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This Frontiers in Medicine issue addresses the science and politics of vaccines. The hypodermic syringe, a classic tool of vaccination, may soon be out-of-date. A global effort is under way to produce a "supervaccine" that would confer, in a single oral dose, lifetime immunity against many of the major infectious diseases. A special section begins on page 1371 and related Reports on pages 1448 and 1451. [Images: needle, Peter Steiner/ The Stock Market; globe, Tom Van Sant/Geosphere Project/The Stock Market. Illustration: E. Carroll]

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J. H. M. SCHMITT, B. M. HAISCH, J. J. DRake

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Vaccines: A Study in Contrasts

This issue of Science—Frontiers in Medicine: Vaccines—presents a striking contrast between the tone of the News articles and the tone of the pieces written by vaccine researchers. Many of the Articles written by researchers have an upbeat tone, reflecting positive assessments of the chances of formulating effective new vaccines. Part of that enthusiasm stems from scientists’ steady progress in demystifying the immune response to foreign antigens, and one aspect of that work is discussed in Sprent and Tough’s Article on how the immune system “remembers” antigens it was exposed to long ago. Another cause for optimism comes from the arsenal of new technologies that are enabling researchers to manipulate the immune response, which are reviewed in an Article by Rabinovich, McInnes, Klein, and Hall.

In the Perspectives section, several researchers show how new knowledge and new technologies are being combined to make vaccines against major infectious diseases. Many of these diseases are caused by pathogens that present multiple targets to the immune system. Advances in recombinant DNA techniques and in peptide and polysaccharide chemistry offer ways to hit many of these targets at once, as discussed by Nussenzieg and Long for malaria vaccines, Sibor for pneumococcal conjugate vaccines, and Glass, Gentsch, and Smith for rotavirus reassortant vaccines. Mekalanos and Sadof also note the importance of recombinant DNA technology in the development of oral vaccines for cholera.

Because even very effective vaccines can fail, researchers must remain vigilant about developing and implementing alternative vaccine strategies. The measles vaccine is a remarkable success story (only 277 cases of measles were reported in the United States in 1993) but, as discussed by Katz and Gellin, the vaccine is far less effective in developing countries. Investigations of why vaccines fail can provide leads for new vaccine strategies, as noted by Hall in her overview of respiratory syncytial virus vaccines. There are currently no vaccines licensed for use in the United States against herpessirus, in part because of concerns about vaccine safety. But, as Plotkin notes, such vaccines are available in other countries—and the public health significance of herpessirus infections is substantial.

All of these contributions offer reasons for hope that we will soon have the knowledge required to make new vaccines against some diseases of major public health significance. But how quickly will that knowledge result in vaccines actually reaching the clinic? That is a difficult question to answer, and the News reports in this issue suggest that it may not be as soon as we would hope. Science’s reporters, led by Jon Cohen, paint a bleak picture of the social mechanisms by which vaccines come to market. Cohen surveyed more than 100 of the world’s leading vaccine researchers, who told him that market disincentives and political disorganization are drastically slowing the process by which vaccines reach the world’s clinics. Ann Gibbons describes how the Children’s Vaccine Initiative, launched just a few years ago to much fanfare, has stumbled badly in its quest to use vaccines to protect the world’s children; Rachel Nowak depicts United States vaccine policy-making in disarray.

How can this political and economic bottleneck be broken, liberating the new knowledge that is rapidly being accumulated? In a Policy Forum, Bloom offers one possible solution. Arguing that the problems are due partly to the huge size and fragmented nature of the vaccine enterprise (involving more than 20 federal agencies, state health departments, vaccine and biotechnology companies, medical societies, and university researchers, among others), he proposes establishing a National Vaccine Commission to take the lead in making and coordinating vaccine policy. The commission would be an independent group whose members would represent the key players in the vaccine enterprise and whose power would derive from the group’s collective expertise and experience in immunization issues. As Bloom envisions it, the establishment of such a commission could be accomplished within existing legislation and funding mechanisms.

If history is a reliable indicator, this conflict between science and politics will not be resolved speedily. But with today’s heightened awareness of cost containment in health care, vaccine researchers may have more reason to hope that their arguments will be heard.

Paula A. Kiberstis, John M. Benditt, and Daniel E. Koshland Jr.
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Embryo Research Guidelines

I would like to clarify two points for readers of Eliot Marshall’s article of 19 August, “Rules on embryo research due out” (News & Comment, p. 1024). First, the report of the National Institutes of Health (NIH) Human Embryo Research Panel, a group of outside experts, is still under development. Therefore, an accurate and complete picture of the panel’s findings and conclusions cannot now be drawn.

The panel’s work, moreover, is one step in a larger policy development process. The process involves a review of the panel report by the Advisory Committee to the Director (ACD) of NIH. This review will continue into the fall and winter. On 1 December, the ACD will deliberate the report in a public session. Only after receiving the advisory committee’s recommendations about the panel report will the NIH make any decisions about which areas of research are acceptable for federal funding and what guidelines (not rules, as the article indicates) will be formulated to govern that research.

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Primates and New Viruses

In a ScienceScope item, “Mystery virus fells donor baboons” (10 June, p. 1523), it is reported that a new, uncharacterized virus triggered an outbreak of encephalitis in baboons and was threatening the colony at the Southwest Foundation for Biomedical Research (SFBR), a primate facility that houses close to 3,000 baboons. In fact, only a few animals have developed an encephalitis-like disease, making it unlikely that the implicated virus is highly virulent in baboons. Moreover, the infectious agent responsible for this outbreak has probably been around for some time, even if it has only recently caught the attention of scientists.

What is of greater concern is that a virus that infects baboons could also be hazardous to humans under the right circumstances. In the past 2 years, two baboon-to-human liver transplants have been conducted (1). The identification of a previously unknown virus in nonhuman primates illustrates the possibility of doing more harm than good through xenograft transplantation: any pathogen carried by a baboon donor would be introduced to the human recipient along with the baboon organ. Most new pandemics arise through inadvertent transmission of viruses from another species (which functions as a natural reservoir) to humans. Surgeons and infectious-disease experts have made good-faith efforts to identify and exclude as organ donors baboons carrying known pathogens such as simian immunodeficiency virus (SIV) and simian T cell leukemia virus; however, it does not follow that the chosen baboons are therefore free from all infectious agents. Baboons carry an abundance of pathogens that are potentially dangerous to humans, including both herpesviruses and retroviruses, which can remain dormant for long periods. Identifying and excluding animals that harbor any number of viruses (some unknown) from transplant studies is virtually impossible.

So far the baboon-to-human liver transplants have been experimental and the human recipients have been terminally ill before transplantation therapy was attempted, but success in any form will likely lead to more investigations and testing until patients begin to recover. It is most disturbing that the public health implications of these studies have not been adequately discussed. One suggestion is to convene virologists, infectious-disease experts, transplant surgeons, and public-policy officials under the guise of the National Institutes of Health (NIH) and the Centers for Disease Control to begin openly discussing the overall risks to the human population. Any panel should be independent of the committees previously constructed by transplantation groups.

At the very least, national guidelines for medical surveillance of transplant recipients and their relatives should be considered: recipients should be quarantined in biosafety conditions for at least 60 days, and all health care personnel could follow accepted NIH guidelines for working with unknown human pathogens. At SFBR, we consider nonhuman primates and their tissues and body fluids to be biohazards and use standard biosafety procedures similar to those required for working with AIDS. Employees of SFBR wear fully protective clothing, including masks and latex gloves, when working with animals or their tissues. We sell these same animals to medical centers, where their tissues may be placed directly into humans along with a cocktail of immunosuppressive drugs. Scientists do not
have the luxury of a crystal ball for predicting the outcomes of these experiments. What we do have is AIDS as a reference point.

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References

The Sobering D₂ Story

The article "A cautionary genetic tale: The sobering story of D₂" by Constance Holden (News, 17 June, p. 1696) sends the wrong message to the field and creates embarrassment for scientists who are pioneering at the forefront of research in the genetics of addictive-compulsive disorders.

The article states that "attempts to replicate [our] finding [about the A1 allele of the D₂ receptor gene] have been largely unsuccessful." A meta-analysis (1) of nine independent studies of a total of 491 heterogeneous alcoholics (severe and less-severe) and 495 heterogeneous control subjects (assessed and unassessed for alcohol abuse) found a statistical association between the D₂ A1 allele and alcoholism that was highly significant: the value of P was 10⁻⁷. When attention was focused on six studies dealing only with a homogenous sample of 158 severe alcoholics, the association was found to be even more striking: the value of P was 10⁻⁸.

The article states that "even those whose research appears to confirm it can't come up with a mechanism for the gene's presumed effects. . . ." In fact, the finding of a genetic marker is only the first step in what may be a long and involved process of continuing research. As in the case of Huntington's chorea, a chromosomal marker first discovered in 1983, adequately marks vulnerability to a disease without knowledge of the gene responsible for its expression. The actual gene was discovered 10 years later. The DRD₃ variants appear to adequately mark vulnerability to addictive-compulsive behaviors, but the mechanism for the specific genetic defect may not be discovered for the next decade. The causative factor may even involve closely linked microsatellites at the DRD₃ locus or possibly distant genes that are in linkage disequilibrium with the DRD₃ gene.

The article quotes psychiatric geneticist Elliott Gershon and his colleagues as saying that, in a study of alcoholics and schizophrenics (whose disorder also involves dopamine transmission) examining the gene instead of the marker, they "found several coding variants," but "the frequency was pretty much the same in the subjects and the controls." In fact, we were also co-authors of that report (2), and the findings were not unexpected. Gershon was referring to exonal anomalies that might alter the structure of the D₂ receptor and hence its ability to bind to its ligand. Our finding (3) suggests an anomaly in the transcriptional process that affects the number of receptors. Gershon's study did not examine anomalies around the 5' promoter region, introns, and the 3' untranslated region, all of which have been shown in a number of other disorders to have mutations that alter transcriptional or translational processes.

The article states that [David Goldman's group] "could find no significant difference between alcoholics and nonalcoholics in the frequency of the suspect allele . . . ." In fact, Goldman's sample (4) excluded severe alcoholic subjects having medical complications. Moreover, the nonalcoholics were not assessed for the presence or absence of alcohol or drug abuse. In contrast, our sample (5) of severe alcoholics had died from alcohol-related pathology. Furthermore, our nonalcoholic control subjects were assessed for the presence of alcohol and drug abuse. Goldman's study, therefore, was not a replication of our first study and has little bearing on it.

Joel Gelertner's group is indirectly quoted as saying that there is little reason to accept Blum and Noble's conclusion. In fact, in the Gelertner study (6), as in Gold- man's, any alcoholic subject showing liver enzyme abnormalities, let alone significant medical problems, was excluded. This is a clear indication that Gelertner's group was excluding severe alcoholics. Furthermore, their paper included no assessment of the control subjects. By excluding the severe alcoholic phenotype, the group was studying the more "environmental" rather than the more "genetic" type of alcoholism.

Holden's article refers to preliminary work by Robert Cloninger and says it "appeared to support the A1 connection, at least with regard to severe alcoholism." Holden then says that "when the group expanded its sample, it found . . . that the association between the D₂ receptor and alcoholism faded out." In their first study (7), Cloninger's group found that 60% of the severe alcoholics in the sample had the D₂ A1 allele, a prevalence that was significantly higher than the nonalcoholic controls. But careful scrutiny of their follow-up paper (8) revealed that the sample of alcoholics in the second study was heterogeneous, including both severe and less severe alcoholics. The inclusion of less severe alcoholics diluted the sample. Moreover, although the group found that the homozy-
gote copies of the D2 dopamine receptor C1 allele were significantly associated (P < 0.002) with their mixed alcohols compared with those of their nonalcoholics, they did not report this finding in the paper.

The article quotes Goldman as stating that "there aren't too many geneticists who would be sanguine about the authenticity of this association." This statement may be true for geneticists who doubt that a single gene can play a major role in complex behaviors such as alcoholism. However, John C. Crabbe and his colleagues (Articles, 17 June, p. 1715), using the quantitative trait loci (QTC) technique, found clear evidence that several responses to alcohol, morphine, and cocaine map to the middle portion of chromosome 9 in the mouse (the DRD2 locus), which suggests that the single locus accounts for all of these associations.

There is increasing evidence from at least 14 laboratories in the United States, the United Kingdom, Canada, France, Japan, and most recently Finland and Australia, that behavioral anomalies ranging from alcoholism to drug abuse (10) to attention deficit hyperactivity disorder to Tourette's Syndrome to obesity to pathological gambling to nicotine abuse are associated with anomalies in the DRD2 locus. Recent studies (10), subsequently confirmed (11), have found an association of the D2A1 allele with components of the evoked potential, including the P300 (a cognitive component), first found by Henri Begleiter's group, to be altered in alcoholics and found by others to be predictive value for substance-abuse liability in children of alcoholics. We are witnessing the birth of a new paradigm in our understanding of the genetic basis of addictive-compulsive behaviors, and from the total evidence available it should be clear that the DRD2 gene will continue to play an important role in these behaviors.

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References

Response: What I conveyed in my article was the majority opinion in the field: that although interest in the D2 dopamine receptor was strong a couple of years ago, the findings as a whole have been too ambiguous to be encouraging. It does not appear at this point that we know enough to pass final judgment on the idea.

Blum and Noble cite a meta-analysis, as if to suggest that there could be no question that their results are being confirmed by other studies. But Gelernter and his colleagues published another meta-analysis last year in the Journal of the American Medical Association (7 April 1993, p. 1673) in which they concluded that ethnic differences in the occurrence of D2 and sampling error were more likely explanations than was alcoholism for differences in the prevalence of the suspect D2 allele.

Much of the division of opinion in the field stems from the fact that different researchers put different constructions on the same data. For example, in the linkage study done at the National Institute of Mental Health (NIMH), P. V. Gejman and other authors, including Gershon, differ with their co-authors Blum and Noble about the significance of the negative finding. Blum and Noble say the result was not surprising, because they believe the genetic difference is likely to be found in some yet unexplored regulatory sequence. The NIMH researchers think that is highly unlikely.

Another disparity concerns Cloninger's work: Blum and Noble strongly imply that Cloninger's expanded sample would have yielded positive results if his alcoholics had been more severely afflicted. Cloninger, however, believes that we simply don't know how to subdivide the subjects in a way that is pertinent to this question. He points out that there is no agreement in the field on the definition of "severe" alcoholism. And the picture is further complicated, he says, by the fact that the D2 association has been reported in "mild" alcoholics with a history of cigarette smoking but no severe medical problems.

One of the greatest areas of disagreement is over selection of controls. Blum and Noble insist that alcoholics must be removed from control groups. Gelernter and others argue that "purifying" the controls would not substantially alter the outcome.

In short, what Blum and Noble seem to be objecting to is not my article, but the opinions of others in the field who hold very different views about the D2 hypothesis, views that were accurately reflected in my reporting.—Constance Holden

Opinion

Since the early 1980's, there has been increasing evidence to associate the bacterium Helicobacter pylori with the occurrence of duodenal and gastric ulcers. Recent studies have even suggested there may be a link with certain types of stomach cancer.

Consequently, diagnosis and treatment of H. pylori infection is now a major health issue. The presence of the bacterium in the stomach can be detected in various ways. But with the growing volume of testing, an accurate, non-invasive diagnostic method is essential.

BreatheMAT measures the CO2 isotope ratio in breath samples to provide sensitive and specific testing for infection by Helicobacter pylori

The new BreathMAT system has been developed by Finnigan MAT to meet this need. Patients ingest 13C-labelled urea which, if H. pylori is present, is metabolised to 13CO2. Samples of breath are taken and the CO2 isotope ratio analyzed on the BreathMAT mass spectrometer. A wide range of other breath tests can be processed using the same BreathMAT system.

Finnigan MAT's expertise in isotope ratio mass spectrometry ensures accurate, high precision analysis. The system has been designed specifically for breath testing in diagnostic and research applications, with full automation to ensure high throughput and productivity in busy laboratories. BreathMAT provides the sensitivity and specificity of mass spectrometry in a compact, cost-effective and easy-to-operate system.

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Machine-Written Summary: Missed Opportunity?

Gerard Salton et al., in their article “Automatic analysis, theme generation, and summarization of machine-readable texts” (3 June, p. 1421), provide an interesting update on automated retrieval and analysis of text. They conclude that “[f]ormal evaluation data on the effectiveness of the methods introduced here are difficult to produce…” The authors miss an opportunity to let readers evaluate the effectiveness of automatic summary writing for themselves by not including, as the last paragraph of their article, a machine-written summary of the article itself. It would be a fine challenge to set the parameters so that the summary would not describe an article about abolition, Greek gods, and the history of India.

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Correction: Ferricyanide and Pattern Formation

In our report (1) on page 192 in the issue of 9 July 1993, “Pattern formation by interacting chemical fronts,” the term “ferrocyanide” should have been “ferricyanide” 11 lines from the end of the first column on page 193 and in the caption of figure 4 on page 194. We thank G. Rabai for pointing out these errors, which in no way change the results or the interpretation of the patterns studied.

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References

Corrections and Clarifications

The Research News article “Pulling hair from the ground” by Virginia Morell (5 Aug., p. 741) should have said that biologist Kate Field of Oregon State University worked with Walt Ream on DNA extraction from ancient hair fragments.

In the News & Comment article “Orphan chimps won’t go back to nature” by Virginia Morell (15 July, p. 312), an incorrect figure was given as the dollar amount the Jane Goodall Institute spends on maintaining orphan chimpanzee sanctuaries. The correct figure is $40,000 per month.
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From a structural point of view, the complex between human growth hormone (hGH) and the extracellular domain of its receptor (hGHP) is one of the best characterized hormone-receptor complexes. One molecule of hGH binds sequentially to two molecules of hGHP, involving separate sites on the hormone molecule and resulting in dimerization of the receptor.

The work of Brian C Cunningham and James A Wells of Genentech Inc, USA, used Biomolecular Interaction Analysis (BIA) to measure the progress of the macromolecular interactions in real-time, allowing the evaluation of the kinetics as well as the affinity of the interactions. By this method it was possible to determine the effect of replacing each of the 30 contact residues in the hGH site 1 structural binding domain with alanine.

The results indicated that only one quarter of the residues account for the major part of the binding energy. Thus the functional binding domain is considerably smaller than the structural binding domain. The results are potentially valuable in the design of hormone analogues for therapeutic purposes, identifying critical residues for the binding interaction and implying that it might be possible to design smaller hormone mimics.

Establishment of a clearly defined experimental situation for the real time BIA studies was aided by the specific immobilization chemistry on the sensor chip. By immobilizing the receptor through a single cysteine residue introduced at a chosen position, the properties of the surface-bound interaction could be closely controlled. This work clearly demonstrates the value of real-time BIA in analysing functional aspects of macromolecular interaction.

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GDP-AIF₅-Gₛ complex, the geometry of the planar AIF₅⁻ complex and the new position of the hydrolytic water molecule were initially identified by F₂ - F₁ maps from models containing protein and GDP only. A planar model for AIF₅⁻ consistent with known crystal structures was constructed and manually fit into the density. After unrestrained positional refinement, the model deviated only slightly from planar geometry with moderate shifts in bond lengths and angles. The model was again refined restricting the AIF₅⁻ in a square planar configuration with 1.78 Å Al–F bond distances (Table 2).


33. The thermal parameter given is the average value for all side chain atoms in the residue. Bₑ is the average B factor for all non-hydrogen atoms in the molecule. The B factor is a measure of the temperature anisotropy of a group of atoms. It is defined as 

   \[ B = \frac{1}{3} (B₁¹ + B₂² + B₃³) \]


36. The changes in the active site region of the GDP-AIF₅⁻ structure relative to the GTPyS-Gi₁,α form are unlikely to be caused by the different temperatures (100 and 300 K, respectively) at which the two data sets were collected. As a control, a selenomethionine-GTPyS-Gi₁,α data set collected at 100 K (a = 0.9802 Å, Table 1) was used to generate F₁ - F₀ and 2F₂ - F₁ maps after partial refinement with the native GTPyS-Gi₁,α model in which Arg178 and Gin504 were replaced with alanine. Electron density corresponding to the position of Arg178 and Gin504, and the water nucleiophile, as seen in the GTPyS-Gi₁,α structure, was observed in these maps. Thus, we conclude that cyrocovalent it self is not sufficient to affect the renaturation of these residues in the GDP-AIF₅⁻ complex.

37. Chung et al. [H.-H. Chung, D. R. Benson, P. G. Schultz, Science 259, 806 (1993)] have shown that replacement of Gin504 with a nitroglycerolate analog in p21⁵⁹⁹ yields an enzyme that has full catalytic activity and retains the ability to be stimulated by GAP. Nitroglutamine is isotropic and isoelectronic with glutamine, but cannot serve as a hydrogen bond donor. Further, it is a weak hydrogen bond acceptor. It may be that nitroglutamine distorts GTP toward the transition state or stabilizes an active conformation state of the protein. It is also possible that the dipole moment of the nitro moiety be exploited to orient the water molecule for nucleophilic attack and to stabilize developing charge in the transition state. The full activity of the nitro mutant suggests that such mechanisms are sufficient to explain the role of Gin504 in the wild-type enzyme as well. However, p21⁵⁹⁹ is a relatively weak enzyme, and much of its activity might be attributed to entropic stabilization of the reactive species in the active site. Additional degrees of rate enhancement could be achieved by several different mechanisms, which might include a hydrogen bond between the phosphates and the nitro group, and between the dipole and hydrogen bond donor groups of a residue that happens to be positioned at the site occupied at Gin504. Thus, we cannot ignore the obvious potential role of hydrogen bonding in transition state stabilization by Gin504 in Gₛ.


49. CCP4, The SERC (UK) Collaborative Computing Project No. 4: A Suite of Programs for Protein Crystallography (Warrington, United Kingdom, Dares- bury Laboratory, 1991).

50. We thank J. Noel and P. Sigler for coordinates of GTPySGₛ-Gₛ: W. Hendrickson and C. Ogata for assistance with the use of the Howard Hughes Medical Institute beamline X4 at the National Synchrotron Light Source and for valuable discussions with regard to MAD phasing; M. Graziano for the first supplies of Gₛ protein for crystallization; C. Nguyen for assistance with mutant protein synthesis; C. Strother for assistance with mass spectrometry; Z. Wang, B. Sutton, M. Mixon, and J. Naismith for help with data collection; and F. Sterrenweis and C. Jones for technical assistance. Supported by NIH grant DK 46231 (S.R.S.); and Welch Foundation grant I-1229 (S.R.S.); NIH grant GM04497, American Cancer Society grant BE30-O, and Welch Foundation grant I-1271 (A.G.G.); and the Lucile P. Markey Charitable Trust and the Raymond Wilke Chair of Molecular Neuropharmacology. Coordin- ates have been deposited with the protein data bank, accession code number 1GA.

18 July 1994; accepted 8 August 1994.
Thermal infrared multispectral “decoration” stretch image of Death Valley, California, during the day, with bands 1, 3, and 5 in blue, green, and red. Colors show spectral differences; temperatures are in dark and light. Quartz-rich materials are red; carbonates are green to blue-green; volcanic rocks, shales, etc. are blue to purple.” [From Remote Geochemical Analysis]

taining to the geochemical evolution of the surface materials. These two approaches are inherently complementary: each provides unique information on different aspects of the surface material, and neither alone will provide sufficient information to completely characterize a surface.

Although field investigation is usually the means of obtaining “ground truth” to verify the results of remote sensing, this has been possible to date only for the case of the Moon. The discussions dealing with the Moon serve as an excellent example of the complementarity of approaches, as we have available each type of remote-sensing data as well as in situ observations and returned samples. I found the lunar chapters especially enlightening, as much of the analysis happened during the Apollo era, before I was old enough to appreciate the scientific value of the data.

A quality of the book is that each chapter stands alone. On the plus side, this means that an individual interested in a single technique can focus on a small number of chapters or can see several different perspectives on a given topic. On the minus side, there is a good deal of redundancy, and information on a given topic may be widely scattered. For example, the properties of surface materials that are responsible for producing spectral features seen in reflectance spectroscopy are discussed in at least four chapters and the composition of Mars as inferred from mid-infrared spectroscopy is discussed in two. Reflectance spectroscopy is dealt with in eight different chapters, and there is no simple division between theory, laboratory work, observations, interpretations, or individual planets.

Despite the inconvenience of having to skip around to find complete treatment of a given subject, the book succeeds remarkably well in its stated purpose. The chapters are authoritative, thorough, and useful at a level appropriate for both the knowledgeable outsider and the active practitioner. In the areas with which I am familiar, the discussions do a good job of summarizing the literature and the state of the field. In the areas with which I am less familiar, the discussions are straightforward and usually clear and contain a large amount of information that I have found useful. I used the book in a course on remote sensing of planetary surfaces this semester and found it to be a most appropriate discussion of compositional remote sensing.

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