[33]

When misfolded proteins escape detection, defective proteins accumulate in the cell. On the other hand, to mistakenly discard proteins in the process of being properly folded would be wasteful.

Inspected By

Biochemists recently discovered that the ER quality control systems use information contained within oligosaccharides (see chapter 8, p. 146) as sensors to monitor the folding status of proteins.[34] This process begins when the ER's machinery attaches an oligosaccharide (abbreviated $Glc_3Man_9GlcNAc_2$) to newly made proteins after they've been manufactured by ribosomes and translocated into the lumen of the ER. Once inside the ER, two Glc units are then trimmed from the oligosaccharide to form $Glc_1Man_9GlcNAc_2$. This modified attachment signifies to the ER's machinery that it's time for chaperones to assist the protein with folding (see chapter 5, p. 105).

Once completed, the remaining Glc residue is cleaved to generate the oligosaccharide $Man_9GlcNAc_2$. This attachment tells the ER's quality control system to scrutinize the newly folded protein for any defects. If improperly folded, the ER's machinery reattaches Glc to the oligosaccharide and sends the protein back to the chaperones for another round of folding.

Moving On Down the Line

Once the protein passes this stage of processing, the ER machinery removes a Man group to generate $Man_8GlcNAc_2$. This marker triggers the ER machinery to send the protein to the Golgi apparatus (see chapter 2,

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Know When to Fold 'Em

Occasionally, the endoplasmic reticulum's (ER's) machinery becomes overwhelmed with unfolded proteins. This glut can stem from the overproduction of proteins or from errors in the oligosaccharide processing steps that guide the ER's quality control operations.[35] If the cell does not effectively deal with the stress on the machinery, the result is catastrophic. Biochemists think the inordinate accumulation of unfolded proteins in the ER contributes to diseases like cancer and neurodegenerative disorders.[36]

When strained this way, the cell responds with something known as the unfolded protein response (UPR). The UPR represents a form of feedback regulation. When too many unfolded proteins are present in the ER, protein synthesis at the rough ER slows down and mRNA molecules that specify the production of proteins processed through the ER are degraded.[37] The UPR can be compared to a waitress who pours soda pop more slowly as the foam rises to the top of the glass.

The UPR represents one more example of the elegant molecular logic that permeates life's chemistry. It also bespeaks foresight and preplanning, indicators of intelligent design.

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p. 40). If, however, the quality control system detects any evidence that proteins with the $Man_8GlcNAc_2$ attachment are misfolded, it targets them for destruction. In other words, the quality control systems of the ER continually monitor the folding status of proteins as they're processed. If the structure of the bound oligosaccharide does not match the expected state of the protein, it triggers either a recycling step or a destruction sequence.

If the ER's machinery deems it necessary to destroy a defective protein, the machinery shuttles the protein from the ER lumen to the cell's cytoplasm. This process is referred to as retro-translocation.[38] Once in the cytoplasm, the defective protein becomes coated with the protein ubiquitin and destroyed by the proteosome (see chapter 6, p. 120).

High-Fidelity Copies

To reproduce a masterpiece requires exacting attention to every imaginable detail. Each nuance of the image must exactly correspond to the original.

The strict biochemical requirements faced by the cell's machinery that manufactures proteins reflect the same impeccable quality control. To be usable, each protein must be an exact replica of the information housed in the gene that specifies the protein's amino acid sequence.

Even though the biomolecular pathways responsible for protein produc-tion display remarkable complexity and chemical elegance, the inherent nature of these chemical and physical processes inevitably causes mistakes to creep into the operation. The need to detect these problems as soon as possible necessitates quality control procedures as stringent as those in any manufacturing plant.

This biochemical quality assurance further highlights the exceptional ingenuity that defines the cell's chemistry and reinforces the conclusion that life has a supernatural basis. Effective and efficient quality control procedures don't just happen. Rather, they are characterized by intentional foresight. Sound quality control systems require careful planning, a detailed understanding of the manufacturing process, the product, and the way that product will be used. All of these features are evident in the qual-ity control activities in the cell. In protein biosynthesis, the placement of quality assurance checkpoints occurs at strategic stages in the production process in a way that ensures reliable protein production while generating manufacturing efficiency.

This chapter focused on some of the purposeful quality assurance pro-cedures associated with protein biosynthesis. Other biochemical systems rely on quality control activities as well. References for a few examples are noted.[39]

Only a designer who exercises thought and care could be so deliberate as to orchestrate effective quality control procedures—whether for a painting's reproduction or for the operations found within the cell. In this context, the cell's quality assurance systems logically compel the conclusion that life's chemistry emanates from the work of a Grand Engineer—One skilled in making exact reproductions. The biochemical fine-tuning displayed by many of the quality control steps associated with protein production and other operations in the cell adds to this analogy. Such precise attention to detail clearly indicates a supreme intelligence at work (see chapter 6).

As biochemists unveil more and more of the cell's elegant artistry, the evidence for a Creator mounts. The next chapter continues to build the case for biochemical intelligent design by considering repeated use of the same patterns in biochemical systems.

Pablo Picasso, *Portrait of Dora Maar* (Reproduced by permission from © 2008 Estate of Pablo Picasso/ Artists Rights Society (ARS), New York; The Bridgeman Art Library)