

SCHEDULE 14A INFORMATION

Proxy Statement Pursuant to Section 14(a) of  
the Securities Exchange Act of 1934

Filed by the Registrant /X/  
Filed by a Party other than the Registrant / /

Check the appropriate box:  
/X/ Preliminary Proxy Statement  
/ / Confidential, for Use of the Commission Only (as permitted  
by Rule 14a-6(e)(2))  
/ / Definitive Proxy Statement  
/ / Definitive Additional Materials  
/ / Soliciting Material under Rule 14a-12

ISIS PHARMACEUTICALS, INC.

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(Name of Registrant as Specified In Its Charter)

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(Name of Person(s) Filing Proxy Statement, if other than the  
Registrant)

Payment of Filing Fee (Check the appropriate box)

/X/ No fee required.  
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1. Title of each class of securities to which transaction  
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2. Aggregate number of securities to which transaction  
applies:  
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Exchange Act Rule 0-11(a)(2) and identify the filing for which  
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1. Amount Previously Paid:  
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2. Form, Schedule or Registration Statement No.:  
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4. Date Filed:  
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ISIS PHARMACEUTICALS, INC.  
2292 FARADAY AVENUE  
CARLSBAD, CA 92008

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NOTICE OF  
2001 ANNUAL MEETING OF STOCKHOLDERS  
AND PROXY STATEMENT  
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Dear Stockholders,

I am pleased to invite you to Isis Pharmaceuticals' 2001 Annual Meeting of Stockholders. We will host the meeting at our offices in Carlsbad, California on Friday, April 6 at 2:30 P.M. In addition to covering the formal items on the agenda, we will review the major developments of the past year and answer your questions.

This booklet includes the agenda for this year's Annual Meeting and the Proxy Statement. The Proxy Statement explains the matters we will discuss in the meeting, and provides general information about Isis Pharmaceuticals.

Your vote is very important. Whether or not you plan to attend the meeting, please complete, date, sign and return the enclosed proxy as soon as possible to ensure your representation at the meeting. We have provided a postage-paid envelope for your convenience. If you plan to attend the meeting and prefer to vote in person, you may still do so even if you have already returned your proxy.

If you are a stockholder of record (that is, if your stock is registered with us in your own name), you may vote by telephone, or electronically through the Internet, by following the instructions included with your proxy card. If your shares are registered in the name of a broker or other nominee, your nominee may be participating in a program provided through ADP Investor Communication Services that allows you to vote by phone or the Internet. If so, the voting form your nominee sends you will provide telephone and Internet instructions.

PLEASE NOTE, HOWEVER, THAT IF A BROKER, BANK OR OTHER NOMINEE HOLDS YOUR SHARES OF RECORD AND YOU WISH TO VOTE AT THE MEETING, YOU MUST OBTAIN A PROXY ISSUED IN YOUR NAME FROM THE BROKER, BANK OR NOMINEE.

We look forward to seeing you at the meeting.

Sincerely,

/s/ B. Lynne Parshall  
SECRETARY

ISIS PHARMACEUTICALS, INC.  
2292 FARADAY AVENUE  
CARLSBAD, CA 92008

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NOTICE OF 2001 ANNUAL MEETING OF STOCKHOLDERS  
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DATE: Friday, April 6

TIME: 2:30 P.M.

PLACE: Isis Pharmaceuticals  
2292 Faraday Avenue  
Carlsbad, CA 92008

Dear Stockholders,

At our 2001 Annual Meeting, we will ask you to:

- Elect two Directors to serve for a three-year term;
- Approve an amendment to our Restated Certificate of Incorporation to increase the authorized number of shares of Common Stock from 50,000,000 to 100,000,000 shares;
- Ratify the selection of Ernst & Young LLP as independent auditors for 2001; and
- Transact any other business that may properly be presented at the Annual Meeting.

The foregoing items of business are more fully described in the enclosed Proxy Statement.

If you were an Isis stockholder of record at the close of business on February 15, 2001 you may vote at the Annual Meeting.

By order of the Board of Directors,

/s/ B. Lynne Parshall  
SECRETARY

Carlsbad, California  
March 6, 2001

ALL STOCKHOLDERS ARE CORDIALLY INVITED TO ATTEND THE MEETING IN PERSON. WHETHER OR NOT YOU EXPECT TO ATTEND THE MEETING, PLEASE COMPLETE, DATE, SIGN AND RETURN THE ENCLOSED PROXY AS PROMPTLY AS POSSIBLE IN ORDER TO ENSURE YOUR REPRESENTATION AT THE MEETING. A RETURN ENVELOPE (WHICH IS POSTAGE PREPAID IF MAILED IN THE UNITED STATES) IS ENCLOSED FOR THAT PURPOSE. ALTERNATIVELY, YOU MAY VOTE BY PHONE OR INTERNET BY FOLLOWING THE INSTRUCTIONS INCLUDED IN THIS PROXY STATEMENT AND WITH YOUR PROXY CARD. EVEN IF YOU HAVE GIVEN YOUR PROXY, YOU MAY STILL VOTE IN PERSON IF YOU ATTEND THE MEETING. PLEASE NOTE, HOWEVER, THAT IF YOUR SHARES ARE HELD OF RECORD BY A BROKER, BANK OR OTHER NOMINEE AND YOU WISH TO VOTE AT THE MEETING, YOU MUST OBTAIN FROM THE RECORD HOLDER A PROXY ISSUED IN YOUR NAME.

ISIS PHARMACEUTICALS, INC.  
2292 FARADAY AVENUE  
CARLSBAD, CA 92008

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PROXY STATEMENT  
INFORMATION ABOUT THE 2001 ANNUAL MEETING AND VOTING  
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GENERAL

The enclosed proxy card has been sent to you by the Board of Directors of Isis Pharmaceuticals, Inc., a Delaware corporation, for use at the 2001 Annual Meeting of Stockholders to be held on Friday, April 6, 2001, at 2:30 P.M. local time, or at any adjournment or postponement thereof, for the purposes stated herein. The Annual Meeting will be held at 2292 Faraday Avenue, Carlsbad, California. This Proxy Statement summarizes the information you will need to know to vote in an informed manner.

VOTING RIGHTS AND OUTSTANDING SHARES

We will begin mailing this Proxy Statement and accompanying proxy card on or about March 6, 2001 to all stockholders who are entitled to vote. Only stockholders who owned our Common Stock at the close of business on February 15, 2001 are entitled to vote at the Annual Meeting. On this record date, we had 40,156,890 shares of our Common Stock outstanding.

Each share of our Common Stock that you own entitles you to one vote. The proxy card indicates the number of shares of our Common Stock that you own. The inspector of election will separately tabulate affirmative and negative votes, abstentions and broker non-votes. Abstentions will count as a cast vote that has the same effect as a negative vote. The inspector of election will count broker non-votes towards a quorum. Except for Proposal 2, broker non-votes will not count towards whether the stockholders have approved a proposal. With respect to Proposal 2, abstentions and broker non-votes will have the same effect as negative votes.

You may vote in one of three ways:

- Attend the 2001 Annual Meeting and vote in person;
- Complete, sign, date and return the enclosed proxy card; or
- Vote by telephone or the Internet by following the instructions included with your proxy card.

SOLICITATION

We will bear the entire cost of solicitation of proxies, including preparation, assembly, printing and mailing of this Proxy Statement, the proxy card and any additional information furnished to stockholders. Copies of solicitation materials will be furnished to banks, brokerage houses, fiduciaries and custodians holding in their names shares of our Common Stock beneficially owned by others to forward to such beneficial owners. We may reimburse persons representing beneficial owners of Common Stock for their costs of forwarding solicitation materials to such beneficial owners. Original solicitation of proxies by mail may be supplemented by telephone, telegram or personal solicitation by directors, officers or other employees of Isis or, at our request, Georgeson Shareholder Communications Inc., a professional proxy solicitation firm. No additional compensation will be paid to directors, officers or other employees for such services, but Georgeson Shareholder Communications Inc. will be paid its customary fee, estimated to be about \$10,000, if it renders solicitation services.

## GENERAL INFORMATION FOR ALL SHARES VOTED VIA THE INTERNET OR BY TELEPHONE

Votes submitted via the Internet or by telephone must be received by 12:00 midnight, Eastern Daylight Time, on April 5, 2001. Submitting your proxy via the Internet or by telephone will not affect your right to vote in person should you decide to attend the Annual Meeting.

### FOR SHARES REGISTERED IN YOUR NAME

If you are a stockholder of record, you may go to <http://www.voteproxy.com> to vote your shares by means of the Internet. The votes represented by such proxy will be generated on the computer screen and you will be prompted to submit or revise your votes as desired. If you are using a touch-tone telephone you may also vote your shares by calling 1-800-PROXIES (1-800-776-9437) and following the recorded instructions. You will be required to provide the control number contained on your proxy card when you vote either by telephone or the Internet, so please have it available at the time you are voting.

### FOR SHARES REGISTERED IN THE NAME OF A BROKER OR BANK

Most beneficial owners whose stock is held in street name receive instructions for voting their shares from their bank, broker or other agent, rather than our proxy card.

A number of brokers and banks are participating in a program provided through ADP Investor Communication Services that allows proxies to vote shares to be granted by means of the telephone and Internet. If your shares are held in an account with a broker or bank participating in the ADP Investor Communication Services program, you may vote your shares telephonically by calling the telephone number shown on the instruction form received from your broker or bank, or via the Internet at ADP Investor Communication Services' web site at <http://www.proxyvote.com>.

### REVOCABILITY OF PROXIES

Once you have submitted your proxy by mail, Internet or telephone, you may revoke it at any time before we exercise it. You may revoke your proxy in any one of three ways:

- You may send in by mail another proxy marked with a later date;
- You may notify our Secretary in writing that you wish to revoke your proxy before the Annual Meeting takes place; or
- You may vote in person at the Annual Meeting. ATTENDANCE at the meeting WILL NOT, by itself, revoke a proxy.

### STOCKHOLDER PROPOSALS

If you have a proposal or director nomination that you would like to be included in our proxy statement and form of proxy for, or to be presented at, the 2002 Annual Meeting of Stockholders, you must send the proposal to Isis by no later than November 6, 2001. Stockholders wishing to submit proposals or director nominations that are not to be included in such proxy statement and proxy must do so no earlier than the close of business on December 7, 2001 and no later than the close of business on January 6, 2002. Stockholders are also advised to review our Bylaws, which contain additional requirements with respect to advance notice of stockholder proposals and director nominations.

### PROPOSAL 1 ELECTION OF DIRECTORS

### INFORMATION ABOUT OUR BOARD OF DIRECTORS

The Board is divided into three classes, each consisting as nearly as possible of one third of the total number of directors. Presently, the Board has six members, each class consisting of two directors.

Each class serves a three-year term, and we hold elections each year at the Annual Meeting to elect the directors whose terms have expired.

During the course of a term, the Board may elect a new director to fill any vacant spot, including a vacancy caused by an increase in the size of the Board. The new director will finish out the term of the director he or she replaced. One Board member, B. Lynne Parshall, was elected in September 2000. Two Board members, Larry Soll and Alan C. Mendelson, resigned in July 2000 and January 2001, respectively.

#### INFORMATION ABOUT THE 2001 ELECTIONS

The Board has nominated two directors for election at the 2001 Annual Meeting. Each of the nominees currently serves as one of our directors. If re-elected, each will serve until the 2004 annual meeting or until his successor is elected and has qualified.

Our stockholders elect directors by a plurality of the votes of the shares present in person or represented by proxy at the meeting and entitled to vote in the election of directors. Shares represented by executed proxies will be voted for the election of the nominees listed below, unless authority to vote in favor of the nominees is withheld. Each person nominated for election has agreed to serve if elected, and we have no reason to believe that any nominee will be unable to serve. However, if any nominee cannot serve, your proxy may vote for another nominee proposed by the Board, or the Board may reduce the number of directors.

We provide below a short biographical description of each of the nominees and of each director whose term of office will continue after the Annual Meeting.

#### BIOGRAPHIES OF NOMINEES FOR ELECTION FOR A THREE-YEAR TERM EXPIRING AT THE 2004

##### ANNUAL MEETING

STANLEY T. CROOKE, M.D., Ph.D., age 56, was a founder of Isis and has been Chief Executive Officer and a director since January 1989. He served as our President from January 1989 to May 1994, and was elected Chairman of the Board in February 1991. SmithKline Beckman Corporation, a pharmaceutical company, employed Dr. Crooke from 1980 until January of 1989, where his titles included President of Research and Development of SmithKline and French Laboratories. Dr. Crooke is Chairman of the Board of Idun Pharmaceuticals, Inc., a pharmaceutical company. He also serves as a director of Valentis, Inc., SYNSORB Biotech Inc., and EPIX Medical, Inc. He is also an adjunct professor of pharmacology at the Baylor College of Medicine and the University of California, San Diego.

MARK B. SKALETSKY, age 52, has served as a director of Isis since January 1989. From May 1993 to January 2001, Mr. Skaletsky served as President and Chief Executive Officer of GelTex Pharmaceuticals, Inc., a biopharmaceutical company. From 1989 to 1993, Mr. Skaletsky was Chairman of Enzytech, Inc., a biopharmaceutical company, and Chief Executive Officer of Enzytech from 1988 to 1993. From 1998 to present, Mr. Skaletsky has been a director of Microcide Pharmaceuticals, Inc., a biotechnology company, and from August 2000 to present, he has been a director of ImmunoGen, Inc., a biotechnology company. He is also currently Chairman of the Biotechnology Industry Organization. In addition, Mr. Skaletsky is a member of the Board of Trustees of Bentley College located in Waltham, MA.

THE BOARD RECOMMENDS THAT YOU VOTE IN FAVOR OF THE ELECTION OF EACH OF THE ABOVE NOMINEES

#### BIOGRAPHIES OF BOARD MEMBERS CONTINUING UNTIL THE 2002 ANNUAL MEETING

B. LYNNE PARSHALL, age 46, has served as a director of Isis since September 2000. She is Executive Vice President and Chief Financial Officer of Isis and has been with Isis since 1991. Prior to joining Isis, Ms. Parshall was a Partner with the law firm of Cooley Godward LLP. Ms. Parshall is on the Board

of Visitors at Stanford University Law School. Ms. Parshall is also a member of the Licensing Executives Society and a member of the American, California and San Diego bar associations.

JOSEPH H. WENDER, age 56, has served as a director of Isis since January 1994. Mr. Wender is currently Senior Director of the Financial Institutions Group at Goldman, Sachs & Co., an investment banking firm. He joined Goldman, Sachs & Co. in 1971 and became a General Partner of that firm in 1982 and a Limited Partner in 1992. He is also a director of First Coastal Bancshares, a bank holding company, and Event 411, an Internet event planning company.

#### BIOGRAPHIES OF BOARD MEMBERS CONTINUING UNTIL THE 2003 ANNUAL MEETING

WILLIAM R. MILLER, age 72, has served as a director of Isis since March 1991. In January 1991, he retired as Vice Chairman of the Board of Directors of Bristol-Myers Squibb Company, a position he had held since 1985. He is Chairman of the Board of Trustees of the Cold Spring Harbor Laboratory. Mr. Miller is also Chairman of the Board of Vion Pharmaceuticals, Inc., a biopharmaceutical company. He is a director of ImClone Systems, Inc. and Transkaryotic Therapies, Inc., both biopharmaceutical companies, and Westvaco Corporation, a paper/packaging/specialty chemical manufacturer.

CHRISTOPHER F.O. GABRIELI, age 41, has served as a director of Isis since May 1994. Mr. Gabrieli was a founder of Isis and served as a director from January 1989 to May 1992. He is currently a manager of the general partners of Bessemer Venture Partners II L.P., Bessemer Venture Partners III L.P., Bessemer Venture Partners IV L.P. and related venture capital partnerships, where he has worked since 1986. He is Chairman of the Board of EPIX Medical, Inc.

#### THE BOARD OF DIRECTOR COMMITTEES AND MEETINGS

The Board of Directors met six times in 2000, including four regularly scheduled meetings, one special meeting and one special telephone meeting, and acted by unanimous written consent five times. The Board of Directors also has Audit, Compensation and Nominating committees. During 2000, all directors attended 100% of the meetings of the Board and the committees on which they served.

The Audit Committee is currently comprised of three directors, Mr. Wender (Chairman), Mr. Gabrieli and Mr. Skaletsky. All members of our Audit Committee are not officers of Isis and are independent directors under currently applicable rules. Mr. Mendelson, an independent director who resigned from the Board in January 2001, served as Chairman of the Audit Committee during 2000. The Audit Committee has adopted a formal written Audit Committee Charter, which was filed as an appendix to our 2000 Proxy Statement. The Audit Committee met eight times in 2000. The Audit Committee:

- Reviews the annual and quarterly financial statements and oversees the annual and quarterly financial reporting processes;
- Selects our independent auditors;
- Oversees the independence of our independent auditors;
- Evaluates our independent auditor's performance; and
- Receives and considers our independent auditor's comments as to controls, adequacy of staff and management performance and procedures in connection with audit and financial controls.

The Compensation Committee is comprised of Mr. Skaletsky (Chairman), Mr. Miller and Mr. Wender, all of whom are non-employee directors of Isis. The committee met two times in 2000 and acted by unanimous written consent twenty times. The Compensation Committee:

- Makes recommendations concerning executive salaries and incentive compensation;

- Awards stock options, bonus stock and rights to purchase restricted stock under our 1989 Stock Option Plan and 2000 Broad-Based Equity Incentive Plan;
- Administers our 1989 Stock Option Plan and 2000 Employee Stock Purchase Plan; and
- Determines executive compensation levels and performs other functions regarding compensation as the Board requests.

The Nominating Committee currently consists of two non-employee directors: Mr. Gabrieli (Chairman) and Mr. Wender. In 2000, the Nominating Committee was comprised of two non-employee directors, Mr. Mendelson and Dr. Soll, both of whom were non-employee directors and have resigned from the Board. The committee did not meet in 2000. The Nominating Committee:

- Interviews, evaluates, nominates and recommends individuals for membership on our Board of Directors and its committees; and
- Considers nominees whom our stockholders may recommend.

In the event a stockholder would like to request the nomination of a director at a meeting, the stockholder must submit written information which provides:

- the name, age, business address and residence address of the proposed nominee;
- the principal occupation or employment of such proposed nominee;
- the class and number of shares of Isis beneficially owned by such proposed nominee; and
- a description of all arrangements or understandings between the stockholder and each proposed nominee and any other person or persons who are to be nominated by the stockholder.

#### PROPOSAL 2

##### APPROVAL OF INCREASE IN NUMBER OF AUTHORIZED SHARES OF COMMON STOCK

The Board of Directors has adopted, subject to stockholder approval, an amendment to Isis' Restated Certificate of Incorporation to increase the authorized number of shares of our Common Stock from 50,000,000 shares to 100,000,000 shares.

The additional Common Stock to be authorized by adoption of the amendment would have rights identical to our currently outstanding Common Stock. Adoption of the proposed amendment and issuance of the Common Stock would not affect the rights of the holders of our Common Stock, Series A Preferred Stock or Series B Preferred Stock, except for effects incidental to increasing the number of shares of our Common Stock outstanding, such as dilution of the earnings per share and voting rights of current holders of our Common Stock. If the amendment is adopted, it will become effective upon filing of a Certificate of Amendment of our Restated Certificate of Incorporation with the Secretary of State of the State of Delaware. The complete text of the Certificate of Amendment to the Restated Certificate that would be filed with the Secretary of State of the State of Delaware is set forth in Exhibit A to this Proxy Statement. However, the text of the Certificate of Amendment is subject to revision to include such changes as may be required by the Secretary of State of the State of Delaware and as the Board deems necessary and advisable to effect the proposed amendment of our Restated Certificate of Incorporation.

In addition to the 40,119,564 shares of Common Stock outstanding at January 12, 2001, we have reserved 2,634,463 shares of Common Stock for possible issuance under a Form S-3 shelf registration statement currently on file with the Securities and Exchange Commission (the "SEC"). Also as of January 12, 2001, there were 7,533,560 shares of Common Stock issuable upon exercise of outstanding options granted under our stock option plans and 3,364,012 shares of Common Stock subject to future issuance under our equity plans. Isis has also issued warrants and convertible debt which, on January 12, 2001, would have been exercisable and convertible into an aggregate of 4,443,500 shares of Common Stock. In addition, we have outstanding 120,150 shares of Series A Preferred Stock and 12,015 shares of Series B Preferred Stock which is convertible into Common Stock on March 31, 2002 and June 30, 2002, respectively. The Preferred Stock converts into Common Stock at a premium to market at the time of conversion. If our Preferred Stock were convertible on January 12, 2001, it would convert into an aggregate of 1,984,345 shares of Common Stock on such date.

Although at present the Board of Directors has no other plans to issue the additional shares of Common Stock other than in the ordinary course of business to employees and directors under our stock option and other equity plans, it desires to have the shares available to provide Isis additional flexibility for business and financial purposes in the future. The additional shares may be used, without further stockholder approval, for various purposes including, without limitation, raising capital, providing equity incentives to employees, directors or consultants, establishing strategic relationships with other companies and expanding our business or product lines through the acquisition of other businesses or products.

Isis could also use the additional shares of Common Stock that would become available for issuance if this proposal were adopted to oppose a hostile takeover attempt or delay or prevent changes in control or management of Isis. For example, without further stockholder approval, the Board could strategically sell shares of Common Stock in a private transaction to purchasers who would oppose a takeover or favor the current Board. Although this proposal to increase the authorized Common Stock has been prompted by business and financial considerations and not by the threat of any hostile takeover attempt, nor is the Board currently aware of any such attempts directed at Isis, nevertheless, stockholders should be aware that approval of this proposal could facilitate future efforts by us to deter or prevent changes in control of Isis, including transactions in which the stockholders might otherwise receive a premium for their shares over then current market prices.

The affirmative vote of the holders of a majority of the outstanding shares of the Common Stock on the record date will be required to approve this amendment to the our Restated Certificate of Incorporation. As a result, abstentions and broker non-votes will have the same effect as negative votes.

THE BOARD OF DIRECTORS RECOMMENDS A VOTE IN FAVOR OF PROPOSAL 2

PROPOSAL 3  
RATIFICATION OF SELECTION OF INDEPENDENT AUDITORS

The Board of Directors has selected Ernst & Young LLP as our independent auditors for the fiscal year ending December 31, 2001, and has requested management to ask for stockholder ratification at the Annual Meeting. Ernst & Young LLP has audited our financial statements since we were founded in 1989. Representatives of Ernst & Young LLP will be at the 2001 Annual Meeting to answer any questions and make a statement should they choose to do so.

Although our Bylaws do not require stockholders to approve our independent auditors, the Board would like to hear the stockholders' opinion as a matter of good corporate practice. If the stockholders vote against Ernst & Young LLP, the Board will reconsider whether or not to keep the firm. However, even if the stockholders ratify the selection, the Board may choose to appoint a different independent

accounting firm at any time during the year if it believes that a change would be in the best interests of Isis and its stockholders.

To ratify the selection of Ernst & Young LLP, the holders of a majority of shares present in person or represented by proxy and entitled to vote at the 2001 Annual Meeting must vote in favor of Proposal 3.

During the fiscal year ended December 31, 2000, the aggregate fees billed by Ernst & Young LLP for the audit of our financial statements for such fiscal year and for the reviews of our interim financial statements was \$55,450.

During the fiscal year ended December 31, 2000, there were no fees billed by Ernst & Young LLP for information technology consulting fees.

During the fiscal year ended December 31, 2000, the aggregate fees billed by Ernst & Young LLP for professional services other than audit and information technology consulting fees was \$28,890.

The Audit Committee has determined the rendering of all other non-audit services by Ernst & Young LLP is compatible with maintaining the auditor's independence.

During the fiscal year ended December 31, 2000, none of the total hours expended on our financial audit by Ernst & Young LLP were provided by persons other than Ernst & Young LLP's full-time permanent employees.

THE BOARD OF DIRECTORS RECOMMENDS A VOTE IN FAVOR OF PROPOSAL 3

SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT

This table outlines the ownership of our Common Stock as of January 12, 2001 by:

- Each director and nominee for director;
- Each executive officer named in the Summary Compensation Table under "Executive Compensation--Compensation of Executive Officers";
- All directors and executive officers as a group; and
- Every entity that we know beneficially owns more than five percent of our Common Stock.

BENEFICIAL OWNER -----	BENEFICIAL OWNERSHIP(1)	
	NUMBER OF SHARES	PERCENT OF TOTAL(2)
-----	-----	-----
Citigroup Inc.(3) .....		
153 Greenwich Street		
New York, NY 10043	8,252,133	20.6
Novartis Pharma AG(4) .....		
Lichtstrasse 35		
CH-4002, Basel		
Switzerland	2,354,150	5.9
Elan International Services, Ltd.(5) .....		
102 St. James Court		
Flatts, Smiths FL 04		
Bermuda	2,176,295	5.3
Stanley T. Crooke(6).....	1,324,291	3.3
Christopher F. O. Gabrieli(7).....	1,269,349	3.2
William R. Miller(8).....	62,500	*
B. Lynne Parshall(9).....	289,070	*
Mark B. Skaletsky(10).....	49,500	*
Joseph H. Wender(11).....	73,500	*
C. Frank Bennett(12).....	116,586	*
Douglas L. Cole(13).....	178,242	*
F. Andrew Dorr(14).....	61,854	*
All directors and executive officers as a group (13 persons)(15).....	3,850,008	9.3
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\* Less than one percent.

(1) This table is based upon information supplied by officers, directors and principal stockholders and Schedules 13D and 13G filed with the SEC. Unless otherwise indicated in the footnotes to this table and subject to community property laws where applicable, Isis believes that each of the stockholders named in this table has sole voting and investment power with respect to the shares indicated as beneficially owned.

(2) Applicable percentages are based on 40,119,564 shares of Common Stock outstanding on January 12, 2001, adjusted as required by rules promulgated by the SEC.

(3) Includes 6,696,638 shares held by Salomon Smith Barney Inc., 1,468,650 shares held by SSB Citi Fund Management LLC, 82,715 shares held by Smith Barney Private Trust Company, and

4,130 shares held by Citibank, N.A., all directly or indirectly wholly-owned subsidiaries of Citigroup Inc.

- (4) Includes 38,053 shares of Common Stock held by Novartis Pharmaceuticals Corporation and 97,097 shares of Common Stock held by Genetic Therapy Inc. Novartis Pharmaceuticals Corporation and Genetic Therapy Inc. are Delaware corporations and are directly or indirectly wholly-owned subsidiaries of Novartis Pharma AG.
- (5) Includes 737,951 shares of Common Stock issuable upon conversion of outstanding convertible notes, and 229,881 shares of Common Stock issuable upon exercise of outstanding warrants. Also includes 910,844 shares and 297,619 shares of Common Stock held by Elan Pharmaceutical Investments Ltd. and Elan Pharmaceutical Investments II, Ltd., respectively, both affiliates of Elan International Services, Ltd. and both wholly-owned subsidiaries of Elan Corporation, plc.
- (6) Includes 288,516 shares of Common Stock issuable upon exercise of options held by Dr. Crooke that are exercisable on or before March 13, 2001 and 18,534 shares of Common Stock issuable upon exercise of options held by Rosanne Crooke, Dr. Crooke's wife, that are exercisable on or before March 13, 2001. Dr. Crooke disclaims beneficial ownership of the shares of Common Stock issuable upon exercise of options held by his wife.
- (7) Includes 759,566 shares of Common Stock held of record by Bessemer Venture Partners II ("BVP II"), 329,479 shares of Common Stock held of record by Bessemer Venture Partners III ("BVP III") and 740 shares of Common Stock held of record by the Gabrieli Family Foundation ("GFF"). Mr. Gabrieli is a Manager of Deer II & Co. LLC and of Deer III & Co. LLC, the General Partners of BVP II and BVP III, respectively, and disclaims beneficial ownership of the shares of Common Stock held of record by or issuable to BVP II and BVP III, except to the extent of his respective interests therein. Mr. Gabrieli is a trustee of GFF and disclaims beneficial ownership of the shares of Common Stock held of record by or issuable to GFF. Also includes 53,000 shares of Common Stock issuable upon exercise of options held by Mr. Gabrieli that are exercisable on or before March 13, 2001.
- (8) Includes 20,500 shares of Common Stock issuable upon exercise of options held by Mr. Miller that are exercisable on or before March 13, 2001
- (9) Includes 269,839 shares of Common Stock issuable upon exercise of options held by Ms. Parshall that are exercisable on or before March 13, 2001, and an aggregate of 18,554 shares of Common Stock issuable upon exercise of options which Ms. Parshall transferred to her daughters that are exercisable on or before March 13, 2001.
- (10) Includes 27,500 shares of Common Stock issuable upon exercise of options held by Mr. Skaletsky that are exercisable on or before March 13, 2001.
- (11) Includes 42,500 shares of Common Stock issuable upon exercise of options held by Mr. Wender that are exercisable on or before March 13, 2001.
- (12) Includes 116,341 shares of Common Stock issuable upon exercise of options held by Dr. Bennett that are exercisable on or before March 13, 2001.
- (13) Includes 175,815 shares of Common Stock issuable upon exercise of options held by Dr. Cole that are exercisable on or before March 13, 2001.
- (14) Includes 61,854 shares of Common Stock issuable upon exercise of options held by Dr. Dorr that are exercisable on or before March 13, 2001.
- (15) Includes an aggregate of 1,467,490 shares issuable upon exercise of options held by all current directors and executive officers as a group that are exercisable on or before March 13, 2001.

## SECTION 16(a) BENEFICIAL OWNERSHIP REPORTING COMPLIANCE

Section 16(a) of the Securities Exchange Act of 1934 (the "1934 Act") requires Isis' directors and executive officers, and persons who own more than ten percent of a registered class of our equity securities, to file with the SEC initial reports of ownership and reports of changes in ownership of Common Stock and other equity securities of Isis. Officers, directors and greater than ten percent stockholders are required by SEC regulation to furnish us with copies of all Section 16(a) forms they file.

To our knowledge, based solely on a review of the copies of such reports furnished to us and written representations that no other reports were required, during the fiscal year ended December 31, 2000, all Section 16(a) filing requirements applicable to our officers, directors and greater than ten percent beneficial owners were complied with.

## EXECUTIVE COMPENSATION

### COMPENSATION OF DIRECTORS

We pay our non-employee directors a fee of \$15,000 per year. We do not pay additional compensation for attending Board or Board committee meetings, but we do reimburse Board members for the expenses they incur to attend the meetings. For the fiscal year ending December 31, 2000, we paid a total of \$82,500 to our non-employee directors. Dr. Larry Soll resigned in July 2000 and therefore only received \$7,500.

Each non-employee director also receives automatic stock option grants under our 1992 Non-Employee Directors' Stock Option Plan (the "Directors' Plan"). The options are non-discretionary and only non-employee directors may receive options under this plan. On July 1 of each year (or the next business day should this date fall on a weekend or holiday), each non-employee director receives an option to purchase 4,000 shares of our Common Stock under the Directors' Plan. On July 1, 2000, options to purchase an aggregate of 20,000 shares of stock were granted pursuant to the Directors' Plan. The fair market value of the Common Stock (and the exercise price of the options) was \$14.3125 per share (based on the closing sales price reported in the Nasdaq National Market on the date of grant). The options vest over a four year period in equal annual installments.

In addition, upon initial election to the Board, each new non-employee director receives an automatic grant of an option to purchase 18,000 shares of our Common Stock pursuant to the Directors' Plan. The exercise price of all stock option grants under the Directors' Plan is equal to 100% of the fair market value of the Common Stock on the date of the grant.

On January 6, 2000, we also granted each non-employee director a stock option under the 2000 Broad Based Equity Incentive Plan (the "2000 Plan") as retention options. Each non-employee director was granted an option to purchase 10,000 shares of our Common Stock, for an aggregate of 60,000 shares of Common Stock, pursuant to the 2000 Plan, on that date. The exercise price of the options was \$6.81 per share. The options vest annually over a four year period in equal annual installments.

COMPENSATION OF EXECUTIVE OFFICERS

The following table outlines the compensation paid to or earned by our Chief Executive Officer and each of our four other highest paid executive officers whose total annual salary and bonus exceeded \$100,000, for the fiscal years ending December 31, 2000, 1999, and 1998.

SUMMARY COMPENSATION TABLE

NAME AND PRINCIPAL POSITION	YEAR	ANNUAL COMPENSATION			LONG-TERM COMPENSATION AWARDS	
		SALARY (\$)	BONUS (\$)(1)	OTHER ANNUAL COMPENSATION (\$)(2)	SECURITIES UNDERLYING OPTIONS (#)	ALL OTHER COMPENSATION (\$)
Stanley T. Crooke..... Chairman, CEO and President	2000	400,008	257,605	0	250,000(3)	0
	1999	400,008	0	0	35,000	0
	1998	361,992	253,400	0	70,000	0
B. Lynne Parshall..... Executive Vice President & Chief Financial Officer	2000	330,168	172,760	0	170,000(3)	0
	1999	307,723	0	0	25,000	0
	1998	265,368	139,315	0	45,000	0
C. Frank Bennett..... Vice President, Antisense Research	2000	210,187	100,913	0	80,000	0
	1999	179,152	0	0	15,000	0
	1998	160,206	57,574	0	14,000	0
Douglas L. Cole..... Vice President, Development Chemistry & Pharmaceuticals	2000	217,300	74,969	0	50,000	0
	1999	204,472	0	0	10,000	0
	1998	202,428	67,357	0	10,000	0
F. Andrew Dorr..... Vice President, Chief Medical Officer	2000	261,372	109,106	0	118,749(4)	0
	1999	238,225	0	0	20,000	0
	1998	198,887	73,833	0	12,000	0

(1) Bonuses are included here in the years they were earned. Bonuses represent compensation for achievements and are not necessarily paid in the year they are earned; i.e., bonuses for 2000 were paid in January 2001.

(2) As permitted by rules promulgated by the SEC, no amounts are shown for any executive officers where the amounts constitute perquisites and do not exceed the lesser of 10% of the sum of the aggregate amount in the Salary and Bonus columns or \$50,000.

(3) Options will fully vest on January 2, 2006; provided, however, that the options will fully vest on January 2, 2002 if certain performance objectives are met prior to that date. As of January 12, 2001, all of the objectives had been met.

(4) Includes 10,000 options granted to Dr. Dorr in August in association with his promotion and 48,749 options issued in a 2 for 1 stock exchange offered to all non-executive officer employees. At the time of the exchange, Dr. Dorr was not an executive officer.

STOCK OPTION GRANTS AND EXERCISES

Executive officers are granted stock options under our 1989 Stock Option Plan and 2000 Plan. As of December 31, 2000, options to purchase a total of 2,045,643 shares of our Common Stock had been granted under the 1989 Stock Option Plan; options to purchase 2,003,791 shares of our Common Stock had been granted under the 2000 Plan; and options to purchase 20,000 shares of our Common Stock had been granted under our Non-Employee Directors Stock Option Plan during 2000.

The following tables show certain information regarding options granted to, exercised by and held at year end December 31, 2000 by each of the executive officers named in the Summary Compensation Table:

OPTION GRANTS IN LAST FISCAL YEAR

NAME	INDIVIDUAL GRANTS				POTENTIAL REALIZABLE VALUE AT ASSUMED ANNUAL RATES OF STOCK PRICE APPRECIATION FOR OPTION TERM(3)	
	NUMBER OF SECURITIES UNDERLYING OPTIONS GRANTED (#)(1)	% OF TOTAL OPTIONS GRANTED TO EMPLOYEES IN FISCAL YEAR(2)	EXERCISE PRICE (\$/SH)	EXPIRATION DATE	5% (\$)	10% (\$)
Stanley T. Crooke.....	250,000(4)	6.2	\$ 6.8125	01-05-10	1,070,715	2,713,189
B. Lynne Parshall.....	170,000(4)	4.2	\$ 6.8125	01-05-10	728,086	1,844,969
C. Frank Bennett.....	60,000 20,000(5)	1.5 0.5	\$ 6.8100 6.2500	01-05-10 12-31-09	257,122 78,585	651,315 199,133
Douglas L. Cole.....	50,000	1.2	\$ 6.8100	01-05-10	214,268	542,762
F. Andrew Dorr.....	48,749(6) 60,000 10,000(7)	1.2 1.5 0.2	\$ 6.8100 6.8100 12.1875	12-31-02 01-05-10 08-15-10	20,679 257,122 76,620	73,444 651,315 194,155

- (1) Options granted in 2000 vest over a four-year period: 25% after the first year and 2.08% per month thereafter except those noted.
- (2) Based on options to purchase an aggregate of 4,046,134 shares granted in 2000 under our 1989 Stock Option Plan and our 2000 Plan. This is not necessarily indicative of the number of options that will be granted in the future.
- (3) The potential realizable value is calculated based on the term of the option at its time of grant, based on the assumption that the market value of the underlying stock increases at the stated values, compounded annually.
- (4) Reflects options that will fully vest on January 2, 2006; provided, however, that the options will fully vest on January 2, 2002 if certain performance objectives are met prior to that date. As of January 12, 2001, all of the objectives had been met.
- (5) Includes 20,000 options granted to Dr. Bennett in January 2000 in connection with his promotion.
- (6) Reflects 48,749 options issued in a 2 for 1 stock exchange offered to all non-executive officer employees. At the time of the exchange, Dr. Dorr was not an executive officer.
- (7) Includes 10,000 options granted to Dr. Dorr in August in association with his promotion.

AGGREGATED OPTION EXERCISES IN LAST FISCAL YEAR AND FY-END OPTION VALUES

NAME	SHARES ACQUIRED ON EXERCISE (#)	VALUE REALIZED (\$)(1)	NUMBER OF SECURITIES UNDERLYING UNEXERCISED OPTIONS AT FISCAL YEAR END (#)	VALUE OF UNEXERCISED IN-THE-MONEY OPTIONS AT FISCAL YEAR END (\$)(2)
			EXERCISABLE/ UNEXERCISABLE	EXERCISABLE/ UNEXERCISABLE
Stanley T. Crooke.....	0	0	281,483/287,659	\$632,923/\$953,125
B. Lynne Parshall.....	62,335	\$1,624,437	283,664/195,564	\$459,986/\$648,125
C. Frank Bennett.....	3,700	\$ 71,906	91,007/91,793	\$4,169/\$316,400
Douglas L. Cole.....	0	0	159,804/58,096	\$635,738/\$190,750
F. Andrew Dorr.....	4,416	\$ 59,600	36,259/110,074	\$85,239/\$329,639

- (1) Fair market value of our Common Stock on the date of exercise minus the exercise price.
- (2) Fair market value of our Common Stock at December 31, 2000 (\$10.625) multiplied by the applicable number of shares minus the aggregate exercise price of the options for the number of shares.

EMPLOYMENT AGREEMENTS, TERMINATION OF EMPLOYMENT AND CHANGE IN CONTROL ARRANGEMENTS

In January 2000, we entered into agreements with certain key employees pursuant to which we agreed to provide the covered employees with severance benefits under certain conditions, including Stanley T. Crooke, B. Lynne Parshall, C. Frank Bennett, Douglas L. Cole and F. Andrew Dorr. In the event that a covered employee's employment is terminated without "cause," as defined in the agreement, by Isis on or before December 31, 2001 (the "Severance Period"), the employee will be eligible to receive a severance payment equal to a minimum of six months of his or her then current base salary, less payroll deductions and withholdings.

In the event that the covered employee's employment is terminated by us during the Severance Period as a result of a reduction of our workforce or the employee elects to terminate his or her employment with Isis as a result of substantial change in his or her primary job duties, the severance payment will be increased to at least nine months of the covered employee's then current base salary, less payroll deductions and withholdings.

In the event that the covered employee's employment is terminated by Isis during the Severance Period as a result of a "change in control" as defined in the agreement, the employee's severance payment will be increased so that he or she will receive a total of 24 months of his or her then current base salary, less payroll deductions and withholdings.

COMPENSATION COMMITTEE REPORT(1)

The Compensation Committee of the Board of Directors consists of Mark B. Skaletsky, Chairman, William R. Miller and Joseph H. Wender, none of whom has ever been an officer or employee of Isis. The Compensation Committee's responsibilities include:

- Making recommendations concerning executive salaries and incentive compensation;
- Awarding stock options, bonus stock and rights to purchase restricted stock under our 1989 Stock Option Plan and the 2001 Broad-Based Equity Incentive Plan;
- Administering our 2001 Employee Stock Purchase Plan; and
- Determining executive compensation levels and performing other functions regarding compensation as the Board of Directors requests.

The full Board of Directors reviews the Compensation Committee's recommendations regarding the compensation of executive officers.

COMPENSATION COMMITTEE INTERLOCKS AND INSIDER PARTICIPATION

As noted above, during the fiscal year ended December 31, 2000, our Compensation Committee was composed of Messrs. Skaletsky, Miller and Wender, none of which have ever been employees or officers of Isis. None of our executive officers serves as a member of the board of directors or compensation committee of any entity that has one or more executive officers serving as a member of our Board of Directors or Compensation Committee.

EXECUTIVE COMPENSATION

We design our executive compensation programs to attract and retain executives who can help us meet our business objectives and to motivate them to enhance long-term stockholder value. The executive officers' annual compensation consists of three elements: cash salary, a cash incentive bonus and stock option grants.

To determine fair compensation, the Compensation Committee reviews historical and current salary, bonus and stock award information for other comparable companies in similar geographic areas and at similar stages of growth and development. The group of comparable companies is not necessarily the same as the companies included in the market indices included in the performance graph in this Proxy Statement. The Compensation Committee also reviews a variety of industry surveys throughout the year, which provide additional information about short and long-term executive compensation. Based in part on this information, the Compensation Committee generally sets salaries, including that of our Chief Executive Officer, at levels comparable to competitive companies of comparable size in similar industries. We structure our management bonus program around both individual and Company performance. We base the total size of the cash bonus pool on our success in meeting performance goals for the year, accounting for changes the Compensation Committee discusses and agrees to during the course of the year.

We use our stock option program to give management employees a substantial economic interest in the long-term appreciation of our Common Stock. We grant existing members of management new options on an annual basis to provide a continuing financial incentive. The size of the individual annual option grants is related to the executive's position and performance in the previous year.

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(1) The material in this report is not "soliciting material," is not deemed filed with the SEC and is not to be incorporated by reference in any filing of Isis under the Securities Act of 1933, as amended (the "1933 Act"), or the 1934 Act.

The following table shows certain information concerning the repricing of options received by the Named Executive Officers during the last ten years.

OPTION REPRICING INFORMATION

NAME	DATE	NUMBER OF SECURITIES UNDERLYING OPTIONS/SARS REPRICED OR AMENDED (#)	MARKET PRICE OF STOCK AT TIME OF REPRICING OR AMENDMENT (\$)	EXERCISE PRICE AT TIME OF REPRICING OR AMENDMENT (\$)	NEW EXERCISE PRICE (\$)	LENGTH OF ORIGINAL OPTION TERM REMAINING AT DATE OF REPRICING OR AMENDMENT
F. Andrew Dorr Vice President, Chief Medical Officer	1-1-00	48,749(1)	6.25	(2)	6.81	(2)

(1) These shares were issued in connection with a stock option exchange program offered to all non-executive officer employees. This program was not offered to executive officers or directors, and Dr. Dorr was not an executive officer at the time he participated. The options were exchanged at a ratio of 2 existing option shares for each 1 exchanged option share (option shares rounded down and each grant calculated individually).

(2) 90,000 options with an exercise price of \$18.125 granted on June 1, 1996 would have been fully vested in five months from the date of the exchange; 7,500 options with an exercise price of \$18.00 granted on January 1, 1997 would have been fully vested in one year from the date of the exchange. The remaining terms of the cancelled options were six years and seven years, respectively.

TAXES

Under Section 162(m) of the Internal Revenue Code of 1986, as amended, we can only deduct up to \$1 million of compensation we pay to certain executive officers each taxable year. However, we may deduct compensation above \$1 million if it is "performance based compensation" within the meaning of the Internal Revenue Code. The Compensation Committee has determined that stock options granted under the 1989 Stock Option Plan with an exercise price at least equal to the fair market value of our Common Stock on the date of grant will be treated as performance-based compensation.

ASSESSMENT OF 2000

We set extremely challenging objectives for 2000. In achieving the majority of those objectives, we made significant progress in the following areas:

- We received \$161 million in cash of which approximately \$137 million was from new sources;
- We initiated a collaboration between our Ibis Therapeutics division and Agouron Pharmaceuticals, Inc., a Pfizer company;
- We completed Phase II clinical trials for ISIS 3521 in non-small cell lung cancer and achieved positive results. The FDA granted Isis fast track review status for ISIS 3521 in non-small cell lung cancer and approved the start of Phase III clinical trials;
- We re-analyzed the Phase IIb results of ISIS 2302 in Crohn's disease using a population pharmacokinetics analysis and determined sufficient activity to initiate a new Phase II trial at higher doses;
- We initiated Phase I clinical trials for ISIS 104838, Isis' first second generation chemistry;

- We initiated GeneTrove-TM- collaborations with the R. W. Johnson Pharmaceutical Research Institute, a member of the Johnson & Johnson family of companies, and AstraZeneca plc and extended our Abbott Laboratories, Inc. collaboration to include commercial scale manufacturing;
- We initiated Phase I/II clinical trials for ISIS 14803 for Hepatitis C;
- We achieved expense reductions of approximately \$9 million as a result of our restructuring plan;
- We identified a drug candidate for Type 2 Diabetics which inhibits the PTP-1B gene;
- We demonstrated that topically delivered ISIS 2302 effectively inhibits ICAM-1 in a SCID mouse model for psoriasis; and
- We were issued 167 worldwide patents this year.

#### COMPENSATION FOR OUR CEO

Dr. Crooke's compensation is determined in accordance with the criteria described above for all executive officers. The Compensation Committee recommended that Dr. Crooke receive a salary increase of 12.5%, to \$450,000 for 2001. Dr. Crooke did not receive a salary increase in 2000. In January 2001, Dr. Crooke received a bonus of \$257,605 for accomplishments in 2000. In January 2000, the Committee also approved an option grant of 250,000 shares of Common Stock for Dr. Crooke, pursuant to our 1989 Stock Option Plan, which will fully vest on January 2, 2006; provided, however, that the option will fully vest on January 2, 2002, if certain performance objectives are met as of that date. As of January 12, 2001, all of the performance objectives had been met. The stock option grant was made on January 6, 2000, at an exercise price of \$6.8125 per share, the fair market value on the date of grant.

Mark B. Skaletsky, Chairman  
William R. Miller  
Joseph H. Wender

## AUDIT COMMITTEE REPORT

The Audit Committee oversees our financial reporting process on behalf of the Board of Directors. Management has the primary responsibility for the financial statements and the reporting process, including the systems of internal controls. In fulfilling its oversight responsibilities, the Audit Committee reviewed the audited financial statements in our Annual Report on Form 10-K for the year ended December 31, 2000 with management, including a discussion of the quality, not just the acceptability, of the accounting principles, the reasonableness of significant judgments, and the clarity of disclosures in the financial statements.

The Audit Committee reviewed with our independent auditors, who are responsible for expressing an opinion on the conformity of our audited financial statements with generally accepted accounting principles, their judgments as to the quality, not just the acceptability, of our accounting principles and any other matters as are required to be discussed with the Audit Committee under generally accepted auditing standards. In addition, the Audit Committee has discussed with the independent auditors the auditors' independence from management and Isis, including the matters in the written disclosures required by the Independence Standards Board. The Audit Committee received from Ernst & Young LLP written disclosure and the letter regarding its independence as required by Independence Standards Board Standard No. 1. The Audit Committee also discussed with our independent auditors the matters required by the Statement on Auditing Standards No. 61.

The Audit Committee discussed with our independent auditors the overall scope and plans for their audit. The Audit Committee meets with the independent auditors, with and without management present, to discuss the results of their examinations, their evaluations of our internal controls, and the overall quality of our financial reporting.

In reliance on the reviews and discussions referred to above, the Audit Committee recommended to the Board of Directors, and the Board has approved, that the audited financial statements be included in the Annual Report on Form 10-K for the year ended December 31, 2000 for filing with the Securities and Exchange Commission. The Audit Committee and the Board have also recommended, subject to stockholder approval, the selection of our independent auditors.

Joseph H. Wender, Audit Committee Chairman  
Mark B. Skaletsky, Audit Committee Member  
Christopher F. O. Gabrieli, Audit Committee Member

PERFORMANCE MEASUREMENT COMPARISON(1)

COMPARISON OF 5 YEAR CUMULATIVE TOTAL RETURN AMONG  
ISIS PHARMACEUTICALS, INC.,  
THE NASDAQ COMPOSITE INDEX (TOTAL RETURN) AND  
THE AMEX BIOTECH INDEX

EDGAR REPRESENTATION OF DATA POINTS USED IN PRINTED GRAPHIC

	DEC-99	DEC-00	DEC-01	DEC-02	DEC-03	DEC-04
Isis Pharmaceuticals Inc.	\$100	\$137	\$94	\$99	\$48	\$81
AMEX Biotech Index	\$100	\$108	\$121	\$138	\$293	\$474
Nasdaq U.S.	\$100	\$123	\$151	\$213	\$395	\$238

SOURCE: GEORGESON SHAREHOLDER COMMUNICATIONS INC.

The above table and chart assume \$100 invested on December 31, 1995 in our Common Stock, the NASDAQ Composite Index (Total Return) and the AMEX Biotech Index. Total return assumes reinvestment of dividends.

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(1) This Section is not "soliciting material," is not deemed filed with the SEC and is not to be incorporated by reference in any filing of Isis under the 1933 Act or the 1934 Act.

CERTAIN TRANSACTIONS

In April 1999, Isis and Elan Corporation, plc formed a joint venture to develop technology for the formulation of oral oligonucleotide drugs. The joint venture, Orasense, Ltd., is a Bermuda limited company which is currently owned 80.1% by Isis and 19.9% by Elan. Isis and Elan each contributed rights to certain oral drug delivery technology to the joint venture. In addition, Isis contributed rights to a proprietary oligonucleotide, which will be the first candidate for oral formulation by Orasense. Isis and Elan will provide development and manufacturing services to Orasense and will be entitled to royalties on any milestone payments and royalties received by Orasense for development of orally formulated oligonucleotide drugs. If Isis enters into an agreement with Orasense for oral formulation of any Isis oligonucleotide drug, Isis will pay Orasense royalties and a portion of certain third party milestone payments with respect to the drug. In conjunction with this transaction, Isis sold 910,844 shares of Isis' Common Stock to Elan International Services ("EIS") for \$15,000,000, and issued a warrant to purchase up to 215,000 shares of Isis' Common Stock at \$24 per share. The term of the warrant is five years. Isis also sold 120,150 shares of Isis' Series A Convertible Preferred Stock to EIS for \$12,015,000. EIS has made available to Isis an \$18,400,000 line of credit under a convertible debt arrangement. Since April 1999, EIS borrowed \$8,962,000 under this convertible debt agreement, which Isis used to provide development funding to Orasense. For the years ended December 31, 2000 and

1999, Isis recorded \$5,217,000 and \$4,402,000, respectively, in revenue from Orasense. For the years ended December 31, 2000 and 1999, Isis recorded \$9,702,000, and \$7,242,000, respectively as equity in the net loss of Orasense.

In January 2000, Isis and Elan Corporation, plc formed a new joint venture to develop an antisense drug to treat patients chronically infected with the Hepatitis C virus (HCV). This new joint venture, HepaSense Ltd., is a Bermuda limited company which is currently owned 80.1% by Isis and 19.9% by Elan. HepaSense plans to develop and commercialize this novel therapeutic for HCV, while investigating delivery of the therapeutic with Elan's proprietary MEDIPAD-Registered Trademark- Drug Delivery System, a disposable subcutaneous infusion device. Isis and Elan have each licensed technology to HepaSense. Isis and Elan will provide development and manufacturing services to HepaSense and will be entitled to royalties on any milestone payments and royalties received by HepaSense for development of HCV drugs. In conjunction with this transaction, Isis sold 298,000 shares of Isis' Common Stock to EIS for \$7,500,000, and issued to EIS a warrant to purchase up to 14,881 shares of Isis' Common Stock at \$50.40 per share. The term of the warrant is five years. Isis also sold 12,015 shares of Isis' Series B Convertible Preferred Stock to EIS for \$12,015,000. EIS has made available to Isis a \$12,015,000 line of credit under a convertible debt arrangement. During the year, Isis borrowed \$1,834,000 under this convertible debt agreement, which Isis used to provide development funding to HepaSense. For the year ended December 31, 2000, Isis recorded \$2,751,000 in revenue from HepaSense and recorded \$6,237,000 as equity in the net loss of HepaSense.

#### OTHER MATTERS

The Board of Directors knows of no other matters that will be presented for consideration at the Annual Meeting. If any other issues are properly brought before the meeting, we will ask our proxy holders to vote on the matters using their best judgment.

For further information about Isis Pharmaceuticals, please request a copy of our Annual Report. The report is the Form 10-K for the year ended December 31, 2000 that we filed with the Securities and Exchange Commission, and is available free of charge. Please send written requests to:

B. Lynne Parshall, Secretary  
Isis Pharmaceuticals, Inc.  
2292 Faraday Avenue  
Carlsbad, CA 92008

By Order of the Board of Directors  
/s/ B. Lynne Parshall  
SECRETARY

March 6, 2001

EXHIBIT A  
CERTIFICATE OF AMENDMENT OF  
RESTATED CERTIFICATE OF INCORPORATION OF  
ISIS PHARMACEUTICALS, INC.

Isis Pharmaceuticals, Inc., a corporation organized and existing under and by virtue of the General Corporation Law of the State of Delaware, does hereby certify:

FIRST: The name of the Corporation is Isis Pharmaceuticals, Inc. (the "Corporation").

SECOND: The date on which the Corporation's original Certificate of Incorporation was filed with the Secretary of State of the State of Delaware is March 25, 1991.

THIRD: The Board of Directors of the Corporation, acting in accordance with the provisions of Sections 141 and 242 of the General Corporation Law of the State of Delaware, adopted resolutions at a meeting held on December 8, 2000 to amend Article V of the Restated Certificate of Incorporation of the Corporation to read in its entirety as follows:

The Corporation is authorized to issue two classes of shares designated respectively "Common Stock" and "Preferred Stock." The total number of shares of all classes of stock which the Corporation has authority to issue is 115,000,000 shares, consisting of 100,000,000 shares of Common Stock, each having a par value of \$.001, and 15,000,000 shares of Preferred Stock, each having a par value of \$.001. The Preferred Stock may be issued in one or more series. The Board of Directors is authorized to fix the number of shares of any such series of Preferred Stock and to determine the designation of any such series (a "Preferred Stock Designation"), subject to (a) such stockholder approvals as may be provided for herein and (b) the number of shares of Preferred Stock authorized at that time by this Article V. Subject to such stockholder approvals as may be provided for herein, the Board of Directors is further authorized to determine or alter the rights, preferences, privileges and restrictions granted to or imposed upon any wholly unissued series of Preferred Stock, and to increase or decrease (but not below the number of shares of such series then outstanding) the number of shares of any series of Preferred Stock. In case the number of shares of any series shall be so decreased, the shares constituting such decrease shall resume the status that they had prior to the adoption of the resolution or amendment originally fixing the number of shares of such series.

FOURTH: The foregoing amendment was submitted to the stockholders of the Corporation for their approval and was duly adopted in accordance with the provisions of Section 242 of the General Corporation Law of the State of Delaware.

IN WITNESS WHEREOF, Isis Pharmaceuticals, Inc. has caused this Certificate of Amendment to be signed by its duly authorized officers this        day of        , 2001.

By: -----  
Stanley T. Crooke  
CHAIRMAN OF THE BOARD OF DIRECTORS  
AND CHIEF EXECUTIVE OFFICER

ISIS PHARMACEUTICALS, INC.  
PROXY SOLICITED BY THE BOARD OF DIRECTORS  
FOR THE ANNUAL MEETING OF STOCKHOLDERS TO BE HELD ON APRIL 6, 2001

The undersigned hereby appoints STANLEY T. CROOKE and B. LYNNE PARSHALL, and each of them, as attorneys and proxies of the undersigned, with full power of substitution, to vote all of the shares of stock of Isis Pharmaceuticals, Inc. (the "Company") which the undersigned may be entitled to vote at the Annual Meeting of Stockholders of the Company to be held at the Company's offices at 2292 Faraday Avenue, Carlsbad, California 92008 on Friday, April 6, 2001 at 2:30 p.m., and at any and all continuations and adjournments thereof, with all powers that the undersigned would possess if personally present, upon and in respect of the following matters and in accordance with the following instructions, with discretionary authority as to any and all other matters that may properly come before the meeting.

UNLESS A CONTRARY DIRECTION IS INDICATED, THIS PROXY WHEN PROPERLY EXECUTED WILL BE VOTED FOR ALL NOMINEES LISTED IN PROPOSAL 1 AND FOR PROPOSALS 2 AND 3 AS MORE SPECIFICALLY DESCRIBED IN THE PROXY STATEMENT. IF SPECIFIC INSTRUCTIONS ARE INDICATED, THIS PROXY WHEN PROPERLY EXECUTED WILL BE VOTED IN ACCORDANCE THEREWITH.

(CONTINUED ON OTHER SIDE)

PLEASE DETACH AND MAIL IN THE ENVELOPE PROVIDED

A /X/ PLEASE MARK YOUR  
VOTES AS IN THIS  
EXAMPLE

FOR all nominees  
listed at right (except  
as marked to the  
contrary below)

WITHHOLD  
AUTHORITY  
to vote for all  
nominees listed at right

Proposal 1: To elect  
two directors to  
hold office until  
the 2004 Annual Meeting  
of Stockholders

/ /

/ /

To withhold authority to vote  
for any nominee(s), write  
such nominee(s) name(s) below:

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

THE BOARD OF DIRECTORS RECOMMENDS A VOTE FOR THE NOMINEES FOR DIRECTOR  
LISTED BELOW

NOMINEES: Stanley T. Crooke  
Mark B. Skaletsky

THE BOARD OF DIRECTORS RECOMMENDS A VOTE FOR PROPOSALS 2 AND 3.

	FOR	AGAINST	ABSTAIN
Proposal 2: To approve an amendment to the Company's Restated Certificate of Incorporation to increase the authorized number of shares of common stock from 50,000,000 to 100,000,000 shares.	/ /	/ /	/ /
Proposal 3: To ratify the selection of Ernst & Young LLP as independent auditors of the Company for its fiscal year ending December 31, 2001.	/ /	/ /	/ /

PLEASE VOTE, DATE AND PROMPTLY RETURN THIS PROXY IN THE ENCLOSED RETURN  
ENVELOPE WHICH IS POSTAGE PREPAID IF MAILED IN THE UNITED STATES.

SIGNATURE \_\_\_\_\_ DATE \_\_\_\_\_

SIGNATURE \_\_\_\_\_ DATE \_\_\_\_\_

(SIGNATURE IF HELD JOINTLY)

NOTE: Please sign exactly as your name appears hereon. If the stock is  
registered in the names of two or more persons, each should sign.  
Executors, administrators, trustees, guardians and attorneys-in-fact  
should add their titles. If signer is a corporation, please give full  
corporate name and have a duly authorized officer sign, stating title.  
If signer is a partnership, please sign in partnership name by authorized  
person.