

SCHEDULE 14A INFORMATION

Proxy Statement Pursuant to Section 14(a) of the Securities Exchange Act of 1934 (Amendment No.)

Filed by the Registrant [X]

Filed by a Party other than the Registrant []

Check the appropriate box:

- [] Preliminary Proxy Statement
[] Confidential, for Use of the Commission Only (as permitted by Rule 14a-6(e)(2))
[X] Definitive Proxy Statement
[] Definitive Additional Materials
[] Soliciting Material Pursuant to Section 240.14a-11(c) or Section 240.14a-12

ISIS PHARMACEUTICALS, INC.

(Name of Registrant as Specified In Its Charter)

(Name of Person(s) Filing Proxy Statement, if Other Than the Registrant)

Payment of Filing Fee (Check the appropriate box):

- [X] No fee required.
[] Fee computed on table below per Exchange Act Rules 14a-6(i)(4) and 0-11.

(1) Title of each class of securities to which transaction applies:

(2) Aggregate number of securities to which transaction applies:

(3) Per unit price or other underlying value of transaction computed pursuant to Exchange Act Rule 0-11 (Set forth the amount on which the filing fee is calculated and state how it was determined):

(4) Proposed maximum aggregate value of transaction:

(5) Total fee paid:

[] Fee paid previously with preliminary materials.

[] Check box if any part of the fee is offset as provided by Exchange Act Rule 0-11(a)(2) and identify the filing for which the offsetting fee was paid previously. Identify the previous filing by registration statement number, or the Form or Schedule and the date of its filing.

(6) Amount Previously Paid:

(7) Form, Schedule or Registration Statement No.:

(8) Filing Party:

(8) Date Filed:

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

NOTICE OF
2000 ANNUAL MEETING OF STOCKHOLDERS
AND PROXY STATEMENT

Dear Stockholders,

I am pleased to invite you to Isis Pharmaceuticals' 2000 Annual Meeting of Stockholders. We will host the meeting at our offices in Carlsbad, California on Thursday, June 8 at 2:00 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.

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,

B. Lynne Parshall
Secretary

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

NOTICE OF 2000 ANNUAL MEETING OF STOCKHOLDERS

Date: Thursday, June 8

Time: 2:00 P.M.

Place: Isis Pharmaceuticals
2292 Faraday Avenue
Carlsbad, CA 92008

Dear Stockholders,

At our 2000 Annual Meeting, we will ask you to:

- Elect three Directors to serve for a three-year term;
- Approve the Company's 2000 Employee Stock Purchase Plan;
- Ratify the selection of Ernst & Young LLP as independent auditors for 2000; 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 April 10, 2000 you may vote at the Annual Meeting.

By order of the Board of Directors,

B. Lynne Parshall
Secretary

Carlsbad, California
April 24, 2000

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. 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

PROXY STATEMENT

INFORMATION ABOUT THE 2000 ANNUAL MEETING AND VOTING

GENERAL

The enclosed proxy card has been sent to you by the Board of Directors of Isis Pharmaceuticals, Inc., a Delaware corporation, so you may vote at the 2000 Annual Meeting of Stockholders. 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 April 24, 2000 to all stockholders who are entitled to vote. Only stockholders who owned our Common Stock at the close of business on April 10, 2000 are entitled to vote at the Annual Meeting. On this record date, we had 35,483,354 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, but not towards whether the stockholders have approved a proposal.

You may vote in one of two ways:

- Attend the 2000 Annual Meeting and vote in person, or
- Simply complete, sign and return the enclosed proxy card.

SOLICITATION

We will pay all the costs associated with soliciting these proxies. In addition to mailing proxy-soliciting material, our directors and employees may also solicit proxies in person, by telephone or by other electronic means of communication. We will ask banks, brokerage houses, fiduciaries, and custodians to forward the proxy material to their principals and to obtain authority to execute proxies. We will then reimburse them for expenses.

REVOCABILITY OF PROXIES

Once you have returned your proxy, 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 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;
- 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 you would like to be included in the Company's proxy statement and form of proxy for or to be presented at the 2001 Annual Meeting of Stockholders, you must send the proposal to Isis by no later than February 7, 2001.

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 eight members, so two classes consist of three directors, and one class consists of two directors. Each class serves a three-year term and we hold elections each year at the Annual Meeting to replace the directors whose term has 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. Two Board members resigned during 1999: Daniel L. Kisner resigned in February and Burkhard Blank resigned in August.

INFORMATION ABOUT THE 2000 ELECTIONS

The Board has nominated three directors for election at the 2000 Annual Meeting. Each of the nominees currently serves as one of our directors. If re-elected, each will serve until the 2003 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. 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.

THE BOARD RECOMMENDS THAT YOU VOTE "IN FAVOR" OF THE ELECTION OF EACH OF THE FOLLOWING NOMINEES.

BIOGRAPHIES OF NOMINEES FOR ELECTION FOR A THREE-YEAR TERM EXPIRING AT THE 2003 ANNUAL MEETING

ALAN C. MENDELSON, age 52, has served as a director of Isis since January 1989. He has been a partner of Cooley Godward LLP since January 1980. Mr. Mendelson served as Acting General Counsel at Cadence Design Systems, Inc., an electronic design automation software company, from November 1995 to June 1996. He is also a director of Axy's Pharmaceuticals, Inc., a biopharmaceutical company, and U.S. Search.com, a public records internet search company.

WILLIAM R. MILLER, age 71, 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 40, 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., and Bessemer Venture Partners IV L.P., related venture capital partnerships, where he has worked since 1986. He is Chairman of the Board of EPIX Medical, Inc., a developer of magnetic resonance imaging contrast agents.

BIOGRAPHIES OF BOARD MEMBERS CONTINUING UNTIL THE 2001 ANNUAL MEETING

STANLEY T. CROOKE, M.D., Ph.D., age 55, was a founder of Isis and has been its CEO 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 director of Valentis, Inc., both pharmaceutical companies, and is a director of SYNORB Biotech Inc., a Canadian pharmaceutical company that develops carbohydrate-based therapeutics, 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 51, has served as a director since January 1989. Since May 1993, Mr. Skaletsky has been President and CEO of GelTex Pharmaceuticals, Inc., a biopharmaceutical company. From 1988 to 1993, Mr. Skaletsky was Chairman and CEO of Enzytech, Inc., a biopharmaceutical company, and Opta Food Ingredients, Inc., a leading innovator, manufacturer and marketer of proprietary texturizing products sold to food processors in North America who focus on the dairy, dressings/sauces, meat and baked goods categories. He is currently Chairman of the Biotechnology Industry Organization, an industry organization. In addition, Mr. Skaletsky is a member of the Board of Trustees of Bentley College located in Waltham, MA.

BIOGRAPHIES OF BOARD MEMBERS CONTINUING UNTIL THE 2002 ANNUAL MEETING

LARRY SOLL, Ph.D., age 57, has served as a director of Isis since July 1992. He was Chairman of the Board of Directors of Synergen, Inc., a biopharmaceutical company, from 1986 to December 1994 and CEO from April 1993 to May 1994. Dr. Soll is a trustee of INVESCO Global Health Sciences, a closed-end investment fund; a director of the INVESCO Family of Mutual Funds, an open-ended mutual fund; and was a director of ImmuLogic Pharmaceuticals Corporation, a biopharmaceutical company, until February 1997.

JOSEPH H. WENDER, age 55, 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.

THE BOARD OF DIRECTOR COMMITTEES AND MEETINGS

The Board of Directors met eight times in 1999, including three regularly scheduled meetings and five special telephone meetings. The Board of Directors also has Audit, Compensation, and Nominating committees.

The Audit Committee is comprised of three independent directors, Mr. Mendelson (Chairman), Mr. Wender and Mr. Skaletsky. The committee met seven times in 1999. The Board of Directors has adopted a written charter for the Audit Committee. A copy of the charter is included as Appendix "A" to this proxy statement. The Audit Committee:

- Recommends engagement of our independent auditors;
- Approves services performed by the auditors (including the review and evaluation of our accounting system and its system of internal controls) in connection with our annual audit;
- Reviews our balance sheet and statement of operations and cash flows for each interim period;
- Reviews any changes in accounting policy that have occurred during the interim period; and
- Reviews any changes in accounting systems and procedures as well as the system of internal controls.

The Compensation Committee is comprised of Mr. Skaletsky (Chairman), Mr. Miller and Mr. Wender. Every member of the Compensation Committee is a non-employee director. The committee met two times in 1999. 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, 2000 Employee Stock Purchase Plan; and
- Determines executive compensation levels and performs other functions regarding compensation as the Board requests.

The Nominating Committee is comprised of two non-employee directors: Mr. Mendelson and Dr. Soll. The Committee did not meet in 1999. The Nominating Committee:

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

During 1999, all directors except Mr. Miller attended at least 75% of the meetings of the Board and the committees on which they served.

SECTION 16(a) BENEFICIAL OWNERSHIP REPORTING COMPLIANCE

Section 16(a) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), requires our directors, executive officers, and holders of more than 10% of our Common Stock to file with the Securities and Exchange Commission (the "SEC") initial reports of ownership and reports of changes in ownership of our Common Stock. We believe that during the fiscal year ended December 31, 1999, our officers and directors complied with all these filing requirements except for David Ecker, an Executive Officer, who inadvertently failed to report the transfer of 1,904 shares each to his daughter and son on April 23, 1999. Now he has reported all his transactions. In making this statement, we relied upon the written representations of our directors and executive officers. Based on stockholder filings, we do not believe the filing requirements of Section 16(a) apply to any other stockholders.

PROPOSAL 2

APPROVAL OF THE 2000 EMPLOYEE STOCK PURCHASE PLAN

Stockholders are requested in this Proposal #2 to approve the 2000 Employee Stock Purchase Plan. The affirmative vote of the holders of a majority of the shares present in person or represented by proxy and entitled to vote at the 2000 Annual Meeting will be required to approve the 2000 Employee Stock Purchase Plan.

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

PURPOSE

The purpose of the 2000 Employee Stock Purchase Plan (the "Plan") is to retain the services of our employees and to provide incentives to exert maximum efforts for the success of the Company by allowing eligible employees to purchase Isis Common Stock through payroll deductions on favorable terms. This Plan was adopted by the Board in January 2000 and supersedes and replaces the Employee Stock Purchase Plan adopted on September 5, 1991.

ADMINISTRATION

The Board administers the Plan. The Board can construe and interpret the Plan and, subject to the provisions of the Plan, determine when and how rights to purchase our Common Stock will be granted pursuant to an Offering, to determine the provisions of each Offering, and to designate which of our affiliates will be eligible to participate in the Plan. The Board can delegate administration of the Plan to a committee composed of at least two members of the Board. The Board has delegated administration of the Plan to the Compensation Committee. The "Board" refers to the Compensation Committee as well as to the Board of Directors itself throughout the remainder of this section.

ELIGIBILITY, PARTICIPATION

Isis employees who work at least 20 hours a week and have been employed for a continuous period set by the Board, but less than 2 years, are eligible to participate in an Offering. Participation in an Offering will terminate automatically upon termination of employment. The Officers of Isis may participate in an Offering, but the Board may limit the participation of certain highly compensated employees. An employee's participation in the Plan (together with other stock purchase plans of Isis or Isis affiliates but not including stock awards option or stock award plans) may not exceed \$25,000 in any calendar year. In addition, any employee owning 5% or more of the total combined voting power of Isis may not participate. Employees desiring to participate in an Offering must provide an appropriate notice to the Company. Employees may terminate participation in any Offering at any time, except as limited by the Board.

TERMS OF OFFERING

Each eligible employee can designate a percentage of his earnings up to 10%, or such lower percentage designated by the Board, during the Offering Period to be deducted and used to purchase Isis Common Stock in the Offering. Payroll deductions will be deposited with the general funds of the Company. The Board may allow certain changes to payroll deduction amounts for an Offering. The Board may also designate a maximum dollar amount for purchases during an Offering.

The Board may also specify a maximum number of shares for an Offering per employee for the Offering and for each purchase date under an Offering.

The purchase price of stock received under the Plan will be the lesser of (i) an amount equal to 85% of the fair market value of the stock on the Offering Date; or (ii) an amount equal to 85% of the fair market value of the stock on the purchase date. On each purchase date under an Offering, each participant's accumulated payroll deductions will be applied to purchase our Common Stock.

DURATION, AMENDMENT AND TERMINATION

The Board may suspend or terminate the Plan at any time. No rights may be granted under the Plan while the Plan is suspended or after it is terminated. Unless sooner terminated, the Plan will terminate in January 2010.

SHARES SUBJECT TO THE PLAN; ADJUSTMENTS UPON CHANGE IN STOCK

200,000 shares of our Common Stock may be granted under the Plan. This amount will be automatically increased as of each January 6, beginning January 6, 2001 and continuing through January 6, 2009, by the lesser of (i) one percent of the total number of shares of Common Stock outstanding on that anniversary date or (ii) 200,000 shares.

If any change is made in the stock under the Plan due to a change in corporate capitalization through reincorporation, stock dividend, stock split, reverse stock split, combination or reclassification of shares, the Plan and any Offering will be appropriately adjusted in the class(es) and maximum number of securities subject to the Plan and price of shares under an the Offering. The Board will make the adjustment and their determination will be final, binding and conclusive.

In the event of: (1) a dissolution, liquidation or sale of all or substantially all of the assets of Isis, (2) a merger or consolidation in which Isis is not the surviving corporation, or (3) a reverse merger in which Isis is the surviving corporation but the shares of Common Stock outstanding immediately preceding the merger are converted by virtue of the merger into other property, whether in the form of securities, cash or otherwise or (4) any other capital reorganization in which more than fifty percent (50%) of the securities of Isis entitled to vote are sold or otherwise exchanged, then any surviving corporation may assume outstanding rights or substitute similar rights for those under the Plan. If the surviving corporation does not assume the outstanding rights or substitutes similar rights, participants' accumulated payroll deductions will be used to purchase Common Stock immediately prior to the transaction described above and the participants' rights under the ongoing Offering will be terminated immediately following that purchase.

TAX INFORMATION

Participation in the Plan is intended to qualify for the favorable federal tax treatment accorded employee stock purchase plans under Section 423 of the Internal Revenue Code. Under these provisions, a participant will be taxed on amounts withheld as if actually received. However, no income will be taxable to a participant until disposition of the shares acquired.

If the stock is disposed of more than two years after the beginning of the Offering and more than one year after the stock is transferred to the participant, the lesser of (i) the excess of the fair market value of the stock at the time of the disposition over the exercise price or (ii) the excess of the fair market value of the stock as of the beginning of the Offering over the exercise price (determined as of the beginning of the Offering period) will be treated as ordinary income. Any further gain or any loss will be taxed as a capital gain or loss.

If the stock is sold or disposed of before the expiration of either of the holding periods described above, the excess of the fair market value of the stock on the exercise date over the exercise price generally will be treated as ordinary income at the time of the disposition, and Isis may, in the future, be required to withhold income taxes relating to the ordinary income from other payments made to the participant. The balance of any gain will be treated as capital gain. Even if the stock is later disposed of for less than its fair market value on the exercise date, the same amount of ordinary income is attributed to the participant and a capital loss is recognized equal to the difference between the sales price and the fair market value of the stock on the exercise date.

Any capital gain or loss realized by a participant upon the disposition of stock acquired under the Plan will be long- or short-term depending on whether the stock has been held for more than one year.

There are no federal income tax consequences to Isis by reason of the grant or exercise of rights under the Plan. Isis generally is entitled to a deduction for amounts taxed as ordinary income to a participant upon disposition by a participant of stock before the expiration of the holding periods described above.

PROPOSAL 3

RATIFICATION OF SELECTION OF INDEPENDENT AUDITORS

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

The Board of Directors has selected Ernst & Young LLP as our independent auditors for the fiscal year ending December 31, 2000, and has requested management to ask for stockholder approval 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 2000 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 approve the selection, the Board may choose to appoint a different independent accounting firm at any time during the year if it feels that any 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 2000 Annual Meeting must 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 February 28, 2000 by:

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

BENEFICIAL OWNER -----	BENEFICIAL OWNERSHIP(1)	
	NUMBER OF SHARES	PERCENT OF TOTAL(2)
Boehringer Ingelheim International GmbH	2,412,607	7.4
Binger Strasse 173 D-55216 Ingelheim Am Rhein GERMANY		
Novartis AG(3)	2,354,150	7.2
Lichtstrasse 35 CH-4002, Basel SWITZERLAND		
Stanley T. Crooke(4)	1,384,583	4.2
Christopher F. O. Gabrieli(5)	1,408,334	4.3
B. Lynne Parshall(6)	345,188	1.0
Alan C. Mendelson(7)	36,407	*
William R. Miller(8)	55,000	*
Mark B. Skaletsky(9)	42,000	*
Larry Soll(10)	45,000	*
Joseph H. Wender(11)	66,000	*
C. Frank Bennett(12)	87,064	*
Debby Jo Blank(13)	33,853	*
David J. Ecker(14)	183,346	*
All directors and executive officers as a group 12.4(12 persons)(15)	3,836,968	11.3

* Less than one percent

(1) We based this table upon information our directors, executive officers and principal stockholders supplied us and filed with the Securities and Exchange Commission on Schedules 13D and 13G. Unless otherwise indicated in the footnotes to this table and subject to community property laws where applicable, each of the stockholders we name in this table has sole voting and investment power for the shares we indicate as beneficially owned. Unless otherwise indicated, the address of each stockholder listed above is in the care of Isis at 2292 Faraday Avenue, Carlsbad, California 92008.

(2) Applicable percentage ownership is based on 32,778,391 shares of Common Stock outstanding on February 28, 2000.

- (3) Includes 2,219,000 shares currently registered to Novartis Pharma AG, 38,053 shares registered to Novartis Pharmaceuticals Corporation, and 97,097 shares registered to Genetic Therapy Inc. Novartis Pharma AG, Novartis Pharmaceuticals Corporation and Genetic Therapy Inc. are all directly or indirectly wholly owned subsidiaries of Novartis AG, a corporation registered in Switzerland. Novartis Pharmaceuticals Corporation and Genetic Therapy, Inc. are Delaware corporations.
- (4) Includes 260,234 shares issuable upon exercise of options held by Dr. Crooke that are exercisable on or before April 28, 2000 and 14,849 shares issuable upon exercise of options held by his wife that are exercisable on or before April 28, 2000. Dr. Crooke disclaims beneficial ownership of the shares issuable upon exercise of options held by his wife.
- (5) Includes 759,566 shares held of record by Bessemer Venture Partners II ("BVP II"), 486,464 shares held of record by Bessemer Venture Partners III ("BVP III") and 740 shares held of record by the Gabrieli Family Foundation ("GFF"). Mr. Gabrieli is a Manager of Deer II & Co. LLC, the general partner of BVP II, and of Deer III & Co. LLC, the general partner of BVP III, and disclaims beneficial ownership of the shares 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 held of record by or issuable to GFF. Also includes 45,500 shares issuable upon exercise of options held by Mr. Gabrieli that are exercisable on or before April 28, 2000.
- (6) Includes 319,499 shares issuable upon exercise of options held by Ms. Parshall that are exercisable on or before April 28, 2000, and an aggregate of 4,000 shares issuable upon exercise of options which Ms. Parshall transferred to her daughters that are exercisable on or before April 28, 2000.
- (7) Includes an aggregate of 620 shares held in trust by Mr. Mendelson's wife for his sons and 30,500 shares issuable upon exercise of options held by Mr. Mendelson that are exercisable on or before April 28, 2000. Mr. Mendelson disclaims beneficial ownership of the shares held in trust by his wife for his sons.
- (8) Includes 13,000 shares issuable upon exercise of options held by Mr. Miller that are exercisable on or before April 28, 2000.
- (9) Includes 20,000 shares issuable upon exercise of options held by Mr. Skaletsky that are exercisable on or before April 28, 2000.
- (10) Includes 45,000 shares issuable upon exercise of options held by Dr. Soll that are exercisable on or before April 28, 2000.
- (11) Includes 35,000 shares issuable upon exercise of options held by Mr. Wender that are exercisable on or before April 28, 2000.
- (12) Includes 86,707 shares issuable upon exercise of options held by Dr. Bennett that are exercisable on or before April 28, 2000.
- (13) Includes 33,853 shares issuable upon exercise of options held by Dr. Blank that are exercisable on or before April 28, 2000.
- (14) Includes 52,648 shares held in the Ecker Family Revocable Trust in which Dr. Ecker is a trustee, 3,587 shares owned by his daughter, and 3,987 shares owned by his son. Also includes 123,124 shares issuable upon exercise of options held by Dr. Ecker that are exercisable on or before April 28, 2000.
- (15) Includes shares described in the notes above, as applicable.

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, 1999, we paid a total of \$101,250 to our non-employee directors. Dr. Burkhard Blank, an affiliate of Boehringer Ingelheim, resigned in August 1999 and therefore only received \$11,250.

We also grant each non-employee director a stock option under the 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), we automatically grant each non-employee director an option to purchase 4,000 shares of our Common Stock. On July 1, 1999, we granted options to purchase an aggregate of 28,000 shares of stock pursuant to the Directors' Plan. The fair market value of the Common Stock (and the exercise price of the options) was \$10.25 per share (based on the closing sales price reported in the Nasdaq National Market on the date of grant).

In addition, upon initial election to the Board, we grant each new Non-Employee Director an option to purchase 18,000 shares of our Common Stock. The exercise price of all the stock options we grant is equal to 100% of the fair market value of the Common Stock on the date of the grant.

As of February 28, 2000, none of the options granted in 1999 under the Directors' Plan had vested.

COMPENSATION OF EXECUTIVE OFFICERS AND OTHER EMPLOYEES

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, 1999, 1998, and 1997.

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 \$(3)
Stanley T. Crooke Chairman, CEO and President	1999	400,008	0	0	35,000	0
	1998	361,992	253,400	0	70,000	0
	1997	310,008	169,531	0	22,500	0
B. Lynne Parshall Executive Vice President & Chief Financial Officer	1999	307,723	0	0	25,000	0
	1998	265,368	139,315	0	45,000	0
	1997	250,344	112,653	0	17,000	0
Debby Jo Blank(4) Executive Vice President	1999	283,289	0	0	125,000(5)	0
David J. Ecker Vice President, Managing Director, Ibis Therapeutics	1999	186,727	0	0	15,000	0
	1998	175,331	65,749	0	10,000	0
	1997	166,981	57,400	0	7,000	0
C. Frank Bennett Vice President, Antisense Research	1999	179,152	0	0	15,000	0
	1998	160,206	57,574	0	14,000	0
	1997	151,138	59,038	0	9,000	0

- (1) Although most of our objectives for 1999 were met or exceeded, with the major exception of achieving positive results in pivotal clinical trials for Crohn's disease, the management of the Company recommended to the Compensation Committee that executive officers be awarded no bonus for 1999 performance against objectives.
- (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 higher of 10% of the sum of the amount in the Salary and Bonus column and \$50,000.
- (3) Does not include excess group term life insurance premiums which do not exceed, for any individual, \$3,200 and which were paid on the same basis as was offered to all salaried employees.
- (4) Dr. Blank joined us on March 15, 1999.
- (5) Options granted upon date of hire at the Executive Vice President option level.

STOCK OPTION GRANTS AND EXERCISES

Executive officers are granted options under the 1989 Stock Option Plan. As of February 28, 2000, options to purchase a total of 7,315,851 shares had been granted and were outstanding under the 1989 Stock Option Plan.

In January 2000, the Compensation Committee adopted a 2000 Broad-Based Equity Incentive Plan (the "2000 Plan") for granting options to employees, including executive officers. 1,990,000 shares of our Common Stock are authorized for issuance under the Plan. As of February 28, 2000, options to purchase a total of 1,981,255 shares had been granted and were outstanding under the 2000 Plan.

The following tables show certain information regarding options granted to, exercised by and held at year end (for the fiscal year ended December 31, 1999) 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)	Base Price (\$/Sh)	Aggregate Dollar Value(\$)	Expiration Date	5%(\$)	10%(\$)
Stanley T. Crooke	35,000	1.9	\$ 12.9375	452,813	12-31-08	284,771	721,667
B. Lynne Parshall	25,000	1.3	\$ 12.9375	323,438	12-31-08	203,408	515,476
Debby Jo Blank	125,000	6.7	\$ 11.6250	1,453,125	3-14-09	913,546	2,314,023
David J. Ecker	15,000	.80	\$ 12.9375	29,063	12-31-08	122,045	309,286
C. Frank Bennett	15,000	.80	\$ 12.9375	29,063	12-31-08	122,045	309,286
All Executive Officers as a Group	230,000			2,481,565			
All Non-Executive Officer Directors as a Group(4)	28,000			287,000			
All Non-Executive Officer Employees as a Group	1,646,475			19,191,339			

(1) Options granted in 1999 vest over a four-year period: 25% after the first year and 2.08% per month thereafter.

(2) Based on options to purchase an aggregate of 1,876,475 shares granted in 1999. Represents the number of options granted under the 1989 Stock Option Plan in 1999 and 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) All the options were granted under the Directors' Plan.

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

Name	Shares	Value	Number of Securities Underlying Unexercised Options at FY-End(#)	Value of Unexercised In-the-Money Options at FY-End (\$)(2)
	Acquired on Exercise(#)	Realized (\$)(1)	Exercisable/Unexercisable	Exercisable/Unexercisable
Stanley T. Crooke	0	0	15,000 /0	\$0 /\$0
			1,642 /0	\$0 /\$0
			30,000 /0	\$0 /\$0
			25,000 /0	\$0 /\$0
			30,000 /0	\$0 /\$0
			24,583 /417	\$55,312 /\$938
			24,583 /417	\$55,312 /\$938
			39,166 /834	\$0 /\$0
			16,406 /6,094	\$0 /\$0
			33,541 /36,459	\$0 /\$0
			0 /35,000	\$0 /\$0
B. Lynne Parshall	0	0	20,000 /0	\$0 /\$0
			59,728 /0	\$29,864 /\$0
			47,500 /0(3)	\$0 /\$0
			18,000 /0	\$0 /\$0
			25,000 /0	\$9,375 /\$0
			20,000 /0	\$0 /\$0
			10,751 /250	\$24,190 /\$563
			7,167 /167	\$16,126 /\$376
			48,000 /12,000	\$0 /\$0
			15,666 /334	\$0 /\$0
			12,395 /4,605	\$0 /\$0
			21,562 /23,438	\$0 /\$0
			0 /25,000	\$0 /\$0
Debby Jo Blank	0	0	0 /125,000	\$0 /\$0
David J. Ecker	0	0	2,975 /0	\$0 /\$0
			9,000 /0	\$0 /\$0
			50,000 /0	\$6,250 /\$0
			15,000 /0	\$0 /\$0
			11,947 /203	\$26,881 /\$457
			17,625 /375	\$0 /\$0
			5,104 /1,896	\$0 /\$0
			4,791 /5,209	\$0 /\$0
			0 /15,000	\$0 /\$0

Name	Shares	Value	Number of Securities Underlying Unexercised Options at FY-End(#)	Value of Unexercised In-the-Money Options at FY-End (\$)(2)
	Acquired on Exercise(#)	Realized (\$)(1)	Exercisable/Unexercisable	Exercisable/Unexercisable
C. Frank Bennett	1,800	\$9,563	1,750 /0	\$0 /\$0
	525	\$3,445	1,500 /0	\$0 /\$0
	2,000	\$16,125	491 /0	\$0 /\$0
			2,534 /225	\$5,702 /\$506
			45,000 /5,000	\$0 /\$0
			11,750 /250	\$0 /\$0
			6,562 /2,438	\$0 /\$0
		6,708 /7,292	\$0 /\$0	
		0 /15,000	\$0 /\$0	

(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, 1999 (\$6.25) multiplied by the applicable number of shares minus the aggregate exercise price of the options for the number of shares.

(3) Includes options to purchase an aggregate of 4,000 shares transferred to Ms. Parshall's daughters.

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. 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 6 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 the Company's 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 9 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.

THE AUDIT COMMITTEE REPORT

The Audit Committee oversees the Company's 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 the Annual Report on Form 10-K for the year ended December 31, 1999 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 the Company's 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 the Company, including the matters in the written disclosures required by the Independence Standards Board.

The Audit Committee discussed with the Company's 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 the Company's internal controls, and the overall quality of the Company's 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, 1999 for filing with the Securities and Exchange Commission. The Audit Committee and the Board have also recommended, subject to stockholder approval, the selection of the Company's independent auditors.

Alan C. Mendelson, Audit Committee Chairman
Mark B. Skaletsky, Audit Committee Member
Joseph H. Wender, Audit Committee Member

March 1, 2000

COMPENSATION COMMITTEE REPORT1

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 2000 Broad-Based Equity Incentive Plan;
- Administering the 2000 Employee Stock Purchase Plan; and
- Determining executive compensation levels and performing other functions regarding compensation as the Board requests.

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

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 on page 20. 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 bonus pool on our success in meeting performance goals for the year, accounting for changes the Compensation Committee discussed and agreed 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.

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.

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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 the Company under the Securities Act of 1933, as amended (the "1933 Act"), or the Exchange Act.

ASSESSMENT OF 1999

We had set challenging objectives for 1999. In achieving the majority of those objectives, we made significant progress in the following areas:

- We received \$35.0 million in equity financing;
- We completed Antisense Target Validation collaborations with Abbott Laboratories and Rhone-Poulenc Rorer;
- We gained approval of Fomivirsen in Europe and Brazil;
- We identified two sensitive tumor types for ISIS 3521: Non-Hodgkin's Lymphoma and Non-Small Cell Lung Cancer;
- We initiated Phase II clinical trials for ISIS 3521;
- We initiated Phase II clinical trials for ISIS 2503 targeting pancreas, breast, lung, colon and neck cancer.
- We initiated Phase IIa clinical trials for a topical formulation for ISIS 2302 for psoriasis, and an enema formulation for ISIS 2302 for ulcerative colitis; and
- We received allowance on our 450th patent.

However, since the Phase III trials for ISIS 2302 in Crohn's Disease failed in 1999, we did not achieve the critical objective of filing a New Drug Application for ISIS 2302.

COMPENSATION FOR OUR CEO

Dr. Crooke's compensation is determined in accordance with the criteria described above for all executive officers. Dr. Crooke and the Compensation Committee agreed that Dr. Crooke would not receive a salary increase for 2000. Although we met or exceeded most of our objectives for 1999, with the major exception of achieving positive results in pivotal clinical trials for Crohn's disease, the management of the Company recommended to the Compensation Committee that no member of management be awarded a bonus for 1999 performance under the management objective program. Therefore, Dr. Crooke received no bonus for 1999. In January 1999, The Committee also approved an option for 35,000 shares of stock for Dr. Crooke, which is within the guidelines for the CEO under our annual stock option grant program.

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

PERFORMANCE MEASUREMENT COMPARISON(1)

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

[PERFORMANCE GRAPH]

	Dec. 1994 -----	Dec. 1995 -----	Dec. 1996 -----	Dec. 1997 -----	Dec. 1998 -----	Dec. 1999 -----
Isis	100	328	450	308	323	156
NASDAQ Composite Index	100	140	172	210	290	532
AMEX Biotechnology Index	100	163	176	198	226	477

The above table and chart assume \$100 invested on December 31, 1994 in the Company's 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 the Company under the 1933 Act or the Exchange Act.

CERTAIN TRANSACTIONS

In 1999, we paid \$1.9 million in interest on a \$22.6 million loan from Boehringer Ingelheim International GmbH in conjunction with a collaborative agreement with Boehringer. Boehringer owns 7.4% of our Common Stock.

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 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 for \$15,000,000, and issued a warrant to purchase up to 215,000 shares of Isis' Common Stock at \$14 per share. The term of the warrant is 5 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 million line of credit under a convertible debt arrangement. During the year, Elan purchased convertible debt from Isis in the amount of \$2,213,000, which Isis used to provide development funding to OraSense. For the year ended December 31, 1999, Isis recorded \$4,402,000 in revenue from OraSense, and recorded \$7,242,000 as equity in the net loss of OraSense.

In January 2000, Isis and Elan Corporation agreed to form a new subsidiary of Isis to develop an antisense drug, ISIS 14803, to treat patients chronically infected with Hepatitis C virus (HCV). The new subsidiary, called HepaSense, is owned 80.1% by Isis and 19.9% by Elan. HepaSense plans to develop and commercialize ISIS 14803 for HCV while investigating delivery of this therapeutic with Elan's proprietary MEDIPAD(R) Drug Delivery System, a disposable subcutaneous infusion device. Isis and Elan have each licensed technology to HepaSense. As part of the transaction, Elan purchased 12,015 shares of Isis' Series B Preferred Stock for \$12,015,000. The Series B Preferred Stock will be convertible in the future into either Isis common stock or stock in HepaSense. Elan will also purchase \$7.5 million of Isis common stock in April 2000 and potentially an additional \$7.5 million of common stock upon completion of a mutually agreed milestone. Both common stock purchases will be purchased at a premium to Isis' market price. In addition, Elan will make available to Isis a \$12.0 million line of credit for Isis' funding commitment to 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 stockholders 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, 1999, 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

B. Lynne Parshall
Secretary

April 24, 2000

APPENDIX A

BOARD OF DIRECTORS
AUDIT COMMITTEE

CHARTER

The general purpose of the Audit Committee is to assist the Board of Directors in the exercise of its fiduciary responsibility to provide oversight of the Company's financial statements and the financial reporting processes, internal accounting and financial controls, the annual independent audit of the Company's financial statements, and other aspects of the financial management of the Company.

The Audit Committee will be appointed by the Board of Directors and will comprise at least three directors, each of whom are independent of management and the Company. All committee members must be financially literate, or shall become financially literate within a reasonable period of time after appointment to the Committee. At least one member shall have accounting or related financial management expertise.

The powers and duties of the Audit Committee include the following:

1. The Audit Committee will oversee the annual and quarterly financial reporting processes.
2. The Audit Committee will select the independent auditor for the Company. The selection shall be proposed by management, confirmed by the Audit Committee and ratified by the stockholders. The Audit Committee will have a clear understanding with management and the independent auditors that the independent auditors are ultimately accountable to the Board and the Audit Committee, as representatives of the Company's stockholders. The Audit Committee shall have the ultimate authority and responsibility to evaluate and, where appropriate, replace the independent auditors.
3. The Audit Committee will discuss with the auditors their independence from management and the Company and the matters included in the written disclosures required by the Independence Standards Board.
4. The Audit Committee will meet with management, the independent auditors, and the internal auditors (when the Company has such a function) prior to their audits to review and discuss the planned scope and objectives of the audits.
5. The Audit Committee will meet with the independent auditors and the internal auditors, with and without management present, after their audits to review and discuss the results of their examinations and appropriate analyses of the financial statements.
6. The Audit Committee will review the recommendations of the independent auditors for improving internal accounting controls and management's responses thereto, primarily as communicated in the annual management letter.
7. The Audit Committee will review and discuss the reports of the independent auditors, with and without management present, as to the state of the Company's financial reporting systems and procedures, the adequacy of internal accounting and financial controls, the integrity and competency of the financial and accounting staff, and other aspects of the financial management of the Company.

8. The Audit Committee will review the interim financial statements with management and the independent auditors prior to the filing of the Company's Quarterly Reports on Form 10-Q. The Audit Committee will also discuss the results of the quarterly reviews and any other matters required to be communicated to the Audit Committee by the independent auditors under generally accepted auditing standards. The Chair of the Audit Committee may represent the entire committee for the purposes of this review.
9. The Audit Committee will review with management and the independent auditors the financial statements to be included in the Company's Annual Report on Form 10-K (or the annual report to stockholders if distributed prior to the filing of Form 10-K), including their judgment about the quality, not just acceptability, of accounting principles, the reasonableness of significant judgments, and the clarity of the disclosures in the financial statements. Also, the Audit Committee will discuss the results of the annual audit and any other matters required to be communicated to the Audit Committee by the independent auditors under generally accepted auditing standards.
10. The Audit Committee will maintain free and open communication between the Audit Committee, directors who are not members of the Audit Committee, the Company's management, the internal auditors, and the independent auditors.
11. The Audit Committee shall have adequate resources and authority to discharge its responsibilities and duties including the following:
 - a. The Audit Committee will have full authority at its own discretion to institute investigations of any matter brought to its attention, with full access to all books, records, facilities and personnel of the Company, including standing authority to retain special counsel or experts.
 - b. The Audit Committee will have the authority to review all aspects of the Company's financial operations on a planned basis.
 - c. The Audit Committee will have the authority to review the Company's policies and procedures and the actual implementation of such policies and procedures with respect to officers' expenses and perquisites.
12. The Audit Committee will report annually to the Board of Directors, outlining the Audit Committee's activities for the past year and its plans for the coming year. In addition, the Audit Committee shall report to the Board of Directors any significant matters as they occur during the year.

ISIS PHARMACEUTICALS, INC.

PROXY SOLICITED BY THE BOARD OF DIRECTORS
FOR THE ANNUAL MEETING OF STOCKHOLDERS TO BE HELD ON JUNE 8, 2000

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 Thursday, June 8, 2000 at 2:00 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 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 WILL BE VOTED IN ACCORDANCE THEREWITH.

(Continued on other side)

SEE REVERSE
SIDE

PLEASE DATE, SIGN AND MAIL YOUR PROXY CARD BACK AS SOON AS POSSIBLE!

ANNUAL MEETING OF STOCKHOLDERS
ISIS PHARMACEUTICALS, INC.

JUNE 8, 2000

Please Detach and Mail in the Envelope Provided

PLEASE MARK YOUR
A [X] 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.
[]

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

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

Proposal 1: To elect
three directors
to hold office
until the 2003 Annual
Meeting of Stockholders.

NOMINEES: Alan C. Mendelson
William R. Miller
Christopher F. O. Gabriell

Proposal 2: Approve the Company's 2000 Employee Stock Purchase Plan. FOR [] AGAINST [] ABSTAIN []

Proposal 3: To ratify the selection of Ernst & Young LLP as Independent auditors of the Company for its fiscal year ending December 31, 2000. [] [] []

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

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 a 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.
