TEACHING BIOTECH MANUFACTURING FACILITY DESIGN AND REGULATORY COMPLIANCE

Better Equipping Students for a Maturing Industry

DAVID E. BLOCK
University of California • Davis, CA 95616

Over the past fifty years, the field of biochemical engineering has evolved tremendously, from early work on fermentation of antibiotics and other small organic molecules to the more recent production of recombinant proteins as human and animal therapeutics.

The curriculum for training biochemical engineers has also evolved. Early courses in fermentation used textbooks such as *Biochemical Engineering*[1] and covered enzymatic reactions, cell growth kinetics (*e.g.,* Monod kinetics), microbial fermentor design, oxygen transfer, and sterilization with a limited analysis of purification of biomolecules. Other similar courses, using books such as *Biochemical Engineering Fundamentals*[2] and more recently *Bioprocess Engineering: Basic Concepts*[3] and *Biochemical Engineering*[4] followed.

Even more recently, courses geared toward purification of molecules produced by fermentation have been added to biochemical engineering curricula, using such texts as *Bioseparations: Downstream Processing for Biotechnology.*[5] These courses have typically focused on the theoretical background of the unit operations, however. Teaching the design of specific equipment has normally been left for the mainstream chemical engineering course on equipment design, using texts such as *Plant Design and Economics for Chemical Engineers.*[6]

The first commercial recombinant protein production (*i.e.,* recombinant human insulin by Eli Lilly) began in 1982. Since then, the number of therapeutic recombinant protein products on the market has grown steadily to over seventy in 2000, with at least 360 more currently in development.[7] This has resulted in a relatively mature industry with very specific training needs. In particular, the industry uses specialized unit operations such as fermentation and chromatography, as well as unique critical utilities. In addition, sanitary design is essential to the successful production of biologics. Regulatory issues such as current Good Manufacturing Practices (cGMP) and validation are also critical, not only to manufacturing biopharmaceuticals, but also to all facets of process development and process engineering in this industry.

For these reasons, in 1997 we initiated a course on Biotech Manufacturing Facility Design and Regulatory Compliance at the University of California, Davis, that covers this material and which is now required of all senior-level biochemical engineering majors.

The course covers material necessary in the design and operation of a facility producing biological products, with emphasis on recombinant proteins. It introduces the students

David E. Block *is an Assistant Professor in the Department of Viticulture and Enology and the Department of Chemical Engineering and Materials Science at the University of California, Davis. He holds a BSE and PhD in Chemical Engineering from the University of Pennsylvania and the University of Minnesota, respectively. Prior to joining the university, he worked in the Biopharamaceuticals Department at Hoffmann-La Roche in Nutley, New Jersey.*

to concepts such as aseptic processing and Good Manufacturing Practices (GMP). After introducing these general design and regulatory issues, each area of a biotech facility is discussed following process flow. In the discussion, general equipment-design issues are included, such as piping and pumpsizing, and pressure-vessel design. The second focus of the course is compliance with current GMP, the laws governing production of human and veterinary drugs, as enforced by the Food and Drug Administration (FDA). Concepts such as validation masterplanning, validation protocols, protocol execution, and change control as they apply to both equipment and process qualification are discussed. Ideas for successful project management and facility startup are introduced throughout the course.

This course is typically taken concurrently with a traditional course in fermentation and a course in biopurification. In the following quarter, students take a bioprocess engineering laboratory course and biotech-related senior design project to complete their area of emphasis.

GOALS

There are five goals for this course. By the completion of the ten weeks of instruction, students are expected to

- *Be familiar with bioprocess equipment, process flow, and interactions between facility areas*
- *Understand aseptic processing and the idea of sanitary design*
- *Be able to specify critical equipment parameters and understand design issues*
- *Understand the importance of GMP in manufacturing*
- *Understand and be able to write validation documentation*

All course lectures, demonstrations, and projects are geared toward these goals. In general, we do not expect a student to complete the course and immediately to be able to perform a detailed design of a piece of equipment. Mentoring by experienced engineers will always be a necessary step in training. The information that the students receive in this course, however, will allow them to identify equipment as they walk through a biotech manufacturing facility, to have a good idea of the critical parameters for each piece of equipment so they can more readily participate in operation and design of the equipment, and to understand the intense regulatory environment in which they will work.

Table 1
Course Outline

1	**Overview of Biotech Facilities**
2	**Overview of Compliance Issues**
3	**Aseptic Processing/Materials**
4	**Piping and Instrumentation Drawings**
5	**Inoculum Preparation**
6	**Media Preparation**
7	Pumps/pipes/valves/filters
8	**Fermentation**
9	Basic design and pressure vessels
10	Oxygen transfer
11	Sterilization
12	**Primary Recovery**
13	Centrifuges, filters
14	Cell Disruption
15	**Buffer Preparation**
16	**Purification—Chromatography**
17	Ultrafiltration/Diafiltration
18	Viral inactivation/removal
19	**Water Systems**
20	Heat exchangers
21	**CIP Systems**
22	**Biowaste Treatment: HVAC**
23	**Basic Control Systems**
	Control and data acquisition
24	**GMP Review**
25	**Validation Master Plan**
26	**Protocols**
27	**Change Control**
28	**Batch Records**

COURSE CONTENT

The general outline for the course in shown in Table 1. After some introductory material, the course outline follows the process flow through a production facility, including the fermentation, purification, and utility areas. The last section of the course focuses on cGMP, including validation and other regulatory documentation. The book used as a text for the course is *Bioprocess Engineering: Systems, Equipment, and Facilities,*[8] which is a compilation of chapters on various parts of a biotech facility written by industrial practitioners.

Introductory Material

Since this is a new area of study for most of the students, a fairly large amount of time (approximately six fifty-minute lectures) is spent on introductory material to give them a strong common background. First there is an introduction to the bioprocess industry and its various segments, which produce everything from bulk chemicals to recombinant proteins. Reasons for the orders-of-magnitude difference in product cost from one end of the spectrum to the other are discussed as a way of getting students to focus on what is different about producing pharmaceuticals. Next is an introduction to regulatory compliance, including a history of the FDA in this country, a brief overview of cGMP and validation, and an idea of the ethical and legal ramifications of noncompliance.

After these overviews, the course focuses on the ideas of sanitary design and aseptic processing that are critical to biopharmaceutical production. Introductory information is given to the students on the two facets of sanitary design: materials of construction (*e.g.*, grades of stainless steel and welding considerations), and design (*e.g.*, pipe sloping, low-point drains, avoidance of dead legs, cleanability of various types of valves and flange connections, and instrument mounting in tanks).

Finally, piping and instrumentation diagrams (P&IDs) are introduced, using actual examples. The types of information contained in these drawings and how to use this information for equipment design and operation are stressed in both class exercises and homework problems (see the class example in Figure 1). Aside from their importance in facility design, P&IDs are a convenient means of introducing and discussing each of the pieces of equipment or systems in the remainder of the course.

Process Areas and Design Details

After completing the introductory material, the next major series of lectures covers design of equipment in each of the process areas in the order of process flow, as shown in the block diagram of a generic facility in Figure 2.

This section of the course begins with the inoculum and media preparation areas of the facility. For inoculum preparation, specialized equipment used for microbial and mammalian cell systems is discussed, such as laminar flow hoods, incubating shakers, and CO_2 incubators. General guidelines are given for inoculum sizes and stages used in industry. For media preparation, a description of various types of media prep systems (*e.g.,* ones using sterile filtration or continuous heat sterilization) is given, along with a detailed discussion of all of the components. Since this is the first time in the course that we come across valves and pumps, a survey is completed of the various types that are available and which ones are typically used for biotech facilities. Next, the process for sizing pipes for turbulent flow with reasonable pressure drops, as well as sizing pumps using a total mechanical energy balance, desired flow rate, and pump curves is explained.

For the fermentation area, we discuss a simplified P&ID for a generic microbial fermentor. Then, as with the media prep area, each component part is considered. This includes a discussion of the sizing and the various aspect ratios of fermentors, of the design of pressure vessels and ASME code, and of the control systems typical for fermentors (*e.g.,* pH, dissolved oxygen, foam, aeration, agitation, temperature). Special lectures are given on oxygen transfer in fermentors (and how it affects design) and on designing for sterilization. Differences between microbial fermentors and mammalian cell bioreactors are then highlighted.

Primary recovery (*i.e.,* separation of cells from the cell-

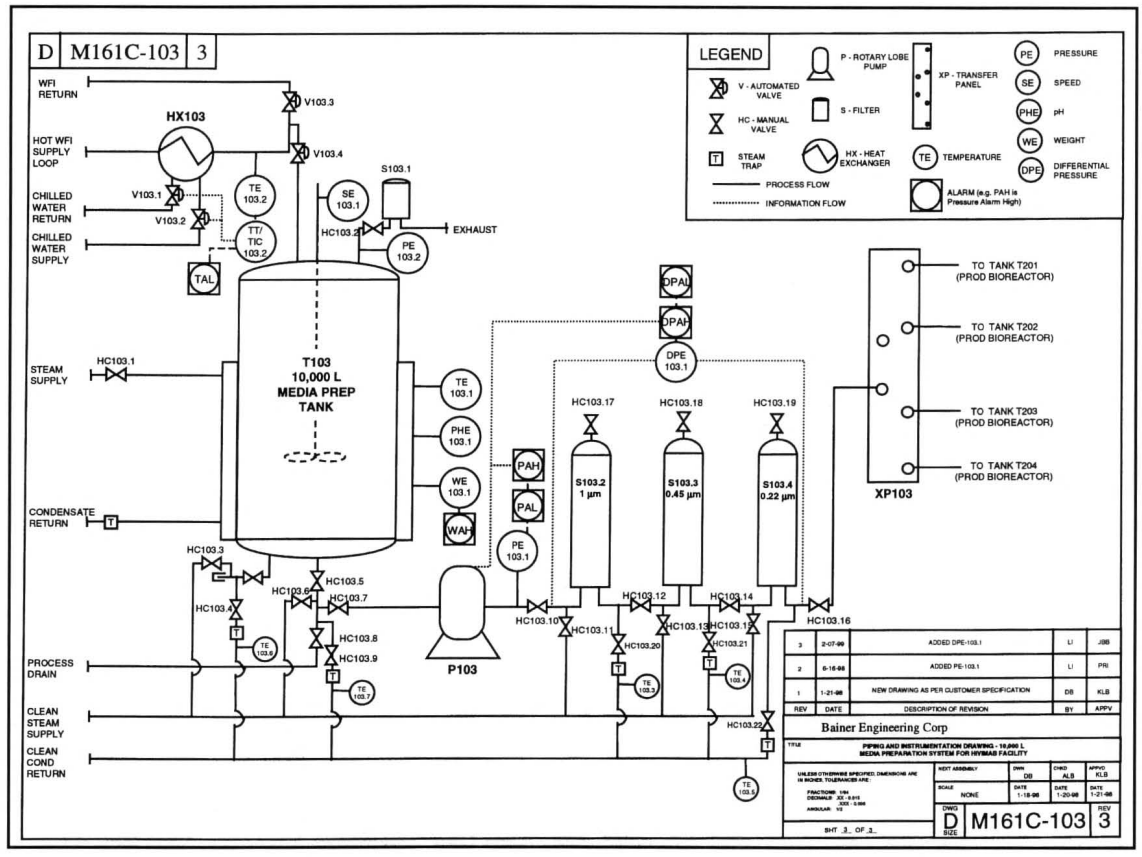

Figure 1. *Example of a piping and instrumentation diagram (P&ID) used in the course. This P&ID for a mammalian cell culture media prep area was used for homework and exam purposes. Each of the student teams generates a similar diagram for different pieces of equipment as part of the quarter-long group project.*

free broth) is covered next. This is mainly a description of tangential flow filtration and centrifugation, the two main means of cell separation currently used in the industry. Again, the important design parameters are stressed, as well as the scale-up issues for each unit operation. Factors affecting the choice between these unit operations are also discussed.

For purification, the discussion centers primarily on chromatography since it is currently the main means of purifying therapeutic recombinant proteins. After discussing the four most common types of chromatography (*i.e.,* ion exchange, hydrophobic interaction, affinity, and gel filtration) and their specific uses, the focus turns again to the equipment. This includes a description of the components of chromatography skids, including specialized valves and sensors. Scale-up and chromatography column sizing is also covered for the various types of columns. Ultrafiltration and diafiltration are then discussed. Since the equipment for these processes is essentially the same as for the primary recovery tangential flow filtration, emphasis is placed on the specific use of the equipment for product concentration or buffer exchange.

Finally, we cover the utilities critical for biotech manufacturing facility operation. While these utilities commonly make up one-third of a facility, they are largely ignored by traditional biochemical engineering courses. USP purified-water production systems are described, as well as Water-for-Injection (WFI) and Clean Steam stills that are fed by the purified-water systems. In discussing WFI systems, heat exchanger design and sizing is covered.

Next, the concept of Clean-in-Place systems, or CIP, is introduced. Cleaning cycles and necessary flow rates and temperatures are discussed. Heating, ventilation, and air conditioning (HVAC) is then covered briefly—only in regard to what it controls in the facility, namely temperature, humidity, room cleanliness (and classification), and pressure. Differential room pressure and HEPA filtration are used in these facilities as a means of maintaining a clean-room environment. Control-system alternatives such as programmable logic controllers (PLCs) and distributed control systems (DCS) are introduced.

Regulatory Compliance

Aside from the introductory material mentioned above, the last section of the course covers regulatory compliance according to cGMP. The bulk of this time is spent in discussion of Validation. Validation is defined as the process of establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.[9] For Validation, facility masterplans are discussed briefly prior to discussing the details of a validation test plan or protocol.

All of the typical activities associated with Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ) are covered in a fair amount of detail. The emphasis here is that testing should be performed to assure that the equipment does what it is designed for: 1)

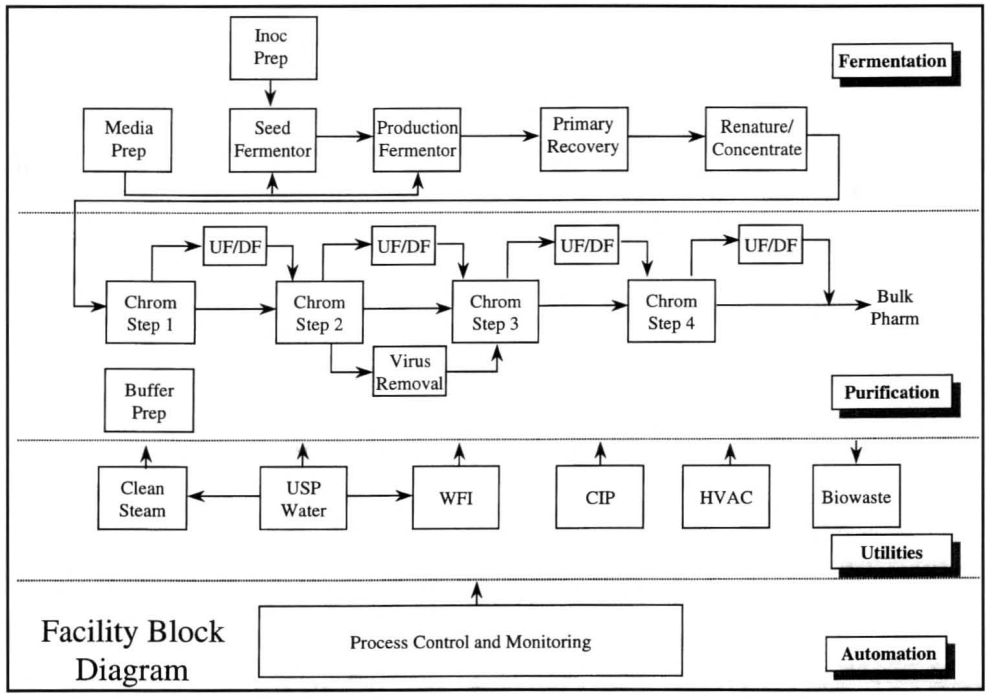

Figure 2. *Block diagram for a generic biotech manufacturing facility. The course developed generally follows the process flow as an outline.*

reproducibly and 2) for good technical reasons. Testing for the sake of testing, and creating paperwork, is discouraged.

CLASS ACTIVITIES, PROJECTS, AND HOMEWORK

In order to reinforce the lecture material and achieve the course goals, several class activities are carried out during the course. For instance, when discussing sanitary fittings and design, various types of valves (*e.g.,* ball, butterfly, diaphragm, and gate), welding samples (*e.g.,* hand and machine welded), flanges or other unions (*e.g.,* threaded joints and sanitary clamps), and objects of various materials (*e.g.,* different grades of stainless steel, brass, glass, and various types of flexible tubing) are brought into the class.

Students work in small teams to determine what the various objects are and whether or not they would be considered cleanable in a biopharmaceutical facility. Aside from being interesting for the students, this activity gives us the opportunity to stress the limitations to design caused by the idea of cleanability and to point out the difference between "clean" and "cleanable."

Another class activity takes place during the introduction of P&IDs when the students are again arbitrarily split up into small groups and are given a list of questions to answer about a P&ID that they have not yet reviewed extensively. They are given a limited time to answer all the questions, forcing them to work together as an actual team (which will be the norm when they enter an industrial environment).

Another major part of the course (30% of the final grade) is a group project. The premise of the project is that the students comprise a central engineering group in a company where a new production facility is entering a detailed design phase. Each group of three students is given one piece of equipment or system in the facility for which they must create a P&ID, write a detailed design specification that could go out for bid, and then write a validation protocol or test plan for the same piece of equipment. This project gives the students an opportunity to use the lecture material from the class as well as to think about a particular unit operation in great detail. It also usually involves interaction with actual equipment vendors to get ideas or to answer questions about the functionality or design of their equipment. This aspect of the course has proven to be quite successful. Former students have specifically pointed to these unique activities as the reason they were offered jobs in the industry.

[Students] see the information disseminated through this course as practical, and mastery of the subject matter allows [them] to make a more rapid transition to industry and thereby to become productive sooner.

Since no actual textbook exists for this topic, homework problems have to be created each year from personal knowledge or limited literature. Problems generally involve sizing the relevant equipment or designing portions of a facility based on design principles covered in lecture. Exams closely follow the form of homework.

DEMONSTRATION PERIODS AND TOURS

To familiarize the students further with the type of equipment discussed in class and to make the course more "hands on," an extra hour each week is set aside for demonstrations. They consist of either a vendor or the instructor demonstrating a piece of equipment, and they follow the flow of the course material, roughly corresponding to the material that is being covered that week in lecture. For example, during the introductory phase of the course, a representative of Arc Machines comes in to demonstrate orbital machine welding, the type of welding predominantly used in piping systems in biotech facilities.

At another time, a representative of ITT PureFlo Valves shows the students a large collection of sanitary diaphragm valves made especially for the biotech industry; full-scale sanitary centrifugal and positive displacement pumps are demonstrated (including assembling/disassembling the pump heads to examine the mechanism of pumping, a discussion of mechanical seals, priming capability, and cavitation) at the pilot winery at UC Davis.

Small autoclavable fermentors have also been used for demonstrations of associated control systems and mixing (with various impeller types and placement, with and without baffles). Tours of local fermentation process development facilities have been used to demonstrate larger sterilize-in-place fermentors. Millipore has brought in both cartridge and small tangential flow filtration units for demonstration. Amersham Pharmacia Biotech covers different types of chromatography resins and brings in pilot-scale process columns.

Finally, programmable logic controllers are demonstrated in-house, both for their functionality and ladder-logic programming. These demonstrations provide a valuable experience for the students that pictures and diagrams alone cannot equal.

In addition to the weekly demonstration periods, one or two plant tours have been scheduled each year to local biotech manufacturing sites. This experience has been extremely useful to the students in integrating the knowledge they have gained from the remainder of the course material.

POTENTIAL LIMITATIONS OF THE APPROACH

To assure that the students taking this course remain marketable in the wider chemical engineering job market, many of the equipment design issues of a mainstream equipment design course are still taught (*e.g.,* pipes, pumps, pressure vessels, heat exchangers)—but the equipment is discussed in the context of a biotech facility. Unit operations and ideas unique to the biotech/pharmaceutical industry, such as fermentation, chromatography, clean utilities, sanitary design, and cGMP, are also stressed throughout the course.

The addition of instruction in reading P&IDs, demonstrations of actual equipment used in processing, and tours of production facilities have been particularly useful and would likely be beneficial in a mainstream chemical engineering equipment design course as well. Students completing this course have received simultaneous job offers from biotech and chemical companies, so it appears that the flexibility of this approach is evident to potential employers.

Teaching a course in this subject does require some knowledge of the industry. This knowledge could be gained from previous industrial experience, extensive reading, collaborative teaching with personnel from local companies, or an industrial sabbatical.

CONCLUSIONS

This new course on biotech manufacturing facility design and regulatory compliance is a unique experience for chemical engineering students who are planning to join the biotech or biopharmaceutical industry after graduation. The reception from students and industry alike has been overwhelmingly favorable. Both groups see the information disseminated through this course as practical, and mastery of the subject matter allows the students to make a more rapid transition to industry and thereby to become productive sooner.

ACKNOWLEDGMENTS

The author would like to acknowledge the support and encouragement of Professors Karen McDonald, Alan Jackman, and Subhash Risbud in the Department of Chemical Engineering and Materials Science at the University of California, Davis, during the development of this new course and its transition to a permanent, required course. Acknowledgment is also extended to the various companies that sent representatives to talk to students over the last four years (Digital Welding Systems, ITT PureFlo Valves, Millipore, Amersham Pharmacia Biotech, Ingold Mettler Toledo, and New Brunswick Scientific) and the companies who allowed us to visit their sites, including Genentech, Chiron, and AgraQuest. The author would also like to thank Professor Michael Delwiche at UC Davis for the demonstration of PLCs in his laboratory.

REFERENCES

1. Aiba, S., A.E. Humphrey, and N.F. Millis, *Biochemical Engineering,* 2nd ed., Academic Press, New York, NY (1973)
2. Bailey, J.E., and D.F. Ollis, *Biochemical Engineering Fundamentals,* 2nd ed., McGraw-Hill, New York, NY (1986)
3. Shuler, M.L., and F. Kargi, *Bioprocess Engineering: Basic Concepts,* Prentice Hall, Englewood Cliffs, NJ (1992)
4. Blanch, H.W., and D.S. Clark, *Biochemical Engineering,* Marcel Dekker, New York, NY (1996)
5. Belter, P.A., E.L. Cussler, and W.-S. Hu, *Bioseparations: Downstream Processing for Biotechnology,* John Wiley & Sons, New York, NY (1988)
6. Peters, M.S., and K.D. Timmerhaus, *Plant Design and Economics for Chemical Engineers,* 3rd ed., McGraw-Hill Book Company, New York, NY (1980)
7. www.phrma.org
8. Lyderson, B.K., N.A. D'Elia, and K.L. Nelson, eds, *Bioprocess Engineering: Systems, Equipment, and Facilities,* John Wiley & Sons, New York, NY (1994)
9. FDA, "Guideline on General Principles of Process Validation" (1987) ❐

ChE books received

Principles of Condensed Matter Physics, by P.M. Chaikin and T.C. Lubensky; Cambridge University Press, 40 West 20th Street, New York, NY 10011-4211; 694 pages, $69.95 (hardback), $47.95 (paperback) (2000)

An Introduction to Nonlinear Chemical Dynamics: Oscillations, Waves, Patterns, and Chaos, by Irving R. Epstein and John A. Pojman; Oxford University Press, 198 Madison Avenue, New York NY 10016; 392 pages, $75 (1998)

Polymers in Sensors: Theory and Practice, edited by Naim Akmal and Arthur M. Usmani; ACS Symposium Series 690; Oxford University Press, 198 Madison Avenue, New York NY 10016; 302 pages (1998)

Energy Storage Systems for Electronics, Edited by Tetsuya Osaka and Madhav Datta; Gordon and Breach Science Publishers; 579 pages, $145 (2000)

Oxford Dictionary of Biochemistry and Molecular Biology, edited by A.D. Smith, S.P. Datta, and G. Howard; Oxford University Press, 198 Madison Ave., New York, NY 10016; 738 pages, $60 (1997)

Fundamentals of Industrial Catalytic Processes, by R.J. Farrauto and C.H. Bartholomew; Blackie Academic & Professional; 754 pages $149 (1997)

Fluid Dynamics and Transport of Droplets and Sprays, by William A. Sirignano; Cambridge University Press, 40 West 20th Street, New York, NY 10011-4211; 311 pages, $80 (1999)

Flow Measurement Handbook: Industrial Designs, Operating Principles, Performance, and Applications, by Roger C. Baker; Cambridge University Press, 40 West 20th Street, New York, NY 10011-4211; 524 pages, $110 (2000)