

UNITED STATES  
SECURITIES AND EXCHANGE COMMISSION  
WASHINGTON, D.C. 20549

SCHEDULE 13G  
(Amendment No. 5)\*

UNDER THE SECURITIES EXCHANGE ACT OF 1934

Isis Pharmaceuticals, Inc.  
(Name of Issuer)

Common Stock  
(Title of Class of Securities)

464330 10 9  
(CUSIP Number)

\*The remainder of this cover page shall be filled out for a reporting person's initial filing on this form with respect to the subject class of securities, and for any subsequent amendment containing information which would alter the disclosures provided in a prior cover page.

The information required in the remainder of this cover page shall not be deemed to be "filed" for the purpose of Section 18 of the Securities Exchange Act of 1934 ("Act") or otherwise subject to the liabilities of that section of the Act but shall be subject to all other provisions of the Act (however, see the Notes).

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13G

CUSIP NO. 464330 10 9

PAGE 2 OF 4 PAGES

1 NAME OF REPORTING PERSONS  
S.S. OR I.R.S. IDENTIFICATION NOS. OF ABOVE PERSONS

STANLEY T. CROOKE 306-42-5073

2 CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP\* (a) [ ]  
(b) [X]

3 SEC USE ONLY

4 CITIZENSHIP OR PLACE OF ORGANIZATION

UNITED STATES

5 SOLE VOTING POWER  
NUMBER OF 1,209,519 (1)

6 SHARED VOTING POWER  
SHARES 0  
BENEFICIALLY OWNED BY

7 SOLE DISPOSITIVE POWER  
EACH REPORTING PERSON WITH 1,209,519 (1)

8 SHARED DISPOSITIVE POWER  
0

9 AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON  
1,209,519 (1)

10 CHECK BOX IF THE AGGREGATE AMOUNT IN ROW (9) EXCLUDES CERTAIN SHARES\*  
11 PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW 9  
4.6%

12 TYPE OF REPORTING PERSON\*  
IN

(1) includes 93,974 shares of Common Stock issuable upon exercise of options exercisable within 60 days. Also includes 6,045 shares issuable upon exercise of stock options held by Rosanne Crooke, Dr. Crooke's wife, exercisable on or before 3/1/97, as to which Dr. Crooke disclaims beneficial ownership.

\*SEE INSTRUCTION BEFORE FILLING OUT!

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ITEM 1.

- (a) Name of Issuer: Isis Pharmaceuticals, Inc. ("Issuer")
- (b) Address of Issuer's Principal Executive Offices: 2292 Faraday Avenue  
Carlsbad, CA 92008

ITEM 2.

- (a) Name of Person Filing: Stanley T. Crooke
- (b) Address of Principal Business Office or, if none,  
Residence: 2292 Faraday Avenue  
Carlsbad, CA 92008
- (c) Citizenship: United States
- (d) Title of Class of Securities: Common Stock
- (e) CUSIP Number: 464330 10 9

ITEM 3. NOT APPLICABLE.

ITEM 4. OWNERSHIP.

- (a) Amount Beneficially Owned: 1,209,519 (2)
- (b) Percent of Class: 4.6%
- (c) Number of shares as to which such person has:
- (i) sole power to vote or to direct the vote: 1,209,519 (2)
  - (ii) shares power to vote or to direct the vote: 0
  - (iii) sole power to dispose or to direct the disposition of: 1,209,519 (2)
  - (iv) shared power to dispose or to direct the disposition of: 0

ITEM 5. OWNERSHIP OF FIVE PERCENT OR LESS OF A CLASS

If this statement is being filed to report the fact that as of the date hereof the reporting person has ceased to be the beneficial owner of more than five percent of the class of securities, check the following:

ITEM 6. OWNERSHIP OF MORE THAN FIVE PERCENT ON BEHALF OF ANOTHER PERSON

Not applicable

ITEM 7. IDENTIFICATION AND CLASSIFICATION OF THE SUBSIDIARY WHICH ACQUIRED THE SECURITY BEING REPORTED ON BY THE PARENT HOLDING COMPANY.

Not applicable.

ITEM 8. IDENTIFICATION AND CLASSIFICATION OF MEMBERS OF THE GROUP

Not applicable.

- (2) includes 93,974 shares of Common Stock issuable upon exercise of options exercisable within 60 days. Also includes 6,045 shares issuable upon exercise of stock options held by Rosanne Crooke, Dr. Crooke's wife, exercisable on or before 3/1/97, as to which Dr. Crooke disclaims beneficial ownership.

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ITEM 9. NOTICE OF DISSOLUTION OF GROUP

Not applicable.

ITEM 10. CERTIFICATION

Not applicable

SIGNATURE

After reasonable inquiry and to the best of my knowledge and belief, I certify that the information set forth in this statement is true, complete and correct.

January 30, 1997

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Date

/s/ Stanley T. Crooke

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Signature

Stanley T. Crooke, Chairman and CEO

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Name/Title