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The Honorable Charles B. Rangel
House of Representatives

Dear Mr. Rangel.

This is the second report in response to your May 9, 1974, request. Our previous report, issued to you on July 23, 1974, dealt with the first three issues in your request and focused on the supply and demand for crude opium and opium derivatives. This report discusses the remaining three issues in your request, namely:

- What have been the U.S efforts toward establishing new legitimate sources of opium? (See pp 1 to 4.)
- What technology is required to increase production of opium from present sources and the extent to which the United States is supporting such technology? (See pp 4 to 7.)
- What is the state of research with respect to synthetic alternatives to codeine and other opium derivatives and the extent to which the United States is supporting such research? (See pp. 7 to 10.)

We contacted officials at (1) the Drug Enforcement Administration, (2) the Special Action Office for Drug Abuse Prevention, (3) the National Academy of Sciences, and (4) the Departments of State, Agriculture; and Health, Education, and Welfare. We also talked to officials in private industry and members of the medical profession

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We found that

- Although its policy is that domestic requirements for opiates will continue to be met through imports, the United States discourages the expansion of legitimate opium production overseas because of illicit diversion problems. New sources could be developed both overseas and at home, but U.S. Government encouragement has been minimal.

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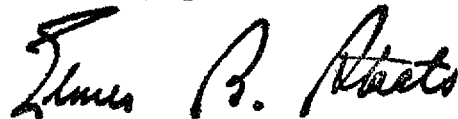
--More opium alkaloids can be produced from present sources by developing improved plant strains and better extraction procedures. The U.N., with U.S. support, is conducting research on the opium poppy, as well as a different strain of alkaloid-rich poppy--*Papaver bracteatum*. Domestically, Government and private industry research is focused on *Papaver bracteatum*.

--A commercially feasible process for producing a synthetic codeine is a least 5 years from realization, according to both Government and private industry officials. Current research reports on synthetic alternatives to the natural opiates state that, while synthetics are currently used in medical treatment, none affords the broad relief provided by codeine. Studies of physicians' opinions and prescribing practices indicate that although synthetic alternatives are being used, the medical profession considers opium-based medications to be superior and necessary.

The enclosure discusses these issues in greater detail.

As requested by your office during the preparation of our first report, we did not obtain formal agency comments. However, we discussed the results of our review with officials of the agencies involved and their comments were considered in preparing this report. We plan no further distribution of this report unless you agree or publicly announce its contents.

Sincerely yours,

A handwritten signature in black ink, appearing to read "James B. Aronson". The signature is written in a cursive, slightly slanted style.

Comptroller General
of the United States

Enclosure

ISSUES CONCERNING NEW LEGITIMATE SOURCES FOR OPIUM,
TECHNOLOGY REQUIRED TO INCREASE PRODUCTION FROM PRESENT
SOURCES, AND THE STATE OF RESEARCH WITH RESPECT TO SYNTHETIC
ALTERNATIVES TO CODEINE AND OTHER OPIUM DERIVATIVES

Historically, the United States has supported severely limiting the worldwide cultivation of opium poppies and has sought controls through multilateral treaties designed to tighten governmental regulation over opium production and export. By 1973 India was the sole producer of licit opium for export in the world market, however, it has been unable to meet U.S. demands. Releases from U.S. stockpiles are providing an interim solution, but new legitimate sources will eventually be needed.

Current U.S. policy, as stated by the U.S. delegate to the United Nation's (U.N.'s) Commission on Narcotic Drugs in February 1974, is that:

- The international community is responsible for assuring adequate supplies of opiates for medical and scientific purposes until suitable nonaddictive or less addictive synthetic substances can be developed and adopted.
- The United States has a vital interest in preventing diversion from licit sources and eliminating all illicit production.
- The United States intends to continue to meet its opium requirements through imports.

WHAT HAVE BEEN THE U S EFFORTS TOWARD
ESTABLISHING NEW LEGITIMATE SOURCES OF OPIUM?

Opium production in India

The United States has always discouraged the expansion of licit opium production without adequate controls to prevent leakage or diversion into the illicit market. India has been reluctant to expand the amount of land allotted for opium cultivation because diversion controls could be weakened. According to one Drug Enforcement Administration (DEA) official, opium production in India has probably peaked at about 1,000 metric tons a year. No U.S. funds have been used directly to encourage opium production in India or any other country.

Exports from other countries

According to Department of State and DEA officials, the United States is not encouraging the establishment of new sources in other countries. One official believed that many countries could begin producing immediately if encouraged to do so, however, the United States has never encouraged this source because local governments have traditionally been unable to control licit production. No evidence indicates that the U.S. will reverse its traditional stand and seek the expansion of opium cultivation by other nations

Despite U.S. protests, the Turkish Government has decided to again cultivate opium poppies for the licit export market. Procurement of opium from Turkey is still authorized under international treaty. State Department officials said unless the U N. International Narcotics Control Board decides that Turkish controls are inadequate, no action will be taken to discourage procurement by member nations. Both the United States and the U N. would provide assistance in establishing controls if asked to do so, according to the State Department.

The seven provinces recently authorized by the Turkish Government to grow opium poppies are the same areas which were cultivated during 1971. One DEA official said that Turkey projects a yield of 200 metric tons of opium from the current crop, but he believes a far greater yield will be produced, resulting in illicit diversion.

According to a recent press report, the Turkish Government is adopting a new method of harvesting poppies. In the old hand method, the poppy pod is lanced and the opium gum collected, in the new "poppy straw process," the whole pod and stalk are collected. Because the farmers would not be allowed to collect opium gum under the new method, U.S. officials believed that, with proper policing, this method could lessen potential illicit diversion

U.S. opium processors are not prohibited from purchasing from Turkey; however, they are not authorized to import or equipped to process poppy straw. They claim that importing straw for processing would be too costly. Regardless of whether the U.S. opium processors can purchase crude opium from Turkey, the world supply of licit opium alkaloids will increase

The U S Comprehensive Drug Abuse Prevention and Control Act of 1970 (21 U.S.C. 801) prohibits importing any narcotic controlled substance except crude opium and coca leaves. However, the act provides that during an emergency in which domestic supplies of controlled substances are inadequate the

Attorney General may authorize such imports. Should the Attorney General declare such an emergency, he could authorize and regulate the importation of processed opium alkaloids such as codeine and morphine base. According to one DEA official, excess processed opium alkaloids have not generally been available for sale on the world market. However, certain countries may now be developing facilities using the poppy straw process for alkaloid extraction and may eventually produce for export.

Opium seized from illicit traffic

The Attorney General is authorized by the act to register and regulate businesses that process crude opium. Procuring crude opium has traditionally been the responsibility and concern of the individual processing companies. The U. S. Government does not participate in negotiations for the sale of opium

Under international treaty, member nations may export opium seized in the illicit market. The U.S. Government has agreed to assist U.S. importers by bringing to their attention significant seizures that foreign governments might agree to export. The U.S. companies would still be responsible for negotiating a sale.

In discussing opium sources with the three companies currently licensed to import and process crude opium, we learned that only one company has imported confiscated opium in the past few years. A second company said it would consider bidding for seized opium, the third was not interested because of the generally lower quality of illicit opium. Since 1970 the Government has issued permits to import seized opium from Afghanistan, Thailand, Pakistan, South Vietnam, and Egypt.

Confiscated opium, however, is unreliable as a continuous source. The maximum amount purchased and imported into the United States in any year, according to DEA statistics, was 29.5 metric tons in 1972. One DEA official said that the amount of confiscated opium available for sale in any year might average 20 metric tons. An industry source agreed with this estimate and indicated that prospective bidding on confiscated opium has increased significantly because of worldwide shortages

Domestic cultivation

The act states that, with proper controls and licensing, opium poppies may be cultivated in the United States for domestic needs, and international treaty sanctions this policy. U.S. officials agree that production could easily be established and controlled to provide for domestic medical and

scientific needs. Such development would make the United States self-sufficient with regard to this vital commodity.

According to the Special Action Office for Drug Abuse Prevention (SAODAP), when our opium supply was threatened during World War II, Government research verified that we could meet our needs for opiates by domestic cultivation. U.S. officials believe, however, that domestic cultivation, even under the most stringent controls, would be inconsistent with the past U.S. position and could cause nations not capable of adequately controlling opium production to enter the market.

As previously stated, U.S. policy is that the United States will meet its opium needs through imports. Officials in SAODAP, DEA, and the Department of State see no need to change that position.

WHAT TECHNOLOGY IS REQUIRED TO INCREASE
PRODUCTION OF OPIUM FROM PRESENT SOURCES
AND THE EXTENT TO WHICH THE
UNITED STATES IS SUPPORTING SUCH TECHNOLOGY?

The opium poppy (*Papaver somniferum*) can be cultivated in many soils and climates, and opium is produced in various countries. In most producing areas, such as India and Turkey, the opium poppy is hand cultivated on small plots and harvested by farmers. Although the poppy can be cultivated and harvested mechanically, it has traditionally been grown in countries where a large unskilled work force is available to perform the extensive labor required to obtain crude opium by incising the poppy pod.

The United States has never provided direct funding to an opium-producing country to support research for increasing production. After World War II the Department of Agriculture and the former Federal Bureau of Narcotics conducted some research related to providing strategic medical supplies in the event opium imports were cut off. This involved experimental planting of poppies, maintaining supplies of poppy seeds, and developing an extraction process to obtain the opium alkaloids. In addition, research published by the Federal Bureau of Narcotics in 1944 dealt with the effects of fertilizers, growing conditions, breeding, and extraction methods on the opium poppy.

In recent years the United States has initiated little research or technology to increase opium production, primarily because until quite recently the United States has received an adequate supply of crude opium from the exporting

countries In fact, the Government has been more concerned with restricting and eradicating the opium poppy because of the illicit opium traffic

Increased production

More opium can be obtained by developing (1) improved plant strains to increase the per plant yield of alkaloids and (2) more efficient extraction procedures.

Little research is being conducted in the United States on improving the poppy plant strain to increase the per plant alkaloid yield. According to private industry sources, the private sector is not funding any opium poppy research

The Third Special Session of the U.N. Commission on Narcotic Drugs noted that further research was needed to improve the poppy straw extraction process. The discussion focused primarily on three alkaloid extraction methods:

- Extraction of alkaloids from poppy straw including the nonincised pod.
- Extraction of alkaloids remaining in the poppy straw after the pod has been incised and the opium gum removed.
- Extraction of alkaloids from the green poppy plant before the pods have ripened.

The only U.S Government program in this area is being sponsored by SAODAP and carried out by the Department of Agriculture This program is comparing the morphine content of green poppy straw to that of dry straw and investigating the feasibility of extracting alkaloids from green straw.

Although the Government is not directly funding opium poppy research in other countries, it made a special contribution to the U.N Fund for Drug Abuse Control (UNFDAC) in February 1974. This contribution included \$800,000 for U.N Narcotics Laboratory research to develop and perfect processes for increased production

In July 1974, a group of world experts sponsored by UNFDAC met in Geneva to draw up guidelines and establish priorities for this program The 3-year project will investigate (1) various straw processes of alkaloid extraction, (2) methods to improve yields of desired alkaloids from selected strains

of opium poppies, and (3) crop development of *Papaver bracteatum*, a different strain of poppy, as a source of codeine. This program will involve seed collection, experimental cultivation, and breeding experiments with the opium poppy and will include all aspects of the growing cycle, environmental conditions, and harvesting procedures.

Papaver bracteatum

Papaver bracteatum is a member of the poppy family, but unlike the annual opium poppy (*Papaver somniferum*), it is a long-lived perennial containing no morphine--the source of heroin. Instead, it contains the alkaloid thebaine. Codeine, the major derivative of imported opium, is currently produced from morphine, but can also be produced by chemical conversion from thebaine.

In addition to its lack of morphine, apparent advantages of *Papaver bracteatum* over the opium poppy include (1) higher yields of codeine per area under cultivation, (2) the elimination of annual plantings, and (3) the potential for better controls over illicit planting and diversion, because the thebaine content of new plantings of *Papaver bracteatum* does not reach a suitable level for harvesting for 2 or 3 years.

Thebaine is a poisonous material which is not used medically, although certain of its derivatives are being produced and marketed for medical and scientific use. However, thebaine could be used to produce compounds with abuse potential. Initial DEA studies indicate that certain thebaine-derived compounds have analgesic potency ranging from 2 to about 1,500 times that of morphine, with a correspondingly high dependency-inducing capacity. Apparently no significant illicit market for these compounds presently exists.

According to one manufacturing company, the techniques for converting thebaine to morphine are relatively complicated and require sophisticated equipment. The process also requires highly flammable chemicals. Consequently, the danger to a clandestine operator is much greater than in converting morphine to heroin.

At least one private concern is interested in developing *Papaver bracteatum* as a domestic source for codeine and believes it could compete with opium imports at current price levels. This processor is doing research on the growth of *Papaver bracteatum* and has some experimental fields growing.

Growing *Papaver bracteatum* in the United States is not prohibited. The alkaloid thebaine, however, is a controlled substance--anyone handling it must be licensed by DEA. Before private industry will make the large financial commitment necessary to set up a commercially feasible operation, they want official U.S. sanctions, including a policy allowing controlled domestic cultivation of *Papaver bracteatum* as a source of codeine.

Private industry and the Department of Agriculture are conducting research to identify the highest thebaine strains and determine cultivation requirements of *Papaver bracteatum*. The Department of Agriculture has also funded four research projects overseas, including two completed projects--a study of *Papaver bracteatum* and related species in Iran and the collection and cultural evaluation of *Papaver bracteatum* and related species in Turkey. Two ongoing projects concern developing strains from *Papaver bracteatum* for alkaloid production in Israel and the screening of *Papaver bracteatum* and related species for alkaloids, mainly thebaine and codeine, in the Netherlands.

In 1972 the United Nations Narcotics Laboratory undertook a research program, financed by UNFDAC, on the use of *Papaver bracteatum* to produce codeine. The United States aids this program through its financial contribution to UNFDAC (\$10 million out of total collections of \$13.45 million) and by the direct participation by U.S. experts. The third meeting of the program working group was held last October at the U.S. Agricultural Research Center in Beltsville, Maryland.

According to officials involved in both private- and Government-sponsored *Papaver bracteatum* research, the evidence has been encouraging, and they foresee *Papaver bracteatum* as a significant future source of codeine.

WHAT IS THE STATE OF RESEARCH WITH RESPECT TO
SYNTHETIC ALTERNATIVES TO CODEINE AND OTHER
OPIUM DERIVATIVES AND THE EXTENT TO WHICH THE
UNITED STATES IS SUPPORTING SUCH RESEARCH?

Synthetic codeine

The availability of a synthetic codeine at a price competitive with natural codeine could eventually eliminate the cultivation of opium poppies for medical purposes. However, no commercially feasible process presently exists.

Codeine was first synthesized in 1952, the feat was only of theoretical importance because of the complexity, inefficiency, and high cost of the process. Improvement in processes have been made, but no one we contacted believed that commercial production was possible in the near future. Government officials felt that, with the rising price of crude opium and the advancing state of chemical research, a new concerted effort should be made to develop a commercially feasible process for producing a synthetic codeine.

Pharmaceutical companies and opium processors are conducting research on a synthetic codeine either in house or through outside contracts. Because of competitive secrecy, no information is available on the extent of this research. The U S. Government also conducts some research within the National Institutes of Health. Government and private industry officials believe that any breakthrough in the commercial production of a synthetic codeine is 5 to 10 years away.

Synthetic alternatives

Synthetic alternatives are being used in all the major therapeutic categories for which opium derivatives have traditionally been prescribed, including the treatment of (1) pain (analgesics), categorized as mild to moderate and moderate to severe, (2) cough (antitussives), and (3) diarrhea (antidiarrheals).

Over the years, various research studies have compared synthetic alternatives to natural opiates. Recently, research studies by two major scientific institutions addressed this subject. One was a report by the World Health Organization (WHO) entitled "Opiates and their Alternatives for Pain and Cough Relief," and the other was a more recent report by the Committee on Problems of Drug Dependence of the National Academy of Sciences (NAS) entitled "Study of Synthetic Substitutes for Opiate Alkaloids."

The WHO report, released in 1972, said that

--For both categories of pain, synthetics can be, and have been, used in place of morphine and codeine.

--For the relief of cough, available synthetics can be used in place of codeine, however, a lack of well-controlled clinical trials in most instances prevented any judgment on their merits.

--For diarrhea, available synthetics are equal or superior to opiates.

The WHO report concluded that "* * * the natural and semi-synthetic opiates may be considered not indispensable in the practice of modern medicine."

The NAS Committee, commissioned by DEA, released its report in August 1974. The report dealt with the availability of synthetic alternatives and the effects and problems that would result from a total worldwide ban on opium cultivation.

In the treatment of both categories of pain, the NAS report agreed with the WHO report that substitutes are available and in use. Likewise, for the treatment of cough and diarrhea, the NAS report lists synthetics which can be and are being used. It also points out that, although the availability of synthetic antitussives may limit the use of opiates, no synthetic provides the broad relief of codeine. Further, in the treatment of mild to moderate pain, nothing has proved superior to the natural product.

As part of the NAS study, physicians' opinions and prescribing practices were surveyed in collaboration with the American Medical Association. Another recent survey, commissioned by private industry and performed by the Lea-Mendota research group, also examined the prescribing practices of physicians and solicited their opinions on the merits and shortcomings of various drugs.

The studies reported similar findings. Synthetic and natural opiates are widely used to treat all categories of pain. Doctors prefer codeine in treating severe coughs; however, various synthetics are also being prescribed. In both surveys, the majority of doctors felt that opium-based analgesics and antitussives were necessary and that the removal of these products would impair treatment of patients.

Statements by private physicians we interviewed tended to support these findings. According to physicians, various synthetics have proved desirable for some therapeutic uses and have been accepted in medical practice, but doctors still believe the natural opiates are superior drugs.

When a new product is discovered, a substantial period of time elapses before it can be marketed. A new product must undergo thorough tests, including tests for dependence liability, under a variety of conditions before its effectiveness can be adequately determined. The product must then prove itself to the practicing physicians if it is to gain acceptance as a suitable replacement for existing drugs.

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