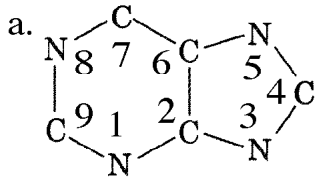
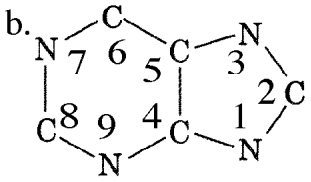
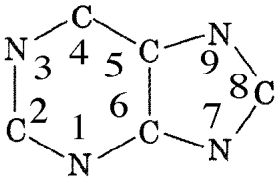
SECTION I

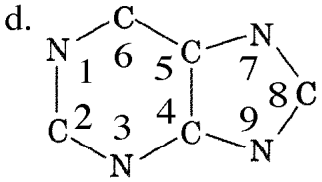
Decide which is the best answer and blacken the corresponding brackets.

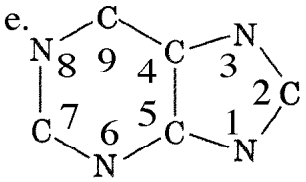
1. Which of the following is the correct numbering scheme for purine bases?

a. 

b. 

c. 

d. 

e. 

2. Ribonucleotide reductase converts (where N is any base):
   - A. dNMP to NMP
   - B. NTP to dNTP
   - C. NDP to dNDP
   - D. dNDP to NDP
   - E. NMP to dNMP

3. Which of the following is true?
   - A. Gout is caused by excess uric acid with multiple possible causes.
   - B. Gout is caused by excess orotic acid leading to its deposition in joints.
   - C. Orotic aciduria leads to mental retardation and orotic acid deposition in the joints.
   - D. Hereditary excess (hyper) HGPRT activity leads to mental retardation and gout.
   - E. Guanine treatment of gout is effective because of feedback inhibition of *de novo* synthesis.

4. Which are equivalent oxidation states of tetrahydrofolate?
   - A. Dihydrofolate, N^{10}-formyl THF, N^5-N^{10}-methylene THF
   - B. N^{10}-formyl THF, N^5-formyl THF, N^5-N^{10}-methenyl THF
   - C. N^5-methyl THF, N^5-formyl THF, N^{10}-formyl THF
   - D. N^5-N^{10}-methylene THF, N^5-N^{10}-methenyl THF, N^5-formyl THF
   - E. N^5-N^{10}-methylene THF, N^5-methyl THF, dihydrofolate

5. Which list is made up of only nucleosides?
   - A. inosine, uridine, adenosine, cytosine
   - B. inosinate, uracyl, adenine, cytosine
   - C. inosine, uracyl, adenine, cytidine
   - D. hypoxanthine, uridylate, adenine, cytidine
   - E. inosine, uridine, adenosine, cytidine

6. Poliovirus infection causes inhibition of translation of cellular mRNAs by:
   - A) Cleavage of eIF4G
   - B) Phosphorylation of eIF2
   - C) Dephosphorylation of eIF4E
   - D) Degradation of cellular mRNAs
   - E) None of the above

SECTION I - Continued
Decide which is the best answer and blacken the corresponding brackets.

7. The poly A binding protein in eukaryotes functions in translation and interacts with:
   A) eIF4E
   B) One of the eIF3 subunits
   C) eIF4G
   D) eIF2
   E) Directly with the cap structure

8. Which of the following statements concerning protein translocation into or across membranes is correct?
   i) In eukaryotic cells, mitochondria, endoplasmic reticulum, and Golgi are competent to translocate proteins from the cytosol into the interior of the organelle.
   ii) Protein translocation across membranes occurs post-translationally.
   iii) Protein translocation across membranes normally involves a translocation machinery that is comprised of receptors and specialized lipid.
   iv) Unidirectionality of protein translocation is due to proteolytic removal of the signal sequence on the trans side of the membrane.
   v) Protein insertion into membranes is usually coupled to protein translocation across the membrane.

9. A mitochondrial matrix targeting signal (MTS) is fused to the mature enzyme form of glycosidase X, which normally resides in the plasma membrane. You discover that this protein is not imported by mitochondria. Why?
   i) The MTS is not dominant over the secretory sorting signal of glycosidase X.
   ii) The MTS is not dominant over the signal sequence of glycosidase X.
   iii) Glycosidase X may be difficult to unfold.
   iv) The MTS is removed by a secretory protease.
   v) Cytosolic chaperones do not recognize secretory proteins.

10. Which of the following is required for polypeptide insertion into the mitochondrial inner membrane?
   i) ATP
   ii) Tom proteins
   iii) Tim proteins
   iv) all of the above
   v) i and iii

11. Ubiquitin is added to proteins and targets them for degradation. Which of the following statements is correct.
   i) Ubiquitin is added to a glycine in the target protein.
   ii) The rate of protein degradation depends on the rate of de-ubiquitination.
   iii) The rate of protein degradation depends on the nature of the C-terminal amino acid of the target protein.
   iv) Ubiquitin targets the protein to the lysosome.
   v) Ubiquitin is involved in the degradation of proteins in the secretory pathway.

12. A knock out of the Ced-4 gene in C. elegans would result in
   i) Inappropriate cell death.
   ii) Activation of Ced-3.
   iii) Inability of Ced-9 to associate with Ced-3.
   iv) Inactivation of Ced-9.
   v) none of the above.

13. Caspase-8 recognizes and cleaves the tetrapeptide sequence ala-ala-val-asp in the protein Bap31, which is part of a complex that recruits procaspase-8. Which amino acid(s) in this sequence, if substituted with an unrelated amino acid, would affect cleavage of Bap31.
   i) Asp
   ii) Val
   iii) P_3-Ala
   iv) P_4-Ala
   v) any of the above.

SECTION I - Continued

Decide which is the best answer and blacken the corresponding brackets.

14. Which of the following is incorrect
    i) Bcl-2 prevents the release of cytochrome c from mitochondria.
    ii) Bcl-2 blocks activation of caspase-8 by the oncogene EIA.
    iii) Bcl-2 blocks activation of caspase-8 by Fas ligand.
    iv) Bcl-2 is located in more than one membrane.
    v) Bcl-2 is an oncogene.

15. Which events would predispose a cell to transformation by myc.
    i) loss of cytochrome c
    ii) loss of Bax
    iii) loss of p53
    iv) i, ii and iii are correct
    v) ii and iii are correct

SECTION II

For each of the statements below ONE or MORE are correct. Decide which combination of statements is correct and blacken the brackets with:

1) If A, B and C are correct
2) If A and C are correct
3) If B and D are correct
4) If D is correct
5) If all are correct

16. Phosphorylation of eIF2 in mammalian cells leads to
    A) Prevention of ternary complex formation
    B) Trapping of eIF2B in a complex with eIF2
    C) Inhibition of cap-dependent and cap-independent translation
    D) Degradation of viral and cellular mRNAs

17. Phosphorylation of eIF2 by GCN2 in yeast leads to
    A) Degradation of viral and cellular mRNAs
    B) Decreased amounts of eIF2-GTP-$tRNA^{met}$
    C) Induction of oligoisoadenylate synthase
    D) Induction of GCN4 mRNA translation

18. Eukaryotic mRNA can be polycistronic because of
    A) Leaky "scanning"
    B) Shine-Dalgarno sequence
    C) Termination and reinitation by ribosomes
    D) Lack of cap structure

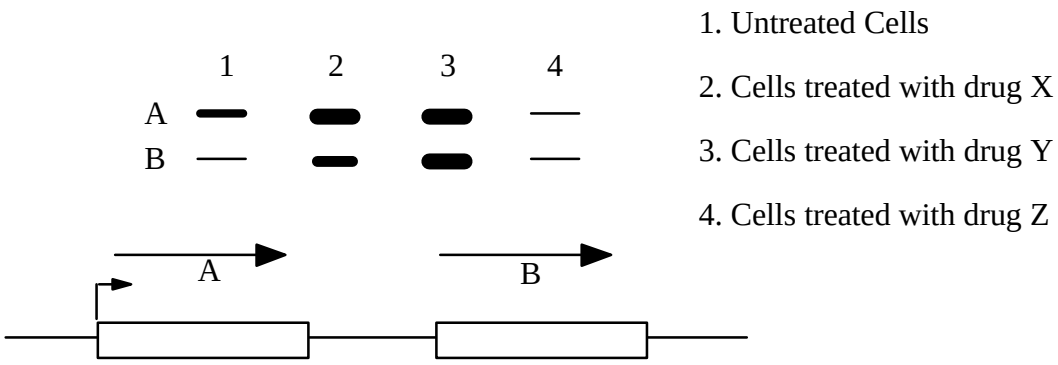
19. The iron responsive element (IRE) in the transferrin receptor mRNA is:
    A) Required for efficient ribosome binding
    B) Recognized by a translational activator
    C) Recognized by hemin
    D) Present in the 3' non-coding region of the mRNA

SECTION II - Continued

For each of the statements below ONE or MORE are correct. Decide which combination of statements is correct and blacken the brackets with:

1) If A, B and C are correct
2) If A and C are correct
3) If B and D are correct
4) If D is correct
5) If all are correct

20. Interpretation of a nuclear run-on transcription assay. Indicate which conclusions can be drawn from the results of this experiment.



(A) There is a transcriptional block in untreated cells.
(B) Drug X stimulates initiation of transcription.
(C) Drug Y stimulates both transcription initiation and elongation.
(D) Drug Z reduces transcription initiation.

21. Attenuation within the tryptophan operon *in vivo* could be affected one way or another by the following manipulations. Assuming that all amino acids are present in high amounts, indicate which of the following manipulations will cause an decrease in readthrough transcription (more attenuation).
(A) deletion of the entire leader region between the transcription start site and the trpE gene
(B) replacement of all the tryptophan codons with alanine codons in the leader coding region.
(C) deletion of the sequence "1" in the leader region.
(D) introducing mutations that increases the stability of the 3:4 hairpin.

22. Regarding rho-dependent termination:
(A) rho is capable of unwinding the RNA.
(B) the polarity of some nonsense mutations may be linked to their effect on rho-dependent termination.
(C) progression of rho along the RNA may be impeded by the presence of ribosomes.
(D) rho functions as a monomer.

23. Regarding the process of antitermination in bacteria,
(A) antitermination within ribosomal operons requires only cellular proteins.
(B) the NusA protein associates with the RNA polymerase in conjunction with the sigma factor
(C) the qut site is recognized as DNA.
(D) antitermination functions better on rho-independent termination sites

24. In the case of a gene that is imprinted,
(A) expression of a particular allele depends on whether it is inherited from the mother or the father.
(B) the pattern of methylation is different on the maternally and paternally inherited alleles.
(C) deletion of the silent allele would not affect the phenotype.
(D) maintenance of the imprint pattern in somatic cells does not require the action of the cytosine methyl-transferase (CMT).

SECTION II - Continued

25. Transcription in eukaryotes: indicate which of the following statements are correct.
    (A) TFIIB can bind to RNA polymerase II and to TFIIF.
    (B) TFIIF can affect transcription initiation but not elongation.
    (C) The Gal4 activation domain can recruit both TFIIB and TFIID.
    (D) The interaction between TFIIH and RNAPII is critical in determining the position of the transcription start site.

26. Transcription in eukaryotes: indicate which of the following statements are correct.
    (A) TFIIH is essential for promoter clearance.
    (B) The kinase that is responsible for the phosphorylation of RNA polymerase II is a cyclin-dependent kinase.
    (C) The function of TFIIH is modulated by TFIIE.
    (D) The helicases present in the TFIIH complex can also play a role in DNA repair.

27. Transcription in eukaryotes: indicate which of the following statements are correct.
    (A) The Gal4 activation domain functions when fused to the Gal4 DNA binding domain, but not when it is fused to the lexA DNA binding domain.
    (B) The reporter plasmid must necessarily contain an open reading frame.
    (C) In the yeast two-hybrid system, the activation domain and the DNA binding domain are present in the same protein.
    (D) A transcriptional activator must necessarily contain a DNA binding domain.

28. Transcription in eukaryotes: indicate which of the following statements are correct.
    (A) DNA methylation is not required for normal development in *Drosophila melanogaster*.
    (B) Repression of a methylated gene involves the recruitment of a histone deacetylase.
    (C) DNA methylation may cause the stable repression of a gene.
    (D) The presence of methylated DNA sequences within a gene invariably correlates with lack of expression.

29. Regarding histone acetylation:
    (A) Although histone acetyl-transferases are found in organisms as distantly related as yeast and man, they do not exhibit any sequence conservation.
    (B) Histone acetyl-transferases act only on lysine and arginine residues.
    (C) The effect of histone acetyl-transferases on transcription can be monitored *in vitro* using "naked" DNA as a template.
    (D) Histone acetylation increases sensitivity to DNase 1.

30. Nuclear receptors.
    (A) The ligand binding domain can exist in three different conformations.
    (B) Nuclear receptors bind to DNA as homo- or hetero-dimers.
    (C) Co-repressor complexes prefer to bind to the apo-ligand binding domain.
    (D) The ligand is usually a hydrophilic molecule.

31. Transcriptional repressors.
    (A) A DNA binding domain may be sufficient, in some situations, to repress transcription of a given reporter.
    (B) Active repression requires that the repressor protein contains both a DNA binding domain and an active repression domain.
    (C) Some transcriptional repressors do not bind to DNA.
    (D) Active repression domains may make contact with TBP, an activation domain or a histone-deacetylase.

32. Enhancers and insulators:
    (A) An enhancer located at equal distance from two promoters may preferentially stimulate one of the two promoters.
    (B) A single insulator can prevent interaction between a promoter and several upstream enhancers.
    (C) One model suggests that insulators are located at the base of chromatin loops.
    (D) An architectural transcription factor can bent DNA and interact with other DNA binding proteins.

33. Silencing
    (A) Position effect variegation refers to the fact that a given gene is expressed in some cells but not in others within the same tissue.
    (B) Position effect variegation may result from the "spreading" of heterochromatin.
    (C) Chromosomal rearrangements may cause a gene to become under the influence of position effect variegation.
    (D) The Sir proteins bind to the locus control region.

SECTION II - Continued

34. Chromatin structure and gene regulation.
    (A) In *in vitro* transcription assays using naked DNA, transcriptional activators can stimulate transcription to the same extent as *in vivo*.
    (B) The DNase sensitivity of the globin locus is higher in erythrocytes than in neuronal cells.
    (C) Chromatin assembled *in vitro* and used in transcription assays exhibits the same level of expression as "naked" DNA.
    (D) In general, the "opening" of the chromatin precedes gene expression.

35. Acetyltransferases and chromatin remodeling complexes.
    (A) All chromatin remodeling complexes contain an ATPase activity.
    (B) Histones are currently the only known substrates for acetyltransferases.
    (C) Acetylation of histones occurs on lysine residues within their amino-terminal domains.
    (D) The process of transcription elongation results in the progressive acetylation of histones within a gene.

36. Chromatin structure and gene regulation.
    (A) Inclusion of a locus control region within a transgene can prevent position effect variegation in transgenic mice.
    (B) In transgenic mice, the locus control region confers tissue-specific gene expression but not copy number dependent gene expression.
    (C) The locus control region of the Beta-globin gene cluster contains at least 4 DNase hypersensitive sites.
    (D) A functional locus control region induces DNA replication of the Beta-globin gene cluster early during S phase in non erythroid cells.

37. More complicated types of genetic switches can be constructed by combining positive and negative controls. Indicate which of the following statements are correct:
    (A) A mutation within the coding sequence for the lactose repressor may be trans-dominant.
    (B) Following addition of lactose to the medium, the lactose repressor protein binds to the operator of the lactose operon.
    (C) Operator-constitutive mutations are cis-dominant.
    (D) The catabolite activator protein (CAP) enables bacteria to use alternative carbon sources in the presence of glucose.

38. In prokaryotes, the process of transcription can involve the following events:
    (A) The formation of a closed promoter complex.
    (B) The unwinding and rewinding of DNA.
    (C) The formation of an RNA-DNA hybrid.
    (D) The synthesis of very short RNA molecules.

39. Transcription in prokaryotes: indicate which of the following statements are correct.
    (A) The change in (Greek letter "sigma") factor can change the DNA binding specificity of RNA polymerase.
    (B) Binding sites for activators interacting with the (Greek letter alpha) factor must be located within 2 base pairs of the -35 element.
    (C) The carboxy-terminal domain of the (Greek letter alpha) makes specific protein -DNA contact with the UP element.
    (D) The core RNA polymerase binds to the promoter to form the "closed complex".

40. The regulation of a bacterial promoters involves several elements. Indicate which of the following statements are correct.
    (A) A binding site which overlaps the -35 or -10 promoter elements can function as an operator.
    (B) Some bacterial proteins can act as either activators or repressors.
    (C) Ligands can modulate gene expression by preventing or helping transcriptional factors to bind to DNA.
    (D) To activate transcription, an activator must be able to interact with one of the subunits of RNA polymerase.

SECTION III

For each of the statements below, ONE or MORE are correct. Decide which combination of statements is correct and blacken the corresponding brackets.

43. You label your protein in vivo with radioactive phosphate [^{32}P] and you believe that your protein is phosphorylated on **only** tyrosine residues. How would you prove this and identify which tyrosine is phosphorylated (you know the sequence of your protein and you have more than one tyrosine in your protein).
    1) Subject your protein to partial alkali hydrolysis and separate amino acids by chromatography.
    2) Subject your protein to acid hydrolysis and separate amino acids by chromatography.
    3) Subject your protein to high temperatures and separate amino acids by chromatography
    4) Cleave your protein with a protease, separate peptides and sequence radioactive peptides.
    5) Separate proteins by SDS polyacrylamide gel electrophoresis and subject to acid treatment

    a) 1 and 4
    b) 1, 2 and 5
    c) 1,4 and 5
    d) 2 and 4
    e) 3 and 4

44. From the 3 D structure of a serine/threonine kinase (A kinase) and a tyrosine kinase (Insulin receptor). Which of the following are true.
    1) In the inactive conformation the kinases are bound to ATP
    2) The 3D structure of a serine/threonine kinase is similar to that of a tyrosine kinase.
    3) Activation of the kinase requires a conformational change
    4) Activation of the kinase is stabilised by phosphorylation of a Tyrosine, Serine or Threonine residue that lies in the ATP binding pocket

    a) 2 and 4
    b) 1 and 2
    c) 1 and 4
    d) 3 and 4
    e) 2 and 3

45. Which of the following are true for CRE binding protein (CREB).
    1) Phosphorylation of CREB on its DNA binding domain is required for recruitment of a coactivator
    2) Phosphorylation of CREB causes it to translocate from the cytoplasm to the nucleus.
    3) Phosphorylation of CREB on its activation domain stimulates transcription
    4) Phosphorylation of CREB is required for recruitment of TFIIB, a general transcription activator to the complex.

    a) 1 and 4
    b) 2 and 3
    c) 3
    d) 3 and 4
    e) 2 and 4

46. The following compounds participate in glycoprotein or proteoglycan biosynthesis:

    1. GMP-sialic acid
    2. Dolichol-P-galactose
    3. GDP-mannose
    4. UDP-iduronic acid

    A. 1
    B. 2 and 4
    C. 3
    D. 1 and 3
    E. 4

SECTION III - Continued

For each of the statements below, ONE or MORE are correct. Decide which combination of statements is correct and blacken the corresponding brackets.

47. The glycopeptide linkages found in mammalian O-linked oligosaccharides are:
    1. Xylose linked to threonine
    2. N-acetylgalactosamine linked to asparagine
    3. N-acetylgalactosamine linked to serine
    4. Galactose linked to either serine or threonine

    A. 1
    B. 2 and 4
    C. 1 and 3
    D. 4
    E. 1, 2 and 3

48. Characteristics of the N-linked oligosaccharides:
    1. All the mannose residues are linked
    2. Phosphate can be added by a specific kinase
    3. The invariant core contains N-acetylglucosamine
    4. They may contain Gal 1,4GlcNAc

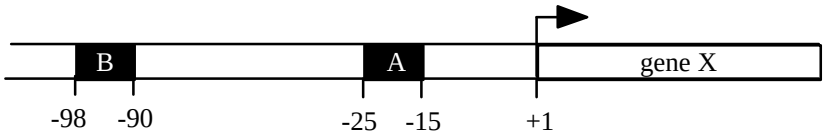
    A. 1
    B. 2
    C. 3
    D. 4
    E. 3 and 4

49. Targeting of lysosomal enzymes to the lysosomes requires
    1. A specific lectin
    2. O-linked oligosaccharides
    3. Mannose -6-phosphate
    4. N-acetylglucosamine

    A. 1
    B. 2 and 4
    C. 3
    D. 1 and 3
    E. 4

SECTION II - Continued

41.



We have cloned a fragment of bacterial DNA that contains the gene coding for protein X. We found that gene X is expressed at high levels only when molecule Y is added to the medium. Upstream of gene X, we found two binding sites, A and B, that are involved in the regulation of gene X. To investigate the roles of sequences A and B, we have isolated a panel of mutations that affect expression of gene X. Our findings can be summarized as follows:

- Using the wild type promoter, gene X expression was found to be very weak in the absence of molecule Y.
- When sequence B was deleted, gene X expression was very low, whether Y was present or not.
- Some mutations in sequence A increased gene X expression when Y was present. However, the same mutations had no effect when Y was absent.

Give the correct interpretation of these results

(A) Sequence B is a binding site for an activator.
(B) Sequence A is a binding site for a repressor.
(C) Molecule Y could be a ligand that help an activator to bind to sequence B.
(D) The -35 and -10 sequences are likely to diverge significantly from the consensus promoter sequences, or the spacing between them is not optimal.

42. You have been hired by Genentech Inc. Your first task is to produce a bacterial strain that can express the lactose operon when both lactose and glucose are present in the medium. Indicate which strategy or strategies would work.
(A) Move away the binding site for the catabolite activator protein, CAP.
(B) Mutate the catabolite activator protein, CAP, to render it capable of binding DNA even in the absence of cAMP.
(C) Delete the gene encoding the lactose repressor.
(D) Modify the -35 and -10 sequences of the lactose operon to make them excellent binding sites for sigma 70.