

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 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):

/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:

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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 JUNE 6, 1997

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, June 6, 1997, 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 ratify the selection of Ernst & Young LLP as independent auditors of the Company for its fiscal year ending December 31, 1997.
3. 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 April 14, 1997, 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 28, 1997

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.

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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 June 6, 1997, 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 28, 1997, 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 1998 Annual Meeting of Stockholders must be received by the Company no later than December 22, 1997 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 April 14, 1997 will be entitled to notice of and to vote at the Annual Meeting. At the close of business on April 14, 1997, the Company had outstanding and entitled to vote 26,352,117 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.

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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 Board) shall 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 is presently composed of nine members with one vacancy. Professor Christoph Hohbach resigned from the Board on December 13, 1996, at which time Stephen K. Carter was elected by the Board to fill the vacancy created by Professor Hohbach's resignation. Dr. Carter resigned from the Board on March 17, 1997, and the Board has not yet elected a replacement to fill the vacancy created by his resignation.

There are three directors in the class whose term of office expires in 1997. All of the nominees for election to this class, Alan C. Mendelson, William R. Miller and Christopher F. O. Gabrieli, are currently directors of the Company. If elected at the Annual Meeting, each of the nominees would serve until the 2000 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 2000 ANNUAL MEETING

Alan C. Mendelson, age 49, has served as a director of the Company since January 1989. He was Secretary of the Company from January 1989 to November 1991. He has been a partner of Cooley Godward LLP, counsel to the Company ("Cooley Godward"), since January 1980. Mr. Mendelson also served as Acting General Counsel of 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, Acuson Corporation, an ultrasound equipment manufacturer, and Elecsys International, Inc., a manufacturer of interconnect products used in advanced electronic equipment.

William R. Miller, age 68, 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 ("Bristol-Myers Squibb"), a pharmaceutical 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 Neurosciences, Inc. ("SIBIA") and of Vion Pharmaceuticals, Inc., both biotechnology companies. He is a director of ImClone Systems, Inc., St. Jude Medical Inc., Transkaryotic Therapies, Inc., Westvaco Corporation, and Xomed Surgical Products, Inc., and is an Advisory Director of Chugai Pharmaceuticals, Inc.

Christopher F. O. Gabrieli, age 37, 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 Deer II & Co. LLC and of Deer III & Co. LLC, the general partners of Bessemer Venture Partners II L.P. and Bessemer Venture Partners III L.P., affiliated venture capital partnerships (collectively "Bessemer"),

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where he has worked since 1986. He is a director of Opta Food Ingredients, a supplier of food ingredients, Epix Medical, Inc. ("Epix Medical"), a developer of magnetic resonance imaging contrast agents, and several privately held health care companies.

DIRECTORS CONTINUING IN OFFICE UNTIL THE 1998 ANNUAL MEETING

Stanley T. Crooke, M.D., Ph.D., age 52, 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 a director of SIBIA, GeneMedicine, Inc., a biotechnology company, and Epix Medical and is an adjunct professor of pharmacology at the Baylor College of Medicine and the University of California, San Diego.

Mark B. Skaletsky, age 48, 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 biotechnology company. From April 1988 to February 1993, Mr. Skaletsky was employed by Enzytech, Inc. ("Enzytech"), a biotechnology company, in a variety of positions, including Chairman of the Board and Chief Executive Officer from April 1988 to February 1993; Enzytech was acquired by Alkermes, Inc. in 1992. Mr. Skaletsky is a director of Charles River Labs, the Biotechnology Industry Organization ("BIO"), and the Massachusetts Biotechnology Council.

DIRECTORS CONTINUING IN OFFICE UNTIL THE 1999 ANNUAL MEETING

Daniel L. Kisner, M.D., age 50, 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 54, has served as a director of the Company since July 1992. He was Chairman of the Board of Directors of Synergen, Inc., ("Synergen"), a biopharmaceutical company, which was acquired by Amgen, Inc., from 1986 to December 1994 and Chief Executive Officer of Synergen from April 1993 to May 1994. Dr. Soll is a trustee of Global Health Sciences, a closed-end investment fund, and was a director of ImmuLogic Pharmaceutical Corporation, a biotechnology company, from March 1993 to February 1997.

Joseph H. Wender, age 52, 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.

BOARD COMMITTEES AND MEETINGS

During the fiscal year ended December 31, 1996, the Board of Directors held five 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, statement of operations, cash flows and stockholders' equity 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 the fiscal year ended December 31, 1996.

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 (the "1989 Plan"), administers the Company's Employee Stock Purchase Plan and

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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 three times during the fiscal year ended December 31, 1996. Alan C. Mendelson resigned from the Compensation Committee on May 31, 1996, at which time Joseph H. Wender was elected.

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. The Nominating Committee is composed of two non-employee directors: Mr. Mendelson and Dr. Soll and did not meet during the year.

During the fiscal year ended December 31, 1996, all directors, other than Professor Hohbach, 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.

COMPLIANCE WITH SECTION 16(a) OF THE SECURITIES EXCHANGE ACT OF 1934

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 the fiscal year ended December 31, 1996, all Section 16(a) filing requirements applicable to its officers, directors and greater than ten percent stockholders were complied with.

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PROPOSAL 2

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, 1997 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 2.

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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 28, 1997 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..... Binger Strasse 173 D-55216 Ingelheim Am Rhein GERMANY	2,408,607	9.2
Novartis AG (3)..... CH-4002, Basel SWITZERLAND	2,257,053	8.6

Christopher F. O. Gabrieli (4).....	1,680,944	6.3
83 Walnut Street Wellesley Hills, MA 02181		
Bessemer Venture Partners (5).....	1,536,465	5.7
1025 Old Country Road Westbury, NY 11590		
Stephen K. Carter (6).....	--	--
Stanley T. Crooke(7).....	1,212,348	4.6
Daniel L. Kisner (8).....	284,666	1.1
Alan C. Mendelson (9).....	23,627	*
William R. Miller (10).....	42,500	*
Mark B. Skaletsky (11).....	28,500	*
Larry Soll (12).....	40,750	*
Joseph H. Wender (13).....	43,750	*
B. Lynne Parshall (14).....	153,744	*
All directors and executive officers as a group (10 persons) (15)	3,510,829	12.8

* 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 26,306,352 shares of Common Stock outstanding on February 28, 1997.
- (3) 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

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registered in Switzerland and a wholly-owned subsidiary of Novartis AG. 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.

- (4) Includes 759,566 shares owned 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 25,916 shares issuable upon exercise of options held by Mr. Gabrieli that are exercisable on or before April 29, 1997.
- (5) 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.
- (6) Excludes shares owned by Boehringer Ingelheim International GmbH ("BII"). Dr. Carter does not, directly or indirectly, have or share voting power or investment power over the shares held by BII and, therefore, disclaims beneficial ownership of such shares. Dr. Carter resigned from the

Company's Board on March 17, 1997.

- (7) Includes 96,642 shares issuable upon exercise of options held by Dr. Crooke that are exercisable on or before April 29, 1997 and 6,206 shares issuable upon exercise of options held by his wife that are exercisable on or before April 29, 1997.
- (8) Includes 280,666 shares issuable upon exercise of options held by Dr. Kisner that are exercisable on or before April 29, 1997 and 2,000 shares each issuable upon exercise of options which Dr. Kisner transferred to his son and daughter that are exercisable on or before April 29, 1997.
- (9) Includes 310 shares held in a trust by Mr. Mendelson's wife for his son, Jonathan, 310 shares held in trust by Mr. Mendelson's wife for his son, David, and 18,000 shares issuable upon exercise of options held by Mr. Mendelson that are exercisable on or before April 29, 1997. Mr. Mendelson disclaims beneficial ownership of the shares held in trust by his wife for his sons.
- (10) Includes 2,500 shares issuable upon exercise of options held by Mr. Miller that are exercisable on or before April 29, 1997.
- (11) Includes 7,500 shares issuable upon exercise of options held by Mr. Skaletsky that are exercisable on or before April 29, 1997.
- (12) Includes 40,750 shares issuable upon exercise of options held by Dr. Soll that are exercisable on or before April 29, 1997.
- (13) Includes 16,750 shares issuable upon exercise of options held by Mr. Wender that are exercisable on or before April 29, 1997.
- (14) Includes 133,612 shares issuable upon exercise of options held by Ms. Parshall that are exercisable on or before April 29, 1997.
- (15) Includes shares described in the notes above, as applicable.

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EXECUTIVE COMPENSATION

COMPENSATION OF DIRECTORS

In the fiscal year ended December 31, 1996, each director of the Company or one of its affiliates who is not otherwise an employee of the Company or any affiliate (a "Non-Employee Director") received a fee of \$15,000 (except that Dr. Carter did not receive a fee for 1996); no additional compensation is paid for attendance at Board or committee meetings. For 1996, the total compensation paid to Non-Employee Directors was \$105,000. 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 1996, 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. Carter 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 \$18.625 per share for all but the option to purchase 18,000 shares granted to Dr. Carter, the exercise price of which was \$18.00 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 28, 1997, none of these options had vested.

COMPENSATION OF EXECUTIVE OFFICERS AND OTHER EMPLOYEES

The following table shows for the fiscal years ending December 31, 1996, 1995 and 1994, 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, 1996:

SUMMARY COMPENSATION TABLE

Name and Principal Position	Year	Annual Compensation			Long-Term Compensation Awards	All Other Compensation (\$) (3)
		Salary (\$)	Bonus (\$)	Other Annual Compensation (\$) (1) (2)	Securities Underlying Options (#)	
Stanley T. Croke	1996	280,344	98,119	0	40,000	0
Chairman and Chief Executive Officer	1995	262,000	116,001	0	50,000	0
	1994	244,860	123,409	0	0	0
Daniel L. Kisner	1996	257,280	77,185	0	25,000	0
President and Chief Operating Officer	1995	242,719	92,112	0	30,000	0
	1994	226,840	97,995	0	90,000 (4)	0
B. Lynne Parshall	1996	236,171	70,851	0	16,000	0
Executive Vice President & Chief Financial Officer	1995	214,743	67,745	0	85,000 (5)	0
	1994	195,834	72,072	0	0	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, 1996.
- (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) Represents the 90,000 options granted in connection to Dr. Kisner's promotion to President on 5-24-94.
- (5) 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 28, 1997, options to purchase a total of 6,132,558 shares had been granted and were outstanding under the 1989 Plan and options to purchase 957,791 shares remained available for grant thereunder.

The following tables show for the fiscal year ended December 31, 1996 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

Individual Grants

Name	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	Potential Realizable Value at Assumed Annual Rates of Stock Price Appreciation for Option Term (3)	
						5% (\$)	10% (\$)
Stanley T. Crooke	40,000	3.10	13.125	525,000	12-31-05	330,055	836,359
Daniel L. Kisner	25,000	1.94	13.125	328,125	12-31-05	206,285	522,725
B. Lynne Parshall	16,000	1.24	13.125	210,000	12-31-05	132,022	334,544

- (1) Options granted in 1996 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 1,291,715 shares granted in 1996. Represents the number of options granted under the 1989 Plan in 1996 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.

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 (#)		Value of Unexercised In-the-Money Options at FY-End (\$ (2))	
			Exercisable/Unexercisable	Exercisable/Unexercisable	Exercisable/Unexercisable	Exercisable/Unexercisable
Stanley T. Crooke	38,500	\$680,688	14,750 /250		\$139,756	/\$2,369
			1,642 /0		\$15,558	/\$0
			23,500 /6,500		\$209,620	/\$57,980
			0 /25,000		\$0	/\$288,500
			18,000 /12,000		\$202,500	/\$135,000
			9,583 /15,417		\$134,162	/\$215,838
			9,583 /15,417		\$134,162	/\$215,838
Daniel L. Kisner	40,000	\$789,259	170,000 /0		\$2,938,571	/\$0
			4,097 /70		\$41,994	/\$718
			0 /50,000		\$0	/\$437,500
			17,625 /4,875		\$171,844	/\$47,531
			0 /25,000		\$0	/\$303,125
			17,500 /7,500		\$196,875	/\$84,375
			45,000 /45,000		\$489,375	/\$489,375
			5,750 /9,250		\$80,500	/\$129,500
B. Lynne Parshall	36,937	\$469,553	5,750 /9,250		\$80,500	/\$129,500
			0 /25,000	(3)	\$0	/\$121,875
			18,666 /1,334		\$177,327	/\$12,673
			59,728 /0		\$731,668	/\$0
			0 /47,500	(4)	\$0	/\$415,625
Daniel L. Kisner	40,000	\$789,259	14,099 /3,901		\$137,465	/\$38,035
			0 /25,000		\$0	/\$303,125
			12,000 /8,000		\$135,000	/\$90,000
			1,750 /9,251		\$24,500	/\$129,514
			1,167 /6,167		\$16,338	/\$86,338
			12,000 /48,000		\$64,500	/\$258,000
			0 /16,000		\$0	/\$78,000

- (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, 1996 (\$18.00) multiplied by the applicable number of shares minus the aggregate exercise price of the options for such number of shares.
- (3) Includes 2,000 options, each, transferred to Dr. Kisner's son and daughter.
- (4) Includes 2,000 options, each, transferred to Ms. Parshall's daughters. Does not include options for 2,500 in aggregate transferred to Ms. Parshall's father and brother for which Ms. Parshall disclaims beneficial ownership.

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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 are currently 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: a 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 Company's 1989 Plan with an exercise price of 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.

1996 was a year in which the Company continued to advance development of its drug candidates. It continued progress in Phase III clinical trials for ISIS

2922, its compound to treat cytomegalovirus-induced retinitis in AIDS patients. The Company also completed Phase IIa trials of ISIS 2302, a compound that inhibits intercellular adhesion molecule-1 (ICAM-1) in Crohn's disease, and continued progress in Phase II in four other indications: ulcerative colitis; psoriasis; rheumatoid arthritis; and renal transplant rejection. In addition, the Company continued preclinical development in other compounds to treat cancer and Hepatitis C.

Isis entered Phase I clinical trials on ISIS 3521/CPG64128A, one of its two cancer compounds targeting solid tumor cancers, in February of 1996, and began Phase I clinical trials on ISIS 5132/CPG69846A, the other cancer compound, in April 1996. Both trials have continued to make progress. The Company also filed an IND on ISIS 5320 to treat HIV in October 1996 and initiated clinical trials in early 1997.

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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.

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Isis' research continues to proceed well. The Company's patenting strategy continued to bear fruit with 42 additional patents issued in 1996. The Company's relationships with its collaborative partners have continued positively. In 1996, the Company achieved the milestone of the completion of its Phase IIa Crohn's disease study and received a \$10 million milestone payment in the form of an equity investment from BII. In October and December of 1996, the Company also accessed the line of credit provisions of the agreement with BII to draw down \$16.2 million of the \$40 million line of credit available.

The Company's continued focus on financial controls resulted in a favorable operating expense profile at a level which was significantly lower than the Company's 1996 original budget.

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 1996 while also improving the quality and precision of purification and analytical methods.

The Compensation Committee approved a 10.6% salary increase for Dr. Crooke for 1997. As a matter of course, the Company does not expect that it will be able to achieve all the objectives set for the year; and in 1996, 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, with relatively more modest increases in base compensation. The Committee approved a bonus of \$98,119 for Dr. Crooke, which was 100% 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 100% of its achievement of objectives, and Dr. Crooke performing at 100% of his achievement of personal objectives. In January 1997, the Committee also approved an option for 22,500 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, 1996, the Company's Compensation Committee was composed of Messrs. Skaletsky, Miller and Wender. Mr. Mendelson resigned from the Compensation Committee on May 31, 1996, at which time Mr. Wender replaced him. Mr. Mendelson was Secretary of the Company from January 1989 to November 1991. He has been a partner of Cooley Godward since 1980. As of February 29, 1997, Mr. Mendelson beneficially owned

23,627 shares of Common Stock (see "Security Ownership of Certain Beneficial Owners and Management"). Fees paid by the Company to Cooley Godward during the fiscal year ended December 31, 1996 for legal services rendered to the Company did not exceed five percent of Cooley Godward's gross revenues for such fiscal year.

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PERFORMANCE MEASUREMENT COMPARISON(1)

COMPARISON OF CUMULATIVE TOTAL RETURN AMONG ISIS PHARMACEUTICALS
THE NASDAQ COMPOSITE INDEX (TOTAL RETURN)
THE CHICAGO BOARD OF OPTIONS BIOTECHNOLOGY INDEX

[GRAPH]

	Dec. 1991	Dec. 1992	Dec. 1993	Dec. 1994	Dec. 1995	Dec. 1996
Isis	100	67	49	29	95	131
NASDAQ Composite Index	100	116	134	130	183	224
CBO-Biotechnology Index	100	78	58	51	83	79

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 Chicago Board of Options Biotechnology 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.

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CERTAIN TRANSACTIONS

In 1996, the Company achieved a milestone specified under the terms of its collaborative agreement with BII. As a result of this accomplishment, in December 1996, BII purchased 409,000 shares of Common Stock for \$10 million in cash. The Company borrowed \$16.2 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 US 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, 1996 was \$16.2 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 28, 1997

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, 1996 IS AVAILABLE WITHOUT CHARGE UPON WRITTEN REQUEST TO: B. LYNNE PARSHALL, SECRETARY, ISIS PHARMACEUTICALS, INC., 2292 FARADAY AVENUE, CARLSBAD, CALIFORNIA 92008.

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ISIS PHARMACEUTICALS, INC.
PROXY SOLICITED BY THE BOARD OF DIRECTORS
FOR THE ANNUAL MEETING OF STOCKHOLDERS TO BE HELD ON JUNE 6, 1997

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, June 6, 1997 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 PROPOSAL 2 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

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

ANNUAL MEETING OF STOCKHOLDERS
ISIS PHARMACEUTICALS, INC.

June 6, 1997

- PLEASE DETACH AND MAIL IN THE ENVELOPE PROVIDED -

PLEASE MARK YOUR
A VOTES AS IN THIS
EXAMPLE

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

PROPOSAL 1: to elect three directors to hold office until the 2000 Annual Meeting of Stockholders.

WITHHOLD AUTHORITY to vote for all nominees listed at right.

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

nominee(s) name(s) below:

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

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

THE BOARD OF DIRECTORS RECOMMENDS A VOTE FOR PROPOSAL 2.

PROPOSAL 2: To ratify the selection of Ernst & Young LLP as independent auditors of the Company for the fiscal year ending December 31, 1997.

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, include title. If a partnership, please sign in partnership name by authorized person.