C1. The common points of control are as follows:

1. DNA-chromatin structure. This includes gene amplification—increase in copy number; gene rearrangement—as in immunoglobulin genes; DNA methylation—attachment of methyl groups, which inhibits transcription; locus control regions—sites that control chromatin conformation.

2. Transcription. This includes transcription factors/response elements—interactions that can activate or inhibit transcription.

3. RNA level. This includes RNA processing—regulation of splicing via SR proteins; RNA stability—regulation of RNA half-life; RNA translation—regulation of the ability of RNAs to be translated.

4. Protein level. This includes feedback inhibition—small molecules that modulate enzyme activity; posttranslational modification—covalent changes to protein structure that affect protein activity.

C2. Response elements are relatively short genetic sequences that are recognized by regulatory transcription factors. After the regulatory transcription factor(s) has bound to the response element, it will affect the rate of transcription, either activating it or repressing it, depending on the action of the regulatory protein. Response elements are typically located in the upstream region near the promoter, but they can be located almost anywhere (i.e., upstream and downstream) and even quite far from the promoter.

C3. Transcription factor modulation refers to different ways that the function of transcription factors can be regulated. The three general ways are the binding of an effector molecule, protein-protein interactions, and posttranslational modifications.

C4. Transactivation occurs when a regulatory transcription factor binds to a response element and activates transcription. Transactivators may interact with TFIID and/or mediator to promote the assembly of RNA polymerase and general transcription factors at the promoter region. They also could alter the structure of chromatin so that RNA polymerase and transcription factors are able to gain access to the promoter. Transinhibition occurs when a regulatory transcription factor inhibits transcription. Transinhibitors or repressors also may interact with TFIID and/or mediator to inhibit RNA polymerase.

C5. A. True.

B. False.

C. True.

D. False, it causes up regulation.

C6. A. DNA binding.

B. DNA binding.

C. Protein dimerization.

C7. Glucocorticoid receptor: binding of an effector molecule and protein-protein interactions

CREB protein: covalent modification and protein-protein interactions

C8. For the glucocorticoid receptor to bind to a GRE, the cell must be exposed to the hormone and it must enter the cell. It binds to the receptor, which releases HSP90. After HSP90 is released, the receptor dimerizes and then enters the nucleus. Once inside the nucleus, the dimer will recognize a pair of GREs and bind to them, thereby leading to the activation of specific genes that have two GREs next to them.

C9. It could be in the DNA-binding domain so that the receptor would not recognize GREs.

It could be in the HSP90 domain so that HSP90 would not be released when the hormone binds.

It could be in the dimerization domain, so that the receptor would not dimerize.

It could be in the nuclear localization domain so that the receptor would not travel into the nucleus.

It could be in the transactivation domain so that the receptor would not activate transcription, even though it could bind to GREs.

C10. Phosphorylation of the CREB protein causes it to act as a transactivator. The unphosphorylated CREB protein can still bind to CREs, but it does not stimulate transcription.

C11. A. No effect.

B. No effect.

C. It would be inhibited.

D. No effect.

C12.A. Eventually, the glucocorticoid hormone will be degraded by the cell. The glucocorticoid receptor binds the hormone with a certain affinity. The binding is a reversible process. Once the concentration of the hormone falls below the affinity of the hormone for the receptor, the receptor will no longer have the glucocorticoid hormone bound to it. When the hormone is released, the glucocorticoid receptor will change its conformation, and it will no longer bind to the DNA.

B. An enzyme known as a phosphatase will eventually cleave the phosphate groups from the CREB protein. When the phosphates are removed, the CREB protein will stop transactivating transcription.

C13. Possibility 2 is the correct one. Since we already know that the E protein and the Id protein form heterodimers with myogenic bHLH, we expect all three proteins to have a leucine zipper. Leucine zippers promote dimer formation. We also need to explain why the Id protein inhibits transcription, while the E protein enhances transcription. As seen in possibility 2, the Id protein does not have a DNA-binding domain. Therefore, if it forms a heterodimer with myogenic bHLH, the heterodimer probably will not bind to the DNA very well. In contrast, when the E protein forms a heterodimer with myogenic bHLH, there will be two DNA-binding domains, which would promote good binding to the DNA. Note: A description of these proteins is found in Chapter 23.

C14. The enhancer found in A would work, but the ones found in B and C would not. The sequence that is recognized by the transcriptional activator is 5′–GTAG–3′ in one strand and 3′–CATC–5′ in the opposite strand. This is the same arrangement found in A. In B and C, however, the arrangement is 5′–GATG–3′ and 3′–CATC–5′. In the arrangement found in B and C, the two middle bases (i.e., A and T) are not in the correct order.

C15. There are four types of bases (A, T, G, and C) and this CRE sequence contains 8 bp, so according to random chance, it should occur every 4^8 bp, which equals every 65,536 bp. If we divide 3 billion by 65,536, this sequence is expected to occur approximately 45,776 times. This is much greater than a few dozen. There are several reasons why the CREB protein does not activate over 45,000 genes.

1. To create a functional CRE, there needs to be two of these sequences close together, because the CREB protein functions as a homodimer.

2. CREs might not be near a gene.

3. The conformation of chromatin containing a CRE might not be accessible to binding by the CREB protein.

C16.
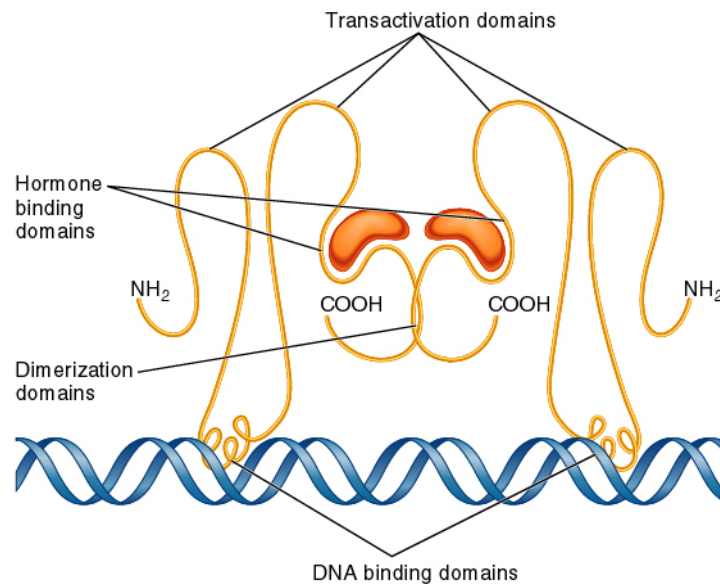
This is one hypothetical drawing of the glucocorticoid receptor. As discussed in your textbook, it forms a homodimer. The dimer shown here has rotational symmetry. If you flip the left side around, it has the same shape as the right side. The hormone-binding, DNA-binding, dimerization, and transactivation domains are labeled. The glucocorticoid hormone is shown in *orange*.

C17. The mutation could cause a defect in the following:

1. adrenaline receptor

2. G protein

3. adenylate cyclase

4. protein kinase A

5. CREB protein

6. CREs of the tyrosine hydroxylase gene

If other genes were properly regulated by the CREB protein, we would conclude that the mutation is probably within the tyrosine hydroxylase gene itself. Perhaps a CRE has been mutated and no longer recognizes the CREB protein.

C18. The 30 nm fiber is the predominant form of chromatin during interphase. The chromatin must be converted from a closed conformation to an open conformation for transcription to take place. This "opening" process involves less packing of the chromatin and may involve changes in the locations of histone proteins. Transcriptional activators recruit histone acetyltransferase and ATP-dependent remodeling enzymes to the region, which leads to a conversion to the open conformation.

C19. The attraction between DNA and histones occurs because the histones are positively charged and the DNA is negatively charged. The covalent attachment of acetyl groups decreases the amount of positive charge on the histone proteins and thereby may decrease the binding of the DNA. In addition, histone acetylation may attract proteins to the region that loosen chromatin compaction.

C20. The binding of the DNA to the core histones could

1. prevent transcriptional activators from recognizing enhancer elements that are required for transcriptional activation.

2. prevent RNA polymerase from binding to the core promoter.

3. prevent RNA polymerase from forming an open complex in which the DNA strands separate.

C21. The function of a locus control region is to control the chromatin conformation in a region containing one or more genes. The control region will govern whether or not the genes in this region are accessible to transcription factors and RNA polymerase.

C22. The translocation breakpoint occurred between the *β*-globin gene and the locus control region. Therefore, the *β*-globin gene is not expressed because it needs the locus control region to allow the chromatin to be in an accessible conformation.

C23. DNA methylation is the attachment of a methyl group to a base within the DNA. In many eukaryotic species, this occurs on cytosine at a CG sequence. After *de novo* methylation has occurred, it is passed from mother to daughter cell via a maintenance methylase. Since DNA replication is semiconservative, the newly made DNA contains one strand that is methylated and one that is not. The maintenance methylase recognizes this hemimethylated DNA and methylates the cytosine in the unmethylated DNA strand.

C24. Perhaps the methylase is responsible for methylating and inhibiting a gene that causes a cell to become a muscle cell. The methylase is inactivated by the mutation.

C25. A CpG island is a stretch of 1,000 to 2,000 bp in length that contains several CG sequences. CpG islands are often located near promoters. When the island is methylated, this inhibits transcription. This inhibition may be the result of the inability of the transcriptional activators to recognize the methylated promoter and/or the effects of methyl-CpG-binding proteins, which may promote a closed chromatin conformation.

C26. The function of splicing factors is to influence the selection of splice sites in RNA. In certain cell types, the concentration of particular splicing factors is higher than in other tissues. The high concentration of particular splicing factors, and the regulation of their activities, may promote the selection of particular splice sites and thereby lead to tissue-specific splicing.

C27. As shown in Figure 15.18, the unique feature of the smooth muscle mRNA for α–tropomyosin is that it contains exon 2. Splicing factors that are only found in smooth muscle cells may recognize the splice junction at the 3′ end of intron 1 and the 5′ end of intron 2 and promote splicing at these sites. This would cause exon 2 to be included in the mRNA. Furthermore, since smooth muscle mRNA does not contain exon 3, a splicing suppressor may bind to the 3′ end of intron 2. This would promote exon skipping so that exon 3 would not be contained in the mRNA.

C28. This person would be unable to make ferritin, because the IRP would always be bound to the IRE. The amount of transferrin receptor mRNA would be high, even in the presence of high amounts of iron, because the IRP would always remain bound to the IRE and stabilize the transferrin receptor mRNA. Such a person would not have any problem taking up iron into his/her cells. In fact, this person would take up a lot of iron via the transferrin receptor, even when the iron concentrations were high. Therefore, he/she would not need more iron in the diet. However, excess iron in the diet would be very toxic for two reasons. First, the person cannot make ferritin, which prevents the toxic buildup of iron in the cytosol. Second, when iron levels are high, the person would continue to synthesize the transferrin receptor, which functions in the uptake of iron.

C29. A cell may need to respond rather quickly to a toxic substance in order to avoid cell death. Translational and posttranslational mechanisms are much faster. By comparison, transcriptional activation takes a lot of time. In this case, it is necessary to up regulate the gene, synthesize the mRNA, and then translate the mRNA to make a functional protein.

C30. A disadvantage of mRNAs with a short half-life is that the cells probably waste a lot of energy making them. If a cell needs the protein encoded by a short-lived mRNA, the cell has to keep transcribing the gene that encodes the mRNA because the mRNAs are quickly degraded. An advantage of short-lived mRNAs is that the cell can rapidly turn off protein synthesis. If a cell no longer needs the polypeptide encoded by a short-lived mRNA, it can stop transcribing the gene, and the mRNA will be quickly degraded. This will shut off the synthesis of more proteins rather quickly. With most long-lived mRNAs, it will take much longer to shut off protein synthesis after transcription has been terminated.

C31. Conditions such as viral infection, nutrient deprivation, heat shock, and toxic heavy metals lead to the phosphorylation of eIF2a. Under these conditions, a cell is in a state where it should not divide because this would not be good for the survival of the multicellular organism of which it is a part.

C32. If mRNA stability is low, this means that it is degraded more rapidly. Therefore, low stability results in a low mRNA concentration. The length of the polyA tail is one factor that affects stability. A longer tail makes mRNA more stable. Certain mRNAs have sequences that affect their half-lives. For example, AREs are found in many short-lived mRNAs. The AREs are recognized by cellular proteins that cause the mRNAs to be rapidly degraded.

C33. The binding of IRP to the IRE inhibits the translation of ferritin mRNA and enhances the stability of the transferrin receptor mRNA. The increase in the stability of transferrin receptor mRNA increases the concentration of this mRNA and ultimately leads to more transferrin receptor protein. Conditions of low iron promote the binding of IRP to the IRE, leading to a decrease in ferritin protein and an increase in transferrin receptor protein. When the iron concentration is high, iron binds to IRP, causing it to be released from the IRE. This allows the ferritin mRNA to be translated and also causes a decrease in the stability of transferrin receptor mRNA. Under these conditions, more ferritin protein is translated, and less transferrin receptor is made.