

SCHEDULE 14A INFORMATION

PROXY STATEMENT PURSUANT TO SECTION 14(A) OF
THE SECURITIES EXCHANGE ACT OF 1934Filed by the Registrant 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))
 Definitive Proxy Statement
 Definitive Additional Materials
 Soliciting Material Pursuant to sec.240.14a-11(c) or sec.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):

- 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):
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- 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.
- (1) Amount Previously Paid:
 (2) Form, Schedule or Registration Statement No.:
 (3) Filing Party:
 (4) Date Filed:

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

NOTICE OF ANNUAL MEETING OF STOCKHOLDERS
TO BE HELD ON MAY 22, 1998

TO THE STOCKHOLDERS OF ISIS PHARMACEUTICALS, INC.:

NOTICE IS HEREBY GIVEN that the Annual Meeting of Stockholders of Isis Pharmaceuticals, Inc., a Delaware corporation (the "Company"), will be held on Friday, May 22, 1998, at 2:00 p.m. at the Company's offices at 2292 Faraday Avenue, Carlsbad, California 92008, for the following purposes:

1. To elect three directors to serve for a three-year term and until their successors are duly elected and qualified.
2. To approve an increase in the number of shares authorized for issuance under the Company's 1989 Stock Option Plan (the "1989 Plan") from 8,200,000 to 10,200,000, to extend the term of the 1989 Plan until January 31, 2008, and to make changes to the stockholder approval requirements of the 1989 Plan.
3. To ratify the selection of Ernst & Young LLP as independent auditors of the Company for its fiscal year ending December 31, 1998.
4. To transact such other business as may properly come before the meeting or any adjournment thereof.

The Board of Directors has fixed the close of business on March 30, 1998 as the record date for the determination of stockholders entitled to notice of and to vote at this Annual Meeting and at any adjournment thereof.

By Order of the Board of Directors

B. Lynne Parshall
Secretary

Carlsbad, California
April 13, 1998

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 CONCERNING SOLICITATION AND VOTING

GENERAL

The enclosed proxy is solicited on behalf of the Board of Directors of Isis Pharmaceuticals, Inc., a Delaware corporation (the "Company"), for use at the Annual Meeting of Stockholders to be held on May 22, 1998, at 2:00 p.m. (the "Annual Meeting"), or at any adjournment thereof, for the purposes set forth herein and in the accompanying Notice of Annual Meeting. The Annual Meeting will be held at the Company's offices at 2292 Faraday Avenue, Carlsbad, California 92008.

SOLICITATION

The Company will bear the entire cost of solicitation of proxies, including preparation, assembly, printing and mailing of this proxy statement, the proxy 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 Common Stock beneficially owned by others to forward to such beneficial owners. The Company 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, facsimile, telegram or personal solicitation by directors, officers or other regular employees of the Company. No additional compensation will be paid to directors, officers or other regular employees for such services.

The Company intends to mail this proxy statement and accompanying proxy card on or about April 13, 1998, to all stockholders entitled to vote at the Annual Meeting.

STOCKHOLDER PROPOSALS

Proposals of stockholders that are intended to be presented at the Company's 1999 Annual Meeting of Stockholders must be received by the Company no later than December 14, 1998 in order to be included in the proxy statement and proxy relating to such annual meeting.

VOTING RIGHTS AND OUTSTANDING SHARES

Only holders of record of Common Stock at the close of business on March 30, 1998 will be entitled to notice of and to vote at the Annual Meeting. At the close of business on March 30, 1998, the Company had outstanding and entitled to vote 26,794,335 shares of Common Stock.

Each holder of record of Common Stock on such date will be entitled to one vote for each share held on all matters to be voted upon at the Annual Meeting. All votes will be tabulated by the inspector of election appointed for the Annual Meeting, who will separately tabulate affirmative and negative votes, abstentions and broker non-votes. Abstentions will be counted towards the tabulation of votes cast on proposals presented to the stockholders and will have the same effect as negative votes. Broker non-votes are counted towards a quorum, but are not counted for any purpose in determining whether a matter has been approved.

REVOCABILITY OF PROXIES

Any person giving a proxy pursuant to this solicitation has the power to revoke it at any time before it is voted. It may be revoked by filing with the Secretary of the Company at the Company's principal executive office, 2292 Faraday Avenue, Carlsbad, California 92008, a written notice of revocation or a duly executed proxy bearing a later date, or it may be revoked by attending the meeting and voting in person. Attendance at the meeting will not, by itself, revoke a proxy.

PROPOSAL 1

ELECTION OF DIRECTORS

The Company's Restated Certificate of Incorporation and Bylaws provide that the Board of Directors shall be divided into three classes, each class consisting, as nearly as possible, of one-third of the total number of directors, with each class having a three-year term. Vacancies on the Board may be filled only by persons elected by a majority of the remaining directors. A director elected by the Board to fill a vacancy (including a vacancy created by an increase in the size of the Board) will serve for the remainder of the full term of the class of directors in which the vacancy occurred and until such director's successor is elected and qualified.

The Board of Directors presently has nine members. Stephen K. Carter resigned from the Board on March 17, 1997. On June 6, 1997, Burkhard Blank was elected by the Board to fill the vacancy created by Dr. Carter's resignation.

There are three directors in the class whose term of office expires in 1998. All of the nominees for election to this class, Burkhard Blank, Stanley T. Crooke and Mark B. Skaletsky, are currently directors of the Company. If elected at the Annual Meeting, each of the nominees would serve until the 2001 annual meeting and until his successor is elected and has qualified, or until his earlier death, resignation or removal.

Directors are elected by a plurality of the votes present in person or represented by proxy and entitled to vote at the Annual Meeting. Shares represented by executed proxies will be voted, if authority to do so is not withheld, for the election of the three nominees named below. In the event that any nominee should be unavailable for election as a result of an unexpected occurrence, such shares will be voted for the election of such substitute nominee as the Board of Directors may propose. Each person nominated for election has agreed to serve if elected, and the Board has no reason to believe that any nominee will be unable to serve.

Set forth below is biographical information for each person nominated and each person whose term of office as a director will continue after the Annual Meeting.

THE BOARD OF DIRECTORS RECOMMENDS A VOTE IN FAVOR OF EACH NAMED NOMINEE.

NOMINEES FOR ELECTION FOR A THREE-YEAR TERM EXPIRING AT THE 2001 ANNUAL MEETING

BURKHARD BLANK, M.D., age 42, has served as a director of the Company since June 1997. Dr. Blank joined Boehringer Ingelheim GmbH in 1986 and was named to his current position, head of the Project Management Division, in 1993. Dr. Blank also serves on the Board of Directors at Cambridge Neuroscience, Inc., a biopharmaceutical company. Pursuant to the terms of an agreement, Boehringer Ingelheim International GmbH ("BII") is entitled to designate a representative reasonably satisfactory to the Company for election to the Company's Board of Directors. Dr. Blank is BII's representative.

STANLEY T. CROOKE, M.D., Ph.D., age 53, was a founder of the Company and has been its Chief Executive Officer and a director since January 1989 and served as its President from January 1989 to May 1994. He was elected Chairman of the Board in February 1991. From 1980 until January 1989, Dr. Crooke was employed by SmithKline Beckman Corporation, a pharmaceutical company, most recently as President of Research and Development of Smith Kline & French Laboratories. Dr. Crooke is Chairman of the Board of GeneMedicine, Inc., and a director of SIBIA Neurosciences, Inc. ("SIBIA"), both biopharmaceutical companies, and EPIX Medical, Inc., ("EPIX") a developer of magnetic resonance imaging contrast agents. 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 49, has served as a director since January 1989. Since May 1993, Mr. Skaletsky has been President and Chief Executive Officer of GelTex Pharmaceuticals, Inc., a biopharmaceutical company. From April 1988 to February 1993, Mr. Skaletsky was employed by Enzytech, Inc., a biopharmaceutical company, in a variety of positions, including Chairman of the Board and Chief Executive Officer from April 1988 to February 1993; Enzytech, Inc. was acquired by Alkermes, Inc. Mr. Skaletsky is a director of Charles River Labs and LeukoSite, Inc., both biopharmaceutical companies, the Biotechnology Industry Organization ("BIO"), an industry organization, and the Massachusetts Biotechnology Council.

DIRECTORS CONTINUING IN OFFICE UNTIL THE 1999 ANNUAL MEETING

DANIEL L. KISNER, M.D., age 51, has served as a director of the Company since March 1991, Chief Operating Officer of the Company since February 1993 and President since May 1994. He was Executive Vice President of the Company from March 1991 until May 1994. From December 1988 until March 1991, he was Division Vice President of Pharmaceutical Development for Abbott Laboratories, a pharmaceutical company. He is also a director of Anesta Corporation, a drug delivery company.

LARRY SOLL, Ph.D., age 55, has served as a director of the Company since July 1992. He was Chairman of the Board of Directors of Synergen, Inc., a biopharmaceutical company, from 1986 to December 1994 and Chief Executive Officer of Synergen 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 53, has served as a director of the Company 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.

DIRECTORS CONTINUING IN OFFICE UNTIL THE 2000 ANNUAL MEETING

ALAN C. MENDELSON, age 50, has served as a director of the Company 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 CoCensys, Inc., a biopharmaceutical company, and Acuson Corporation, an ultrasound equipment manufacturer.

WILLIAM R. MILLER, age 69, has served as a director of the Company since March 1991. In January 1991, he retired as Vice Chairman of the Board of Directors of Bristol-Myers Squibb Company, which position he had held since 1985. He is Vice Chairman of the Board of Trustees of the Cold Spring Harbor Laboratory. Mr. Miller is also Chairman of the Board of SIBIA and Vion Pharmaceuticals, Inc., both biopharmaceutical companies. He is a director of ImClone Systems, Inc., a biopharmaceutical company, St. Jude Medical, Inc., a diversified medical device company, Transkaryotic Therapies, Inc., a biopharmaceutical company, Westvaco Corporation, a paper/packaging/specialty chemicals manufacturer, and Xomed Surgical Products, Inc., a medical device company.

CHRISTOPHER F. O. GABRIELI, age 38, has served as a director of the Company since May 1994. He was a founder of the Company and previously 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 (collectively "Bessemer"), where he has worked since 1986. He is on the Board of EPIX, where he serves as Chairman, and several privately held healthcare companies.

BOARD COMMITTEES AND MEETINGS

During 1997, the Board of Directors held six meetings. The Board has an Audit and Financing Committee, a Compensation Committee and a Nominating Committee.

The Audit and Financing Committee recommends engagement of the Company's independent auditors and approves services performed by such auditors, including the review and evaluation of the Company's accounting system and its system of internal controls in connection with the Company's annual audit. The Audit and Financing Committee also reviews the Company's balance sheet and statements of operations and cash flows for each interim period, and any changes in accounting policy that have occurred during the interim period, and assists the management of the Company in reviewing financing opportunities for the Company, in making recommendations to the Board, and in implementing financing projects as approved by the Board. The Audit and Financing Committee is composed of Messrs. Mendelson (Chairman), Wender and Skaletsky and met eight times during 1997.

The Compensation Committee makes recommendations concerning executive salaries and incentive compensation, awards stock options, bonus stock and rights to purchase restricted stock under the Company's 1989 Stock Option Plan, administers the Company's Employee Stock Purchase Plan and otherwise determines executive compensation levels and performs such other functions regarding compensation as the Board may delegate. The Compensation Committee is composed of Messrs. Skaletsky (Chairman), Miller and Wender and met two times during 1997.

The Nominating Committee interviews, evaluates, nominates and recommends individuals for membership on the Company's Board of Directors and committees thereof. The Nominating Committee will consider nominees recommended by stockholders. See "Information Concerning Solicitation and Voting - Stockholder Proposals." The Nominating Committee is composed of two non-employee directors: Mr. Mendelson and Dr. Soll. The Nominating Committee did not meet during the year.

During 1997, all directors, other than Drs. Carter and Blank, attended at least 80% of the meetings of the Board and the committees on which they served, held during the period for which they were directors or committee members.

SECTION 16(a) BENEFICIAL OWNERSHIP REPORTING COMPLIANCE

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

To the Company's knowledge, based solely on a review of the copies of such reports furnished to the Company and written representations from its officers and directors that no other reports were required, during 1997, all Section 16(a) filing requirements applicable to its officers, directors and greater than ten percent stockholders were satisfied.

PROPOSAL 2

AMENDMENT OF THE 1989 STOCK OPTION PLAN TO INCREASE SHARES

In June 1989, the Board of Directors adopted, and the stockholders subsequently approved, the Company's 1989 Stock Option Plan (the "1989 Plan"). In February 1998, the Board approved an amendment to the 1989 Plan, subject to stockholder approval, to increase the number of shares authorized for issuance under the 1989 Plan by 2,000,000 to an aggregate of 10,200,000 shares, to extend the term of the 1989 Plan until January 31, 2008, and to make changes to the stockholder approval requirements of the 1989 Plan.

Stockholders are requested in this Proposal 2 to approve the increase in the number of shares authorized for issuance under the 1989 Plan, the extension of the plan term and the changes to the stockholder approval requirements. 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 Annual Meeting will be required to approve the 1989 Plan, as amended. Abstentions will be counted toward the tabulation of votes cast and will have the same effect as negative votes. Broker non-votes are not counted for any purpose in determining whether this matter has been approved.

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

The essential features of the 1989 Plan, as amended, are outlined below.

PURPOSE

The 1989 Plan was adopted to provide a means by which employees (including officers) and directors of and consultants to the Company may be given an opportunity to benefit from increases in value of the Common Stock of the Company through the granting of incentive and supplemental (or nonstatutory) stock options, stock bonuses and rights to purchase restricted stock (collectively, the "Stock Awards"). Incentive stock options granted under the 1989 Plan are intended to qualify as "incentive stock options" within the meaning of Section 422 of the Internal Revenue Code of 1986, as amended (the "Code"). Supplemental stock options granted under the 1989 Plan are intended not to qualify as incentive stock options under the Code. See "Federal Income Tax Information" for a discussion of the tax treatment of incentive and supplemental stock options. As of December 31, 1997, options to purchase an aggregate of 6,097,056 shares had been granted and were outstanding under the 1989 Plan, options to purchase an aggregate of 1,398,791 shares had been exercised under the 1989 Plan, and 704,225 shares remained available for grant thereunder.

ADMINISTRATION

The 1989 Plan authorizes the Board of Directors of the Company to administer the 1989 Plan or to delegate administration to a committee. The Board has delegated administration of the 1989 Plan to the Compensation Committee of the Board, and the Compensation Committee has delegated administration of the 1989 Plan to the Non-Management Stock Option Committee with respect to certain option grants to certain employees, none of whom is subject to Section 16 of the Exchange Act. Each person serving on the Compensation Committee is a "non-employee director" within the meaning of Rule 16b-3 of the Exchange Act and an "outside director" within the meaning of Section 162(m) of the Code. As used herein with respect to the 1989 Plan, the "Board" refers to the Compensation Committee and the Non-Management Stock Option Committee as well as to the Board of Directors itself.

The Board has the power to construe and interpret the 1989 Plan and, subject to the provisions of the 1989 Plan, to select the persons to whom stock awards are to be made, to designate the number of shares to be covered by each Stock Award, to determine whether an option is an incentive stock option or a supplemental stock option, to establish vesting schedules, to specify the exercise price and the type of consideration to be paid to the Company upon exercise or purchase, and, subject to certain restrictions, to specify any other terms.

ELIGIBILITY

Incentive stock options may be granted under the 1989 Plan only to key employees (including officers) of the Company. Key employees (including officers), directors and consultants are eligible to receive Stock Awards other than incentive stock options under the 1989 Plan.

No incentive stock option may be granted under the 1989 Plan to any person who, at the time of the grant, owns (or is deemed to own) stock possessing more than 10% of the total combined voting power of all classes of stock of the Company, unless the option exercise price is at least 110% of the fair market value of the stock subject to the option on the date of grant, and the term of the option does not exceed five years from the date of grant. In addition, the aggregate fair market value, determined at the time of grant, of the shares of Common Stock with respect to which such options are exercisable for the first time by an optionee during any calendar year may not exceed \$100,000. Further, the 1989 Plan contains a per-employee, per-calendar year limitation equal to 294,873 shares.

STOCK SUBJECT TO THE 1989 PLAN

Subject to stockholder approval of this Proposal 2, 10,200,000 shares are reserved for issuance under the 1989 Plan. If Stock Awards granted under the 1989 Plan expire or otherwise terminate without being exercised, the Common Stock not purchased pursuant to such Stock Awards again becomes available for issuance under the 1989 Plan.

TERMS OF OPTIONS

The following is a description of the permissible terms of options under the 1989 Plan. Individual option grants may be more restrictive as to any or all of the permissible terms described below.

Exercise Price; Payment. The exercise price of incentive stock options under the 1989 Plan may not be less than the fair market value of the Common Stock subject to the option on the date of the option grant, and in some cases may not be less than 110% of such fair market value (see "Eligibility" above). The exercise price of supplemental stock options under the 1989 Plan may not be less than 85% of the fair market value. The Company has routinely granted options at 100% of the fair market value. At February 27, 1998, the closing price of the Common Stock as reported on the Nasdaq National Market was \$13.4375 per share.

The exercise price of options granted under the 1989 Plan must be paid either: (i) in cash at the time the option is exercised; or (ii) at the discretion of the Board, (a) pursuant to a deferred payment arrangement or (b) in any other form of legal consideration acceptable to the Board. Since 1991, the Board has not authorized any form of payment for option exercise other than cash or pursuant to a "same-day sale" program developed pursuant to Regulation T of the Federal Reserve Board.

Transferability. Under the 1989 Plan, an incentive stock option may not be transferred by the optionee other than by will or by the laws of descent and distribution. Supplemental stock options may be transferred for limited estate planning purposes or by will or the laws of descent and distribution.

Option Exercise. Options granted under the 1989 Plan may become exercisable in cumulative increments ("vest") as determined by the Board. Shares covered by currently outstanding options under the 1989 Plan typically vest at the rate of 25% per year after year one and 2.08% per month thereafter during the optionee's employment or service as a consultant or director. Shares covered by options granted in the future under the 1989 Plan may be subject to different vesting terms. The Board has the power to accelerate the time during which an option may be exercised. In addition, options granted under the 1989 Plan may permit exercise prior to vesting. To date, the Company has not granted options which permit exercise prior to vesting.

Term. The maximum term of options under the 1989 Plan is ten years, except that in certain cases the maximum term is five years (see "Eligibility"). With certain exceptions, options under the 1989 Plan terminate three months after the optionee ceases to render services to the Company.

ADJUSTMENT PROVISIONS

If there is any change in the stock subject to the 1989 Plan or subject to any Stock Award granted under the 1989 Plan (through merger, consolidation, reorganization, recapitalization, stock dividend, dividend in property other than cash, stock split, liquidating dividend, combination of shares, exchange of shares, change in corporate structure or otherwise), the 1989 Plan and the Stock Awards outstanding thereunder will be appropriately adjusted as to the class and the maximum number of shares, the maximum number of shares which may be granted to an employee during a calendar year and price per share of stock subject to the 1989 Plan and such Stock Awards.

EFFECT OF CERTAIN CORPORATE EVENTS

The 1989 Plan provides that, in the event of a dissolution or liquidation of the Company, or of a specified type of merger or other corporate reorganization, to the extent permitted by law, any surviving corporation will be required to either assume any Stock Awards outstanding under the 1989 Plan or substitute similar Stock Awards

for those outstanding under the 1989 Plan, or such outstanding Stock Awards will continue in full force and effect. In the event that any surviving corporation declines to assume or continue the Stock Awards outstanding under the 1989 Plan, or to substitute similar Stock Awards, then, with respect to Stock Awards held by persons then performing services as employees or as consultants or directors for the Company, the time during which such Stock Awards may be exercised will be accelerated and the Stock Awards terminated if not exercised during such time.

DURATION, AMENDMENT AND TERMINATION

The Board may suspend or terminate the 1989 Plan without stockholder approval or ratification at any time or from time to time. Subject to stockholder approval of this Proposal 2, unless sooner terminated, the 1989 Plan will terminate on January 31, 2008 (instead of December 31, 2000).

The Board may also amend the 1989 Plan at any time or from time to time. Subject to stockholder approval of this Proposal 2, no amendment will be effective unless approved by the stockholders of the Company within 12 months before or after its adoption by the Board if such amendment requires stockholder approval in order to comply with Rule 16b-3, Section 422(b) of the Code or any Nasdaq or securities exchange requirements. Prior to the proposed amendment, a plan amendment required approval by the stockholders of the Company within 12 months before or after its adoption by the Board if the amendment would: (i) modify the requirements as to eligibility for participation (to the extent such modification requires stockholder approval in order for the Plan to satisfy Section 422(b) of the Code, if applicable, or Rule 16b-3 of the Exchange Act); (ii) increase the number of shares reserved for Stock Awards under the Plan; or (iii) modify any other provision of the Plan in any other way if such modification requires stockholder approval in order to comply with Rule 16b-3 or satisfy the requirements of Section 422(b) of the Code.

FEDERAL INCOME TAX INFORMATION

Incentive Stock Options. Incentive stock options under the 1989 Plan are intended to be eligible for the favorable federal income tax treatment accorded "incentive stock options" under the Code.

Slightly different rules may apply to optionees who acquire stock subject to certain repurchase options or whose stock is subject to forfeiture under Section 16(b) of the Exchange Act.

Supplemental Stock Options. Supplemental stock options granted under the 1989 Plan generally have the following federal income tax consequences:

There are no tax consequences to the optionee or the Company by reason of the grant of a supplemental stock option. Upon exercise of a supplemental stock option, the optionee normally will recognize taxable ordinary income equal to the excess of the stock's fair market value on the date of exercise over the option exercise price. Generally, with respect to employees, the Company is required to withhold from regular wages or supplemental wage payments an amount based on the ordinary income recognized. Subject to the requirement of reasonableness, the provisions of Section 162(m) of the Code, and the satisfaction of a tax-reporting obligation, the Company will generally be entitled to a business expense deduction equal to the taxable ordinary income realized by the optionee. Upon disposition of the stock, the optionee will recognize a capital gain or loss equal to the difference between the selling price and the sum of the amount paid for such stock plus any amount recognized as ordinary income upon exercise of the option. Such gain or loss will be long-term, mid-term or short-term depending on how long the stock was held. Slightly different rules apply to optionees who acquire stock subject to certain repurchase options or who are subject to Section 16(b) of the Exchange Act.

Stock Bonuses and Restricted Stock. Stock bonuses and restricted stock purchases granted under the 1989 Plan have the following federal income tax consequences:

Upon acquisition of the stock, the recipient normally will recognize taxable ordinary income equal to the excess of the stock's fair market value over the purchase price, if any. However, to the extent the stock is subject to certain types of vesting restrictions, the taxable event will be delayed until the vesting restrictions lapse unless the recipient elects to be taxed on receipt of the stock. With respect to employees, the Company is generally required to withhold from regular wages or supplemental wage payments an amount based on the ordinary income recognized. Generally, the Company will be entitled to a business expense deduction equal to the taxable ordinary income realized by the optionee. Upon disposition of the stock, the optionee will recognize a capital gain or loss equal to the difference between the selling price and the sum of the amount paid for such stock plus any amount recognized as ordinary income upon acquisition (or vesting) of the stock. Such gain or loss will be long-term, mid-term or short-term depending on how long the stock was held. Slightly different rules may apply to optionees who acquire stock subject to certain repurchase options or who are subject to Section 16(b) of the Exchange Act.

Potential Limitation on Company Deductions. Section 162(m) of the Code denies a deduction to any publicly held corporation for compensation paid to certain employees in a taxable year to the extent that compensation exceeds \$1 million for such employee. It is possible that compensation attributable to stock options, stock bonuses and restricted stock purchases, when combined with all other types of compensation received by a covered employee from the Company, may cause this limitation to be exceeded in any particular year. Certain kinds of compensation, including qualified "performance-based compensation," are disregarded for purposes of the deduction limitation.

The table under Stock Option Grants and Exercises presents certain information with respect to options granted under the 1989 Plan for 1997.

PROPOSAL 3

RATIFICATION OF SELECTION OF INDEPENDENT AUDITORS

The Board of Directors has selected Ernst & Young LLP as the Company's independent auditors for the fiscal year ending December 31, 1998 and has further directed that management submit the selection of independent auditors for ratification by the stockholders at the Annual Meeting. Ernst & Young LLP has audited the Company's financial statements since its inception in 1989. Representatives of Ernst & Young LLP are expected to be present at the Annual Meeting, will have an opportunity to make a statement if they so desire and will be available to respond to appropriate questions.

Stockholder ratification of the selection of Ernst & Young LLP as the Company's independent auditors is not required by the Company's Bylaws or otherwise. However, the Board is submitting the selection of Ernst & Young LLP to the stockholders for ratification as a matter of good corporate practice. If the stockholders fail to ratify the selection, the Board will reconsider whether or not to retain that firm. Even if the selection is ratified, the Board in its discretion may direct the appointment of a different independent accounting firm at any time during the year if the Board determines that such a change would be in the best interests of the Company and its stockholders.

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 Annual Meeting will be required to ratify the selection of Ernst & Young LLP.

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

SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT

The following table sets forth certain information regarding the ownership of the Company's Common Stock as of February 27, 1998 by: (i) each director and nominee for director; (ii) each executive officer named in the Summary Compensation Table under "Executive Compensation--Compensation of Executive Officers;" (iii) all directors and executive officers of the Company as a group; and (iv) all those known by the Company to be beneficial owners of more than five percent of its Common Stock.

BENEFICIAL OWNER	BENEFICIAL OWNERSHIP(1)	
	NUMBER OF SHARES	PERCENT OF TOTAL(2)
Boehringer Ingelheim International GmbH(3) Binger Strasse 173 D-55216 Ingelheim Am Rhein GERMANY	2,412,607	9.0
Novartis AG(4) Lichtstrasse 35 CH-4002, Basel SWITZERLAND	2,257,053	8.4
Christopher F. O. Gabrieli(5) 83 Walnut Street Wellesley Hills, MA 02181	1,687,944	6.2
Bessemer Venture Partners(6) 1025 Old Country Road Westbury, NY 11590	1,536,465	5.6
Burkhard Blank(7)	--	--
Stanley T. Crooke(8)	1,277,677	4.7
Daniel L. Kisner(9)	403,916	1.5
Alan C. Mendelson(10)	27,527	*
William R. Miller(11)	46,500	*
Mark B. Skaletsky(12)	32,500	*
Larry Soll(13)	46,500	*
Joseph H. Wender(14)	54,750	*
B. Lynne Parshall(15)	259,257	*
All directors and executive officers as a group (10 persons)(16)	3,835,571	13.6

* Less than one percent

- (1) This table is based upon information supplied by directors, executive officers and principal stockholders and Schedule 13Ds and 13Gs filed with the SEC. Unless otherwise indicated in the footnotes to this table and subject to community property laws where applicable, 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 percentage ownership is based on 26,760,742 shares of Common Stock outstanding on February 27, 1998.
- (3) Includes 4,000 shares held of record by Prof. Christoph Hohbach, a former director of the Company, and for which BII has sole voting and investment power.

- (4) Novartis AG, a corporation registered in Switzerland, is the successor of Ciba-Geigy Limited in which 2,219,000 shares are currently registered. All shares of Common Stock of the Company that are owned by Novartis AG as successor of Ciba-Geigy Limited will be transferred to Novartis Produkte AG, a corporation registered in Switzerland and a wholly-owned subsidiary of Novartis AG. Also includes 38,053 shares held by Novartis Corporation, a New York corporation (formerly known as Ciba-Geigy Corporation), that is a wholly-owned subsidiary of Novartis AG.
- (5) Includes 759,566 shares held of record by Bessemer Venture Partners II L.P. ("BVP II"), 335,485 shares held of record by Bessemer Venture Partners III L.P. ("BVP III") and 350 shares held of record by the Gabrieli Family Foundation ("GFF"). Also includes 434,639 shares issuable upon exercise of Class A Warrants held of record by BVP III and 1,123 shares issuable upon exercise of Class A Warrants held of record by 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 an aggregate of 1,610 shares and an aggregate of 5,165 shares issuable upon exercise of Class A Warrants held of record by seven stockholders who have agreed to vote such shares as directed by BVP III; Mr. Gabrieli also disclaims beneficial ownership of such shares. Also includes 2,246 shares issuable upon exercise of Class A Warrants held by Mr. Gabrieli and 32,916 shares issuable upon exercise of options held by Mr. Gabrieli that are exercisable on or before April 28, 1998.
- (6) Includes 759,566 shares held of record by BVP II, 335,485 shares held of record by BVP III and 434,639 shares issuable upon exercise of Class A Warrants held of record by BVP III. Also includes an aggregate of 1,610 shares and an aggregate of 5,165 shares issuable upon exercise of Class A Warrants held of record by seven stockholders who have agreed to vote such shares as directed by BVP III; BVP III disclaims beneficial ownership of such shares.
- (7) Excludes shares beneficially owned by BII. Dr. Blank does not, directly or indirectly, have or share voting power or investment power over the shares beneficially owned by BII.
- (8) Includes 159,173 shares issuable upon exercise of options held by Dr. Crooke that are exercisable on or before April 28, 1998 and 9,004 shares issuable upon exercise of options held by his wife that are exercisable on or before April 28, 1998. Dr. Crooke disclaims beneficial ownership of the shares issuable upon exercise of options held by his wife.
- (9) Includes 399,916 shares issuable upon exercise of options held by Dr. Kisner that are exercisable on or before April 28, 1998 and an aggregate of 4,000 shares issuable upon exercise of options which Dr. Kisner transferred to his son and daughter that are exercisable on or before April 28, 1998.
- (10) Includes an aggregate of 620 shares held in trust by Mr. Mendelson's wife for his sons and 22,000 shares issuable upon exercise of options held by Mr. Mendelson that are exercisable on or before April 28, 1998. Mr. Mendelson disclaims beneficial ownership of the shares held in trust by his wife for his sons.
- (11) Includes 4,500 shares issuable upon exercise of options held by Mr. Miller that are exercisable on or before April 28, 1998.
- (12) Includes 11,500 shares issuable upon exercise of options held by Mr. Skaletsky that are exercisable on or before April 28, 1998.
- (13) Includes 46,500 shares issuable upon exercise of options held by Dr. Soll that are exercisable on or before April 28, 1998.
- (14) Includes 23,750 shares issuable upon exercise of options held by Mr. Wender that are exercisable on or before April 28, 1998.
- (15) Includes 235,125 shares issuable upon exercise of options held by Ms. Parshall that are exercisable on or before April 28, 1998, 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, 1998.
- (16) Includes shares described in the notes above, as applicable.

EXECUTIVE COMPENSATION

COMPENSATION OF DIRECTORS

In the fiscal year ended December 31, 1997, each director of the Company who is not otherwise an employee of the Company (a "Non-Employee Director") received a fee of \$15,000 (except that Dr. Carter received \$3,750 and Dr. Blank received \$7,500); no additional compensation is paid for attendance at Board or committee meetings. For 1997, the total compensation paid to Non-Employee Directors was \$101,250. The members of the Board of Directors are also reimbursed for their expenses incurred in connection with attendance at Board meetings in accordance with Company policy.

Each Non-Employee Director also receives stock option grants under the 1992 Non-Employee Directors' Stock Option Plan (the "Directors' Plan"). Only Non-Employee Directors are eligible to receive options under the Directors' Plan. Option grants under the Directors' Plan are non-discretionary. On July 1 of each year (or the next business day should such date be a weekend or holiday), each Non-Employee Director is automatically granted under the Directors' Plan an option to purchase 4,000 shares of Common Stock of the Company. In addition, each new Non-Employee Director is granted an option to purchase 18,000 shares of the Company's Common Stock upon initial election to the Board of Directors. The exercise price of all such stock options granted is equal to 100% of the fair market value of the Common Stock on the date such option is granted.

In 1997, the Company granted options to purchase an aggregate of 46,000 shares of stock to Non-Employee Directors pursuant to automatic grants under the Directors' Plan, including a grant of 18,000 shares granted to Dr. Blank upon being elected to the Board of Directors. The fair market value of the Common Stock on the date of these grants (and the exercise price of such options) was \$14.375 per share for all but the option to purchase 18,000 shares granted to Dr. Blank, the exercise price of which was \$15.50 per share (based in each case on the closing sales price reported in the Nasdaq National Market on the date of grant). As of February 27, 1998, none of these options had vested.

COMPENSATION OF EXECUTIVE OFFICERS AND OTHER EMPLOYEES

The following table shows for the fiscal years ending December 31, 1997, 1996 and 1995, certain compensation paid by the Company, including salary, bonuses, stock options, and certain other compensation, to its Chief Executive Officer and each of its two other most highly compensated executive officers whose total annual salary and bonus exceeded \$100,000 in the year ended December 31, 1997:

SUMMARY COMPENSATION TABLE

Name and Principal Position	Year	Annual Compensation			Long-Term Compensation Awards	
		Salary (\$)	Bonus (\$)	Other Annual Compensation (\$)(1)(2)	Securities Underlying Options (#)	All Other Compensation (\$)(3)
Stanley T. Crooke Chairman and Chief Executive Officer	1997	310,008	169,531	0	22,500	0
	1996	280,344	98,119	0	40,000	0
	1995	262,000	116,001	0	50,000	0
Daniel L. Kisner President and Chief Operating Officer	1997	272,712	122,724	0	18,000	0
	1996	257,280	77,185	0	25,000	0
	1995	242,719	92,112	0	30,000	0
B. Lynne Parshall Executive Vice President & Chief Financial Officer	1997	250,344	112,653	0	17,000	0
	1996	236,171	70,851	0	16,000	0
	1995	214,743	67,745	0	85,000(4)	0

(1) As permitted by rules promulgated by the SEC, no amounts are shown where such 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.

(2) None of the persons listed in the table held restricted stock as of December 31, 1997.

(3) Does not include excess group term life insurance premiums which do not exceed, for any individual, \$3,000 and which were paid on the same basis as was offered to all salaried employees.

(4) Includes 60,000 options granted in connection to Ms. Parshall's promotion to Executive Vice President on 12-14-95.

STOCK OPTION GRANTS AND EXERCISES

The Company grants options to its executive officers under its 1989 Plan. As of February 27, 1998, options to purchase a total of 6,758,081 shares had been granted and were outstanding under the 1989 Plan and, subject to stockholder approval of Proposal 2, options to purchase 1,971,359 shares remained available for grant thereunder.

The following tables show for the fiscal year ended December 31, 1997 certain information regarding options granted to, exercised by and held at year end 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	22,500	2.20	18.00	405,000	12-31-06	254,614	645,191
Daniel L. Kisner	18,000	1.76	18.00	324,000	12-31-06	203,691	516,153
B. Lynne Parshall	17,000	1.66	18.00	306,000	12-31-06	192,375	487,478
All Executive Officers as a Group	57,500			1,035,000			
All Non-Executive Officer Directors as a Group(4)	46,000			681,500			
All Non-Executive Officer Employees as a Group(5)	966,828			16,312,156			

- (1) Options granted in 1997 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 1,024,328 shares granted in 1997. Represents the number of options granted under the 1989 Plan in 1997 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.
- (4) All such options were granted under the 1992 Non-Employee Directors' Stock Option Plan.
- (5) Includes an option to purchase 35,000 shares granted under the 1989 Plan to a consultant, which option expired on December 31, 1997.

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 FY-End(#) ----- Exercisable/ Unexercisable	Value of Unexercised In-the-Money Options at FY-End \$(2) ----- Exercisable/ Unexercisable
Stanley T. Crooke	0	0	15,000/0	\$56,813/\$0
			1,642/0	\$6,219/\$0
			29,500/500	\$95,359/\$1,616
			0/25,000	\$0/\$146,313
			24,000/6,000	\$133,500/\$33,375
			14,583/10,417	\$121,221/\$86,591
			14,583/10,417	\$121,221/\$86,591
			19,166/20,834	\$0/\$0
		0/22,500	\$0/\$0	
Daniel L. Kisner	0	0	170,000/0	\$1,971,696/\$0
			4,167/0	\$19,012/\$0
			0/50,000	\$0/\$153,125
			22,125/375	\$89,883/\$1,523
			0/25,000	\$0/\$160,398
			23,750/1,250	\$132,109/\$6,953
			63,000/27,000	\$326,813/\$140,063
			8,750/6,250	\$72,734/\$51,953
			8,750/2,250	\$72,734/\$51,953
			7,979/17,021(3)	\$0/\$0
		0/18,000	\$0/\$0	
B. Lynne Parshall	0	0	20,000/0	\$76,250/\$0
			59,728/0	\$391,965/\$0
			0/47,500(4)	\$0/\$145,469
			17,700/300	\$71,906/\$1,219
			0/25,000	\$0/\$160,938
			16,000/4,000	\$89,000/\$22,250
			4,751/6,250	\$39,493/\$51,953
			3,167/4,167	\$26,326/\$34,638
			24,000/36,000	\$0/\$0
			7,666/8,334	\$0/\$0
		0/17,000	\$0/\$0	

- (1) Fair market value of the Company's Common Stock on the date of exercise minus the exercise price.
- (2) Fair market value of the Company's Common Stock at December 31, 1997 (\$12.3125) multiplied by the applicable number of shares minus the aggregate exercise price of the options for such number of shares.
- (3) Includes options to purchase an aggregate of 4,000 shares transferred to Dr. Kisner's son and daughter.
- (4) Includes options to purchase an aggregate of 4,000 shares transferred to Ms. Parshall's daughters.

COMPENSATION COMMITTEE REPORT(1)

The Compensation Committee of the Board of Directors (the "Committee") consists of Mark B. Skaletsky (Chairman), William R. Miller and Joseph H. Wender, none of whom have ever been officers or employees of the Company. The Committee is responsible for setting and administering the Company's policies governing employee compensation and administering the Company's employee benefit plans, including the 1989 Plan and the Employee Stock Purchase Plan. The Committee evaluates the performance of management and determines compensation policies and levels. The full Board of Directors reviews the Committee's recommendations regarding the compensation of executive officers.

The Company's executive compensation programs are designed to attract and retain executives capable of leading the Company to meet its business objectives and to motivate them to enhance long-term stockholder value. Annual compensation for the Company's executive officers consists of three elements: cash salary, a cash incentive bonus and stock option grants.

As in previous years, the Committee reviewed 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 Committee also reviewed a variety of industry surveys which provided additional information about short- and long-term executive compensation. The Committee reviews this information throughout the year when and as it becomes available. Based in part on this information, the Committee generally sets salaries, including that of the Chief Executive Officer, at levels comparable to competitive companies of comparable size in similar industries. The Company's management by objective bonus program is tied to both individual and Company performance. The total size of the bonus pool is based upon the Company's performance in meeting its performance objectives for the year, taking into account changes discussed and agreed to by the Committee during the course of the year. Individual bonus amounts are based on a combination of corporate performance and individual performance.

The Company uses its stock option program to further align the interests of stockholders and management by creating common incentives related to the possession by management of a substantial economic interest in the long-term appreciation of the Company's Common Stock. New options are granted to existing members of management on an annual basis to provide a continuing financial incentive. The size of option grant is related to the executive's position and performance in the previous year.

Section 162(m) of the Code limits the Company to a deduction for federal income tax purposes of no more than \$1 million of compensation paid to certain executive officers in a taxable year. Compensation above \$1 million may be deducted if it is "performance-based compensation" within the meaning of the Code. The Compensation Committee has determined that stock options granted under the 1989 Plan with an exercise price at least equal to the fair market value of the Company's Common Stock on the date of grant will be treated as performance-based compensation.

1997 was a year in which the Company continued to advance development of its drug candidates. It completed Phase III clinical trials for fomivirsen (ISIS 2922), its compound to treat cytomegalovirus-induced retinitis in AIDS patients. The Company entered into an agreement granting CIBA Vision exclusive worldwide distribution rights for ISIS 2922. Under the terms of this agreement, Isis received a \$5 million upfront payment and is eligible to receive an additional \$15 million in pre-commercial fees and milestone payments through the time of regulatory approval in the U.S. and Europe. The Company also completed preclinical development and filed an IND for ISIS 13312, a second generation antisense compound to treat CMV retinitis. Following its Phase IIa study, the Company also began large scale, pivotal-quality trials of ISIS 2302, a compound directed against Crohn's disease and four other possible indications: ulcerative colitis; psoriasis; rheumatoid arthritis, and renal transplant rejection.

Isis also initiated Phase II clinical trials for ISIS 3521, an anticancer compound, in August 1997, following safety and efficacy results from Phase I clinical trials which produced antitumor activity in patients with ovarian and lung cancer and lymphoma. Isis also completed Phase I clinical trials on ISIS 5132, an anticancer compound, in June 1997. After evaluating data from this study regarding the safety, pharmacokinetics, and potential antitumor activity of ISIS 5132, Isis initiated Phase II clinical trials for this drug in November 1997. Isis also began Phase I clinical trials on ISIS 2503, another anticancer compound.

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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.

Isis' research continued to proceed well. The Company's patenting strategy continued to bear fruit with nearly 50 additional patents issued in 1997. The Company's relationships with its collaborative partners have continued positively. In 1997, the Company received an aggregate of \$4 million in milestone payments from Novartis for the start of Phase II studies for each of ISIS 3521 and ISIS 5132.

The Company completed a \$25 million private debt financing in October 1997, with an institutional investor on favorable terms.

The Company continued its focus on manufacturing scale-up by forging successful relationships with industry vendors which, in combination with Isis' efforts, significantly decreased the cost and increased the scale of manufacturing in 1997 while also improving the quality and precision of purification and analytical methods.

The Compensation Committee approved a 17% salary increase for Dr. Crooke for 1998. This increase in salary for Dr. Crooke, and his option award, resulted from an industry-wide analysis of Dr. Crooke's cash compensation and stock option position. In 1997, the Company met or exceeded most of its performance objectives. The Committee continues to believe that a significant cash bonus program to reward performance is an appropriate method of executive compensation. The Committee approved a bonus of \$169,531 for Dr. Crooke, which was 156% of the 35% bonus guideline for the CEO under the Company's management by objective (MBO) program, based on the Company performing at the level of 125% of its achievement of objectives, and Dr. Crooke performing at 125% of his achievement of personal objectives. In December 1997, the Committee amended options to purchase an aggregate of 55,000 shares to extend the option terms for an additional five years. In January 1998, the Committee also approved an option for 70,000 shares of stock for Dr. Crooke, which is within the guidelines for the CEO under Isis' annual stock option grant program.

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

COMPENSATION COMMITTEE INTERLOCKS AND INSIDER PARTICIPATION

As noted above, during the fiscal year ended December 31, 1997, the Company's Compensation Committee was composed of Messrs. Skaletsky, Miller and Wender.

PERFORMANCE MEASUREMENT COMPARISON(1)

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

[GRAPHIC OMITTED]

	Dec. 1992	Dec. 1993	Dec. 1994	Dec. 1995	Dec. 1996	Dec. 1997
Isis	100	73	43	142	195	133
NASDAQ Composite Index	100	116	112	158	193	236
AMEX BIOTECH Index	100	68	48	78	85	95

The above table and chart assume \$100 invested on December 31, 1991 in the Company's Common Stock, the NASDAQ Composite Index (Total Return) and the AMEX Biotech Index. Total return assumes reinvestment of dividends.

- (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 June 1997, the Company borrowed an additional \$6.4 million under a \$40 million line of credit made available under the terms of its collaborative agreement with BII. The funds will be used for the purpose of funding research and development costs associated with the collaboration. Borrowings under the line of credit bear interest at the seven year U.S. interbanking rate plus 2.0%, determined at the time each advance is made. Interest payments are due twice each year with principal repayment due seven years after the advance date. The principal may be repaid in cash or stock, at the Company's option. If the Company elects to repay the loan in shares of Isis Common Stock, repayment will be made at a share price equal to 90% of the average market value over the 20 trading days preceding the maturity date. The balance under this line of credit as of December 31, 1997 was \$22.6 million.

OTHER MATTERS

The Board of Directors knows of no other matters that will be presented for consideration at the Annual Meeting. If any other matters are properly brought before the meeting, it is the intention of the persons named in the accompanying proxy to vote on such matters in accordance with their best judgment.

By Order of the Board of Directors

B. Lynne Parshall
Secretary

April 13, 1998

A COPY OF THE COMPANY'S ANNUAL REPORT TO THE SECURITIES AND EXCHANGE COMMISSION ON FORM 10-K FOR THE FISCAL YEAR ENDED DECEMBER 31, 1997 IS AVAILABLE WITHOUT CHARGE UPON WRITTEN REQUEST TO: B. LYNNE PARSHALL, SECRETARY, ISIS PHARMACEUTICALS, INC., 2292 FARADAY AVENUE, CARLSBAD, CALIFORNIA 92008.

ISIS PHARMACEUTICALS, INC.

PROXY SOLICITED BY THE BOARD OF DIRECTORS

FOR THE ANNUAL MEETING OF STOCKHOLDERS TO BE HELD ON MAY 22, 1998

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, May 22, 1998 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.

MAY 22, 1998

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

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

Proposal 1: to elect three directors to hold office until the 2001 Annual Meeting of Stockholders. []

Nominees: Burkhard Blank
Stanley T. Crooke
Mark B. Skaletsky

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

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

Proposal 2: To approve an increase in the number of shares authorized for issuance under the Company's 1989 Stock Option Plan (the "1989 Plan") from 8,200,000 to 10,200,000, to extend the term of the 1989 Plan until January 31, 2008, and to make changes to the stockholder approval requirements of the 1989 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, 1998.

[] FOR [] AGAINST [] ABSTAIN

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.