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Josef Fried, Kenneth J. Ryan, and Patricia Jones Tsuchitani, Editors; American Steroid Chemistry and Biochemistry Delegation; Committee on Scholarly Communication with the People's Republic of China; National Academy of Sciences

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Oral Contraceptives and Steroid Chemistry in the People's Republic of China

A Trip Report of the American Steroid Chemistry and Biochemistry Delegation

Edited by JOSEF FRIED, KENNETH J. RYAN, and PATRICIA JONES TSUCHITANI

Submitted to the Committee on Scholarly Communication with the People's Republic of China

NATIONAL ACADEMY OF SCIENCES
Washington, D.C. 1977

NOTICE: The views expressed in this report are those of the members of the Steroid Chemistry and Biochemistry Delegation and are in no way the official views of the Committee on Scholarly Communication with the People's Republic of China or its sponsoring organizations--the American Council of Learned Societies, the National Academy of Sciences, and the Social Science Research Council.

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The Committee represents American scholars in the natural, medical, and social sciences, as well as the humanities. It advises individuals and institutions on means of communicating with their Chinese colleagues, on China's international scholarly activities, and on the state of China's scientific and scholarly pursuits. Members of the Committee are scholars from a broad range of fields, including China studies.

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CONTRIBUTORS

LELAND CHINN, Research Fellow and Chairman of the Sexual Disorders and Reproduction Research Committee, G.D. Searle & Co., Chicago, Illinois

JACK FISHMAN, Director, Institute for Steroid Research, Montefiore Hospital and Medical Center, Bronx, New York

JOSEF FRIED, *Chairman of the Delegation*, Chairman, Department of Chemistry, University of Chicago, Chicago, Illinois

PERCY G. (ROD) HOLTON, Assistant Vice-president, Syntex Corporation, Palo Alto, California

DAVID M. LAMPTON, Assistant Professor, Department of Political Science, Ohio State University, Columbus, Ohio

MORTIMER LIPSETT, Director, Clinical Center, and Associate Director for Clinical Care, National Institutes of Health, Bethesda, Maryland

W. HENRY MOSLEY, Chairman, Department of Population Dynamics, School of Hygiene and Public Health, Johns Hopkins University, Baltimore, Maryland

KENNETH J. RYAN, Chairman, Department of Obstetrics and Gynecology, Harvard Medical School, and Chief of Staff, Boston Hospital for Women, Boston, Massachusetts

JEAN CHEN SHIH, Assistant Professor, Biological Sciences-Biochemistry Section, School of Pharmacy, University of Southern California, Los Angeles, California

PATRICIA JONES TSUCHITANI, Staff Officer, Committee on Scholarly Communication with the People's Republic of China, National Academy of Sciences, Washington, D.C.

MONROE WALL, Vice-president, Research Triangle Institute, Research Triangle Park, North Carolina

PREFACE

The American Steroid Chemistry and Biochemistry Delegation, composed of nine scientists, a China scholar specializing in the politics of Chinese health care, and a staff officer of the Committee on Scholarly Communication with the People's Republic of China, spent 19 days in China, from October 10 to October 29, 1976. The delegation was organized under the auspices of the Committee on Scholarly Communication with the People's Republic of China (CSCPRC), which is sponsored jointly by the American Council of Learned Societies, the Social Science Research Council, and the National Academy of Sciences.

The proposal for an exchange in steroid chemistry and biochemistry originated in 1974 with a CSCPRC suggestion to hold a two-week workshop in the United States the following year, in which Chinese and American scientists would participate. The major topics of the proposed workshop were to be chemistry of natural and synthetic steroids as applied in medicinal chemistry, progestational and estrogenic compounds of interest in birth control, and the biochemistry of steroids. The Chinese responded by suggesting that instead, a delegation of American steroid chemists and biochemists visit research institutes, hospitals, and laboratories in China. The CSCPRC therefore proposed such a delegation as part of its 1976 exchange program.

The scientific members of the Delegation represented the fields of steroid chemistry, steroid biochemistry, chemistry of natural products, processing and production of steroid products, endocrinology, oncology, obstetrics and gynecology, human reproduction, and epidemiology. Their major interests were in two areas: steroid raw materials processing and production and the biochemical, physiological, and medical aspects of steroid chemicals.

In addition, there was a strong interest on the part of all the Delegation members in the birth-planning and policy aspects of the principal steroid chemical product, the oral contraceptive. While the visit was devoted primarily to investigating the chemical research on steroids and their clinical uses, the Delegation members had several opportunities to discuss with their Chinese colleagues the population and health policies involved in the use of oral contraceptives.

This report focuses on four areas: (1) the administration of research and public health programs, including the process of drug control and approval; (2) research and production of steroid chemicals;

(3) the clinical applications of steroid hormones; and (4) the chemistry, pharmacology, and medical applications of natural products. In addition to the technical sections of the report, there is an extensive list of the institutions visited, with detailed information on facilities and personnel.

In China, the host for the Delegation was the Scientific and Technical Association of the People's Republic of China (STAPRC), which is the CSCPRC's exchange partner. A staff member of the STAPRC's Bureau of Foreign Affairs, Su Feng-lin, was responsible for coordinating the visit and traveling with the Delegation throughout their stay. Mr. Su arranged visits to research institutes, hospitals, pharmaceutical factories, and other medical units in Peking, Kweilin, Kwangchow, and Shanghai, in cooperation with the local branches of the STAPRC in those cities. He also arranged opportunities for the Delegation members and Chinese scientists to participate in discussion sessions on topics of mutual interest, such as the development of the contraceptive drug anordrin.

Two other people traveled with the Delegation as interpreters. Chu Li-chung, a biochemist at the Peking Institute of Zoology, was indispensable as scientific interpreter. Su Ch'üan-ch'ang, a staff member of the Peking Municipal Bureau of Science and Technology, also aided in interpreting. In Peking, the vice-chairman of the Scientific and Technical Association, Professor Chou P'ei-yüan, hosted a banquet for the Delegation, which was attended by other officials of the STAPRC such as Chu Yung-hang, deputy director of the Bureau of Foreign Affairs, and Feng Yin-fu, deputy chief of division in the Bureau of Foreign Affairs.

The Delegation would like to express its appreciation to the STAPRC, to Su Feng-lin, and to our two interpreters, Chu Li-chung and Su Ch'üan-ch'ang for their assistance in arranging the itinerary. Since the Delegation included two subgroups with distinct interests, it was often difficult to coordinate schedules and arrange special visits for each subgroup. Although this visit was limited, the members of the Delegation had the opportunity to visit the major research institutes and hospitals active in steroid chemistry research and the clinical application of steroids. This report is a record of that visit and of the impressions of the Delegation members on the major topics of interest.

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1

INTRODUCTION

The People's Republic of China probably produces and uses more steroid contraceptives than any other nation in the world. An interest in their methods for transforming indigenous plant materials into hormones, for organizing a highly efficient pharmaceutical industry over a relatively short period of time, and for disseminating drugs widely in the health care sector prompted the trip of our Delegation on steroid chemistry and biochemistry.

Although the marriage of traditional Chinese and Western medicine is proclaimed as an objective of Mao Tse-tung's revolutionary line, a notable exception has been in the use of birth control drugs where efficacy can readily be determined even in the absence of sophisticated clinical trials. There are no herbal medicines competing with the birth control pill or intrauterine device (IUD) in China at this time.

The emphasis on population control as a policy matter undoubtedly provides the impetus for the high level and extent of steroid chemistry and pharmaceutical manufacturing in the People's Republic of China. It is useful to note in this regard that Chinese population policy has vacillated over the last 28 years. In the very early 1950's, and then toward the end of that same decade, Peking asserted that an expanding population was a major asset. In 1957-58, the early 1960's, and during the present post-Cultural Revolution periods, the limitation of births and the avoidance of "reproductive anarchy" have been natural objectives.* Future continuity in birth control policy will depend on leadership commitment, economic conditions, and political stability.

Of special interest is the gearing of all scientific and technical efforts to practical applications related to general public needs. The underpinning for the Chinese effort is largely derived from the basic research of Western nations. Fundamental research is not extensive in China today. The striking accomplishment of Chinese scientists has been the ability to utilize Western methods to their own advantage in rapidly developing extensive production of steroid hormones. Original

*For more on population policy, see John S. Aird, "Population Policy and Demographic Prospects in the People's Republic of China," in *People's Republic of China: An Economic Assessment* (Washington, D.C.: Joint Economic Committee, 1972), pp. 220-331.

chemical or biological research is a rarity in China except for the studies in the Institute of Organic Chemistry in Shanghai, which is engaged in new approaches to the synthesis of polypeptides, proteins, and polyribonucleotides. This work is in the mainstream of current Western research and is an encouraging sign for the future of Chinese science.

The present trend to use science largely for practical ends is, however, a worldwide trend. Emphasis on the practical is politically necessary in China and politically seductive in the West. The value of fundamental studies cannot be gainsaid if one is to avoid compromise in our potential to cope with the ever increasing demand by the public for scientifically based technological advance. Our Delegation was impressed with the capacity of the Chinese to mobilize their technical and scientific resources to cope with significant social needs in population and other health-related problems. It is hoped that innovative basic research will also eventually develop a more important role in the scientific endeavors of the People's Republic of China.

Because of the time at which the Delegation visited the People's Republic, our mission was importantly affected by the momentous political changes that occurred in October 1976. In the months immediately preceding our arrival, five major leaders of the Chinese Revolution had died: Tung Pi-wu, K'ang Sheng, Chou En-lai, Chu Teh, and, of course, Chairman Mao Tse-tung. In addition, the acting premier, Teng Hsiao-p'ing, had been purged in April and had become the object of a national criticism campaign. These events, especially the passing of Chairman Mao Tse-tung, had created a leadership vacuum at the top, a struggle for power, and great uncertainty among the Chinese people.

As our delegation deplaned in Peking on the evening of October 10, 1976, we knew very little about the events that had occurred and the Central Committee decisions that had been made a mere two days before our arrival. These decisions not only affected our mission, but will, in all probability, affect the future of Sino-American relations and the course of development in China. On October 8, the Politburo of the Central Committee of the Chinese Communist Party had adopted resolutions which named Hua Kuo-feng chairman of the Chinese Communist Party and chairman of the Military Affairs Commission. In addition, Hua Kuo-feng was given responsibility for collecting and editing the *Selected Works of Mao Tse-tung* and the *Collected Works of Mao Tse-tung*. Immediately preceding these resolutions, four opposition leaders, conspicuously including Chairman Mao Tse-tung's wife, Chiang Ch'ing, were arrested. In short, by the time we stepped off the plane the succession issue had already been momentarily resolved. The line that began to crystallize in the days immediately following our arrival had a salutory effect on our mission.

The emerging policy line was articulated by Chou P'ei-yüan, vice-chairman of the Scientific and Technical Association of the People's Republic of China and vice-president of Peking University, in his opening remarks at the October 12 banquet welcoming us to China. Chou P'ei-yüan said that the leadership of China wished to strengthen Sino-American ties and that it was his expectation that scientific and cultural interchange between the two nations would grow. As our trip

progressed, other dimensions of the line began to emerge as well. For instance, at the Canton Trade Fair there was a quotation from Chairman Mao Tse-tung asserting that China should use foreign trade and technology to her benefit. Finally, by the time we reached Shanghai, where massive demonstrations against "the gang of four" were occurring, we were told flatly that one of the "crimes" of the "gang" had been its opposition to close relations with the United States.

Our Delegation appeared to be a beneficiary of this set of policies. The generally open and frank discussions that we had in almost all of the institutions visited were an important indication of this. Our Chinese hosts showed a willingness to explain the process by which decisions relating to pharmaceutical research, production, testing, and distribution are made. Of course, we would like to know a great deal more; the gaps in our knowledge are great, but progress was made.

In conclusion, our mission entered the People's Republic of China during a time of domestic leadership and policy change. While these alterations were carried out in quarters well beyond our vision, they made it possible for the Delegation to assess the work going on in the steroid, biochemical, medical, and public health areas. No less importantly, we caught a glimpse of how decisions in these vital areas are made. The American Steroid and Biochemistry Delegation hopes and believes that our presence during this important period contributed to mutual friendship, understanding, and scientific exchange between the United States and China.

2

ADMINISTRATION OF RESEARCH AND PUBLIC HEALTH PROGRAMS

INTRODUCTION

During our brief stay in the People's Republic of China we sought to obtain systematic and reliable information that would enable us to begin to answer the following sets of questions: (1) How are decisions about drug safety, distribution, production levels, and price made, and what have been the implicit or explicit trade-offs? (2) How do the pharmaceutical, research, health, and population bureaucracies interrelate, how is interagency coordination achieved, and what have been the successes and problems encountered in this regard? (3) How are decisions made to initiate research in some areas and discontinue it in others? (4) How extensive has decentralization of both drug research and pharmaceutical production become in the post-Cultural Revolution period? If decentralization has occurred, what tangible consequences has it had? (5) What mechanisms exist to assure public health and environmental quality, and what kinds of problems arise in the process of trying to achieve results in these areas?

While there was much that we were unable to learn, if for no other reason than we did not meet relevant government officials, we were able to find out a great deal from the factory managers, researchers, doctors, and administrators with whom we spoke.

THE PROCESS OF CLINICAL TRIAL, DRUG APPROVAL, AND DISTRIBUTION

Professor Carl Djerassi noted after his 1973 trip to China that

> The entire question of initiation of clinical experimentation, the extent of real informed consent of the patient ... and the precise interaction of scientists, clinicians and government cadres in releasing a drug to the public provides a subject which merits much more exchange between Chinese and foreign specialists.*

*Carl Djerassi, "Some Observations on Current Fertility Control in China," *China Quarterly* 57 (1974):52-53.

While we were unable to secure comprehensive and detailed information with respect to all these queries, the following findings should help clarify the picture. We received the most detailed and reliable answers to questions in this vein from our hosts at the Shanghai Institute of Physiology, the Shanghai International Peace Women and Children Protection Hospital, and the Shanghai Scientific Exchange Station; largely consistent information was furnished in Peking at the Institute of Materia Medica.

The process of drug development, clinical trial, and distribution begins with a research institute developing, for instance, a promising contraceptive agent. This had occurred at both the Shanghai Institute of Physiology, where scientists had developed the "combination" oral contraceptive, and the Shanghai Institute of Materia Medica, where they had done much of the work on a new agent called anordrin (or pill no. 53).* Once the institute in question had conducted animal activity, toxicity, and dosage studies, it informed the Provincial (or Municipal in the case of Shanghai†) Revolutionary Committee's Bureau of Public Health. The Bureau of Public Health, in turn, called a provincial-level "symposium" (*ta hui*) to which were invited representatives of the Bureau's Office of Drug Control (*Yao-wu Chien-chiu-so*), the hospitals that might be involved in clinical trials, the research institute that had developed the agent, and pharmaceutical plants. The purpose of the symposium was to decide if the research results warranted clinical trial and, if so, how such trials were to be conducted. In addition, formal approval of the Bureau of Public Health was required before clinical trials could begin (see Figure 1).‡ Unfortunately, we were unable to discover either the precise standards against which the test results were evaluated in these discussions or the degree to which local Bureau of Public Health approval was contingent upon compliance with general standards that may exist at the national level. Our sense was that no such universal standards exist.

Presuming that approval is forthcoming from both the local symposium and the Bureau of Public Health, as was the case for both the combination pill and anordrin, the agent is assigned to a hospital for clinical trial. The combination pill was assigned to the Shanghai International Peace Women and Children Protection Hospital for clinical trial. In the case of anordrin, the Shanghai Sixth People's Hospital was involved.§ In Peking, the Institute of Materia Medica appeared to rely on the three hospitals affiliated with the Academy of Medical Sciences (Capital, Fu Wai, and the Cancer Hospitals) to conduct clinical trials.

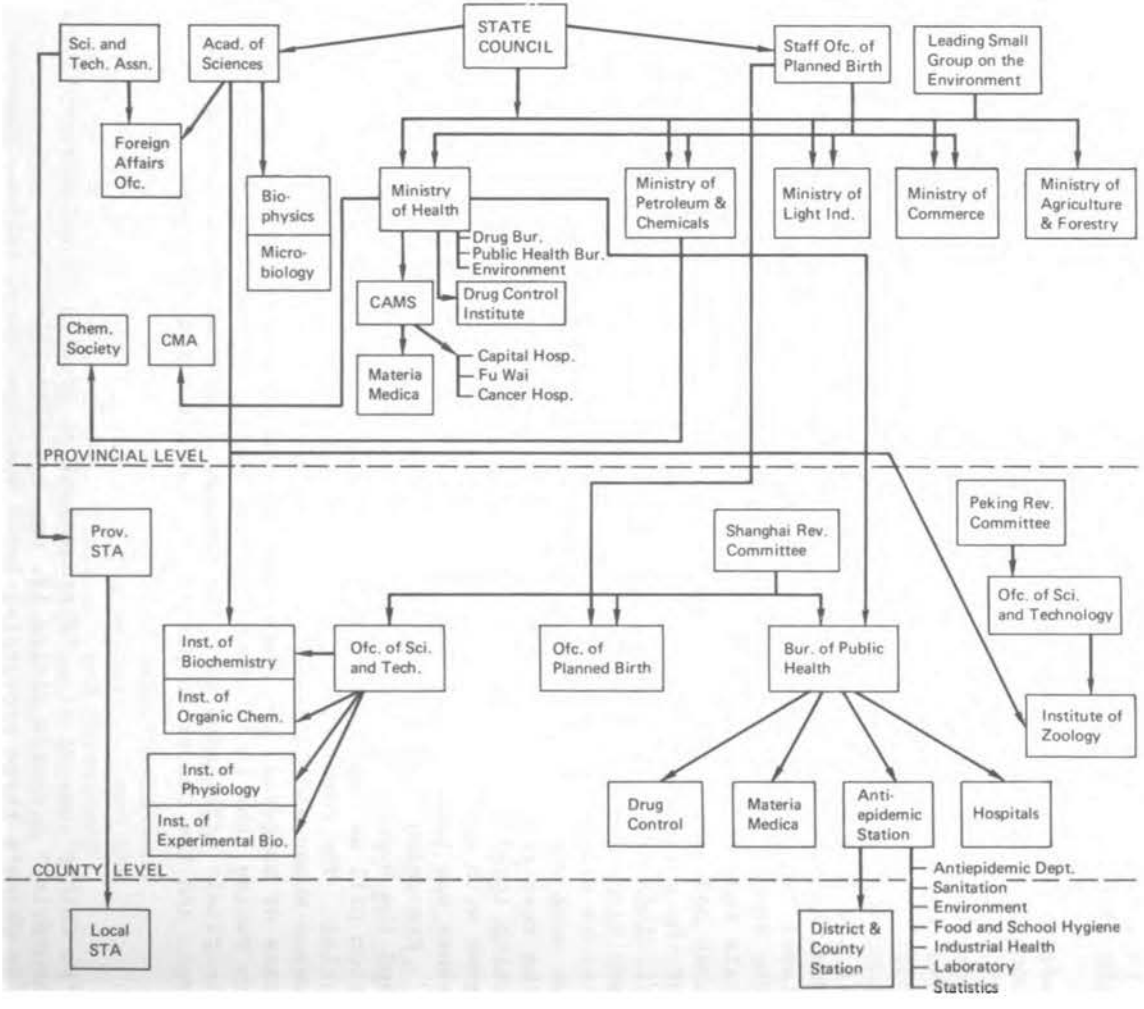
*Ku Chih-p'ing, *et al.*, "Pharmacological Studies of a Contraceptive Drug Anordrin," *Scientia Sinica* 18, no. 2 (1975):261-270.

†In China's three provincial-level municipalities, Peking, Shanghai, and Tientsin, the Municipal Bureau of Public Health serves the same functions as the Provincial Bureaus in the provinces.

‡We were told this at the International Peace Women and Children Protection Hospital, Shanghai, October 25, 1976.

§Ku Chih-p'ing, *et al.*, p. 270.

FIGURE 1


STATE COUNCIL
Sci. and Tech. Assn.
Acad. of Sciences
Staff Ofc. of Planned Birth
Leading Small Group on the Environment
Foreign Affairs Ofc.
Bio-physics
Micro-biology
Ministry of Health
Drug Bur.
Public Health Bur.
Environment
Drug Control Institute
CAMS
Materia Medica
Capital Hosp.
Fu Wai
Cancer Hosp.
Ministry of Petroleum & Chemicals
Ministry of Light Ind.
Ministry of Commerce
Ministry of Agriculture & Forestry
Chem. Society
CMA
PROVINCIAL LEVEL
Prov. STA
Peking Rev. Committee
Shanghai Rev. Committee
Ofc. of Sci. and Technology
Inst. of Biochemistry
Inst. of Organic Chem.
Ofc. of Sci. and Tech.
Ofc. of Planned Birth
Bur. of Public Health
Institute of Zoology
Inst. of Physiology
Inst. of Experimental Bio.
Drug Control
Materia Medica
Anti-epidemic Station
Hospitals
COUNTY LEVEL
Antiepidemic Dept.
Sanitation
Environment
Food and School Hygiene
Industrial Health
Laboratory
Statistics
Local STA
District & County Station

We were told at the Shanghai International Peace Women and Children Protection Hospital that individuals serviced by the hospital and its subordinate units were asked to take part in the clinical trials. Prospective subjects who considered pregnancy undesirable were excluded. We were also told that the hospital informed all prospective subjects that the state would assume responsibility for any difficulties that might arise from their participation in the trials. During the clinical trials for the combination pill, 2,000 women were observed over an aggregate of 10,000 menstrual cycles. We learned in lectures at the Shanghai Scientific and Technical Exchange Station that, in the case of anordrin, 6,000 cycles had been observed. The data for these clinical trials were collected and recorded by local (basic-level) health units. It was simply impossible to assess the reliability of such a data gathering system.

After the clinical trial data on the combination pill were gathered, another city-wide symposium was convened by the Bureau of Public Health to decide whether or not the drug should be "popularized" in Shanghai and its environs. The same process applied to anordrin as well. In addition to those invited to the first symposium, patients who had taken the drug were also invited. Local popularization of the pill required both symposium approval and formal assent from the Provincial or Municipal Bureau of Public Health. Finally, the fact of local distribution had to be registered with the national Ministry of Public Health in Peking. Unfortunately, we were unable to speak with anyone who could tell us authoritatively what standards had to be met in order to secure the Provincial or Municipal Bureau of Public Health's approval.

If a new drug is to be distributed nationally (or cross-provincially), it must secure the approval of the national Ministry of Public Health.* In the case of an oral contraceptive agent, once it is approved by the Ministry of Public Health, approval must also be secured from the State Council's Staff Office for Planned Birth (see Figure 1).† The Staff Office for Planned Birth is a supra-Ministry body designed to coordinate the diverse activities of the health system and pharmaceutical industry in order to achieve the objective of lowering China's birth rate. Before the Staff Office rendered its decision regarding national distribution of anordrin, for instance, it solicited and received reports from the research institute in Shanghai, the Shanghai Bureau of Public Health and its Office of Drug Control, the local symposium, and the Ministry of Public Health. Once approval was given to anordrin (and, once again, we could not ascertain the criteria by which approval was determined), the Staff Office for Planned Birth, in conjunction with the drug manufacturers, fixed production and distribution schedules.

Coming from a pharmaceutical system in which the period of time necessary to develop, test, and distribute a drug is measured in decades, we were naturally interested in how long it took the Chinese to go through the process reported above. At the Shanghai Scientific and

*We were told this at the Institute of Materia Medica in Peking, October 13, 1976.

†We were told this at the Shanghai Scientific and Technical Exchange Station, October 27, 1976.

Technical Exchange Station we were told that clinical trials on anordrin (pill no. 53) began in 1971, that the Shanghai-level symposium was held in June 1973 to approve local popularization, and that the State Council's Staff Office for Planned Birth approved the compound for national distribution in January 1974. The short time separating Shanghai's approval of popularization and approval of national distribution by the Staff Office for Planned Birth would suggest that neither the Staff Office nor the Ministry of Public Health ran extensive tests. They appear to have relied upon the reports of provincial-level organizations.

Several conclusions emerge from the above findings: First, there appears to be substantial local autonomy in testing new compounds and moving to clinical trials involving humans. The risk this entails is a function of the standards imposed at the local symposium. This is a subject about which the Delegation was unable to secure adequate information. Generally, however, the Delegation members did feel that the Chinese had moved too rapidly from the laboratory to clinical trial in the case of the combination pill. No less significantly, it appears that both the Ministry of Public Health and the State Council's Staff Office for Planned Birth are highly dependent upon locally generated clinical trial and test data. Before one can fully evaluate the system, one needs a much better understanding of both the standards that are applied at the local level and the reliability of the clinical trial data.

Another important point is that national (or cross-provincial) distribution requires approval by the Ministry of Public Health and, in the case of oral contraceptives, the State Council's Staff Office for Planned Birth. At least in form, the distinction between interprovincial and intraprovincial distribution is similar to the distinction made in the United States between interstate and intrastate distribution. This suggests that China is not simply a loose collection of provincial-level drug testers and producers who distribute pharmaceutical agents in the absence of central supervision.

The one exception to this generalization about central supervision is Chinese traditional herbal medicine. We learned that since many of these herbal preparations are grown, produced, and used entirely within one province or within provinces in close proximity, the approval of the Ministry of Public Health is waived. There does not appear to be another, separate agency which exercises control over herbal medicines.

Another important conclusion is that the speed with which a contraceptive agent moves from the laboratory to clinical trial and on to public distribution in China appears to be much faster than elsewhere. This seems to reflect several factors: (1) The Chinese with whom we spoke repeatedly seemed less concerned about relatively rare and difficult to document side effects. (2) Extensive testing of the major steroid components has occurred elsewhere, and it may be argued that extensive additional testing is unnecessary. (3) Finally, it is clear that birth control is a high-priority endeavor and has the full weight of political commitment behind it.

DRUG PRICING AND QUALITY CONTROL

We spent a very productive afternoon on October 27 at the Shanghai Pharmaceutical Factory No. 4, where approximately 500 tons of antibiotics (streptomycin and chloromycetin) are produced annually. Besides wanting to find out how the Chinese handle complex chemical processes in an industrial setting, we were anxious to learn how decisions relating to drug price and quantity are made. Also, we wanted to get a clear idea of how, administratively, quality is assured. The information obtained in Shanghai was more detailed than, but consistent with, explanations given at the Peking Pharmaceutical Products Factory.

At the Shanghai Pharmaceutical Factory No. 4 we were told that the prices of pharmaceuticals are fixed by the Ministry of Commerce (*Shang-yeh-pu*), the Ministry of Public Health (*Wei-sheng-pu*), and the Ministry of Petroleum and Chemical Industries (*Shih-you Hua Kung-pu*) in "consultation" with one another. While the "responsible person" with whom we spoke did not specify whether, and to what degree, these various agencies disagreed about price, he did say that prices were calculated on the basis of *costs*. Total costs were calculated on the basis of expenditures for personnel, equipment, buildings, material inputs, and commercial and handling charges. The price at which the drug is sold is designed to cover these expenses. Contraceptives, however, are provided to the public at no cost and are financed out of national resources. We were told that there is one price for each drug throughout the country. It occurred to us that, if this is so, relatively efficient drug manufacturers would have a "profit" because their actual costs would be below those of the standard unit that was the basis for determining the national price. We were told by the responsible person that this occurs *but* these profits are *not* retained by the enterprise. They are all allegedly remitted to the central treasury. These funds, apparently, do not constitute a reservoir out of which local management can acquire resources for plant expansion or other capital, welfare, or operating needs.* All resources for expansion, we were told, had to be allocated through the central plan.

It would seem, at first glance, that such a procedure would necessarily reduce incentives for efficiency. However, before one could reach such a conclusion, one would need to know the criteria by which central capital investment funds are distributed through the plan. Also, one needs to assess what kinds of noneconomic incentives for efficiency may exist. These are two areas that we were unable to explore.

We relentlessly pursued questions relating to the assurance of drug quality control, and to some degree, our hosts did not fully understand why we seemed so intent on identifying an agency of enforcement. While the absence of a direct profit motive probably removes one source of quality control problems, human error and the effects of having to meet

*This *may* only apply to this industry. For a discussion of the possible importance of retained profits in the 1950's see Audrey Donnithorne, "Comment: Centralization and Decentralization in China's Fiscal Management," *China Quarterly* 66 (1976):333-334.

a quota may constitute other sources of difficulty. In both the Peking and Shanghai pharmaceutical factories, we were told that the primary responsibility for drug quality control rests with the production unit itself. In addition, however, the Peking and Shanghai Bureaus of Public Health, and their subordinate Drug Control Offices, make "frequent" (in Peking every three months) inspections of the final products in order to assure compliance with standards. While we were not told specifically what standards the Drug Control Offices enforce, we learned at the Shanghai Pharmaceutical Factory No. 4 that its drugs were in compliance with the standards of the British pharmacopoeia. We also learned that no drugs had ever been pulled off retail shelves because a subsequent check had revealed product defects. In sum, the Chinese seem to have an organizational structure that makes assurance of drug quality possible. Without having seen the system in operation over time and without having a firm sense of what standards have to be met, it is impossible to speak with assurance about the degree to which standards are, in fact, enforced and what uniformity of quality is thereby assured.

THE RESEARCH PROCESS: PRIORITIES, FUNDING, TASK ASSIGNMENT, DECENTRALIZATION, AND COORDINATION

While the Delegation saw several research institutes during its stay, the visits to the Shanghai Institute of Organic Chemistry and the Shanghai Institute of Biochemistry were most productive in clarifying questions relating to the administration of research in China. In addition, a long conversation with a staff member of the Academy of Sciences in Peking clarified several important issues relating to the old State Scientific and Technological Commission and the relationship between the Academy of Sciences and the Scientific and Technical Association of China.

Perhaps the most significant conclusion to emerge from our discussions was that the Chinese Academy of Sciences (*Chung-kuo K'o-hsueh-yuan*) appears to be at least as important in the formulation and administration of research policy after the Cultural Revolution as it had been prior to that movement. In one important respect, the Academy appears to have acquired additional authority. Prior to the Cultural Revolution, the major scientific policy-making body in the People's Republic of China was the State Scientific and Technological Commission. In 1966-67 this organization became the target of critics who asserted that the Commission had been overly responsive to scientific researchers and had been insufficiently sensitive to more "practical" problems requiring scientific attention. By 1967 the Commission had ceased to be mentioned, leaving analysts abroad wondering where scientific policy was being made and what difficulties may have underlain the Commission's disappearance. In Peking we received information answering some of these questions.

The major reason for the elimination of the State Scientific and Technological Commission, and absorption of its responsibilities by the Chinese Academy of Sciences, was administrative. Prior to the Cultural Revolution, it had proven cumbersome and time consuming to have one

organization, such as the State Scientific and Technological Commission, setting research priorities and another body, such as the Academy of Sciences, overseeing the actual implementation of such guidelines. As it was summed up to us, the State Scientific and Technological Commission was "divorced from reality." It had no line responsibilities, and yet it had intervened in "operational" questions with which it was ill prepared to cope. Consequently, the Academy of Sciences assumed its responsibilities, and the State Scientific and Technological Commission was expunged from the organizational map.

A second trend in research administration that has puzzled foreign observers has been the substance behind the apparent decentralization of research institutes in the post-Cultural Revolution period. What operational significance has there been to the "sending down" of approximately 43 research institutes so that either they are under the "dual leadership" of local authorities and the Chinese Academy of Sciences or under exclusive local control?* Three of the institutes that we visited (the Shanghai Institute of Organic Chemistry, the Shanghai Institute of Biochemistry, and the Peking Institute of Zoology), were under the dual leadership of the Academy of Sciences and the Shanghai or Peking Revolutionary Committee. While in Shanghai we asked a responsible person of the Institute of Biochemistry what operational significance dual leadership had and how it worked. Although the Institute of Biochemistry may be a special case (because of its fame as the site where crystalline insulin was synthesized), we were told that the Academy of Sciences provided all of the budgetary resources for research projects and had the last word on which research endeavors would be pursued. The role of the Shanghai authorities was essentially oversight of the centrally determined guidelines. It was suggested to the responsible person that this practice was similar to the system in the United States, where national granting agencies provide the resources, set the guidelines under which the research is to be conducted, and then charge a specific local agency (e.g., a university research foundation) with the responsibility of assuring compliance.

A third area of interest to our Delegation concerned the process by which research projects are initiated and terminated. We found out the most in this regard at the Shanghai Institute of Biochemistry, the Shanghai Institute of Organic Chemistry, and the Institute of Microbiology in Peking. The consistent formulation of how projects got started was "from either national or local initiative." We were always told that projects either could be assigned by the Academy of Sciences or proposed by the research institute with the hope that the Academy would agree to support it and incorporate it into the research plan. In either case, the Academy of Sciences has the final word. At the Institute of Organic Chemistry in Shanghai, we were given an example of how this process works. In the early 1960's, the Shanghai Institute of Organic Chemistry was given a "highly theoretical" assignment to conduct research on biocatalysts. Shortly thereafter, the Ta-ch'ing oil fields were discovered

*Susan S. Nunn, "Research Institutes in the People's Republic of China," *U.S.-China Business Review*, March-April 1976, p. 42.

and developed, and it became apparent that the high paraffin content of the Ta-ch'ing oil reduced its marketability. Someone at the Institute working on the biocatalyst project suggested that it might be possible to devise a process whereby this undesired paraffin could be extracted and converted into a protein supplement for livestock. This would then create a useful product and, at the same time, increase the value of Ta-ch'ing oil. With this idea, the Institute of Organic Chemistry made a formal proposal to the Academy of Sciences, and the project was approved. The person with whom we spoke, however, did not specify what resources went along with project approval, other than the paraffin.

The information that we received on project termination was even less specific. At the Institute of Microbiology in Peking we were told that the Academy of Sciences "consulted" with the research unit and applied "general standards" in evaluating each project. While it was clear that the Academy terminated projects, we were unable to get any precise information on what criteria were used in reaching such a decision.

In a complex, centrally controlled research system, coordination of activities and professional contact is critical. To what extent do researchers in one locality or in one discipline coordinate their activities with (and exchange information with) institutes and individuals engaged in closely related work? While a quick tour makes it difficult to speak with certainty, several indications of possible difficulty were noted: First, both the Peking Institute of Zoology and the Shanghai Institute of Biochemistry were engaged in research dealing with the problem of how to make carp spawn in captivity, yet it was not apparent that the two organizations were coordinating their work. Second, in Peking we repeatedly asked researchers in one discipline whether or not they ever interacted with colleagues outside their own institute, or even those working within the same city. The answer was no. Finally, in Shanghai, the Institutes of Biochemistry, Physiology, and Experimental Biology were all located at the same complex of buildings, yet each organization had its own instruments, which might duplicate those readily available nearby. It appears that what coordination exists is task oriented; there appears to be little coordination by field. This may well reflect the importance attached to "practical application." Were the Chinese to begin to give more emphasis to pure or basic research, one would expect field organization to assume added importance.

BUREAUCRATIC INTERRELATIONSHIPS AND DECISION MAKING

One of the fascinating aspects of studying pharmaceutical production in China is that it is a policy area that impinges upon several organizational chains: the Ministry of Petroleum and Chemical Industries (and its subordinate pharmaceutical plants), the Academy of Sciences, the Ministry of Public Health, and at least two State Council Offices (the Staff Office for Planned Birth and the Leading Small Group on the Environment). One of the Delegation's aims was to identify these agencies and to specify how they interrelate. Equally important was the aim of identifying which values predominated when, and if, organizational conflict occurred. We were more successful at identifying the

organizational system, per se, than the values which guided interorganizational behavior.

In China, as elsewhere, the cooperation and assent of large numbers of organizations and individuals is required in order to develop and distribute any new pharmaceutical product. In the West, particularly the United States, this fact has made it difficult to develop and market new agents. China's leadership has dealt with this problem in several ways: First, there is extensive use of provincial-level symposia (*ta hui*), which bring together representatives of affected agencies and sectors of the society to make recommendations on whether any given product should be taken to clinical trial and whether or not such an agent, once tested, should be introduced into the human population on a limited scale (popularized locally). At the national level, the State Council's Staff Office for Planned Birth is a high-level interdepartmental committee that makes authoritative decisions about nationwide distribution of steroid contraceptives. The Ministry of Public Health makes these decisions for noncontraceptive agents. We wondered whether or not representatives of various agencies and sectors of the society ever had differences of opinion concerning what constituted "acceptable risk" or "adequate testing." While we were told at the Shanghai Institute of Organic Chemistry that "all views were discussed," it seemed clear, in the cases that we were told about, that bureaucratic immobilization was not the general outcome, as is frequently the case with interagency committees elsewhere. The constrained nature of conflict is particularly remarkable because there appear to be no across-the-board standards for safety that any drug must meet. The costs and benefits of each drug seem to be weighed in each decision.

If the above is true, a critical gap in our knowledge is lack of information on how the Chinese have been able to arrest (or control) bureaucratic immobilization. While we were certainly being speculative, it appeared to the Delegation that shared values are an important part of the answer. No one in the decision-making process has a direct or personal economic stake in the outcome.* The costs of research have been borne by the government, and any direct profit incentive is absent. Of no less importance is the fact that government policy is highly supportive of rapid progress in developing contraceptive products. That limitation of births is a high priority would seem to be reflected in the speed with which steroid contraceptives have been developed, tested, and distributed. Two good examples of this are the combination pill and anordrin. While one cannot be certain, such a pattern of organizational behavior and such priorities would seem to reflect the assessment of the Chinese leadership that unrestrained population growth is a far greater problem than the potential risk to presumably small sectors of the population from the use of such drugs. Notions of "adequate safety" must be measured against the costs of nonaction. One would predict that

*This is not to suggest, however, that bureaucratic participants are indifferent to the outcomes of decisions. Many factors, besides economic stake, may give an organizational actor a perceived stake in an outcome.

as China's birthrate falls, as she becomes more economically prosperous, and as her bureaucracies become more complex, there will be an increase in the time required to get any pharmaceutical agent approved.

A second characteristic of the system that appears to make it possible for drugs to move rapidly from the laboratory to the pharmacy is the limited number of points at which the approval process may be influenced. Elsewhere, any public or institutional interest group can enter the decision process through the courts, the legislative branch, or independent agencies. In China, however, there are few extrabureaucratic impediments to implementing a decision. This does not mean that this is a conflict-free process; it only means that the arenas in which conflict occurs are less numerous.

In conclusion, China has a complex organizational system in which conflict is constrained by several factors: reduction of personal stakes in decisions, shared values, on-the-spot meetings to which relevant individuals and groups are invited, and the fact that few extrabureaucratic points of leverage exist. Such a system has increased the speed with which drugs, especially contraceptive agents, can be developed and distributed. However, a system designed to maximize the speed with which agents reach the population faces a necessary trade-off concerning the degree to which the long-term side effects can be evaluated. One can reasonably expect that in China, as elsewhere, there will be an undercurrent of tension about the kinds of trade-offs that should be made.

BROADER ASPECTS OF PUBLIC HEALTH AND ENVIRONMENTAL QUALITY

While the focus of our attention was primarily directed toward pharmaceutical issues, such a concern inevitably brought us into contact with persons and organizations whose health mission was considerably broader, individuals responsible for public health and environmental quality. Because the literature on public health in China is already extensive, we shall concentrate only on new information. Perhaps the single most productive visit we had was to the Shanghai Municipal Antiepidemic Station (*Shang-hai-shih Wei-sheng Fang-i-chan*), an organization roughly equivalent to a state department of public health in the United States. There are 10 county (*hsien*) and 10 district (*ch'ü*) antiepidemic stations under the municipal station's authority (see Figure 1). The Antiepidemic Station, and its approximately 400 employees, is responsible for the public health of Shanghai's approximately 10 million residents. While at the Station we learned much about urban-rural differences in the Shanghai area, municipal disease rates, enforcement of national environmental quality standards, the role of the State Council's Leading Small Group on the Environment, and how food purity is assured. In the process, of course, we learned something about administration, politics, and the importance of economic constraints.

One of the most productive areas of discussion concerned municipal disease rates. We were candidly told that the 1975 prevalence rate for malaria in Shanghai was 0.05 percent, which works out to 5,000 cases, if one assumes a population of 10 million persons. This prevalence rate

was said to represent a 93.5 percent reduction over the rate for 1965. Furthermore, we learned that *all* of the reported cases were concentrated in the rural counties surrounding the urban core. The 1975 rate for typhoid was said to be 10/100,000, which works out to 1,000 cases. The responsible person, however, went on to say that there had been approximately 600 reported cases of typhoid in 1975. We did not pursue the reason for the inconsistency. The present life expectancy for females in Shanghai was asserted to be 73.8 years and that for males 69.3 years. As other individuals and groups have reported, the infant mortality rate is said to be 11.85/1,000 live births.* There was one reported case of polio in greater Shanghai during 1975.

A second productive area of discussion concerned the Station's responsibilities in the area of air and water quality, a regime concern since at least 1973.† We were told that the Ministry of Public Health (especially its Bureau of Environmental Control and its affiliated Academy of Medical Sciences) and the State Council's Leading Small Group on the Environment (*Ling-tao Hsiao-tzu Huan-ching Pao-hu*) had established 40 national standards for air quality and 50 pertaining to water. For instance, the Ministry of Public Health had standards for discharge rates of phenol and cyanide. Local variances could be granted by local authorities, with the approval of the Ministry of Public Health, depending on local conditions (e.g., rate of water flow and total drainage area). Unfortunately, we were not given the standards themselves, nor were we able to observe how strict enforcement was; we simply do not know how frequently variances are granted. We were told, however, that achieving the standards is an arduous task and that Soochow Creek is still below standard, despite persistent efforts.‡

One would expect that the establishment and enforcement of such standards is intensely political; the composition of the Leading Small Group would suggest this. We were told that the Leading Small Group is composed of representatives from (at least) the Ministry of Public Health, the State Planning Commission, the Commission on State Capital

*This rate may well be too low for two reasons: First, because infants leave the hospital after 5-7 days, deaths which occur after that time may be underreported. Second, a Chinese official was recently quoted by Agence France Presse as saying that he was uncertain what China's population was because there is a system-wide underreporting of deaths. Provinces, he said, wanted to obtain the "best possible" rations of rice, clothing, and other goods and they had "a tendency" to record births and be more "discreet" about deaths. (*Foreign Broadcast Information Service: People's Republic of China* 214 (1976):E-15.)

†Charles P. Ridley, *China's Scientific Policies: Implications for International Cooperation* (Stanford: Hoover Institution, 1976), pp. 57-58.

‡In fact, it would appear that the environment still takes a back seat to economic growth when the two come into conflict. For more on official Chinese statements in this regard see Kieran Broadbent, "Agriculture, Environment and Current Policy in China," *Asian Survey* 16, no. 5 (1976): 411-426.

Construction, the Ministry of the Metallurgical Industry, the Ministry of Public Security, the Ministry of Agriculture and Forestry, the Ministries of Light and Heavy Industry, and the Ministries concerned with Transportation and Communications. We asked whether conflict over priorities occurred, and we were told frankly that it did. While given no specific examples, we learned that such disputes are resolved "at a higher level," *presumably* at least at the level of the Standing Committee of the State Council. One would surmise, though we were not told this, that economic constraints are the major source of friction.

Finally, in our discussions at the Antiepidemic Station we were told about the procedures by which food quality is monitored and assured. First, the Station has responsibility for checking the bacterial count in restaurants once per month. The Station has the authority to close any noncomplying facility, though such authority has "rarely" been exercised. Closure is generally unnecessary because almost all food prepared in restaurants is supplied out of central warehouses on a daily basis. Consequently, food spoilage at individual restaurants is not a frequent problem. The Antiepidemic Station not only monitors restaurants, it also checks canned goods for metal residues such as tin, lead, and copper. If such material is found in canned products, health officials talk to the involved factory and, depending on the nature and level of contamination, decide what to do. Never, however, have canned goods been removed from retail shelves.

In sum, Shanghai has a very highly developed public health apparatus. In fact, it is so developed that one must be careful in drawing conclusions about the situation elsewhere. While the organizational structure is comparable to that found in Western countries, we do not know what standards are enforced with what regularity. It seems clear, however, that scarce resources affect the degree to which excessively strict and rigid standards could be enforced. The composition of the Leading Small Group, the plants we observed contaminating the environment, and the fact that Soochow Creek is still a problem all suggest that assuring environmental quality in China, as elsewhere, is an intensely political process in which there is a necessary trade-off between immediate needs for production and the long-term effects such production has on the environment. As the economy grows, and other values assume importance, one would expect to see stronger enforcement.

CONCLUSIONS

The Delegation reached a number of conclusions about the administration of the Chinese pharmaceutical, public health, population, and research bureaucracies:

1. Looking at the organizational structure of the Chinese system, it is clear that there is a complex and finely articulated bureaucracy in which central control is important. Drugs which cross provincial boundaries must be approved by the central administration. Equally important is the fact that the decentralization of research institutes in the post-Cultural Revolution period has not visibly affected the degree to

which research decisions are ultimately a function of central priorities. Finally, there are national environmental standards. In short, an autarchic view of the Chinese system, in this area, would seem to be unwarranted.

2. It is important to note that the degree of local autonomy, and the safeguards of the system, cannot be determined just from looking at organizational structure. One needs to know the values and standards that guide actual decisions. These were dimensions of the Chinese system that were difficult to observe as outsiders on a brief tour.

3. The implicit logic undergirding the heavy reliance upon interdepartmental committees and symposia would seem to be that various organizations have potentially divergent perspectives and information and that any final policy must reflect their inputs. This would lead one to expect that conflict and compromise exist, though such processes were not observed. If such conflict does indeed occur, it makes the speed with which drugs are developed and distributed all the more remarkable. The presence of shared values, lack of personal stakes in outcomes, a limited number of points at which decisions may be obstructed, and a clear government policy favoring rapid drug development and distribution seem to account for the speed with which the Chinese system moves. Conflict was admitted in the area of environmental quality.

4. The price of drugs reflects the regime's estimate of what the true costs of production and distribution are. While contraceptives are supplied by the government free of charge, other pharmaceutical agents do not appear to be subsidized, *if* one assumes that the regime's estimate of costs roughly corresponds with what marketplace costs would be.

In short, our Delegation went some distance in answering the questions posed at the outset of this report. As the Chinese say, this is merely the first step in a journey of 10,000 li.

3

STEROID CHEMISTRY: RESEARCH AND PRODUCTION

The policy decision made in the 1950's to apply the methods of contraception developed in the Western world, particularly in the United States, for curbing the population growth in the People's Republic of China has had an immense effect on the development of research, development, and production facilities in that country. It was decided at an early stage that the employment of Western research and technology adapted to the Chinese scene would bring about the quickest results. The work described in the following pages therefore represents imaginative adaptations of published work rather than original contributions to steroid chemistry.

INVESTIGATIONS ON PRECURSORS FOR STEROID HORMONE SYNTHESIS

Diosgenin

Early investigations centered around the use of diosgenin and yamogenin. Also examined were tokorogenin, stated to be a 1α,2β,3α-trihydroxy-5β-sapogenin,* and gitogenin, a 2α,3β-dihydroxy-5α-sapogenin, among others. The so-called "sinodiosgenin" from *Dioscorea sativa* was shown to be a 3β-D-glucopyranoside by molecular rotation data.

Varieties of *Dioscorea* studied, with name, region of origin, and diosgenin content were

D. gingibransis	Yunnan	2.2%
雲南黃薑 Huang jiang Yellow ginger		
D. nipponica Makino	Northeast provinces	2.0%
東北穿地龍 Chuan ti lung Ground-penetrating dragon		

*L. F. Fieser and M. Fieser list it as 1β- (*Steroids* [New York: Holt, Rinehart, and Winston, 1959], p. 831).

D. *nipponica* Makino	Inner Mongolia	2.1%
内蒙古穿地龙 Chuan ti lung		
D. *tokoro* Makino	Inner Mongolia	1.2-1.8%

The two strains of *D. nipponica* Makino were stated by representatives at the Chinese Export Commodities Fair in Kwangchow to be the sources of commercial diosgenin. They are also found in Chekiang (1.2-1.7%) and Kiangsu (1.2%).

Hecogenin and Tigogenin

Since the Cultural Revolution in 1967 there has been an intensive search for raw materials suitable for increased steroid hormone production. There are many species of *Agave* which grow in China that are used for hard fiber, particularly on the large island of Hainan. This island is located in semitropical latitudes and *Agave* grows well. Other species of *Agave* probably grow in some of the dry desert regions of western China. An analysis was conducted on a number of *Agave* species or subspecies. The results are shown in Table 1. A paper largely in Chinese has been published on these studies in *Acta Chimica Sinica* 33, no. 2, p. 149 (1975). The paper gives the detailed infrared patterns of a number of these sapogenins and, in some cases, the proton magnetic resonance (PMR) data. Of particular interest from a theoretical viewpoint is the fact that 12-epirockogenin was isolated. This sapogenin heretofore had never been found in nature. In addition several rare sapogenins, hainangenin, and hongguangenin have been found in some of these species. In Table 1, sapogenins denoted by an asterisk are the main constituents. The primary constituent of interest to the Chinese is hecogenin, which is prepared in bulk and used for the production of cortisone by the Glaxo process. We discovered at a later date while visiting the Kwangchow Fair that hecogenin was not available for export. Referring to Table 1, it can be seen that all the varieties contain mixtures of tigogenin and hecogenin. In most of the species of *Agave*, hecogenin is the major constituent. In at least one instance, however, tigogenin was the major product. The presence of tigogenin and its 25β-isomer, neotigogenin, in a mixture containing hecogenin can cause considerable problems in the isolation of the latter sapogenin in an inexpensive manner. In other countries of the world the successful utilization of the waste material from fiber processing has been predicated on the availability of varieties that were high in hecogenin and in which tigogenin was low or almost absent. Hence, a good grade of hecogenin acetate could readily be obtained by crystallization.

An analytical method for the analysis of hecogenin in the presence of 9-dehydrohecogenin was presented. The mixture is treated with hydroxylamine hydrochloride and then titrated with base. 9-dehydrohecogenin does not react under these conditions. The production of tigogenin from the varieties where it is a major constituent, such as *A. angustifoliana*, was discussed. It was stated that tigogenin is also available in bulk for the production of anabolic steroids. However,

TABLE 1 Sapogenins Found in Various *Agave* Species Grown in China

Sapogenin	*Agave* Species			
	A. americana	*A. americana* Variety	*A. sisalana*	*A. angustifoliana*
Tigogenone		+		
Neotigogenone				
Tigogenin	+	+	+	+*
Hecogenin	+*	+*	+*	
Sisalagenin			+	+
Δ^9-Hecogenin	+	+		
Rockogenin	+	+	+	
12-Epirockogenin	+			
Gitogenin	+			
Chlorogenin	+	+	+	
Neochlorogenin				
Manogenin	+			
Hainangenin		+	+	
Hongguangenin		+	+	

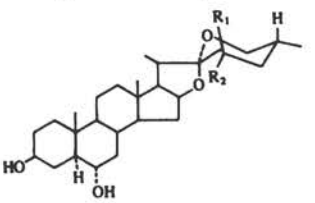
TABLE 2 Occurrence of Sapogenins in Various *Agave* Leaves at Various Stages of Maturity, % of Total Sapogenin

	Bud Tips	Young Leaf	Mature Leaf	Flowering Leaf
Total sapogenin, % dry weight	0.6	0.8	0.9	2.6
Tigogenin	28	17	6	7
Hecogenin	33	45	66	64
9-Dehydrohecogenin	6	5	4	5
Rockogenin	1	2	1	2
Chlorogenin	11	10	9	4
Manogenin	2	4	3	4

further discussions at the Kwangchow Fair indicated that it was not available for export.

The occurrence of some of the major steroids in *Agave* leaves of varying maturity is shown in Table 2. This is an interesting study showing that as the leaf becomes older, the hecogenin content increases. For example, it increases from 33 percent in very young leaves to 66 percent in older leaves. On the other hand, the tigogenin content, which is almost equal to hecogenin at early stages, rapidly decreases as the plant matures. From this one could conclude that tigogenin is the primary product formed and hecogenin is produced later by a hydroxylation and oxidation process. It is fortunate that this process occurs, since from a practical viewpoint it is only the mature leaf that can be utilized for about seven years for fiber production. After flowering, the plant dies, so this process is the terminal stage.

The structures of two interesting new sapogenins that have been found in *Agave sisalana*, i.e., hainangenin and hongguangenin, are shown below. These two sapogenins represent a very interesting hydroxylation in the side chain. The structures were established by nuclear magnetic resonance (NMR). It can be seen that both hainangenin and hongguangenin are hydroxylated at the 23 position of the side chain. In the case of the former the hydroxyl is in the axial position; in the case of the latter the hydroxyl is in the equatorial position as shown.



Hainangenin: $R_1 = OH, R_2 = H$
Hongguangenin: $R_1 = H, R_2 = OH$

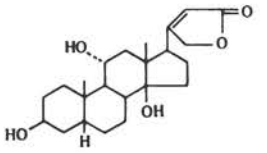
The following potential sources for the production of steroid hormones were investigated but have not been developed to the stage of commercial production.

Solasodine

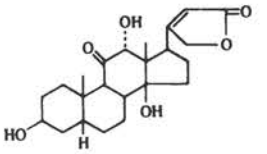
In studies on *Solanum* species, the dried berries of *S. khasianum* from Hunan province showed 2.06 percent of the steroid alkaloid solasodine, while the dried berries of *S. aviculare* showed contents of that alkaloid varying from 0.88 percent to 1.22 percent.

Cardiac Glycosides

In studies on cardenolides, caudogenin, sarmentogenin, and Δ^{14}-sarmentogenin were isolated from *Strophanthus divaricatus* grown in Kwangtung.



(Sarmentogenin)

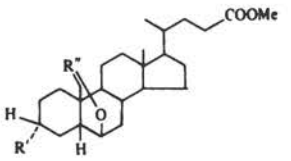


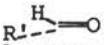
(Caudogenin)

Work was also carried out on thevetigenin from *Thevetia pernoviana* and digitoxigenin as well as on constituents of a variety of *Corchorus* species.

Hyodesoxycholic Acid

In experiments with bile acids, hyodesoxycholic acid was successfully converted to progesterone and 6α-methylprogesterone (*vide infra*), but compounds of the general type



where R' = OH or  , R" = H_2 or =O, could not be successfully transformed into 19-norsteroids, since bromination of the 3-ketone gave the 2-bromo derivative, instead of the anticipated 4-bromination.

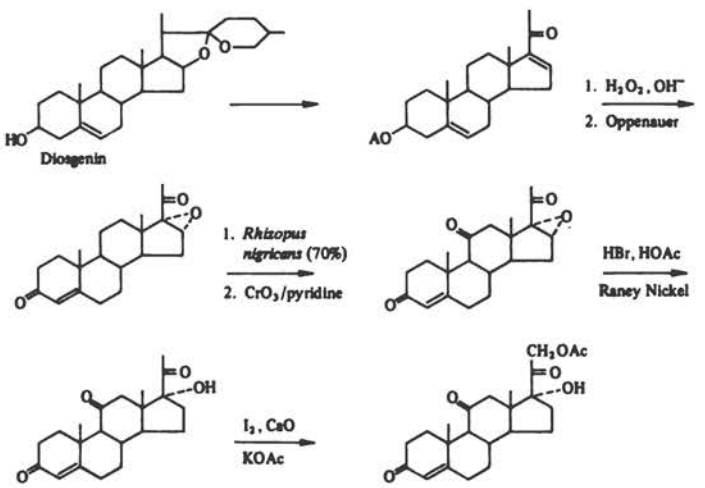
Ergosterol

Workers at the Institute of Microbiology in Peking have been studying ergosterol as a raw material for vitamin D_2 production. Yeasts and

filamentous fungi contain a high percentage of ergosterol. A number of genera have been surveyed, but only the yeasts produce really high yields. The *Saccharomyces* give yields > 2 percent, and some species of *Schizosaccharomyces* produce 1-2 percent. Accordingly, the genus *Saccharomyces* was selected for study. In studies with *S. carlsbergensis*, data were presented that showed that the ergosterol content did not increase as rapidly as the dry weight, but as the number of dead cells increased, the ergosterol content increased as well. It was concluded, therefore, that ergosterol is produced by yeast metabolism in later growth stages. Between pH 3 and pH 8 the ergosterol content remained fairly constant. The cell growth, however, was significantly affected. Ergosterol content increased with an increase in aeration, using shake flasks. The effect of ultraviolet radiation on the ergosterol production of the *S. carlsbergensis* was tested. Exposure times of 20, 30, 60, and 80 s were used, and there was an obvious linear relationship between survival efficiency and exposure to radiation. Increasing the radiation time increased the ergosterol content by more than 10 percent. Optimal conditions for improving the recovery of ergosterol were studied. A temperature of 60°C was found to be optimal for the extraction of the sterol. The recovery efficiency also increased with increasing pH values, 8-10 being optimal. Yields of 4 percent were obtained with *S. carlsbergensis* at a pH of 8, a temperature of 60°C, and an incubation time of 10 hours, after which yields fell off sharply.

CORTICOID SYNTHESIS (COMMENCED IN 1958)

Cortisone

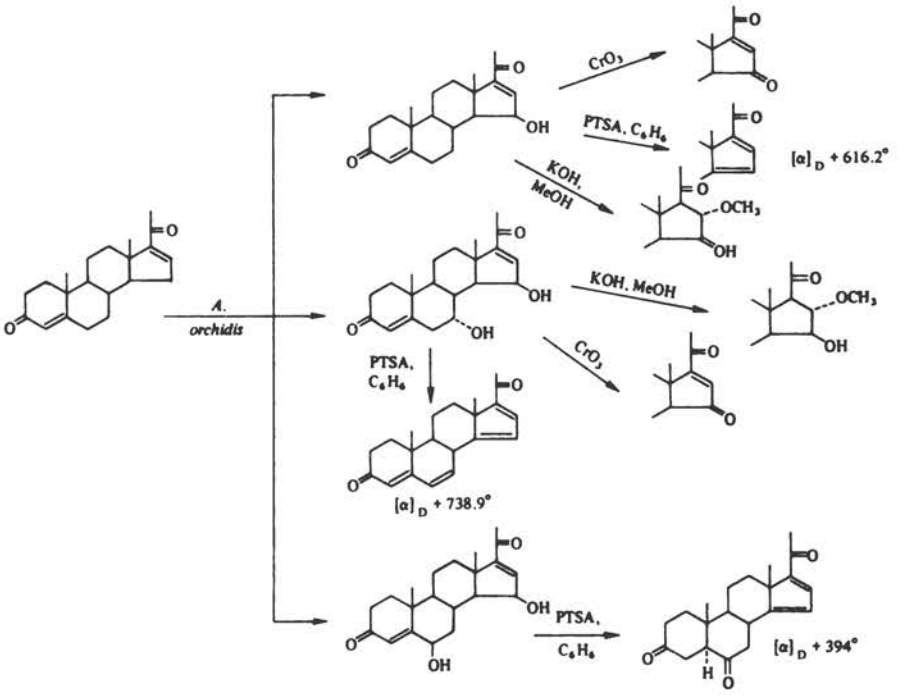


Studies on the conversion of compound "S" to cortisol were conducted principally with *Cunninghanella echinulata*, *elegans*, and *bainieri*. In all, 97 varieties were tested, and all possessed the ability to 11β-hydroxylate to some extent.

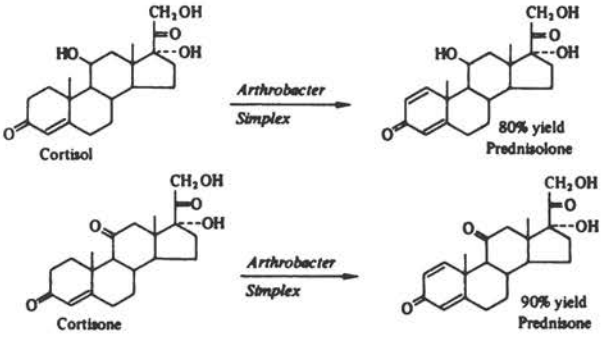
Thirty-three varieties of *Absidia* were evaluated for 11α-hydroxylation ability, of which 73 percent were effective.

Fermentation of Δ^{16}*-Progesterone by Absidia orchidis*

This reaction takes a different course. Three products were obtained, the structures of which were demonstrated by further transformations:



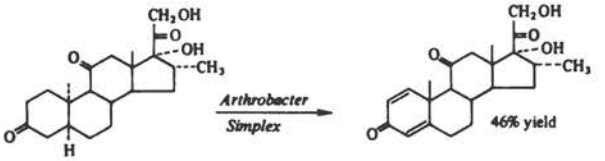
Prednisone, Prednisolone, and Other 1,2-Dehydrosteroids



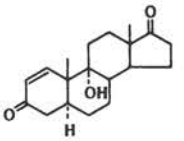
Other Transformations (i)

Whereas

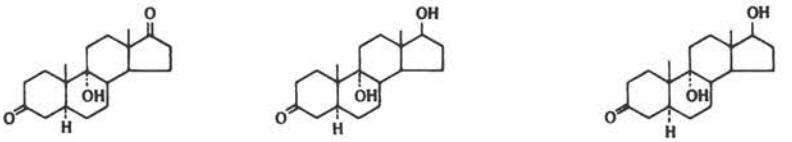
and



I, in contrast, on fermentation with *A. simplex* gives 50 percent of



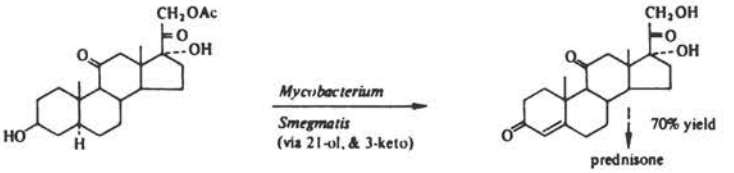
together with smaller amounts of



the structures of which were distinguished by NMR and proved by interconversions.

Other Transformations (ii)

Hecogenin-derived intermediate converted to prednisone:

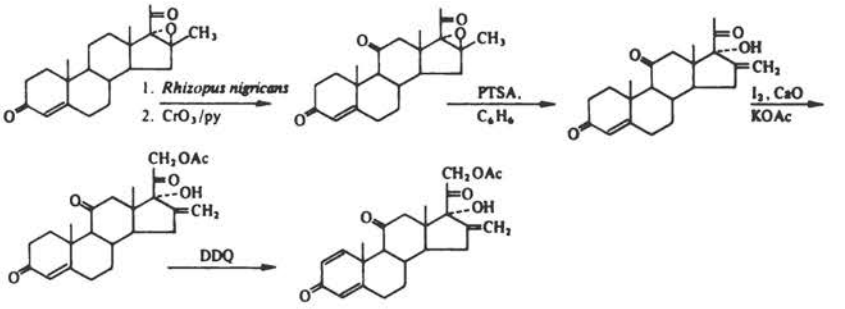


together with some $\Delta^{1,4}$.

Arthrobacter simplex gave

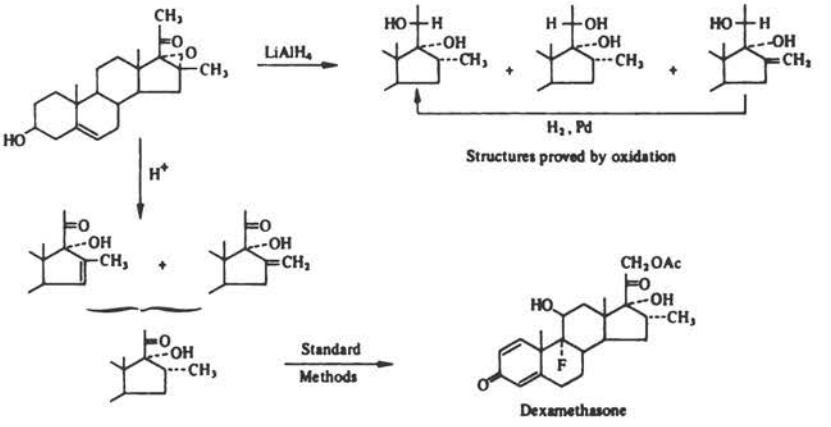
and other *Mycobacterium* species gave a mixture.

16-Methyleneprednisone

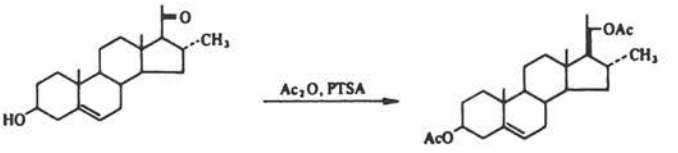


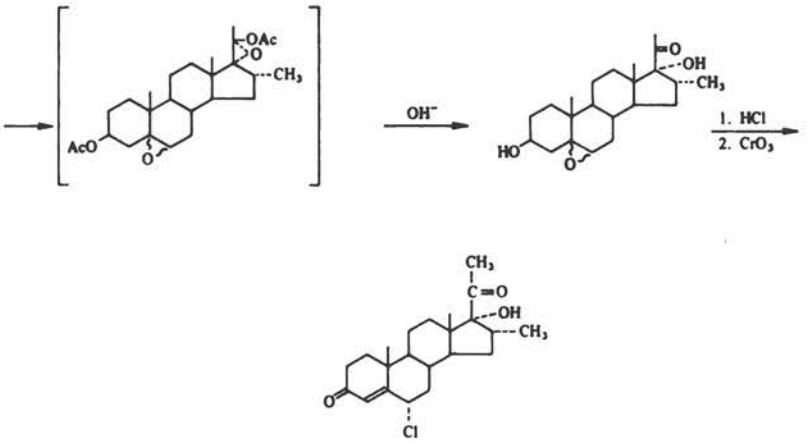
16-Methyleneprednisone was stated to be an end product.

Dexamethasone

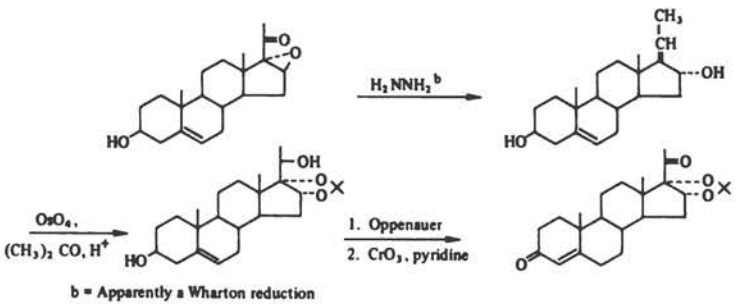


Approaches to 6-Substituted 16α-Methyl Corticoids

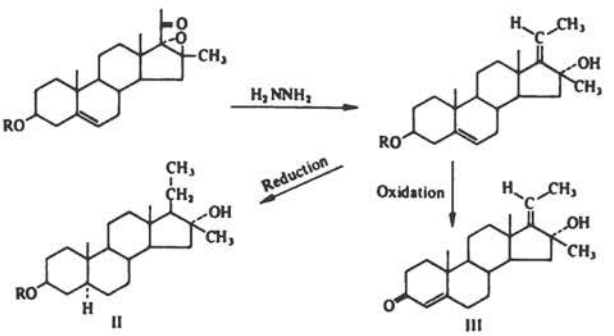




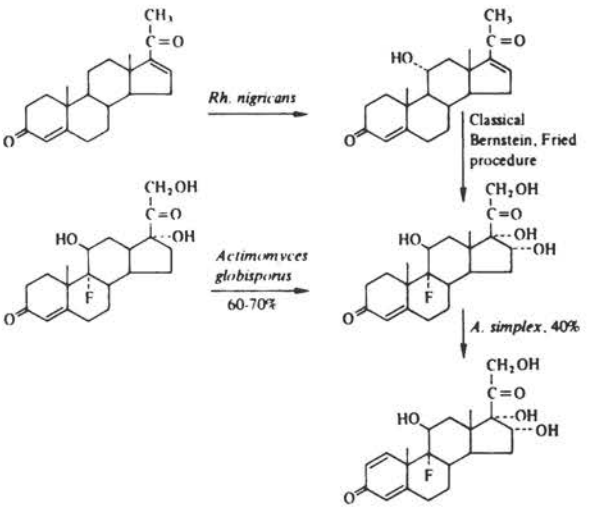
Approaches to 16α-Hydroxysteroids



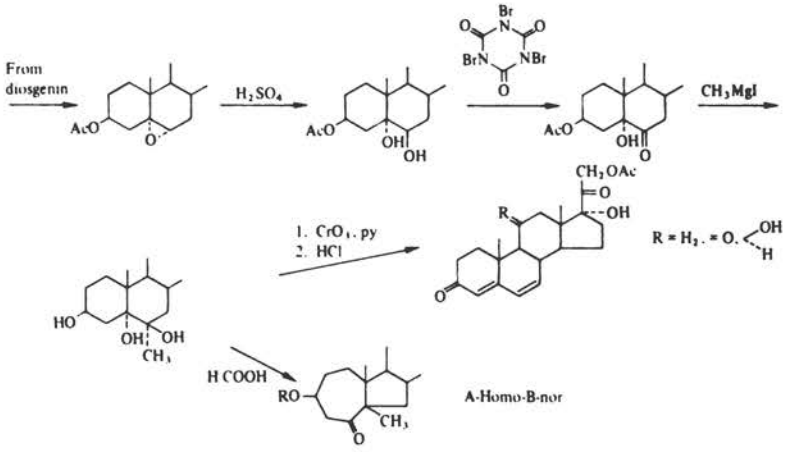
In the 16-methyl series, an analogous reduction produced the *cis*- and *trans*-allylic alcohols. The latter was further converted to the compounds II and III.



Triamcinolone

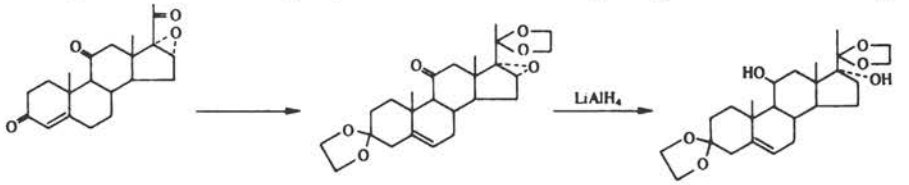


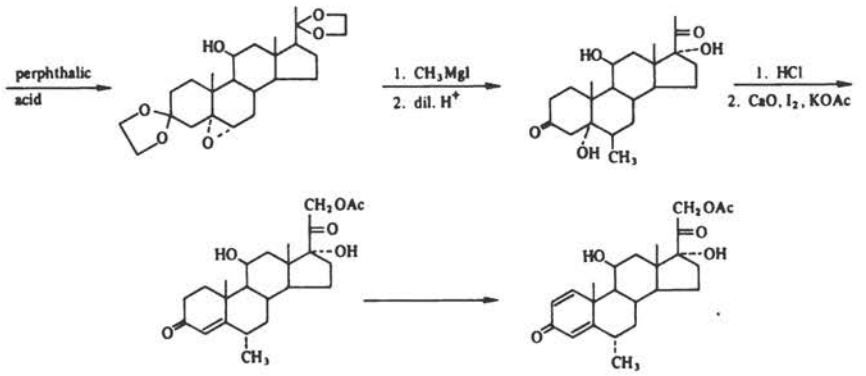
Approaches to 6-Methylsteroids



6α-Methylprednisolone

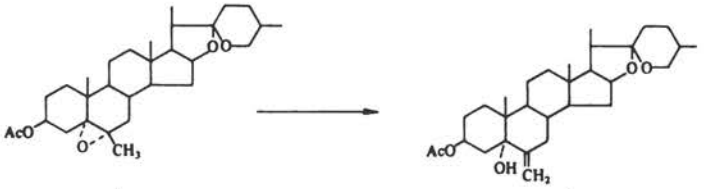
This compound has been prepared in an 11-step sequence from diosgenin:





Miscellaneous Studies

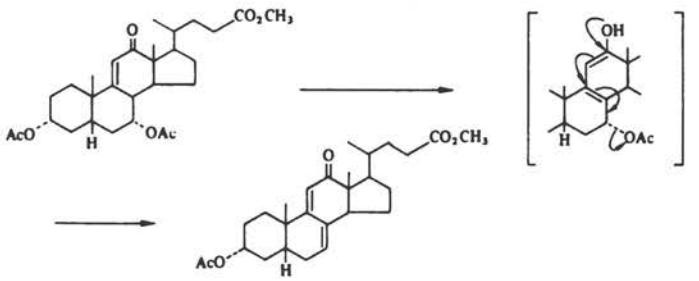
The ring opening of a 16β-methyl-16α,17α-epoxide by *p*-toluenesulfonic acid to give the corresponding 17α-hydroxy-16-methylene compound has been described earlier. Analogously, the 6β-methyl-5α,6α-epoxide (I) was converted to the 5α-hydroxy-6-methylene compound (II):



I II

The epoxide derived from II was converted to the A-homo-B-nor-compound.

Various 1,6 eliminations were described, e.g.,

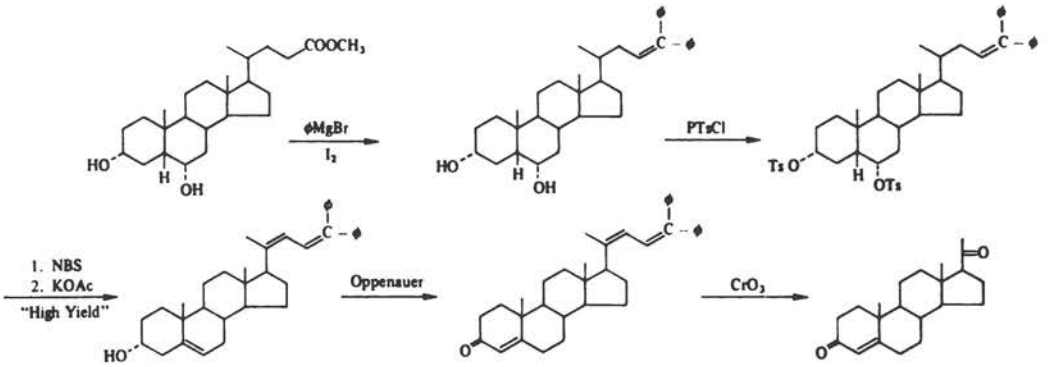


and

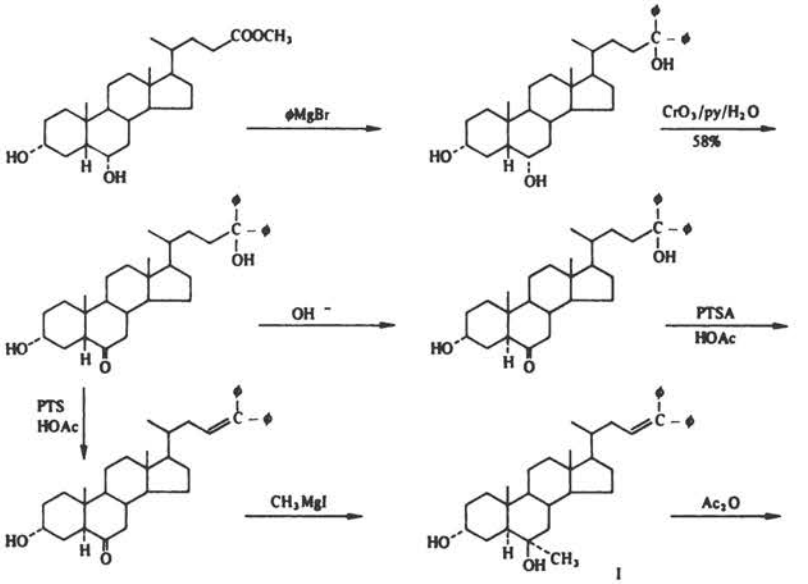
x = AcO-, Cl-

SYNTHESIS OF ORAL CONTRACEPTIVES

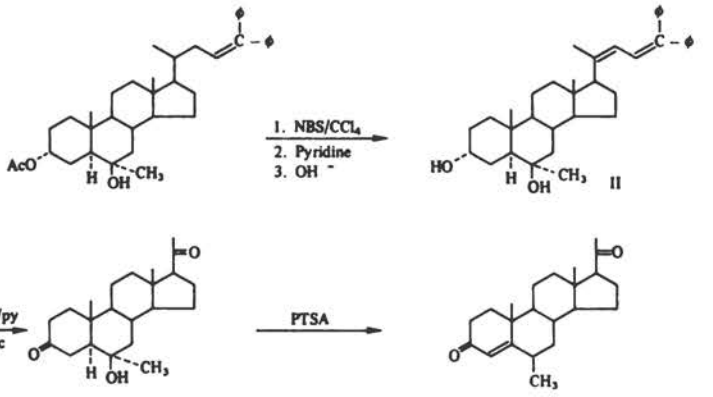
Progesterone from Hyodesoxycholic Acid



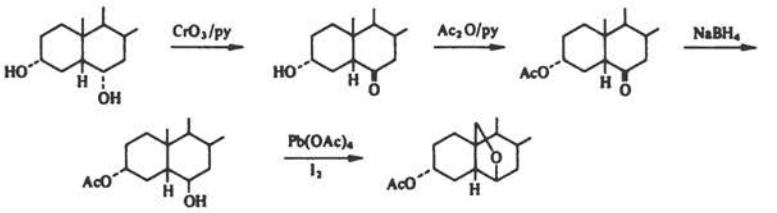
6α-Methylprogesterone from Hyodesoxycholic Acid



I

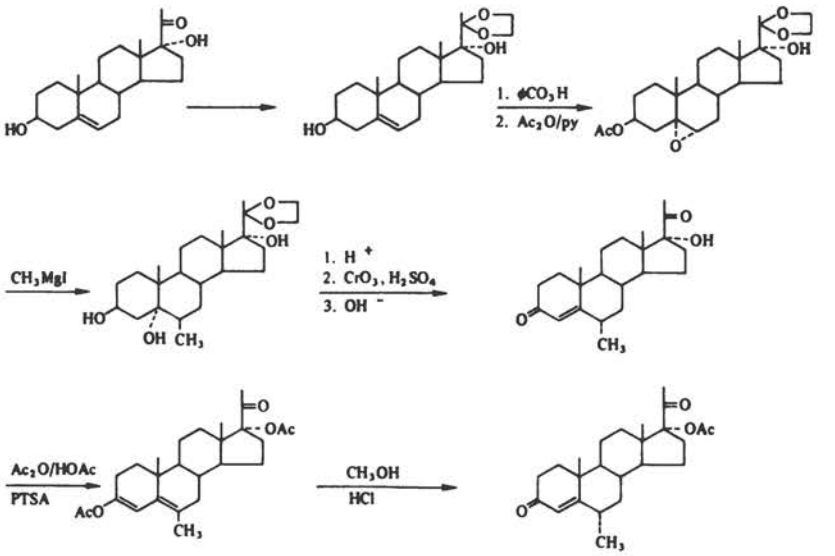


Attempts to Produce 19-Nor-Compounds from Hyodesoxycholic Acid

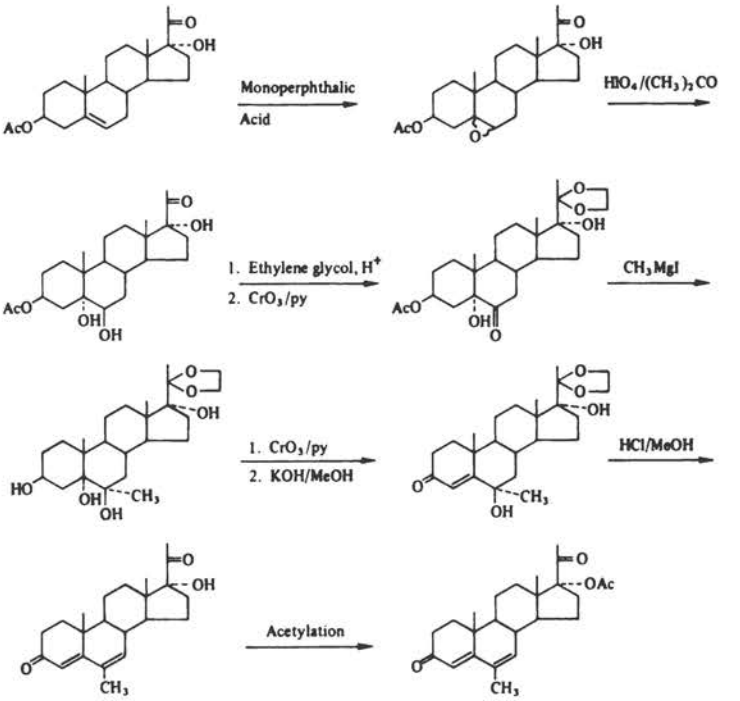


Progestational Agents from Diosgenin-Based Intermediates

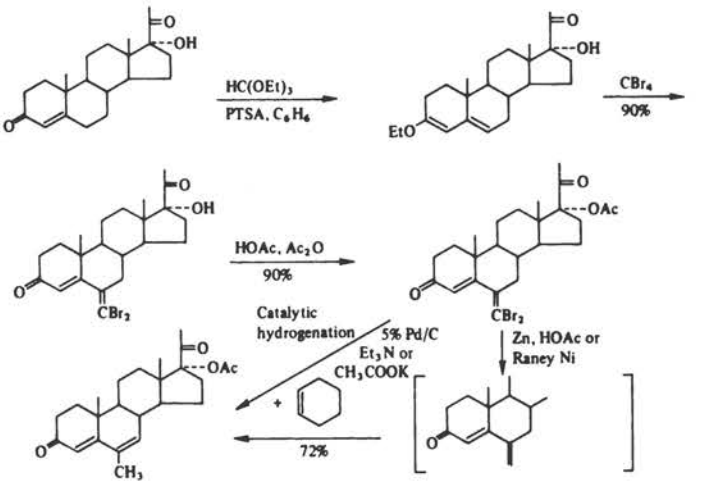
6α-Methyl-17-Acetoxyprogesterone



Δ^6-*Methyl-17α-Acetoxyprogesterone (Megestrol Acetate)*

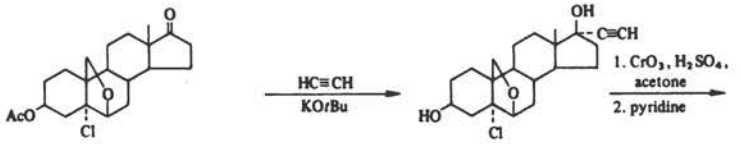


A better method has now been introduced:

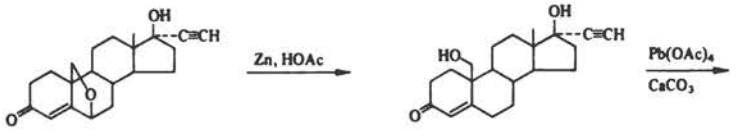


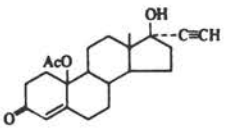
Normal hydrogenation conditions using $Pd/CaCO_3$ (or $BaCO_3$ or $SrCO_3$) gave the 6α-methyl compound, i.e., no Δ^6.

Routes to 19-Norsteroids

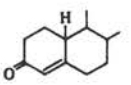


Production intermediate from norethindrone synthesis

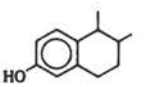




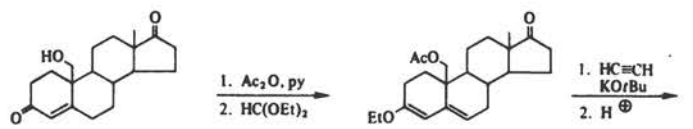
Presumably convertible by Zn-AcOH to



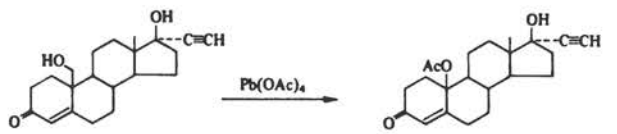
and by heat to



Alternatively,

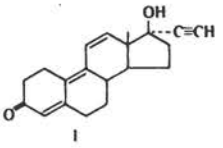


Production intermediate from norethindrone synthesis

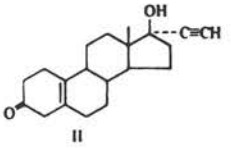


The overall yield from diosgenin is 19 percent. This compound is now undergoing preclinical and clinical testing.

Norgestrienone (I) is being developed as a short-acting contraceptive in combination with mestranol. It is stated to be more effective than norethynodrel (II).

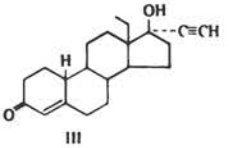


I

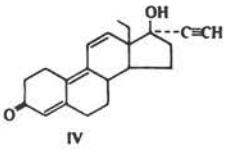


II

dl-Norgestrel (III) is made commercially and d-norgestrel is made on a pilot plant scale. The syntheses have been extended to produce 18-methylnorgestrienone (IV), and the dl compound is being used in clinical trials as a postcoital pill that operates by an antiimplantation mechanism.

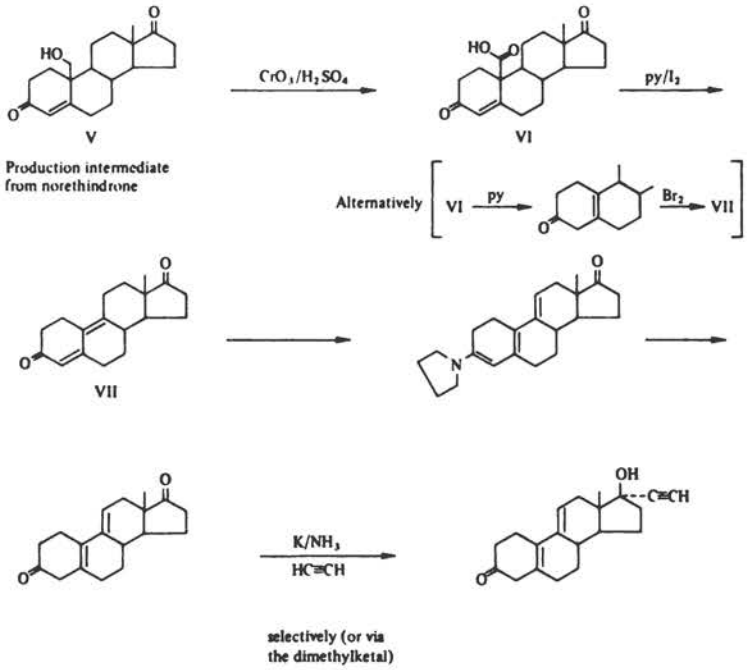


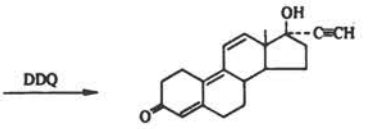
III



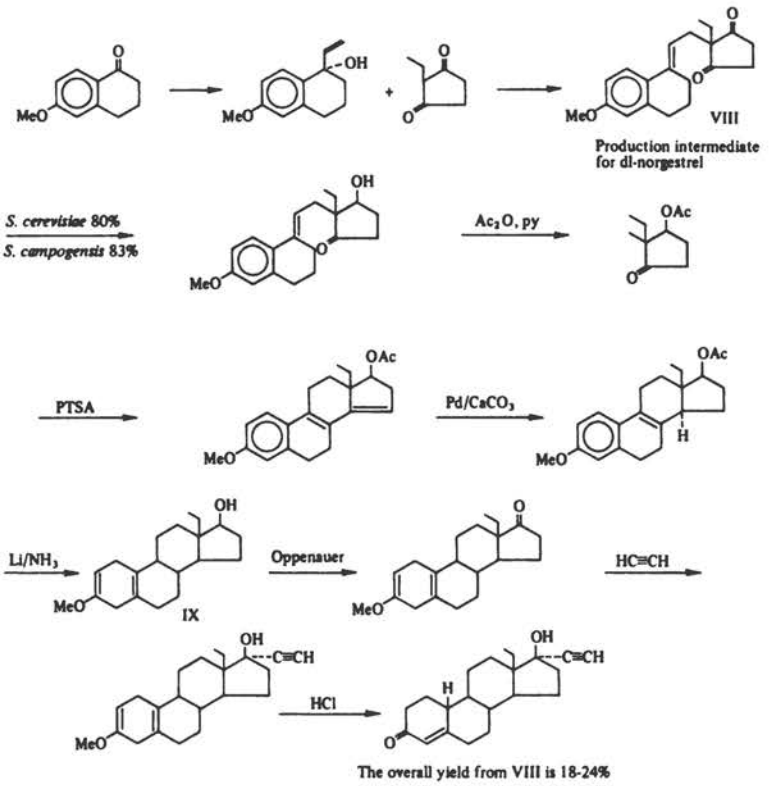
IV

Norgestrienone Process





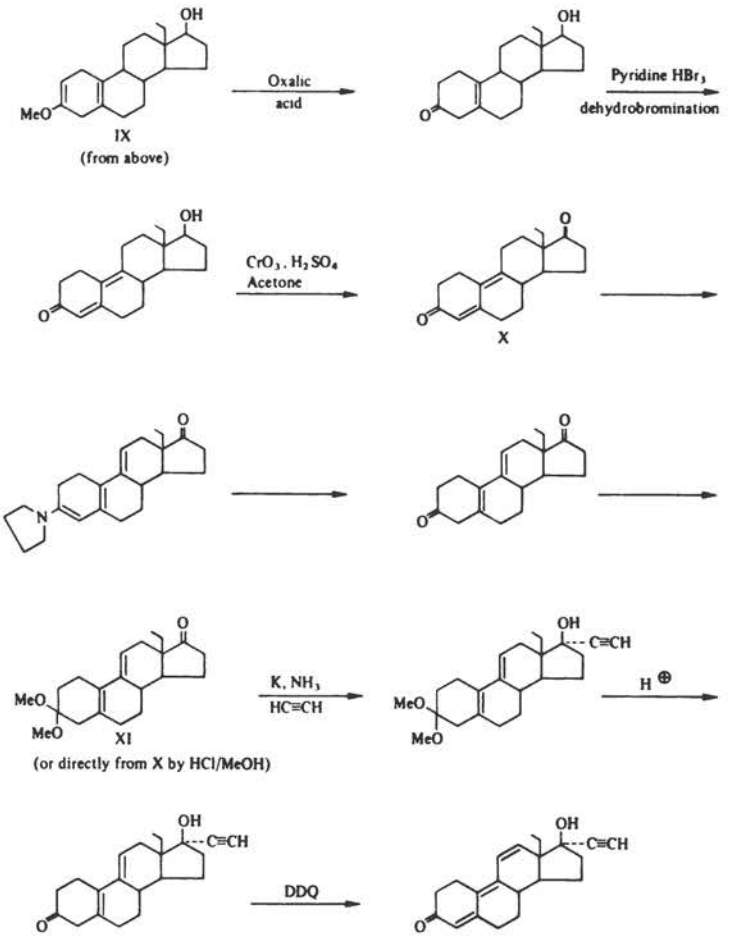
d-Norgestrel Process



One hundred cultures, consisting of 22 species of eight genera, were tested, and it was found that all species of *Saccharomyces* had the ability to varying extents to effect the reduction.

With *S. campogensis* the maximum yield was 83 percent after 55 hours of fermentation time. Thereafter, yields fell off markedly, falling to 55 percent after 66 hours. Optimal concentration was 0.5 percent (500 mg/100 ml). At 750 mg/100 ml, the yield was only 45 percent. Yields were lowest at a pH 5 (the lowest level tested), rising to a maximum at a pH 8.5 (71 percent after 44 hours).

d-18-Methylnorgestrienone Process

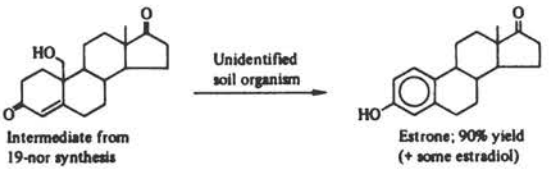


The overall yield in 11 isolated steps from VIII (secodione) is 7 percent and from XI is 4.2 percent.

The syntheses of norgestrienone and dl-18-methyl-norgestrienone are reported in *Acta Chimica Sinica* 33, p. 139 (1975).

Ring A Aromatization

It is known that androsta-1,4-diene-3,17-dione and androsta-4,6-diene-3,17-dione can be converted to estrone by chemical means (e.g., pyrolysis). However, the following microbiological conversion is efficient and used commercially:



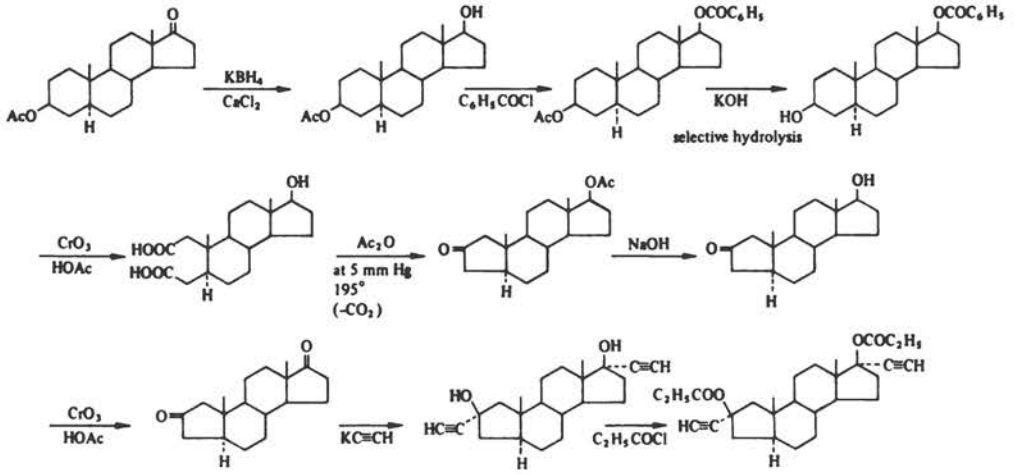
Similarly,

Synthesis of Anordrin, the Active Ingredient of Pill No. 53

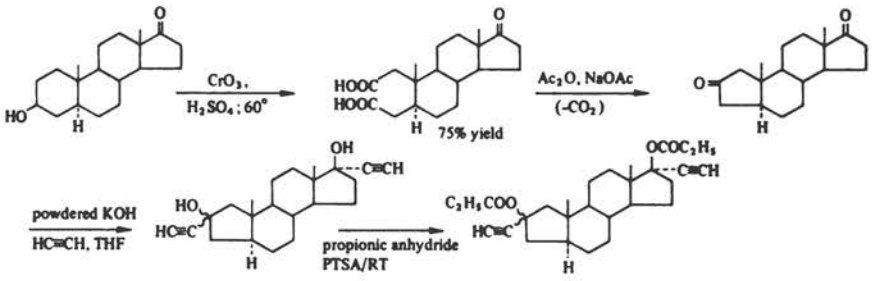
The chemical name of this compound is 2α,17α-diethinyl-A-norandrostane-2β,17β-diol dipropionate.

The basic structure from which the dipropionate anordrin is derived is an invention that the French chemist Jean Jacques made about 20 years ago. The compound as its acetate ester was investigated by Gregory Pincus and later, on the basis of his findings, by a major U.S. drug house. Because of its alleged estrogenicity the drug was discarded as a contraceptive in the United States.

The original synthesis was as follows:



Since this sequence employed too many steps, a new route was developed from isoandrosterone (derived from isoandrosterone acetate) as follows:



The overall yield from isoandrosterone acetate is 36% of theory.

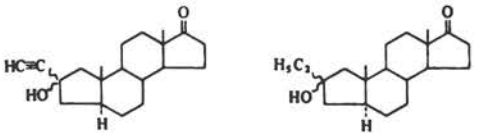
Two stereoisomers are formed at C_2, the ratio of which depends on the ethynylation conditions:

		α	β
HC≡CK	0-5°	8	1
HC≡CK	25°	4	1
KOH, HC≡CH	0-5°	8	1
KOH, HC≡CH	25°	1.4	1

So that low-temperature ethynylation favors the α isomer.

Under conditions that produce an 8:1 ratio, the crude product can be esterified directly, and the final product isolated by direct crystallization. It is assayed qualitatively by thin-layer chromatography.

The stereochemistry was proved by the following conversions of the 2α- and 2β-ethinyl derivatives.

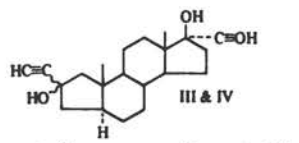


Ia; m.p. 207-8° --------→ Ib; m.p. 168-170°
IIa; m.p. 236-7° --------→ IIb; m.p. 171-3°

	δ 18-H	δ 19-H	
Ia	0.86	0.93	+0.04
Ib	0.86	0.97	
IIa	0.86	0.86	-0.11
IIb	0.86	0.75	

The loss of deshielding, passing from IIa to IIb indicates that IIa possesses a 2β-ethinyl group so that Ia is α-.

Ethynylation of Ia and IIa, respectively, gives the following results:

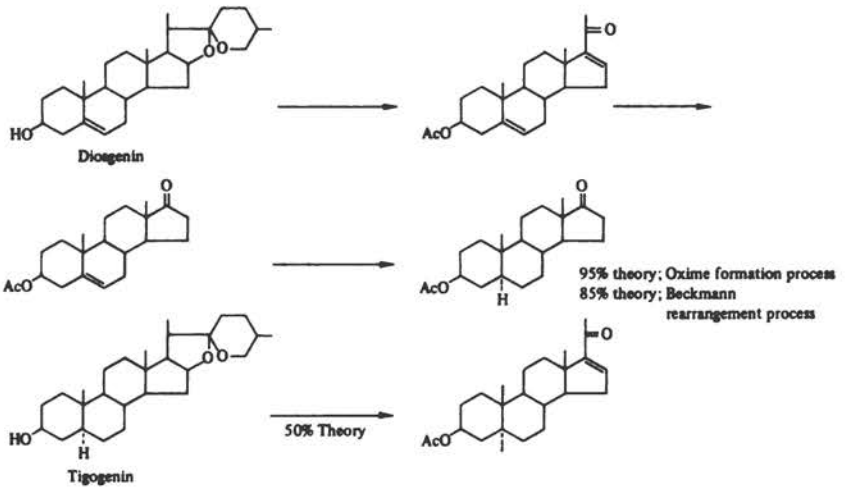


Ia ⟶ III IIa ⟶ IV

	δ 18-H	δ 19-H
III	0.85	0.93
IV	0.85	0.85

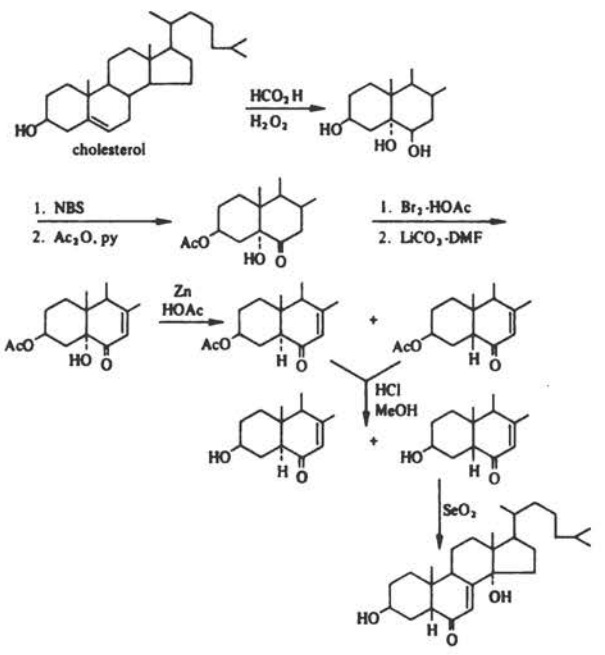
Therefore, III is α- and IV is β-. Propionylation of III gives anordrin.

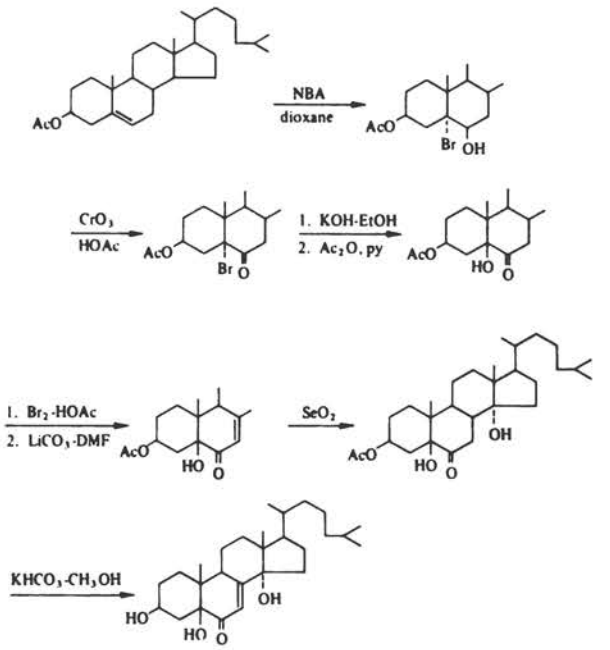
The epiandrosterone acetate used as starting material is conveniently prepared from diosgenin or, better yet, from tigogenin, both of which are relatively abundant:



Ecdysone Analogues

In connection with their efforts toward improved silk yields in sericulture, several ecdysone analogues have been synthesized starting with cholesterol:





3β, 5β, 14α-Trihydroxy-Δ^7-cholesten-6-one

PLANT FACILITIES FOR PRODUCTION

Despite considerable effort to obtain permission to visit a factory in which steroid drugs are produced, the Delegation was unsuccessful in visiting such a facility. We were, however, given the opportunity to visit the Pharmaceutical Factory No. 4 in Shanghai, which is geared to the large-scale production of drugs by both chemical synthesis and fermentation, two types of technology that are essential as well for large-scale steroid production. We therefore felt that the observations made in such a plant would be relevant also with respect to the capabilities of the Chinese for steroid production. In the following, therefore, we shall describe our visit to this factory.

We also visited that part of a pharmaceutical production facility in Peking concerned with turning out products in their final pharmaceutical form, such as ampules and tablets. Although of less importance than the actual production of the raw materials, a visit to this plant supplemented the observations made in Shanghai and served to give us an acceptable impression of pharmaceutical production in the People's Republic of China.

Visit to Pharmaceutical Factory No. 4 in Shanghai

The factory has been in existence for over 100 years. It was formerly owned by foreign capitalist interests and prior to liberation employed

only 160 people. Production was restricted to simple remedies such as eyedrops, cough syrups, and tinctures of camphor and ginger. As there was no chemical industry at that time, all of the raw materials had to be imported. During the Great Leap Forward the factory underwent great change in order to become self-reliant. Synthetic chemical production to make chloramphenicol was begun, and drugs were prepared from bile acids. Streptomycin production was commenced, and although there were many difficulties in making antibiotics, these obstacles were overcome. Imports of raw materials were no longer necessary.

After the Cultural Revolution, the factory took another step forward. Chloramphenicol, streptomycin, dihydrostreptomycin, and kanamycin are now produced as well as phenobarbital and other medicinal products.

The volume of production has increased manyfold so that greater than 500 tons of antibiotics are produced annually and the factory employs 1,600 people. It is able to meet all domestic requirements and have some material for export. Through the efforts of the employees and through technical innovation the quality of the products has been improved.

Since government today lays stress on the rural areas and medicine prices being progressively reduced, the factory has responded by lowering costs, conserving utilities, and making use of waste products.

We visited the streptomycin plant, which was constructed in 1958. The mild steel fermenters were fabricated in Shanghai. It consists of ten 50,000-l fermenters with ten 5,000-l and ten 500-l vessels for inoculum production. The fermentation cycle is 160 hours, and the product is isolated in batches using two ion-exchange resin adsorptions. After the first adsorption the streptomycin is liberated at a pH of 4.5, and after the second, at neutrality. It is then isolated by spray drying. The product conforms to British Pharmacopoeia (BP) quality and assays at 730 units per mg (800 units per mg is equal to 100 percent; BP minimum is equal to 700 units per mg).

Chloramphenicol production is carried out from p-nitroacetophenone in a five-story production plant with gravity feed to each production level. The plant was constructed in 1958 with glass-lined reactors up to 1,000 gal capacity manufactured in Shanghai. Utilities are controlled from central consoles equipped with temperature recorders. The reactors appeared to be of standard design, apart from fully removable manhole covers. Agitators were of the impeller type with single fixed speed motors and the reactors were single jacketed. Intermediates were isolated in 36-in. open-top centrifuges and the final product in 48-in. centrifuges, one of which was of the bottom dump type.

The plant relied on open windows to provide ventilation. Throughout the factory there seemed to be a complete absence of safety equipment, i.e., hard hats, goggles, etc., and an absence of guardrails on stairways. Both the streptomycin and chloramphenicol plants were managed by young woman supervisors, each of whom had been about 10 years at the factory and appeared completely competent. The majority of the process workers were also female.

The factory does not possess its own pilot plant. When new products are introduced, the scale-up work is done in collaboration with the pilot plant of the Shanghai Institute of Organic Chemistry.

Production targets are set annually by the state. Cost calculations are carried out on the same principles as in the West, but overhead charges will probably be lower because of smaller allocations for certain items, such as depreciation, and the elimination of other items, such as taxation, coupled with lower personnel costs.

Although the physical aspect of the buildings was primitive and substandard, the equipment was adequate and well maintained. On the basis of this evidence there is every reason to believe that the Chinese can produce complex organic chemicals (such as steroids) in a competent and economic fashion.

Visit to Peking Pharmaceutical Plant

This plant manufactures intermediates and finished drugs and packages them for distribution. More than 2,000 workers are employed, 50 percent of them women. Two hundred different finished items are produced as well as 30 intermediates. Specifications are according to British Pharmacopoeia. This plant was developed from a hospital supply company for the Eighth Route Army. In 1949 there was very little equipment and a labor force of 100 people. The total production amounted to 1,000,000 ampules and 2,000,000 tablets per year. Since Liberation the facilities have increased substantially. The plant now can produce 1,000,000 ampules in 1.5 days and 2,000,000 tablets in 1 day. Production costs have been substantially lowered. Thus, the cost of penicillin was reduced from 1.5 yuan for 200,000 units to 0.14 yuan, and the cost of 250-mg tetracycline from 1.7 yuan to 0.05 yuan.

Most of the automated equipment that we saw was designed and made by in-house machinists. Its efficiency appeared similar to that of equipment in U.S. plants around 20 years ago. The tablet-making facilities were surrounded by the dust of the various ingredients. The workers all wore masks, but it is hazardous to be constantly exposed to, for instance, aureomycin dust. Visual inspection of filled ampules showed them to be filled to widely differing levels.

STEROIDS FOR EXPORT

A visit to the Chinese Export Commodities Fair at Kwangchow gave us an indication of the large number and wide variety of drugs, including, of course, steroids, being produced in China. While the number and variety of items on exhibit is impressive, inquiry with the representatives from both the Tientsin and Shanghai branches indicated that only very few items are actually available for export.

In its catalog, the Tientsin branch of the China National Chemicals Import and Export Corporation lists the following bulk steroids:

Diosgenin, melting point (mp) 195° min	20 kg lots
Dexamethasone acetate BP 1963	100 g lots
Hydrocortisone BP 1968	2 kg lots
Methyl testosterone BP 1968	5 kg lots

Prednisolone BP 1963/1968	100 g/5 kg lots
Progesterone BP 1968	5 kg lots
Testosterone BP 1963	100 g/5 kg lots

The catalog from the Shanghai branch lists the following steroids:

Digoxin BP 1973	10 g lots
Hecogenin, mp 250°	20 kg lots
Testosterone propionate BP 1968	5 kg lots

Specific inquiry with the official representatives as to the availability of the above items revealed that only diosgenin and hydrocortisone were available in the quantities indicated. It is likely, however, that most of the other drugs on display, which include essentially a full line of pharmaceuticals, are available for use in China. It is well worth pointing out that such specialty steroid formulation as hydrocortisone acetate, prednisolone sodium phosphate, dexamethasone sodium phosphate, triamcinolone acetonide acetate, and fluorohydrocortisone are available in the People's Republic of China.

In passing, it is worth noting that China produces a rather complete range of basic pharmaceutical products including antibiotics (penicillin, streptomycin, tetracycline, griseofulvin, etc.), a wide range of sulfas, tranquillizers (diazepam and reserpine), etc.

In an interview with a commercial representative of the Tientsin branch, we were informed that the plant had been damaged by the recent Tangshan earthquake but that vigorous efforts were being made to get it back into production. Diosgenin supplies were limited owing to flooding and plant damage. Prices were expected to be higher than they were in the spring when an American company purchased several tons at $102.80 per kilo. The Chinese are aware of recent developments in Mexico and appear to be thinking of a price approaching $150 per kilo, although they were advised that prices of starting materials and intermediates will fall.

Their prices are subject to negotiation, but they appeared to agree that typical "starting prices," if material were available, would be as follows: dexamethasone acetate, 9,000 yuan per kilo; hydrocortisone, 1,400 yuan per kilo; prednisolone, 1,700 yuan per kilo; methyltestosterone, 1,500 yuan per kilo; and progesterone, 650 yuan per kilo. Their pricing policy is made just competitive with Western pricing and may not be an accurate reflection of their costs. Since deliveries are said to be often erratic, they appear to be content to sell surplus materials rather than establish themselves as a powerful force in the bulk steroid markets.

We asked for and received a sample of diosgenin as offered for export. The sample was analyzed for us through the courtesy of Syntex Corporation. It is quite evident from this analysis that the sample represents material of high quality.

We also had occasion to obtain analytical data from the same source on two finished products. The first was pill no. 1 in tablet form, stated to contain norethindrone (0.625 mg) and ethynyl estradiol (0.035 mg). Analyses performed on 10 individual tablets indicated considerable

individual variations in the content of the active ingredient in the case of norethindrone but good conformity with the stated content in the case of ethinyl estradiol.

We also obtained a polyethylene envelope containing the so-called "paper pill" which was labeled pill no. 1 thin type, serial no. 72035, produced in Shanghai Pharmaceutical Plant No. 7. Analysis of eight tablets for their content of the two constituents showed small individual variations, but the content of both ingredients was considerably lower than was indicated. An average of 74 percent of the indicated amount of norethindrone and 64 percent of that of ethinyl estradiol were the average figures found.

4

MEDICAL APPLICATIONS OF STEROID HORMONES

INTRODUCTION: CLINICAL TRIALS AND EPIDEMIOLOGY

Information about the general process of new contraceptive drug development from the laboratory stage through clinical trials to mass distribution was developed from several sources. The general overall process of new drug development was described by Chang Chün-t'ien director of scientific research of the Institute of Materia Medica in Peking. The most extensive detailed information about clinical trials was described by the staff of the International Peace Women and Children Protection Hospital in Shanghai. A general overview of the entire process of new contraceptive development was provided at a special seminar conducted at the Shanghai Scientific and Technical Exchange Station. At this seminar we were given a detailed picture of the development of the new contraceptive anordrin (pill no. 53), including chemical synthesis, pharmacology, animal studies, and clinical trials.

Additional information about special studies on various contraceptives was obtained from the endocrinology department of the Peking Institute of Zoology, where studies in reproductive physiology focused on use of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and luteinizing hormone-releasing hormone (LHRH) in promoting fertility in domestic animals, including pisciculture and prostaglandin in pregnancy termination. At the Shanghai Institute of Organic Chemistry there were extensive presentations on the synthesis of steroid compounds as potential contraceptive agents. The Shanghai Institute of Physiology reported on physiological studies of a new oral contraceptive combining two progestational hormones, quinegestanol acetate and megestrol acetate. At the Shanghai Institute of Experimental Biology we received reports from the Department of Physiology and Reproduction on studies with trichosanthin, a drug extracted from Chinese herbal medicines that is utilized for induced abortions.

Chang Chün-t'ien gave the following general picture of procedures for new drug development in the contraceptive field. Candidate drugs, for example, steroidal compounds, may be synthesized by the Institute of Organic Chemistry, or plant extracts prepared by the Institute of Materia Medica. These are initially screened for an antifertility effect in animals. Apparently, this is done in rats, although specific procedures were not described. It was noted elsewhere that more than

100 steroidal compounds were screened before anordrin was selected. After an active agent is found, more extensive physiologic studies will be carried out to determine its mechanism of action, for example, whether it inhibits ovulation, prevents implantation, or has other effects. These studies do not include measurement of gonadotrophin levels. Further, they do not have the capability of measuring hormone binding to receptor sites.

After determining that the agent is active and elucidating the mechanism of action and the dose response, animal toxicity studies are carried out. There are no standardized procedures or regulations regarding what toxicity tests should be undertaken or how they should be conducted. The toxicity tests generally would include determining the acute toxic effects and lethal dose and studies of subacute and chronic toxicity. Animals utilized are mice, rats, dogs, and monkeys. Observations include the general appearance of the animals; blood chemistry; tests of liver, renal, and cardiac function; histological studies; and searches for tumors. Teratogenic tests are also conducted through three generations of animals.

When moving to clinical trials, a "three-in-one group" is formed, consisting in the early stages of the group responsible for synthesis or preparation of the compound, pharmacologists, and clinicians. This group will review the animal studies and then decide on procedures for clinical trials, the first step being tests for safety. On this latter point, the Shanghai International Peace Women and Children Protection Hospital staff reported that the medical personnel will take the medication first in order to assure other participants in clinical trials of its safety.

In recruiting patients for clinical trials, the patients are always informed that the clinicians are testing a new drug. They are told of the expected benefits of the new drug as well as the possibility that there might be failures, including pregnancy. Patients are assured that the hospital will take care of all unintended pregnancies (with induced abortion). There are no specific procedures for informed consent, but on several occasions we were assured that patients are always informed if they are participating in clinical trials.

If the preliminary intensive observation under direct hospital supervision proves satisfactory, large-scale studies are then developed. Again, a three-in-one group is formed. This time it may include not only the pharmacologists and clinicians but also workers from the basic units that will be participating in the large-scale studies. The preliminary data will again be reviewed, and a large-scale study will be designed. This will include establishment of dosage schedules, procedures and standardized forms for data collection, and procedures for the management of anticipated side effects.

The involvement of dozens or hundreds of small clinics in the basic units permits a rapid accumulation of a large series of patients for a full-scale clinical evaluation. A completed study will generally involve several thousand cases with more than ten thousand cycles of observation. The clinicians and other technicians conducting the study will generally visit the basic units to assess the quality of data

collection. When sufficient data have been collected, they will be statistically analyzed.

It should be noted that in spite of repeated questioning at a variety of institutes, we were not able to elicit any examples of controlled clinical trials. Obviously, in contraceptive investigations, placebo-controlled trials could not be done. However, there is no evidence that comparative controlled trials were undertaken. The general pattern, rather, was to collect a series of cases and simply analyze their experience for comparison with clinical observations made elsewhere on other occasions.

The side effects of primary interest are the commonly reported ones that generally result in lower acceptability, for example, menstrual disorders, vomiting, and weight gain. Blood pressure is also carefully monitored.

We could not obtain evidence of a satisfactory search for the rare adverse side effects that have been associated with oral contraceptive use, such as thromboembolism, coronary artery disease, or stroke. It was observed that coronary disease is quite infrequent even among Chinese men, and therefore it might be exceedingly difficult to detect any problem of this nature among Chinese women. Apparently, thromboembolism is also quite uncommon among Chinese women. While there is a concern regarding pill use and hypertension, there was no evidence that there has been any systemic search for an association with stroke. We were told that in cancer-screening surveys there was an investigation of the association of pill use with cancer, but none had been found.

It is worthwhile highlighting several issues that are relevant to the approaches to new contraceptive developments in the People's Republic of China. First, it is clear that they are using multiple approaches to the problem.

The first approach by the synthesis of candidate compounds in an organic chemistry laboratory is by far the most tedious, since it can involve screening of hundreds of compounds before a potentially active agent is found. Even after an active compound is established, extensive studies consuming several years will be required to establish its mechanism of action, as well as its safety in both acute and chronic studies. Given current drug development regulations in the United States, it is probable that this approach would take 15 years or more from the time an active compound has been detected until a new contraceptive is brought to the market.

Because of a lack of regulations and defined procedures for new drug development prior to utilization in humans, the Chinese scientists are able to bring a potentially effective new compound to the production stage much more rapidly. While this undoubtedly has short-run advantages, some concern must be expressed regarding the possibility of long-run difficulties. For example, in the case of anordrin the data with which we were presented really do not give an adequate explanation for its mechanism of action, nor are adequate data available on the absorption, metabolism, and excretion of the drug. This being the case, one might have some concern about potential adverse effects of this drug if it is used by very large numbers of women, particularly because of the high dosage schedules that are required. These remarks are not

meant to discount the concern of Chinese investigators regarding the safety of new contraceptive drugs; rather, they are meant only to highlight the fact that in the absence of standardized requirements for new drug development, human trials can be initiated at an earlier stage than would currently seem appropriate under U.S. drug development regulations.

A second approach to contraceptive development would appear to be clinical trials with variations in the dosage schedule of the currently available oral contraceptive hormone. Chinese scientists have already demonstrated considerable success in this approach through their initiative in successfully reducing the estrogen content of the combined pill from 50 μg to 35 μg and in reducing the progesterone content to one-half and even one-fourth the usual dose used in the Western world. The novel approach to administering progestagens on the fifth day of the cycle and then only with intercourse is thus consistent with other initiatives of this type.

It is of interest to note that apparently, the Chinese are able to initiate human trials of this nature without great difficulty. We were repeatedly assured that the women were informed that they were participating in clinical studies. Given the general regimentation of the Chinese society, it is not at all clear to an outsider how much free choice the women can exercise in this informed consent. On the other hand, with the ready availability of abortions in case of accidental pregnancy, it would appear that this particular undesired effect is not a serious problem. As was noted above, the initial studies with the intermittent progesterone utilizing only a single preparation were reported to result in a high frequency of undesired pregnancies. Apparently, these events did not result in termination of this line of investigation.

The third approach to new contraceptive development bypasses some of the problems involved in initiating human investigations of new drugs. Specifically, since the herbal medicines under investigation are already being used clinically in humans, one does not run into the problem of resolving the ethical issues of initiating clinical trials. Because there are thousands of herbal medicines in use in China, this indeed is a "rich treasure house" that will undoubtedly keep Chinese pharmacologists busy for years to come.

To be weighed against the advantages of this multifaceted approach to contraceptive development are two distinct and what we believe to be serious handicaps. First is the apparent lack of any epidemiological expertise in the design and evaluation of clinical trials. As was noted above, this may not be a serious handicap if one is simply attempting to produce a gross effect such as preventing a conception, terminating a pregnancy, or curing a cancer. However, for a more critical evaluation of the comparative advantages and disadvantages of two drugs or the therapeutic significance of various Chinese or Western medicines, there is no alternative to rigorously designed clinical trials. As an example, there are thousands of herbs that are purported to have a broad variety of different properties. We were told of current research on one herb that presumably had some efficacy in the treatment of chronic bronchitis. As far as could be determined, none of the clinical trials involved controlled studies. Such a deficiency is quite serious in attempting

to assess the efficacy of a pharmacologic agent in a disease that tends to have a highly variable course, including remissions, even without treatment.

As another example, at the Shanghai Tumor Hospital we were presented with data comparing the efficacy of two surgical procedures, the radical mastectomy (Halsted) and the extended radical for breast cancer. This study had several weaknesses in design. In particular, the two procedures were not being done concurrently in time, but rather, the extended radical was being compared with historical data on the Halsted procedure. Also, patients were not randomly allocated to the treatment groups. In fact, cases that were too ill for the extended procedure were assigned to the Halsted procedure, obviously biasing the results.

The lack of an epidemiological approach also means that it is exceedingly unlikely that one can establish the association of a given drug with relatively infrequent or rare adverse side effects. The classical method for developing an association between some incriminated agent and a rare adverse effect (for example, smoking and lung cancer or oral contraceptives and thromboembolism) is through retrospective case control studies. We specifically inquired extensively at every institution we visited regarding whether this type of epidemiological investigation had even been undertaken for any health problem in China. The answers were uniformly negative, with one exception at the Shanghai Tumor Hospital. We were told that there is a "cancer control station" in Shanghai that may undertake these types of studies. The clinicians at the Tumor Hospital, however, were unaware of any specific studies of this nature being carried out in China.

At this stage in the development of the Chinese health care system, concern with rare side effects of hormonal contraceptives may not be a priority. On the other hand, the same epidemiological techniques are crucial in establishing etiologic factors in cancer and chronic disease. China has peculiarly high frequencies of liver, nasopharyngeal, and esophageal cancers in certain geographic regions of the country. We heard reports of massive screening surveys involving hundreds of thousands of participants that were designed to provide early detection and treatment as well as establish the incidence of these tumors. We could find no reports or clinicians who were aware, however, that in-depth epidemiological studies were undertaken in conjunction with these surveys to attempt to establish etiologic factors.

The above observations having been made, it should be noted that a long listing of research institutes in medical sciences in the People's Republic of China indicates that there are five research institutes in epidemiology. Obviously, our group did not visit any of these institutes. However, it is perhaps remarkable that none of the clinicians and other researchers whom we spoke with seemed to be aware of any epidemiological research in their respective fields.

CONTRACEPTIVES IN CURRENT USE

"Planned birth" programs continue to have a high priority for China, and the development of contraceptives ranks prominently in the list of

objectives of research institutes along with agents for the control of cancer, cardiovascular diseases, influenza, bronchitis, and infections. It is therefore not surprising that the greatest application of steroid use in China is for oral contraceptives (Table 3). Although the marriage of "traditional" and Western medicine is often proclaimed as an objective of the Mao Revolutionary Line, a notable exception is for birth control, where the oral contraceptive and intrauterine device are clearly preferred and utilized.

The Steroid Delegation visited two maternity hospitals (250 and 300 beds) in Peking and Shanghai, two large urban general hospitals (700 and 750 beds) associated with medical schools in Canton and Shanghai, and a commune hospital of 70 beds in Kwangtung province and interviewed staff representatives of two small urban hospitals (400 to 450 beds) in Kweilin, one of which was associated with a medical school. All of the units had ambulatory services and specialized birth control clinics. In the absence of systematic data from governmental offices, the information obtained provides a cross section of the contraceptive methods used for family planning in several urban centers of eastern China.

Two oral contraceptive pills are apparently universally available. These are designated simply pill no. 1 and pill no. 2. Pill no. 1 (one-fourth dose) contains norethindrone (0.625 mg) and ethinyl estradiol (0.035 mg). Pill no. 2 (one-fourth dose) contains megestrol (1.0 mg) and ethinyl estradiol (0.035 mg). Both of these are also available at the "one-half dose" level, which contains twice the amount of the progestational agent but with ethinyl estradiol at only 0.0375 mg. Both of these products are available in the "paper pill" formulation in the Shanghai area.

We saw other steroid contraceptives that were available only in limited areas. In Peking there was a preparation called norgestrel containing norgestrel (0.03 mg) and ethinyl estradiol (0.3 mg). This preparation was unknown to physicians in the Shanghai, Kwangchow, and Kweilin areas. One point of interest is that norgestrel is obtained entirely by chemical synthesis rather than being derived from an extract of a natural product.

In the Shanghai area a new contraceptive called anordrin was being utilized. (This is described elsewhere in this report.) This was a 7.5 mg enteric, coated tablet that was called the "vacation pill" and was designed for use at the time of coitus for couples who were together only infrequently.

Also in the Shanghai area there was limited use of a new combined progestational pill. This contained megestrol (0.5 mg) and quinegestanol acetate (0.8 mg). This pill was also designed for intermittent use at the time of coitus. This development is described in detail elsewhere in this report.

At one urban hospital they did have supplies of a long-acting progestational injection. This injection contained 17α-hydroxyprogesterone caproate (250 mg) with estradiol valerate (5 mg) and was designed as a once-a-month injection. According to clinicians whom we saw, this had limited use because of problems with side effects, particularly irregular menstrual bleeding.

TABLE 3 Steroid Contraceptives Available in the People's Republic of China

Name	Composition	Comment
Pill no. 1		
One-fourth dose	Norethindrone, 0.625 mg Ethinyl estradiol, 0.035 mg	Also available as paper pill in Shanghai
One-half dose	Norethindrone, 1.25 mg Ethinyl estradiol, 0.0375 mg	
Pill no. 2		
One-fourth dose	Megestrol, 1.0 mg Ethinyl estradiol, 0.035 mg	Also available as paper pill in Shanghai
One-half dose	Megestrol, 2.0 mg Ethinyl estradiol, 0.0375 mg	
Norgestrel	Norgestrel, 0.03 mg Ethinyl estradiol, 0.3 mg	Available only in Peking
Anordrin	7.5 mg enteric coated	Vacation pill; available only in Shanghai
"Combined progesterone"	Megestrol, 0.5 mg Quinegestanol acetate, 0.8 mg	For intermittent use; available only in Shanghai
Injection no. 1	17α-hydroxyprogesterone caproate, 250 mg Estradiol valerate, 5 mg	Monthly injection

In addition to steroidal contraceptives, a variety of other fertility control methods were available. The intrauterine contraceptive device most used was the steel spring ring, although at one hospital we saw a triple loop. Condoms, diaphragms, and vaginal creams were also available.

In addition to contraceptive services, all of the medical facilities we visited provided abortions and female sterilizations. Abortions were commonly done by suction curettage. We did observe some second trimester abortions being done with the use of the Chinese herbal medicine, trichosanthin. (This preparation is described elsewhere in this report.)

All contraceptive techniques except for condoms and vaginal creams, which can be purchased at the pharmacy, are provided free of charge. There is considerable variation in the popularity of different methods according to locality. Generally, it would appear that in the urban areas, oral contraceptives are most popular. In the rural areas we visited, apparently the intrauterine device is more popular, presumably because it is more convenient and requires less motivation than taking a pill daily.

There are variations in recommended contraceptives according to the patient's condition. At the Peking Maternity Hospital we were told that newly married women are generally advised to use oral contraceptives or condoms. For postpartum women after the first or second child, the intrauterine device or oral contraceptives are advised. After the second child, if the woman is under 35 years, sterilization is advised up to the age of 40. After the age of 40, the IUD or condom is recommended. Pills are not advised after the age of 40 because of the high frequency of hypertension in this age group, as has been reported in clinical trials.

In addition to free contraceptive services, there is also subsidized leave. For example, a women gets two days of paid leave for an IUD insertion. Abortions are provided free with two weeks of paid leave. We were told that most abortions are done for birth spacing and only "occasionally" are they done in the case of a first pregnancy. We were told that abortions for illegitimacy are rare. The most common indication is "contraceptive failure." Women do have repeated abortions, although we were not able to obtain the frequency of repeat abortions.

While contraception is widely practiced, it appears that abortions also play a very important role in the low fertility rates reported in China. This conclusion is based on the fact that in each of the hospitals (except in the Luo Gang Commune, where no data were available) the ratio of abortions to live births was about 1 to 1. Assuming that the catchment area for abortions is the same as for deliveries, this is indicative of a major contribution of abortion to declining fertility. In this regard, it is difficult to interpret the significance of the oft repeated statement that abortions are largely being done for contraceptive failure. Specifically, we were not able to determine whether this was actual failure of a method in practice or failure of intent to use a method.

The frequency of sterilization is difficult to assess. Generally, the ratio of sterilizations to live births being done in the hospitals we

visited was about 1 to 10. It is unlikely that this represents a reasonable estimate, since many sterilizations are done in neighborhood clinics or other basic units. It should be noted that the sterilization technique generally utilized was the minilaparotomy under acupuncture anesthesia. The laparoscopy technique so popular in the United States was not used.

The contraindications for pill use include acute and chronic liver disease, kidney disease, elevated blood pressure, acute carditis, uterine myoma, and ovarian cyst. The oral contraceptive is not recommended for use during breast-feeding and is now seldom used over age 40.

The highly effective social methods for birth control reported previously from China, such as late marriage, small family norms, child spacing, taboos on premarital sex, and deemphasis of the "need" for any male offspring, coupled with an extensive delivery system of contraceptives, results in high acceptance rates. Most hospitals reported high percentages (50 percent or more) of first pregnancies, and although grand multiparas are still seen, our visits to several busy obstetrical floors revealed all women having only their first or second child. The local birth rates quoted (but not verified) at all of these institutions in the urban centers was 14 to 15 per 1,000.

Although population control was stressed in the areas we visited, it was noted that more leeway in family size is tolerated in less densely populated areas, especially in the autonomous regions and among minority groups.

In substance, China has developed adequate family planning methods for effective contraception and is self-sufficient in production and delivery of these methods. Steroid hormones play a significant role in the contraceptive program; however, it would be difficult to say that oral contraceptives are a predominant factor in the low birth rates attributed to China. Chinese physicians and scientists are searching for alternative steroid compounds for fertility control that would minimize or eliminate the side effects associated with estrogen as well as simplify use and increase acceptability. As in the Western world, physicians in China are concerned with the adverse side effects of oral contraceptives and with contraceptive failures.

SPECIFIC NEW CONTRACEPTIVE DEVELOPMENTS: ANORDRIN

Anordrin (A-morandrostane-2α,17α-diethinyl-2β,17β-dioldipropionate) is a new steroidal contraceptive hormone synthesized by the Institute of Organic Chemistry in Shanghai. Synthesis of steroidal derivatives was begun around 1965 and several hundred compounds were screened before anordrin was selected. This contraceptive is also called the vacation pill and apparently has been developed for married couples who live apart for extensive periods and only come together perhaps once or twice a year for vacations, generally for a one-month period. The instructions are that on first use the pill is to be taken immediately after coitus with a second dose the following morning. Thereafter, the pill is to be taken each time with intercourse.

The stated advantages of this pill are that it does not require chronic administration of steroidal hormones. Further, it can be initiated and used any time during the menstrual cycle. When asked about why this preparation was chosen only as a vacation pill rather than for general use, the answer was that it was likely to be taken more frequently during an individual cycle on vacation. Effectiveness apparently relates to frequency of use within a given cycle. The failure rate is apparently higher with isolated sporadic use. Regular use on a series of cycles is not recommended, both because of the relatively high dosages of this compound required (7.5 mg per dose) and because of the fact that it substantially alters the menstrual pattern in the cycle in which it is utilized.

It is worth noting that this pill, as well as the combined progestational drug to be discussed below, was developed to take into account the specific social needs of China. In China all jobs are controlled by the state, and workers are assigned to their place of work and duties by the government. While this system guarantees full employment and eliminates inflation, there are apparently a substantial number of married couples who live separately and are able to meet one another only on vacation for one month in a year. This situation is apparently frequent enough so that special contraceptive modalities are being developed to meet these needs.

Extensive pharmacologic studies of anordrin were carried out by the Institute of Physiology in Shanghai. Single doses of 5 to 10 mg/kg in rats, mice, rabbits, hamsters, and dogs prevented pregnancy when given one to nine days after mating. The dose can be as low as 2 mg/kg in mice and rabbits. Anordrin is uterotropic in the rat, having a potency 2.8 percent that of ethinyl estradiol. It is also slightly antiestrogenic, again as measured by uterine weight. It markedly inhibits deciduoma formation in the rat. Four days after induction of pseudopregnancy, decidual weight was decreased 50 percent. Anordrin had no progestational effect on the rabbit endometrium.

Acute toxicity was examined in female mongrels and rhesus monkeys. Anordrin, given at 75 mg/kg/d for three days, caused no changes in serum cholesterol, blood count, urinalysis, or liver function tests.

Subacute toxicity was examined in the dog using the steroid at a dose of 15 mg/kg twice a week for six months. Blood chemistries, electrocardiograms, and hepatic and renal functions remained normal.

Chronic toxicity was examined in the rat by using a dose of 1 mg/kg twice a week for six months and then 2 mg/kg twice a week for a year and a half. No alterations were detected in any of the organs at postmortem.

The compound was tested for teratogenicity by giving 2 mg/kg seven to nine days after mating in rats. No fetal abnormalities were detected. At higher doses of the compound, mating behavior remained normal.

The absorption and distribution of ^{14}C-labeled anordrin was studied in rats and mice. It is poorly absorbed, 80 percent being recovered from the feces and gastrointestinal tract in 24 hours. Most of the urinary ^{14}C appeared during the 12 hours after administration.

It is slowly metabolized from the blood and most of the material present in plasma was said to be unchanged anordrin based on a single

thin-layer chromatogram. There were obvious discrepancies in the data, the half-life in plasma being long and the biologic half-life based on urinary ^{14}C being less than eight hours. The data suggested the possibility of enterohepatic circulation. Radioactivity was present in pituitary, oviduct, and stomach.

In the rabbit, anordrin slowed transport of the zygote. The blastocysts reaching the uterus were smaller than normal and were degenerating. Similar observations were made in rats.

Antiprogesteronal effects were also confirmed when anordrin was administered in combination with a progesterone. With very small doses of anordrin there was apparently a synergy of the progestational effects, but with large doses, an antiprogestational effect was reported. It would be of interest to test the compound and the 2,17-dihydroxy derivative in a progesterone receptor assay. At the present time there are no data on the metabolism of anordrin.

The utilization of anordrin in clinical trials was decided by the three-in-one group. It was not clear how the dosage for human use was established. Animal work indicating that dosages in the range of 1 to 5 mg/kg were required would imply that 50 to 100 mg might be required as an effective human dose. As was noted earlier, a 7.5-mg dose was established; however, the instructions were that with first intercourse the pill should be taken immediately after coitus and again the next morning. Also, the pill is recommended only for couples who will have frequent intercourse (six to eight times) within a given cycle, because of the observation that it will be less efficacious if used sporadically. This regimen, therefore, would tend to assure a cumulative dose of 50 or more milligrams within a one to three or four week period. The 7.5-mg tablet is enteric coated.

In clinical trials with 6,756 cycles where the pill was used in multiple doses, it was found to be 99.5 percent effective in preventing pregnancy. A more intensive investigation of 750 of these cycles, when records were complete, revealed that in 511 (68.1 percent), the tablets were taken in the midcycle and in 43.7 percent, tablets were actually taken on the fourteenth day. Because the other women had effective protection when the tablets were taken at other times, it was concluded that administration at any time in the cycle results in efficacy.

A major side effect of anordrin is prolongation of the menstrual cycle. In 3,870 cycles, 18 percent of the women had 30- to 45-day cycles. The Chinese investigators did not comment on the psychological effect that the delayed period had on these women in terms of their concern about potential pregnancies.

There was no evidence of any significant effect on the duration of bleeding or the amount of menstrual bleeding. Other side effects reported among 2,164 cycles were nausea, 3.6 percent; vomiting, 1.7 percent; dizziness and fatigue, 2.9 percent; leukorrhea, 2.1 percent; and other complaints, less than 1 percent.

Safety was determined among 109 who used the drug "continuously." (It is not clear whether this meant daily or regularly with intercourse in each successive cycle.) Fifty-two women used the drug for 69 cycles, 36 women for 10 to 12 cycles, and the remainder for a longer period.

The general physical examination; blood chemistry, liver, and kidney function tests; and cervical smears were normal.

Regarding return of fertility, nine out of ten women who had used the drug continuously achieved a desired pregnancy within the first cycle after cessation of the drug. There was no evidence of an effect on lactation in 20 cases.

In detailed studies of the menstrual cycles, it was shown that the pattern of response was different, depending on whether anordrin was given before, during, or after ovulation, or continuously. To evaluate the responses, basal body temperatures, endometrial biopsy, and plasma progesterone were followed. When the pill was taken during the follicular phase (days 4 to 9), some women ovulated, others did not. There was a short luteal phase, and plasma progesterone reached a peak of 4 to 5 mg/ml (normal is 9). When anordrin was given at midcycle, ovulation occurred, but there was often a low plasma progesterone, a short luteal phase, and a delay in the evolution of the secretory pattern of the endometrium. When anordrin was given during the late luteal phase, there were no discernible changes. Its continuous use commonly resulted in anovulatory cycles. Among eight subjects who took the pill "continuously," endometrial biopsy showed no evidence of estrogenic activity. There was evidence of inhibition of glandular development indicative of antiprogestational activity.

The Chinese investigators concluded that while anordrin may have had an effect on inhibiting ovulation, this was inconsistent. The major effects are the inhibition of action of progesterone as well as a direct physiologic effect on the uterus. The primary mechanism of action is assumed to be anti-implantation.

Interestingly, the Chinese investigators had not yet studied this drug as an abortifacient in early pregnancy; they did note that some women who had an unsuspected pregnancy when initiating anordrin did indeed report an abortion. On this basis, there is a plan to initiate clinical trials with this agent as an abortifacient.

The clinical trials with anordrin began in 1971. By June 1973, enough clinical data had been accumulated to call together a symposium of investigators and workers to review the results and recommend the drug for general use. The recommendations of this symposium were forwarded to the Office of Planned Births of the State Council, which gave its approval for general use in January 1974. Anordrin has now been approved for national use, but apparently at the present time its availability is limited. The actual number of users in Shanghai was not known.

The above studies of the oral contraceptives were given in some detail because they illustrate the extent of the biology, pharmacology, and clinical testing by what is perhaps the most sophisticated group in China. Anordrin is now available on demand, and the physicians in Shanghai were unaware of any clinical trials or follow-up surveys.

It is appropriate to remark on the commitment of the scientists to develop improved methods of contraception. They do not consider the estrogen-progestin OC as ideal, although their reported side effects are low. But Chairman Mao was particularly concerned with the health of women and saw the necessity for family planning. These statements

were quoted to us on many occasions and would seem to have the force of policy.

COMBINED QUINEGESTANOL ACETATE-MEGESTROL ACETATE CONTRACEPTIVE

Although the efficacy of continuous low-dose progesterone in preventing pregnancy is well established, the approach of using a combination of two progestational agents for fertility control is a novel one. This combination pill was designed to avoid estrogens and to provide a contraceptive that could be useful for those married couples who live apart and meet only irregularly as well as those living together. Rather than a continuous dose regimen, the pill was developed to be used only with coitus. The method is an outgrowth of "learning from the people" and "the open door policy" where scientists visited women and asked about problems in contraceptive use. The result was an attempt to improve convenience and minimize side effects (discontinuous use and removal of estrogen).

The trials started by prescribing quinegestanol acetate alone on day 5 of the cycle and with each coital act at different dosage levels up to 1.6 mg per pill. This use of a single agent was not very effective in preventing pregnancies and megestrol acetate was added in a trial and error fashion until the present dose of 0.5 mg megestrol acetate and 0.8 mg quinegestanol acetate was arrived at.

Clinical experience for two years with 2,000 women and 10,000 cycles revealed an effectiveness of 98.1 percent in preventing pregnancy if at least eight pills were taken each month.

Breakthrough bleeding occurs in 5-7 percent of cases and is treated with 0.015 mg of ethinyl estradiol each day for 3-5 days. Gastrointestinal side effects occurred in 8 percent of subjects, while 2 percent had significant nausea. Menses are prolonged over 36 days in 24 percent of cases and over 40 days in 7 percent. Basal body temperature curves indicated that ovulation was blocked 80 percent of the time. During initial tests the pill was most effective if taken 24-72 hours prior to coitus and less than 60 percent effective if taken at the time of or following coitus. The present program is to start the pill on day 5 of the cycle and on each day of coitus. Endometrial biopsies on day 21 of the cycle revealed impaired gland development and diminished glycogen. Urinary pregnanediol was determined by gas chromatography on overnight samples, and the levels revealed anovulation in 60 percent of the cases.

Animal studies were initiated to determine the mechanism of action. The animals (rabbits) received the same dose as that used in the clinical trials rather than a lower dose proportional to the body weight of the animals. The pill was given at varying intervals (Table 4) prior to, at, or after coitus. It is clear that the pill is most effective if taken 24 to 48 hours prior to coitus. Ovulation was inhibited 90 percent of the time, but the pregnancy rate was zero. The medication did not prevent human chorionic gonadotropin (HCG) induced ovulation (Table 5) but interfered with implantation. Studies also revealed that zygote transport was accelerated and that the blastocyst arrived prematurely in the uterus, where it stopped dividing and degenerated. By obtaining

TABLE 4 Effect of Quinegestanol-Megestrol Pill on Pregnancy in Rabbits

Number of Pills	Hours Relative to Time of Coitus	Pregnancy Rate, %
0	--	100
1	-72	60
1	-48	0
1	-24	0
1	- 8	42
1	0	66
2	0	
1	+ 8	71
1	+ 8	
1	+24	66
1	+36	
1	0	
1	+ 8	50
1	+24	

TABLE 5 Effect of Quinegestanol-Megestrol Pill on HCG-Induced Ovulation and Pregnancies in Rabbits

HCG	Pill	Ovulation	Implantation	Birth
9	--	8	7	7
5	5	5	1	0

Figures in columns refer to number of animals.

TABLE 6 Effect of Quinegestanol-Megestrol Pill on Zygote Transport in Rabbits

Recipient Rabbit	Number of Animals	Number of Eggs		Fetuses at 28 Days
		Transferred	Implanted	
Control	5	40	57%	43%
Combination pill	5	33	3%	0

fertilized eggs from untreated animals and transplanting them to those who had received HCG with or without the pill, it could be demonstrated that the primary effect was on the genital tract rather than the egg itself, a desynchronization between the zygote and the uterus (Table 6) resulting in an anti-implantation effect.

The influence of this pill on sperm capacitation was tested by obtaining sperm from the genital tract of control or treated rabbits and transferring it to nontreated does after induced ovulation. Fertilization was checked 38 hours later and was 64 percent for sperm from the control and 35 percent for the sperm from the treated animals.

It is clear from these studies that this combination pill can operate at many points in the reproductive process, blocking ovulation and implantation and impairing zygote transport and sperm capacitation as well as interfering with the reproductive cycle.

When the clinical studies were completed, a symposium was organized in Shanghai to review the data and consider the drug for general use. This method has been approved by the Office of Planned Births but is available only in the Shanghai area because of limited production. It remains to be seen how popular it will become.

USE OF STEROID HORMONES IN OBSTETRICS AND GYNECOLOGY

Aside from their use as contraceptive drugs, steroid hormones are not often prescribed for obstetrical or gynecological problems in China. In Western countries, estrogens and/or progestins are used extensively for menopause, endometriosis, and dysfunctional uterine bleeding, conditions more apt to be treated with herbal medicines or acupuncture in China.

The major gynecological problems in China include leiomyomata, ovarian cancer, cancer of the cervix, and choriocarcinoma. There was no emphasis on the menopause, which is only rarely treated with estrogens and more often attended to with herbal medicines. There appeared to be little data on the incidence, severity, or response of menopausal symptoms. Osteoporosis was not singled out as a major problem. Cancer of the endometrium is rare, and absence of estrogen use in the menopause is noteworthy in this regard. Dysfunctional bleeding is treated with herbal medicines and in acupuncture clinics. Chinese gynecologists are

familiar with the efficacy of synthetic progestins but rarely use them for this condition.

Endometriosis, which is ordinarily considered a consequence of delayed childbearing, was reported rarely although physicians were familiar with the diagnosis and occasionally had used norlutin or megestrol for its treatment.

Infertility evaluation in China includes all of the standard procedures used in Western countries but relies heavily on traditional medicine and acupuncture. Clomiphene, but not gonadotropins, has been used for ovulation induction.

Although steroid hormones are generally available, their use in obstetrics and gynecology is quite limited.

STEROIDS IN GENERAL MEDICINE

It was not possible to obtain accurate information about the use of steroids other than the contraceptives. Glucocorticoids are rarely used in rheumatoid arthritis but apparently are used in other diseases such as the nephrotic syndrome. There is a broad range of oral and injectable glucocorticoids available: cortisol acetate, prednisone, dexamethasone, fluococortisol, prednisolone sodium phosphate, and dexamethasone sodium phosphate. Triamcinolone acetonide, synthesized in China, is available for topical application.

Androgens are readily available in the pharmacies and in the hospitals. They are used as an anabolic agent for ill-defined conditions and are used in young women with metastatic breast cancer. Androgens are apparently not used for impotence, a field that has been left to traditional Chinese medicine.

Spironolactone, synthesized in China, is used for the treatment of essential hypertension, although no effort is made to separate out the low-renin hypertensive group. Spironolactone is not used in the diagnosis of primary aldosteronism, which is diagnosed by the classical criteria of hypokalemia and hypertension.

Estrogens and glucocorticoids are used in the treatment of women with breast cancer. Estrogens are given to the postmenopausal patient with soft tissue disease, and glucocorticoids are used for patients with hypercalcemia.

In general, apart from contraceptives, steroids are used as in the West without original inputs from the scientists in China. Diagnosis of diseases of steroid excess or deficiency are relatively unsophisticated, utilizing only such analytic techniques as urinary 17-ketosteroids and hydroxycorticoids and plasma cortisol.

CLINICAL APPLICATIONS OF STEROID BIOCHEMISTRY

A number of very specialized analytical and biochemical research techniques play an essential role in steroid hormone research leading to the eventual clinical use of these agents. Some of the techniques are designed to provide information on the concentration of gonadal and

pituitary hormones in body fluids. Perturbations in these concentrations as well as studies of hormone-receptor interactions provide essential information on the nature of the activity of steroidal contraceptive agents and help identify the location within the complex endocrine reproductive cycle where the interference occurs. Bioassays of newly synthesized agents as well as studies of their metabolic transformation and pharmacokinetics by use of radiolabeled substrates are an intimate part of all steroid hormone research in the developed countries. From the information supplied to us in the People's Republic of China, the steroid contraceptive development program in that country has been associated with only a minor use of the above technologies.

The analytical procedures that were disclosed to us included the measurement of estrone, estradiol, estriol, and pregnanediol in normal human pregnancy and nonpregnancy urine. This was accomplished by hydrolysis with acid, extraction with organic solvent, derivatization, and gas chromatography. The instruments used were manufactured in China, and the values reported were in accord with our experience except that the nonpregnancy estriol values appeared to be excessively high. No routine radioimmunoassays for these substances, which would permit their measurement in plasma, were noted, and this represents a significant lack in the technologies required for the development and use of new steroidal agents. It is clear that the concept and competence for radioimmunoassays are present in China. Specific examples reported were a working radioimmunoassay for human chorionic gonadotropin and a modified immunoassay for α-fetoprotein which has found wide application in the screening for liver cancer.

An exceptionally important role in current steroid research is the study of hormone-receptor interactions. Despite the importance of this technique in the rapid testing of the activity of new synthetic steroid hormones and its well-documented utility in determining the treatment modality in breast cancer, no such work is presently being carried out in China. That the capacity for such studies does exist was exemplified by the study of the binding of synthetic insulin derivatives to insulin receptors, which is being carried out in the Peking Institute of Zoology and which is theoretically comparable to steroid hormone-receptor studies.

A single example of the use of radiolabeled steroid for metabolic and pharmacokinetic studies was that of ^{14}C-labeled anordrin, a synthetic steroidal oral contraceptive whose excretion, metabolism, and plasma levels were monitored via its radioactivity. Of the vast array of bioassays for steroid hormones known, examples of two of the most common ones were reported. These were the uterotrophic assay for estrogenic activity and deciduoma formation for progestational activity.

The above represents the sum of steroid biochemical research techniques that are in use in China at this time. It is meager in comparison to the United States and other developed countries, but we believe it reflects the "borrowed" nature of the current Chinese steroid hormone program. Should they set out on new research efforts in this field, these methodologies will have to be expanded and it appears that the capacity for their extension in quantity and sophistication does exist.

5

NATURAL PRODUCTS: CHEMISTRY, PHARMACOLOGY, AND MEDICAL APPLICATIONS

ANTITUMOR AGENTS

Studies in this area were under investigation both at the Institute of Materia Medica in Peking and the Shanghai Institute of Materia Medica.

Camptothecin and Analogues

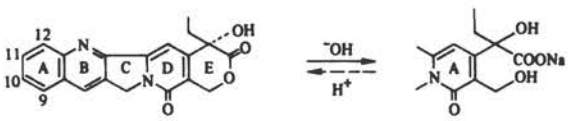
Camptothecin was first isolated from a tree which is a native of China called *Camptotheca acuminata*. (M. E. Wall, *et al.*, *Journal of the American Chemical Society* 88, p. 3888, 1966). Seeds from the fruit of this tree were sent to the United States many years ago, germinated, and grown in a U.S. Department of Agriculture Botanical Garden at Chico, California. Material from several trees growing in this botanical garden was collected and extracted, and the initial isolation was made at the Research Triangle Institute.

Camptothecin is a unique alkaloid with marked activity against experimental animal leukemia and solid tumor systems. Extensive clinical trials in the United States were not encouraging, and further work was abandoned. Accordingly, it was of great interest to find that camptothecin was being actively studied in the clinic in China. In addition, there was strong interest in the synthesis of camptothecin and analogues at the Shanghai Institute of Materia Medica.

Pharmacology and Clinical Findings

All studies were carried out with camptothecin as the sodium salt. This is the form in which the drug has been used in the United States. The manner in which sodium salt is formed is shown in Figure 2. Camptothecin is a very water-insoluble compound. In the presence of a base it can be quantitatively converted to the sodium salt by ring opening of the lactone as shown. The sodium salt is administered intravenously in man. When it was given by the intraperitoneal (IP) route in mice, there was a considerable degree of activity of the sodium salt against experimental leukemia, presumably by ring closure under slightly acidic conditions to regenerate the original camptothecin. Experimentally,

FIGURE 2



there is no question that this occurs, although the yield is far from quantitative. The real question, however, is whether this process really takes place effectively in man when camptothecin is administered intravenously. In the United States we are now studying methods to introduce solubilizing groups in ring A by total synthesis. The Chinese are also doing some work in making ring A analogues although not for the same purpose.

Animal Pharmacology

Camptothecin was tested in China in a number of animal tumors, including sarcoma 180, Walker 256, B22, and a number of other types. The normal dose in rodents was 1 mg/kg/d. In some cases, particularly with the Walker 256, very effective reduction in tumor growth occurred. A particularly interesting development was the use of monoammonium glycyrrhetate, a product produced from the licorice root, as a vehicle for the administration of camptothecin, which resulted in a considerable decrease in toxicity. For example, when camptothecin was administered IP, the median lethal dose (LD_{50}) of camptothecin was 140 mg/kg, whereas it was reduced to 83.6 mg/kg in the presence of 500 mg/kg of the glycyrrhetate given subcutaneously while the camptothecin was given IP. Giving both drugs together by the IP route also markedly increased life prolongation.

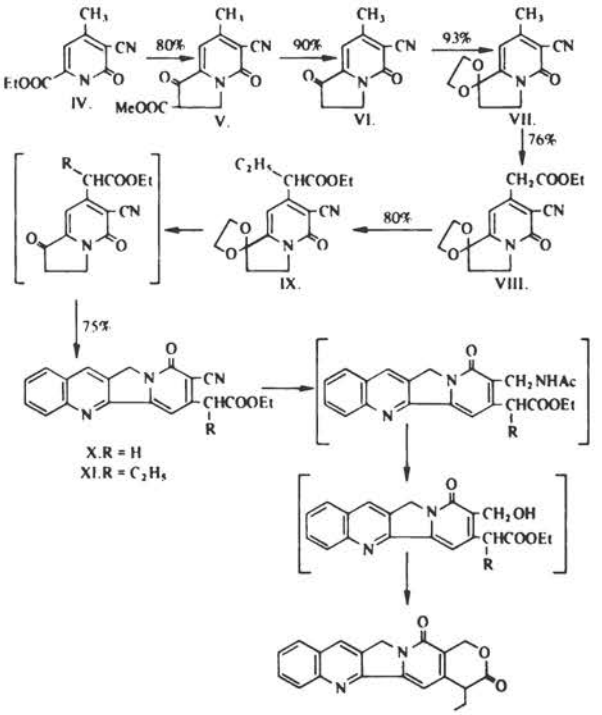
Clinical Use

In China, camptothecin is considered useful for stomach cancer and is in active use in the clinic. The regimen is 20 or 40 mg every day by the intravenous route for two weeks, and 14 injections during this period are made either every day or every other day. However, we did not see any actual hard tabular data. One interesting question that arose during the discussion was whether camptothecin is used as a folk medicine in China. The answer was no.

Chemistry

Two recent papers on camptothecin chemistry have appeared. One is concerned with the total synthesis of camptothecin (*Kexue Tungbao* 21, p. 40, 1976) and the other with studies on derivatives of camptothecin (*Acta Chimica Sinica* 23, p. 71, 1975).

FIGURE 3



Total Synthesis

The synthesis of camptothecin is shown in Figure 3. The pyridone used as starting material is readily prepared by the reaction of $CH_3COCH_2COCOOEt$ with the appropriate nitrile. Reaction of the pyridone (cf. Figure 2) with methylacrylate in the presence of dimethylformamide (DMF) and potassium carbonate gives the bicyclic product V in high yield. Decarboxylation by treatment with hydrochloric acid produces the bicyclic ketone VI, which is converted to the ethylene ketal VII in the standard way. The latter can then be reacted with diethyl carbonate in the presence of toluene sodium hydride to afford VIII, again in high yield, which on alkylation with ethyl iodide gives product IX. It should be noted that at this point rings C and D are fully elaborated and all of the substituents required to form ring E are in place.

After removal of the protective ketal grouping, the resulting ketone, which is somewhat unstable, is treated without isolation with *o*-aminobenzaldehyde in acetic acid containing a trace of hydrochloric acid. This Friedländer condensation proceeds in 75 percent yield, and it will be noted that the rings A, B, C, and D are now fully formed. At this point the nitrile is reduced to the corresponding amine with Raney nickel in the presence of acetic acid and acetic anhydride. The acetylated Raney

nickel reduction product is not isolated but is treated after deacetylation with cold sodium nitrite and dilute sulfuric acid to form the corresponding primary alcohol as shown. Under the acid conditions, ring lactonization will occur to give desoxycamptothecin XII. Desoxycamptothecin was produced in Wall's laboratory by conversion of camptothecin to the corresponding chloro compound, followed by reduction. It was found to be inactive as an antitumor agent, although it is a strong inhibitor of DNA or RNA synthesis. When air is bubbled through a DMF solution of desoxycamptothecin in the presence of cuprous chloride, the hydroxyl group is introduced, yielding camptothecin. This hydroxylation reaction and, in fact, many of the other steps are not novel but are similar in one respect or another to various camptothecin syntheses that have been published in the United States during the last six years. It is worth noting that almost all of the published syntheses are rather low yielding. In contrast, the interest of the Chinese is in a practical synthesis. Novelty or lack of it is of no concern to them. Accordingly, they seem to have done the necessary research and development, which has not been pursued in the United States, where research on camptothecin has been mainly in academic hands.

In another study, not discussed in detail during our visit but published in *Acta Chimica Sinica*, camptothecin was converted to a number of 12-substituted derivatives, including the 12-amino, 12-hydroxy, 12-ethoxy, 12-cyano, 12-carboxy, 12-carbomethoxy, and 12-mercapto analogues. Precursor for all these compounds was 12-nitro, obtained by nitration of the alkaloid in sulfuric acid. The latter on catalytic hydrogenation yielded the corresponding 12-aminocamptothecin, which on diazotization followed by the appropriate substitution reactions yielded all of the remaining compounds. Only partial and sketchy pharmacological data were available. The 12-chloro analogue was active against leukemia no. 615. The 12-hydroxy and 12-methoxy analogues seemed to be more active against Ehrlich ascites carcinoma than camptothecin itself.

Harringtonine and Analogues

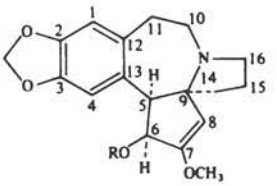
This active antitumor alkaloid and its analogues were under investigation at both the Institute of Materia Medica in Peking and Shanghai Institute of Materia Medica. Harringtonine and some of its analogues were first isolated about seven years ago by C. R. Smith, Jr., R. G. Powell, and co-workers at the Northern Regional Research Laboratory, Peoria, Illinois, from various *Cephalotaxus* species. Working with *Cephalotaxus hainansis* Li, the Chinese scientists have carried out extensive investigations.

Isolation

Various *Cephalotaxus* species have been studied in the United States both in terms of types of alkaloids present and their antitumor activity. The Peking group, using "improved methods," isolated 11 alkaloids, of

which eight were found in quantities sufficient to test for antitumor activity. Four of these alkaloids, namely harringtonine, homoharringtonine, isoharringtonine, and oxyharringtonine, were active antitumor agents. The structures of these compounds are shown in Figure 4. All the alkaloids are esters derived from the parent alkaloid cephalotaxine.

FIGURE 4



Cephalotaxine, R = H

Harringtonine, $R = -C(=O)-C(OH)(CH_2CO_2CH_3)-CH_2CH_2C(OH)(CH_3)_2$

Isoharringtonine, $R = -C(=O)-C(OH)(HO)(CHCO_2CH_3)-CH_2CH_2CH(CH_3)_2$

Homoharringtonine, $R = -C(=O)-C(OH)(CH_2CO_2CH_3)-CH_2CH_2CH_2C(OH)(CH_3)_2$

Desoxyharringtonine, $R = -C(=O)-C(OH)(CH_2CO_2CH_3)-CH_2CH_2CH(CH_3)_2$

Pharmacology

As has been mentioned, the harringtonine alkaloids were first isolated by U.S. workers who found them to be highly active in certain animal leukemia systems. The Chinese workers have confirmed these findings. In addition, all four alkaloids have received clinical study in China. In contrast, in the United States, the decision to carry out large-scale isolation and clinical studies is still under consideration. Side effects found by the Chinese include mild intestinal reactions, which disappeared as soon as the drug was discontinued. There was some alopecia, but hair growth was restored after discontinuation of treatment. The conclusions were that harringtonine might have useful therapeutic effects in man, particularly in some forms of leukemia.

In animal investigations the effects of harringtonine on L615 and L7212 animal leukemia were studied. The former is a reticular cell leukemia. At doses of 1-2 mg, it produced a 54 percent reduction in tumor size, and in the Walker WM256 tumor system it produced a reduction of 34 percent. The LD_{50} in mice was 4.5 mg/kg, and the effective dosage was around 1-2 mg/kg. Toxic reactions include an adverse effect on the spleen index. Harringtonine is also an immunosuppressive agent. In man, out

of a total of 31 cases of granular leukemia, seven showed complete remission; there were 18 partial remissions and six failures. The dosage was about 22 ng/kg/d given in glucose solution, and treatment was continued for 57 days. The results of studies on 31 patients with various forms of leukemia is shown in Table 7.

TABLE 7 Clinical Trials with 41 Patients with Various Forms of Leukemia

Leukemia Form	Number of Subjects	Complete Remission	Partial Remission	No Effect
Acute myelocytic	26	3	17	6
Acute monocytic	2	1	1	
Acute myologenous	5	1	4	
Acute lymphatic	6		3	3

Synthesis of Harringtonine Analogues

The group at the Shanghai Institute of Materia Medica is studying the partial synthesis of harringtonine and analogues by esterifying cephalotaxine with synthetic acids with their acid chlorides. A description of this work has been published in *Acta Chimica Sinica* 23, p. 75 (1975).

Nitrocaphane

Much work in chemical synthesis and in clinical studies has been carried out at Shanghai on a nitrogen mustard called nitrocaphane. This compound is 2-bis-(-chloroethyl)-amino-methyl-5-nitrophenylalanine and hence is an analogue of the well-known phenylalanine nitrogen mustards. Results with a sizable number of patients in the clinic are shown in Table 8.

TABLE 8 Effect of Nitrocaphane

	Number of Patients	Effect	
		Good	Partial
Nitrocaphane	443	68	121
Nitrocaphane Combined therapy	117	23	45

These patients had various malignant tumors with therapeutic effectiveness usually seen in squamous cell carcinoma and the undifferentiated cell types. Objective response rates were as follows: nasopharyngeal carcinoma, 78%; malignant lymphoma, 77%; female genital cancer, 72%; breast carcinoma, 68%; carcinoma of head and neck, 63%; brain tumor and other central nervous system neoplasms, 48%. The therapeutic action was rapid, but the duration of remission was relatively short, lasting only about one month. Side reactions were mainly anorexia, vomiting, nausea, bone marrow depression, and alopecia.

PROTEINS AND POLYPEPTIDES

Members of the Department of Endocrinology at the Peking Institute of Zoology are working with small peptide hormones. In accord with the teachings of Chairman Mao that theory must be integrated with practice, they undertook a problem of practical endocrinology. The carp, a major food fish in China, doesn't spawn in confinement. It has been necessary to use human chorionic gonadotrophin (HCG) and an extract of fish pituitaries, the latter presumably as a source of FSH, to induce spawning. In 1973, they began work with LRH as an agent to induce spawning. This decapeptide is active at 1 mg/kg. The Shanghai Institute of Biochemistry synthesized the D-Ala^6 nonapeptide previously described by American workers and showed that it was effective at several nanograms per kilogram. This material is now in wide use throughout China. In one of the four species of carp, a small amount of fish pituitary is still necessary.

The next topic discussed was a study of the effect of LRH on the carp ovary. The justification for this theoretical work is found in the following quotation from Chairman Mao. "Perception only solves the problem of phenomena; theory above can solve the problem of essence. The solving of both of these problems is not reparable in the slightest degree from practice."

Following injection of labeled LRH, they demonstrated localization in gonadotrophs by electron microscopy (EM) autoradiography. They also found depletion of small secretory granules by staining with periodic acid Schiff (PAS) reagent. These granules differed in staining characteristics from large granules that were not depleted by LRH. They postulated that the large secretory granules contained FSH but could give no convincing support for this. In a series of studies of the carp ovary after LRH, they demonstrated by histochemical techniques that 3 β-hydroxysteroid-dehydrogenase, glucose-6-phosphatase, and alkaline and acid phosphatases increased. It was clear that the important accolade in this work was the acceptance of the use of LRH by the peasants.

Other workers at the Institute of Zoology were studying insulin action. Insulin analogues were synthesized at the Institute of Biochemistry in Shanghai and labeled with either ^{125}I or ^{131}I for binding studies. The group has compared the binding of insulin analogues to fat cell membranes with their biologic activity, using the hypoglycemic shock bioassay. The binding curves indicated a limit of sensitivity of

about 50 pg. At Shanghai, in the Institute of Biochemistry, they have performed three-dimensional structural analysis of insulin using both 2.5- and 1.8-Å resolution. The models derived from this were essentially the same. A series of insulin derivatives have been prepared and tested. These may be summarized: C-terminal hexapeptide removed, 10 percent activity; C-terminal octapeptide removed, no activity; C_{23}-glycine replaced with l-amino acid, no activity; C_{23}-glycine replaced with D-amino acid, some activity; and phenylalanine replaced by nonaromatic amino acid, loss of activity. They demonstrated the necessity for an aromatic structure in place of Phe.

When Gly-Phe was added to the desoctoinsulin, activity decreased to 20 percent. When D-Ala-Phe was added to the desoctoinsulin, the activity was 40 percent that of natural insulin. When the terminal five amino acids were removed, complete activity was retained.

They theorized that the reason for loss of activity when the Gly^{23} was replaced was that the spatial configuration of the terminal "hook" was affected. Use of D-amino acids retained the initial spatial configuration.

The Institute of Biochemistry synthesizes oxytocin, vasopressin, angiotension II, thyrotropin-releasing hormone (TRH), and other peptides for use throughout the country.

A Protein Abortifacient

In accordance with Chairman Mao's teaching that Chinese medicine is a treasure house, the staff of the Institute of Experimental Biology, Shanghai, decided to study a plant described in a sixteenth century compendium of Materia Medica. The root of the plant induced menstrual flow and was also used to cure retention of fetal membranes. The plant identified for study, *Trichosanthes kirilowii*, family Cucurbitacea, was one of seven ingredients that were inserted vaginally.

The work was begun in 1973. A bioassay was developed using abortion of the 12-day pregnant mouse. Chromatography of an acetone extract over CM-sephadex G-50 yielded three components of which one peak was active. Chromatography of this peak on SDS-polyacrylamide yielded three bands, one of which was active. The calculated molecular weight was 18,000. On isoelectric focusing, the active component had a ρI of 9.4. The protein purification techniques were of high quality. Final purity of the trichosanthine (TS) was assumed from a single band in polyacrylamide gel electrophoresis and by immunoelectrophoresis against an antibody prepared in the sheep.

A variety of studies with TS were undertaken. The crude TS was labeled with ^{131}I. When the material was given intravenously, it was cleared rapidly with 100 percent of the radioactivity appearing in the urine in 24 hours. After intramuscular injection, only 40 percent was excreted in 24 hours. When given intraamniotically, there was no excretion of ^{131}I. They then examined the distribution of TS using indirect immunofluorescence. The drug was shown to be localized in the placenta. At 30 minutes, there was specific fluorescence in fetal vessels and to a lesser extent in the fetal red blood cells. At 24 hours, there was

specific fluorescence only in the cytoplasm of the trophoblast, none in the nucleus, and also in the villus, which then degenerated. This work was done using the active peak from the sephadex column.

^{131}I-labeled TS was localized in the kidney, liver, bowel, and placenta. By immunoautoradiography of the human placenta, there were specific granules in the margin of the villi. They then studied the effects of TS in 13 macaca rhesus monkeys and examined the monkeys 11 to 48 hours after injection. The villi showed injury with vesicular buds detached from the villi; the nuclei of the syncytiotrophoblasts were pyknotic and plump. Twenty-four hours after injection, there were severe injury and vacuolization; fibrin was noted in the intervillous space, and there were cell fragments. The spiral arterioles of the decidua were congested, and it was suggested that a deficiency of nutrition hastened the death of the placenta. The evidence was that the effect on the syncytiotrophoblast was decisive and that the hindrance to circulation was secondary. The cytotrophoblast and mesenchymal cells were unaffected at 48 hours; eventually the cytotrophoblast showed damage.

In human studies, HCG was measured by radioimmunoassay, using a double antibody technique with a detection limit of 10 ng/ml. Several hours after intramuscular or intraamniotic injection of TS, plasma HCG decreased, and after 24 hours the value was about half the original. Three days after the injection, it was near the threshold value. The hanges in urinary pregnanediol and estradiol were approximately parallel to the changes in chorionic gonadotrophin.

The effect of TS on the human trophoblast in tissue culture was studied by measuring chorionic gonadotrophin in the culture medium. The purified material was added to a 3-day culture at a concentration of 50 µg/3 ml. A small rise in HCG was seen four hours after adding TS. After that, there was no further rise, whereas there was a normal increase of HCG in control cultures. At 24 hours the cells had disintegrated, and at 48 hours most of the cells were gone. When TS was added to a mixed culture of placental and amnion cells, the amnion cells were normal three days later, but the placental cells had degenerated. Even with 100 µg of TS, the amnion cells were unaffected. However, even as little as 1 µg of TS had obvious effects on the human trophoblast. It was also suggested that the final mechanism of abortion was via the prostaglandins because when TS was given to mice in late gestation, prostaglandin inhibitors delayed abortion.

TS caused no changes in liver, kidney, or blood count in mice, dogs, or monkeys. The LD_{50} of the crude material was 2.6 mg per mouse. The cause of death was unknown. In man, the dose of the acetone precipitate is 5 to 8 mg. It is about 95 percent effective in causing abortion in three days in second trimester subjects. The injection causes local inflammation, tenderness, and fever to 38°C for one to two days. TS is also used for aborting dead fetuses, in treatment of ectopic pregnancy, and as an adjunct to therapy of choriocarcinoma. Data about efficacy in the last two conditions were not available. In view of its specificity of localization, it should be examined in human trophoblastic disease.

Trichosanthin is now being manufactured at a pharmaceutical plant and is freely available. No further clinical trials are planned. But in the words of the scientists, "We have progressed from theory to practice."

α-Fetoprotein

Liver cancer is an important cancer in China. It is not clear what the pathologic substrate is, but it does not seem to be alcoholic cirrhosis. Nevertheless, a history of liver disease is obtained frequently in patients with hepatic carcinoma.

In one presentation, a survey of almost 500,000 people for elevated α-fetoprotein was discussed. In order to do this, they developed a countercurrent immunoelectrophoresis kit using ^{125}I-alpha-fetoprotein (AFP). Normal subjects had less than 25 ng/ml; patients with hepatitis were below 300 ng/ml, the level used as the cutoff point for diagnosis. Barefoot doctors were taught to use the apparatus in the field using radioautography to measure the amounts of AFP present. The material was iodinated in Shanghai.

Results of the AFP screening are shown in Tables 9 and 10. Table 10 also indicates the level of diagnostic instrumentation available in Shanghai. In other work, the physicochemical properties of fetal and cancer AFP were compared. They were identical in molecular weights, polyacrylamide gel electrophoresis, isoelectric focusing, thermal inactivation, enthalpy and entropy of activation, amino acid composition, and composition of cyanogen bromide (CNBR) cleaved peptide fragments. Some of these data may be found in *China Medical Journal* 8, pp. 454 and 463 (1973).

TABLE 9 Results of AFP Screening

		Persons Examined	AFP Cases[a]	Incidence (per 100,000)
Natural population	Workers	281,795	32	11.36
	Commune members	135,849	25	18.40
	Total	417,644	57	13.65
Persons with liver diseases or history of liver diseases	Workers	921	2	217.16
	Commune members	75,739	251	331.40
	Total	76,660	253	330.03

[a]Positive.

TABLE 10 Comparison between the Mass Survey Group and the Clinical Group

	Mass Survey Group, %	Clinical Group, %
Without symptoms	53.5	0.4
General conditions fair	40.0	36.7
Radioactive isotope scanning positive	37.5	88.7
Ultrasonic detection positive	68.9	83.7
LDH and AKP isoenzymes positive	52.4	80.2
AKP positive (> 13 King's units)	54.5	70.3
Resection rate	20.6	8.0

APPENDIX A: DELEGATION ITINERARY

PEKING

Sunday, October 10

Arrive in Peking on Iran Airlines flight no. 801

Monday, October 11

All day	Peking Institute of Zoology, Academia Sinica

Tuesday, October 12

Morning	Institute of Microbiology, Academia Sinica
Afternoon	Palace Museum
Evening	Welcoming banquet hosted by Scientific and Technical Association at the Peking Duck Restaurant (Host: Chou P'ei-yüan)

Wednesday, October 13

All day	Institute of Materia Medica, Chinese Academy of Medical Sciences
Evening	Discussion with Chinese scientists at Peking Hotel

Thursday, October 14

Morning	Peking Maternity Hospital

Afternoon	Three groups: 1. Peking Pharmaceutical Factory 2. Summer Palace 3. Lectures by Delegation members
Evening	Reception given by U.S. Liaison Office

Friday, October 15

All day	Great Wall and Ming Tombs
Evening	Banquet for the STAPRC hosted by the Steroid Chemistry and Biochemistry Delegation at the Chengtu Restaurant

KWEILIN

Saturday, October 16

7:40 a.m.	Depart for Kweilin on CAAC flight no. 139, arriving at 12:55 p.m. (one-hour stopover in Changsha)
Afternoon	Visit to Seven Star Cave
Evening	Banquet hosted by vice-chairman of Revolutionary Committee of Kweilin

Sunday, October 17

All day	Boat ride on the Li River
Evening	Acrobatic performance

Monday, October 18

Morning	Kwangsi Chuang Autonomous Region Institute of Botany
Afternoon	Discussion with six doctors from hospitals in Kweilin
Evening	Film on Kweilin scenery

KWANGCHOW

Tuesday, October 19

Morning	Visit to Reed Flute Cave, Kweilin
1:45 p.m.	Depart on CAAC flight no. 338 for Kwangchow, arriving at 3:05 p.m.
Afternoon	Kwangtung Museum
Evening	Song and dance performance by Kwangtung People's Liberation Army Troupe

Wednesday, October 20

Morning	Chung-shan Medical College
Afternoon	Canton Trade Fair
Evening	Banquet at Pan Hsi Restaurant hosted by Kwangtung Provincial Science and Technology Association

Thursday, October 21

Morning	Visit to Lou Gang People's Commune near Kwangchow
4:05 p.m.	Depart on CAAC flight no. 535 for Shanghai, arriving at 6:00 p.m.

SHANGHAI

Friday, October 22

Morning	Two groups: 1. Shanghai Industrial Exhibit 2. Shopping and sight-seeing in Shanghai
Afternoon	Shanghai Institute of Organic Chemistry, Academia Sinica
Evening	Banquet hosted by a member of the Standing Committee of the Shanghai Municipal Revolutionary Committee

Saturday, October 23

Morning	Two groups: 1. Shanghai Institute of Organic Chemistry 2. Shanghai Antiepidemic Station
Afternoon	Two groups: 1. Shanghai Institute of Organic Chemistry 2. Shanghai Institute of Physiology

Sunday, October 24

All day	May 7 Cadre School for Scientific and Technical Workers

Monday, October 25

Morning	Shanghai International Peace Women and Children Protection Hospital
Afternoon	Two groups: 1. Shanghai Institute of Organic Chemistry 2. Shanghai Institute of Experimental Biology

Tuesday, October 26

Morning	Two groups: 1. Shanghai Institute of Materia Medica 2. Chung Shan Hospital, Shanghai Second Medical College
Afternoon	Shanghai Institute of Biochemistry
Evening	Film: White Haired Girl (Ballet)

Wednesday, October 27

Morning	Lectures on the pharmacology, synthesis, and clinical research on contraceptive no. 53, anordrin, at Shanghai Scientific and Technical Exchange Station
Afternoon	Two groups: 1. Shanghai Tumor Hospital 2. Shanghai Pharmaceutical Factory No. 4

Thursday, October 28

Morning	Three groups: 1. Lectures given by Delegation members at the Shanghai Science and Technology Exchange Station 2. Dr. Monroe Wall, revisit to Shanghai Institute of Materia Medica 3. Tsao Yang New Workers' Village
Afternoon	Free time

Friday, October 29

9:55 a.m.	Depart on CAAC flight no. 923 for Tokyo

APPENDIX B: RESEARCH INSTITUTES, HOSPITALS, AND FACTORIES VISITED

PEKING

Chinese Hosts at the Welcoming Banquet in Peking

周培源
Chou P'ei-yüan
Vice-chairman
Scientific and Technical Association

朱永行
Chu Yung-hang
Deputy Director
Bureau of Foreign Affairs
Scientific and Technical Association

冯因夏
Feng Yin-fu
Deputy Chief of Division
Bureau of Foreign Affairs
Scientific and Technical Association

苏风林
Su Feng-lin
Staff Member
Bureau of Foreign Affairs
Scientific and Technical Association

李明德
Li Ming-te
Staff Member
Bureau of Foreign Affairs
Scientific and Technical Association

苏全昌
Su Ch'üan-ch'ang
Interpreter
Peking Municipal Bureau of Science and Technology

王津
Wang Chin
Responsible Member
Institute of Materia Medica

Chang Chün-t'ien
Director of Scientific Research
Institute of Materia Medica

Ch'ien Yen-wen
Responsible Member, Administration
Peking Institute of Zoology

Ts'ao Yung-ch'i
Researcher
Peking Institute of Zoology

Chu Li-chung
Researcher
Peking Institute of Zoology
(Interpreter assigned to the Delegation)

Fa Yu-hua
Researcher
Institute of Microbiology

Hu Feng-hsien
Ministry of Foreign Affairs

Peking Institute of Zoology, Academia Sinica

After Liberation, two institutes were founded, one in zoology and one in entomology, both affiliated with the Academia Sinica. In 1962 the two institutes were merged, but during the course of the Cultural Revolution, in the move to decentralize the Academy, the new institute was put under the dual jurisdiction of the Academy and the Peking Municipal Revolutionary Committee.

At present there are more than 500 staff members, including over 300 scientific and technical research workers. Fifty percent of the staff are women. Seventy to eighty percent of the research is of an applied nature.

The institute is organized into ten research departments:

The Department of Insect Taxonomy, the Department of Vertebrate Taxonomy, and the Department of Invertebrate Zoology are concerned mainly with taxonomy. Their task is to investigate the animal resources of the country and compile data for a descriptive study.

The Department of Insect Physiology and the Department of Insect Ecology concentrate on insect control, particularly on studies of the most important agricultural pests, such as the parasitic wasp and the ladybug.

The Department of Insecticides and Toxicology does research on increasing the efficiency of insecticides and pheromones and on the beneficial effects of insects (e.g., studies on the juvenile hormone, particularly in relation to silkworms and silk production).

The Department of Animal Ecology does research in pastoral areas, particularly with regard to rodent pests.

The Department of Cell Biology conducts studies on the origin of cells and in the area of tumor immunology.

The Department of Endocrinology is concerned with reproductive physiology, particularly with investigating whether the gonadotrophins FSH, LH, etc., can promote fertility in animals of economic importance, such as the lamb, horse, and cow. These hormones are also used to induce spawning in fish. The Department also carries out studies on the physiology of acupuncture and its mechanism of action and is investigating insulin.

The Technology Department manufactures various instruments used in the institute, such as the electron microscope, high-speed ultracentrifuge, and gas chromatograph, and maintains and repairs these machines. Lectures presented were the following:

- Studies on the Application and the Physiological Action of LRH in Chinese Farm Fishes by Means of Histochemistry and Electron Microscopy by Chang Ch'ung-li
- The Actions of Prostaglandins in Termination of Early Pregnancy by Ch'en Ta-yüan
- Research upon the Relationship between Adrenal Corticosteroids and Acupuncture Anesthesia by Chu Ch'eng

The people whom we met at the Institute included

钱燕文 — Ch'ien Yen-wen
Responsible Member
Administration

张致一 — Chang Chih-i
Responsible Member
Department of Endocrinology

刘以训 — Liu I-hsün
Researcher
Department of Endocrinology

陈大元 — Ch'en Ta-yüan
Researcher
Department of Endocrinology

祝诚 — Chu Ch'eng
Researcher
Department of Endocrinology

张崇理 — Chang Ch'ung-li
Researcher
Department of Endocrinology

Institute of Microbiology, Academia Sinica

The institute, which is under the direct jurisdiction of the Academia Sinica, was founded in 1958 as an amalgamation of the Institute of Applied Microbiology and the National Culture Preservation Unit. Work is conducted in three major research areas: (1) medicinal studies, (2) classification of microbiological systems, and (3) basic research. Three hundred research workers are divided into four laboratories and a pilot plant: (1) laboratory for classification of microorganisms, which includes work on (a) collection of cultures, (b) exchange of cultures and systematic classifications, and (c) new antibiotics; (2) laboratory of genetics and virology, which includes work on the synthesis of T-RNA *in vitro* and studies on viral diseases; (3) laboratory concerned with application of microbial enzymes; and (4) fermentation laboratory, which includes studies on beneficial organisms, microbial products, and transformation of steroids. Lectures presented were the following:

- Studies on Ergosterol Production by Yeasts by Mao Kuei-chen
- Microbiological Transformation of Steroids by Fa Yu-hua

The people we met included

Leng Ping
Responsible Member
Institute of Microbiology

Mao Kuei-chen
Responsible Member
Administration

Fa Yu-hua
Researcher

Institute of Materia Medica, Chinese Academy of Medical Sciences

This institute was founded in 1958 and is one of seven research institutes of the Chinese Academy of Medical Sciences, which, in turn, belongs to the Ministry of Public Health. There are presently 300 scientific research workers divided into eight departments: botany, phytochemistry, pharmacology, synthetic chemistry, analysis, cancer research, antibiotics, and cultivation of medicinal plants. In addition, the institute operates an experimental plantation for medicinal herbs in the Peking suburbs.

The main task of the institute is to supply new drugs for common diseases, such as cancer, cardiovascular disease, influenza, and bronchitis. The staff is also studying contraceptives and antibiotics. Lectures presented to the Delegation were the following:

- Studies on the Steroidal Sapogenins of *Agave* by Ts'ung P'u-chu
- Some Pharmacological Actions of Fructus *Schisandra* by Pao T'ien-t'ung

- Isolation and Determination of the Chemical Structures of Some Constituents of Fructus *Schisandra* by Li Lien-niang
- The Structure, Determination, and Total Synthesis of Anisodine by Hsieh Ching-hsi
- Studies on the Production of Erometrine by *Claviceps microcephala* in Submerged Culture by Yang Yün-p'eng
- Investigation of the Antitumor Constituents of *Cephalotaxus hainansis* Li
  1. Isolation and Identification of the Alkaloids in the Plant by Hsüeh Chih
  2. Pharmacologic and Clinical Studies by Chi Hsiu-chüan

In addition to the above lecturers, our hosts at the institute were

Wang Chin
Responsible Member of the Institute

Chang Chün-t'ien
Director of Scientific Research

Peking Maternity Hospital

This is the OB-GYN hospital for the city of Peking. It has 250 beds and a medical staff of 273, of whom 97 percent are women doctors. The three major divisions are: Medical, Administrative, and Supply. Within the Medical Department are facilities for outpatients, OB-GYN wards, surgical wards, beds for infants, labor rooms, and technical laboratories for clinical work, cytology, pharmacology, psychology, pathology, physical therapy, and diagnostic X-ray. There are also facilities for consultation, prenatal care, immunization, and taking cervical smears for cancer and a fertility clinic.

There are approximately 700 outpatient visits per day, and the outpatient department is open six and one-half days a week. The birthrate is 350-400 per month, or approximately 4,500 deliveries a year. The average birth weight is 3,300 g. The mortality rate for newborns is 0.63 percent; the stillbirth rate is 0.2 percent; and the premature birthrate is 5.8 percent.

The main tasks of the hospital are (1) prevention; (2) serving the workers, peasants, and soldiers; (3) combining Chinese traditional and Western medicine; and (4) putting stress on the rural areas. The hospital trains barefoot doctors and offers short training courses for doctors from other hospitals.

The most commonly used contraceptive in this hospital is the norgestrel pill. For women who are newly married, the doctors recommend the oral contraceptive or condom. For women who have had one or two babies, the oral contraceptive or IUD is recommended. For women who have had two babies, have grown children, and are still under the age of 35, sterilization is recommended. After the age of 40, the IUD or condom is recommended. The doctors do not recommend that women over 40 take the pill or be sterilized.

Chinese traditional medicine is used to treat infertility and to treat the symptoms of menopause. Estrogens are not used in the menopause.

There are no medical students in this hospital. Interns come from among medical school graduates or from other hospitals to train for one year. Residents must have at least seven years training.

The people whom we met were

陳文珍 Ch'en Wen-chen
Deputy Chief
Peking Maternity Hospital

刘近富 Liu Chin-fu
Chief
Maternity Department

范惠民 Fan Hui-min
Chief
Planned Parenthood Department

Peking Pharmaceutical Products Factory

This factory, located in the northeastern part of Peking, manufactures chemical intermediates and finished drugs and packages them for distribution. Of the 2,000 workers, 50 percent are women. The products include ampules, tablets, infusions, synthetic vitamin C, and PAS. More than 200 finished products are manufactured, as well as 30 intermediates.

This factory has a history dating back to the Eighth Route Army in 1940. At that time, a hospital supply factory with about 100 people served with the Eighth Route Army. In 1949, these 100 people moved to Peking and built the plant and equipment themselves. Total production was only 1 million ampules and 2 million tablets per year. Today, with 2,000 workers, the production amounts to 1 million ampules in 1.5 days and 2 million tablets in one day. Production costs have been lowered substantially, the cost of penicillin being reduced from 1.5 to 0.14 yuan per 200,000 units and the cost of tetracycline reduced from 1.7 to 0.05 yuan per 250 mg.

Quality control is exercised by the Peking Municipal Bureau of Health, which inspects the factory every three months.

KWEILIN

Hosts for Our Visit in Kweilin

崔金才 Ts'ui Chin-ts'ai
Vice-chairman
Revolutionary Committee
Kweilin

索志英

So Chih-ying
Chief
Science and Technology Bureau
Revolutionary Committee
Kweilin

陈志辉

Ch'en Chih-hui
Deputy Chief
Science and Technology Bureau
Revolutionary Committee
Kweilin

吴鸿礼

Wu Hung-li
Staff Member
Foreign Affairs Department
Revolutionary Committee
Kweilin

禹伟民

Yü Wei-min
Staff Member
Foreign Affairs Department
Revolutionary Committee
Kweilin

刘小红

Liu Hsiao-hung
Student
Peking Foreign Language Institute

Discussion with Doctors from Kweilin Hospitals

During our three-day stay in Kweilin, an area noted for its scenic beauty, we did not have an opportunity to visit any medical facilities. We did arrange, however, a discussion one afternoon with seven physicians from the obstetrics and gynecology services of the Kweilin People's Hospital, the Kweilin Workers' Hospital, and the Kweilin Medical College Hospital.

Kweilin is located in the northeastern part of Kwangsi Chuang Autonomous Region. The city has seven general hospitals, with the largest having 600 beds and the others having from 300 to 500 beds. The People's Hospital has 450 beds, and the Workers' Hospital, 400 beds. In addition, there are about 250 commune and factory medical clinics located throughout the city and immediate surroundings.

In the People's Hospital and Workers' Hospital, there are about 80 to 100 beds in each allotted to obstetrical and gynecological cases, although neither hospital has a separate OB-GYN department. Each hospital performs about 2,000 deliveries per year. The average birth weight is 3.05 kg. The neonatal mortality rate is reported to be 0.3 percent. Approximately 3 percent of deliveries are by Caesarian section. Almost all births within the city occur within the hospital.

In the surrounding areas, trained midwives are available in every production team for home deliveries. Less than 50 percent of births are first births, reflecting a somewhat higher fertility in the rural areas than in the urban areas. The average age of the women at first birth is about 25 years.

Each of the two hospitals performs about 2,000 abortions per year (the same number as deliveries). Most are first trimester abortions. Also, each hospital performs about 200 to 500 sterilizations per year.

Family-planning services are delivered primarily at the level of the basic unit--the production team--largely by midwives who do both abortions and IUD insertions, as well as distribution of oral contraceptives. Some of the production teams have reported that 90 to 100 percent of the women are using some form of contraception. The most popular contraceptive method in this area is the IUD, which is usually inserted three months postpartum. Pills are less popular because of their "inconvenience" for rural women. The IUD is reported to have about a 4 to 10 percent failure rate, including pregnancies and expulsions.

The physicians reported that the oral contraceptive was introduced into this area in 1964. Clinical trials were not carried out in this area, prior to introduction of the pill into clinical use, because of adequate experience elsewhere in China. The physicians described three ways in which they learn of new drugs: popularization through a government-organized short course, informal communication among doctors, and organization of a group of physicians from one hospital to visit another hospital to learn special techniques and problems.

The physicians who participated in the discussion were

苏国太

Su Kuo-t'ai
Deputy Chief
Kweilin People's Hospital

林月英 (女)

Lin Yüeh-ying
Doctor, Maternity Department
Kweilin People's Hospital

張志英 (女)

Chang Chih-ying
Doctor, Maternity Department
Kweilin People's Hospital

郑宏志

Cheng Chih-hung
Chief, Maternity Hospital
Kweilin Workers' Hospital

楊碧清 (女)

Yang Pi-ch'ing
Doctor, Maternity Department
Kweilin Workers' Hospital

方以生

Fang I-sheng
Doctor
Kweilin Medical College Hospital

Kwangsi Chuang Autonomous Region Institute of Botany

This is a provincial research institute located about 30 km from the city of Kweilin. Prior to 1949 the institute was a part of Kwangsi University and had only five people on the staff, whose function was teaching, not research. At present there is a staff of 170, of whom 60 are workers, 80 are technicians, and 30 are administrators. Of the 80 technicians, about 60 are college graduates.

The programs of the institute cover phytochemistry, plant production, cultivation, and geobotany. There are four major areas of concern: Chinese medicinal herbs, taxonomy, chemistry, and collections. There are three research departments: botanical resources, cultivation, and phytochemistry.

The most important task is to study and exploit the plant resources of Kwangsi, which include 282 families, 1,671 genera, 6,047 species, and 200,000 collections. The living plant collection at the institute includes about 2,000 species, two-thirds of which are medicinal herbs. There is a library with 60,000 books (this figure probably includes journals). The institute has an experimental field of about 800 mou.

After 1969, since the Cultural Revolution, the institute has reported 29 research results, of which 27 are in areas of applied production. The institute staff has established 16 scientific experiment base stations in the rural areas and more than 30 scientific communication bases all over the province. Some of these stations are outside the province and there is cooperation with Peking, Hangchow, and Wuhan.

Two of the principal people who greeted us at the institute were

倪兴仁

Ni Hsing-jen
Vice-chairman
Revolutionary Committee

李树刚

Li Shu-kang
Professor of Taxonomy

KWANGCHOW

Hosts for Our Visit in Kwangchow

韓风鸣

Han Feng-ming
Deputy Chief
Scientific and Technical Association
Kwangtung Province

于侃

Yü K'an
Responsible Member of the Office
Scientific and Technical Association
Kwangtung Province

吴秀独

Wu Hsiu-ch'iang
Responsible Member
Foreign Affairs Department
Scientific and Technical Association
Kwangtung Province

陳华燮

Ch'en Hua-hsieh
Responsible Member
Cancer Hospital

Chung-shan Medical College, No. 1 Affiliated Hospital

This is one of five hospitals affiliated with the medical college. It is a general hospital with 700 beds and 1,100 staff members. Approximately 2,400 patients are treated daily in the outpatient department. The four tasks of the hospital are teaching, treatment, research, and training of lower-level workers.

Medical training in Chung-shan Medical College is a three-year program. About half the medical students come to the No. 1 Hospital for clinical training. In addition, the medical students spend about one year out of the three-year program in the countryside learning to serve the people. This is consistent with the policy of "open door" education, which was a result of the Cultural Revolution.

The No. 1 Hospital gives training in continuing education for physicians from the countryside and training for barefoot doctors. Each year the hospital accepts about 200 physicians from the countryside for a one-year training course. To train barefoot doctors, the hospital set up a 50-bed branch hospital in the countryside, which has trained 200 barefoot doctors to date.

Putting stress on the rural areas, the hospital sends out two medical teams to the countryside each year. Since 1969, more than 200 medical personnel have gone to the villages to give medical care and teach preventive measures.

We visited the obstetrical ward, which has 108 beds with three sections: obstetric and infant care, postpartum, and fertility control surgery. This hospital performs about 120 deliveries per month, 20-30 tubal ligations per month, and about 10 abortions per day.

Our hosts at Chung-shan Medical College were

梁贵尚

K'uang Ho-ling
Professor
Internal Medicine

黄承达

Huang Ch'eng-ta
Deputy Chief
Surgery

邓世南

Cheng Shih-lan
Chief
Eye, Ear, Nose, and Throat

SHANGHAI

Hosts for Our Visit in Shanghai

杨序昭 Yang Hsü-chao
Member
Shanghai Revolutionary Committee

许言 Hsü Yen
Responsible Member
Shanghai Science and Technology Association

郝洪贵 Hao Hung-kuei
Responsible Member
Administrative Office
Shanghai Science and Technology Association

陆关虎 Lu Kuan-hu
Staff Member
Shanghai Science and Technology Association

沈金荣 Shen Chin-jung
Staff Member
Shanghai Science and Technology Association

Shanghai Institute of Organic Chemistry, Academia Sinica

We visited this institute for four half-days; the first half-day was devoted to a general introduction to the work of the institute and a tour of the facilities. During the remaining three half-days, institute research staff members gave presentations on five topics: early work in steroid chemistry, microbiological transformations, synthesis of oral contraceptives, synthesis of ecdysone and ecdysone analogues, and synthesis of prostaglandins.

The institute was founded in 1950. Prior to Liberation there was no institute for organic chemistry in China, and there were only 20 organic chemists in the city of Shanghai. Today the institute staff numbers 1,200, of which 600 are research workers. About one-third of those 600 are women.

Before the Cultural Revolution, the institute was under the direct administration of the Academia Sinica in Peking. Today it is under the joint administration of the Academic Sinica and the Shanghai Municipal Revolutionary Committee.

The present research program embraces six areas:

1. Natural products: steroids, prostaglandins, nucleic acids, insulin, nucleotides, proteins from petroleum, and pheromones

2. Heteroelemental organic chemistry: perfluoropolyethylene, polytetrafluoroethylene, perfluorosurfactants, metal-organic compounds as catalysts, and boron chemistry
3. Extractives: phase-transfer agents and ion-exchange membranes
4. Liquid crystals: mainly cholesterol-based compounds used for diagnosis
5. Analytical chemistry: the institute has built its own instruments for elemental analysis and high-pressure liquid chromatography
6. Biochemistry

The people whom we met during our visit were

汪　　猷 — Wang Yu
Director

黄维垣 — Huang Wei-yüan
Researcher
Organic Chemistry

刘铸晋 — Liu Chu-chin
Researcher
Liquid Crystals

周维善 — Chou Wei-shan
Researcher
Steroid Chemistry

陶正城 — T'ao Cheng-o
Researcher
Steroid Chemistry

甾体化学 — Ch'en Chao-jung
Lecturer
Steroid Chemistry

微生物转化 — Chang Li-ch'ing
Lecturer
Microorganism Transformation

口服避孕药 — Wang Chung-ch'i
Lecturer
Oral Contraceptives

蜕皮激素 — Hsia K'o-min
Lecturer
Juvenile Hormone

前列腺素 — Liu Chih-yü
Lecturer
Prostaglandins

Shanghai Institute of Biochemistry, Academia Sinica

Like the Shanghai Institute of Organic Chemistry, this institute is under the dual jurisdiction of the Academia Sinica in Peking and the Shanghai Municipal Revolutionary Committee. It was established in 1950 as the Institute of Physiology and Biochemistry, which was then divided in 1958 into two separate institutes.

There are six major areas of the research institute: (1) chemistry of proteins and peptides (insulin structure and activity, polypeptide synthesis, and the combination of solid-phase and homogeneous peptide synthesis); (2) synthesis of nucleic acids; (3) immobilized enzymes; (4) cancer research; (5) mechanism of action of acupuncture anesthesia; and (6) plant viruses in rice, wheat, oranges, and mulberry. There is a biochemical products prep lab in which many common biochemicals, including protected amino acids and nucleotides, are made.

Our hosts for the visit and those who presented lectures were

Wang Ying-lai
Vice-chairman
Revolutionary Committee

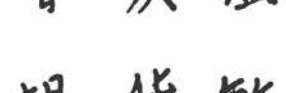
Kung Yü-t'ing
Researcher
Proteins and Polypeptides

P'an Chia-hsiu
Researcher
Proteins and Polypeptides

Tu Yü-ts'ang
Researcher
Proteins and Polypeptides

Chu Shang-ch'uan
Researcher
Structure and Function of Insulin

Tseng Ch'ing-i
Researcher
Cancer



Hu Hua-ming
Chief
Administration

Sha Hao-chung
Member
Workers' Propaganda Team for
Mao Tse-tung Thought
Chief
Scientific Research and Production
Department

Shanghai Institute of Materia Medica

This institute was originally affiliated with the Academia Sinica in Peking but was transferred to the jurisdiction of Shanghai Municipality. There are 500 staff members, of whom 400 are scientific research workers.

The Institute is divided into six research departments: (1) organic chemistry, (2) phytochemistry, (3) pharmacology, (4) antibiotics, (5) analytical chemistry, and (6) contraceptives. In addition, there is a workshop that produces antibiotics and intermediates.

The main research task of the institute is to work on the common diseases such as cancer, chronic bronchitis, and coronary disease and on contraception. Study of various contraceptive agents is approached from three aspects: study of Chinese traditional medicinal herbs; organic chemistry, particularly structure and synthesis of medicinal agents from natural sources; and research on antibiotics.

Our hosts for the visit to this institute were

高怡生 — Kao I-sheng
Responsible Member
Revolutionary Committee
Chairman
Synthetic Drug Research Laboratory

白東魯 — Pai Tung-lu
Vice-chairman
Synthetic Drug Research Laboratory

胥　彬 — Hsü Pin
Chairman
Pharmacology Research Laboratory

顧芝萍 (女) — Ku Chih-p'ing
Responsible Member
Pharmacology Division
Contraceptive Research Laboratory

賀贤国 — Ho Hsien-kuo
Vice-chairman
Phytochemistry Research Laboratory

陆敬心 — Lu Ching-hsin
Responsible Member
Administrative Office

Shanghai Institute of Physiology

This institute, which was administered by the Academia Sinica in Peking before the Cultural Revolution, is now solely under the jurisdiction of the Shanghai Municipal Revolutionary Committee. It is thus one of the research institutes affected by the decentralization of the Academy.

It is located in the building complex that also houses the Shanghai Institute of Biochemistry and the Shanghai Institute of Experimental Biology.

The institute was founded in 1950 as the Institute of Physiology and Biochemistry of the Academia Sinica, with 20 research workers. In 1958 it was divided into two institutes: Physiology and Biochemistry. The Institute of Physiology was placed under the jurisdiction of Shanghai Municipality, as was mentioned above.

The staff of the institute numbers about 360 and is divided among five departments and a pilot plant (workshop): (1) neuromuscular physiology (muscular disease, backache, coronary disease, and neurotoxin, especially snake venom); (2) brain research (acupuncture anesthesia mechanism of action, learning and memory in relation to the mental development of children); (3) physiology of sense organs (influence of loud noise on hearing in connection with environmental control), physiology of vision (color perception and electroretinogram), and bionics (study of the making of artificial hands); (4) high-altitude physiology (study of the adaptation of the human body in high altitudes and the prevention of mountain sickness); and (5) physiology of reproduction (contraceptives).

Our hosts at the institute and those who presented lectures were

蔡睟盎

Ts'ai Ts'ui-ang
Vice-chairman
Revolutionary Committee
Division Responsible Member
Scientific Research and Production Division

周祥生

Chou Hsiang-sheng
Member
Workers' Propaganda Team for Mao Tse-tung Thought
Deputy Division Responsible Member
Scientific Research and Production Division

譚德培

T'an Te-p'ei
Responsible Member
Brain Research Laboratory

趙志奇

Chao Chih-ch'i
Responsible Member
Brain Research Laboratory

英建屏

Ying Chien-p'ing
Scientific Researcher
Brain Research Laboratory

谢衷明

Hsieh Chung-ming
Responsible Member
Reproductive Physiology Research Laboratory

危友民 — Wei Yu-min
Scientific Researcher
Reproductive Physiology Research Laboratory

鮑　璚 — Pao Chün
Scientific Researcher
Reproductive Physiology Research Laboratory

潘堯萍 — P'an Mao-p'ing
Factory Worker

徐秉烜 — Hsü Ping-hsüan
Scientific Researcher
Brain Research Laboratory

唐良全 — T'ang Liang-ch'üan
Worker
Scientific Research and Production Division
Revolutionary Committee

Shanghai Institute of Experimental Biology

Like the Shanghai Institute of Physiology, the Shanghai Institute of Experimental Biology was originally affiliated with the Academia Sinica in Peking but during the Cultural Revolution was transferred to the control of the Shanghai Municipality. It is in the same building complex as are the Institutes of Physiology and Biochemistry.

There are three research departments: (1) antitumor research, with three sections working on tumor immunology (immunotherapy, particularly in liver cancer), nucleic acids of tumors (to determine the derivatives of nucleic acids and the mechanism of carcinogenesis), and viral and chemical carcinogens; (2) physiology of reproduction (investigation of abortion induction with plant proteins; and (3) structure and function of chromosomes and nucleic acids.

The three departments, therefore, concentrate their research on the fields of cancer, reproduction, and genetics. The staff numbers about 300.

Our hosts at the institute and those who gave presentations were

毛祖成 — Mao Tsu-ch'eng
Vice-chairman
Revolutionary Committee

林志春 — Lin Chih-ch'un
Responsible Member
Scientific Research and Production Division

徐国仁 Hsü Kuo-jen
Vice-chairman
Second Research Laboratory

曾弥白 Tseng Mi-pai
Research Worker
Experimental Morphology

熊用周 Hsiung Yung-chou
Research Worker
Organ Morphology and Immunology

蒋天骥 Chiang T'ien-chi
Research Worker
Chemistry, Gas Chromatography

高　慧 Kao Hui
Researcher
Radio Autography

王亚辉 Wang Ya-hui
Researcher
Immunochemistry

Shanghai International Peace Women and Children Protection Hospital

This is a specialized hospital for obstetrical and gynecological services with 400 beds and four departments: obstetrics, gynecology, birth control, and neonatal. There are approximately 60 doctors and 200 nurses among the staff. This hospital performs about 3,000 deliveries per year, 2,000 abortions per year, and 1,000 tubal ligations per year. The most common contraceptive recommended by the physicians is pill no. 1.

The hospital sends medical teams to the countryside, to the factories, and to the suburbs of Shanghai. It gives instruction about medical care and educates women about menstruation, pregnancy, labor, and lactation. It propagates birth control methods and gives regular gynecological exams. It also trains barefoot doctors.

Our hosts during our visit to this hospital were

張佩珠 Chang P'ei-chu
Deputy Chairman
Revolutionary Committee

陳美朴 Ch'en Mei-p'u
Doctor
Maternity Department

王世瑄 Wang Shih-hsüan
Doctor
Maternity Department

陳惠英 Ch'en Hui-ying
Doctor
Pediatrics Department

杨秉炎 Yang Ping-yen
Doctor
Pathology Department

陳惠贤 Ch'en Hui-hsien
Doctor
Planned Parenthood

薛葵宝 Hsüeh K'uei-pao
Staff Member
Revolutionary Committee

Chung Shan Medical College Hospital, Shanghai

This hospital, founded in 1936, is affiliated with the Shanghai First Medical College. It has 750 beds, 253 physicians, 354 nurses, and 194 technicians. It is a general hospital with departments of medicine, surgery, OB-GYN, radiology, and Chinese traditional medicine.

The hospital performs about 1,000 deliveries annually, and about 30 to 40 abortions per month. The most commonly prescribed contraceptives were pill no. 1 and pill no. 2. This hospital does not engage in clinical research with contraceptive techniques.

This hospital is only one of five hospitals affiliated with the Shanghai First Medical College. The other hospitals include a 750-bed general hospital and three specialized hospitals: pediatrics (200 beds); ear, nose, and throat (200 beds); and OB-GYN (300 beds).

Our hosts for the visit were

仇红宝 Ch'ou Hung-pao
Vice-chairman
Revolutionary Committee

范安国 Fan An-kuo
Member
Revolutionary Committee

周毓棻 Chou Yü-fen
Chief
Obstetrics and Gynecology

庄汉忠 Chuang Han-chung
Chief
Laboratory

褚駿仁 Chu Chün-jen
Deputy Chief
Cardiovascular

Shanghai Tumor Hospital

This is a specialized cancer hospital for the city of Shanghai, and it also serves as a referral hospital for cancer cases from other parts of the country. Within the hospital is a tumor research institute.

The staff of the hospital numbers over 700 with 420 beds and departments specializing in surgery, internal medicine, radiotherapy, gynecology, pathology, and radioisotope ultrasonic detection and an outpatient clinic and clinical laboratories. Last year over 5,000 people from all over China were treated at the hospital. Every day 800 to 900 outpatients are seen, among whom about 400 come for radiotherapy.

The departments specialize in the following ways: Surgery includes thyroid, breast, soft tissue, and gastrointestinal cancers; radiotherapy includes nasopharyngeal and esophageal cancers; gynecology includes cervical cancer and choriocarcinoma; and internal medicine includes liver cancer (treatment with Chinese traditional medicine and Western medicine).

The hospital sends medical teams to the countryside to establish a network for tumor diagnosis. In the past few years, 47 teams have been sent out, more than 450 medical personnel participating.

The hospital now runs a college for doctors who come for postgraduate training, barefoot doctors, and factory doctors. There are classes for doctors trained in Western medicine to learn Chinese traditional medicine.

The most common cancers seen in this hospital are esophageal and nasopharyngeal, because this is a referral hospital for cases from all over China.

The most common cancers in Shanghai, in order of importance, are the following: stomach, lung, liver, esophageal, rectal-colon, rectal, and colon. For men the incidence of stomach cancer is highest, followed by lung and liver cancers. For women, the incidence of cervical cancer is highest, followed by breast, stomach, and lung cancers.

According to the doctors at the Shanghai Tumor Hospital, the other research institutes on cancer in the city of Shanghai are the Shanghai Institute of Biochemistry, the Shanghai Institute of Materia Medica (Division of Tumor Pharmacology), and a research institute located in the Tumor Hospital itself. Cooperative work among all these institutes in Shanghai is now under way.

Our hosts at the Shanghai Tumor Hospital were

Li Yüeh-yün
Surgery

Yü Lu-i
Internal Medicine

Ts'ao Shih-lung
Radiology

Ch'en Mei-fang
Radiology

严根宝 Yen Keng-pao
Administration

谢超义 Hsieh Ch'ao-i
Administration

Shanghai Municipal Antiepidemic Station

The Shanghai Antiepidemic Station, which operates under the Municipal Bureau of Health, is responsible for the prevention of infectious diseases and the control of environmental hygiene. Our visit to this station gave us an overview of epidemic and disease control measures as they are conducted in urban areas.

The station has eight departments: antiepidemic, disinfection, environmental hygiene, food and school hygiene, industrial hygiene, laboratory for bacteriology and virology, statistics and data collection, and administration. Of the more than 400 staff members, three-fourths are doctors and medical technicians.

The major activities of the station include water and food management, environmental hygiene, surveillance for selected infectious diseases, and periodic vaccinations. The work of the station is augmented by a network of coordinated activities extending to the smallest urban administrative units. For example, smaller antiepidemic stations are located in each of the 10 districts of Shanghai and in each of the 10 surrounding rural counties. Disease control activities are also carried out by hospitals. Every neighborhood and commune has a group engaged in health protection work. Every basic unit, such as a factory or production brigade, has a health protection group. Barefoot doctors are also engaged in preventive activities.

Our hosts at the Shanghai Antiepidemic Station were

蒋兴权 Chiang Hsing-ch'üan
Chairman
Revolutionary Committee

夏万兴 Hsia Wan-hsing
Staff Member
Administration

梅展 Mei Chan
Staff Member
Quarantine Department

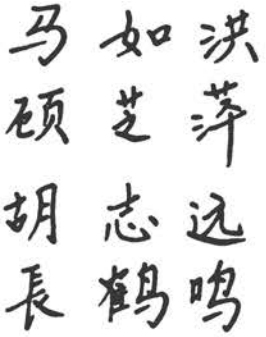
史济德 Shih Chi-te
Staff Member
Environment/Sanitation Department

席德基 Hsi Te-chi
Staff Member
Sterilization Department

Shanghai Lectures on Pill No. 53, Anordrin

On the morning of Wednesday, October 27, the Delegation was invited to the Shanghai Scientific and Technical Exchange Station to hear lectures presented by Chinese scientists on the development of the new contraceptive drug anordrin, otherwise known as pill no. 53. Information about this drug appears in chapter 4 of this report under the heading, "Specific New Contraceptive Developments: Anordrin."

Those who presented lectures on anordrin were



Ma Ju-hung
Shanghai Institute of Materia Medica

Ku Chih-p'ing
Shanghai Institute of Materia Medica

Hu Chih-yüan
Shanghai No. 6 People's Hospital

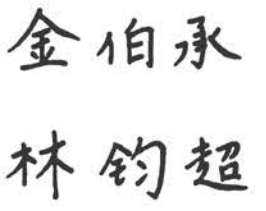
Ch'ang Ho-ming
Shanghai Institute of Medical Industry

Shanghai Pharmaceutical Factory No. 4

This factory has been in existence for over 100 years. It was formerly owned by foreign capitalist interests and prior to Liberation employed only 160 people. Production was restricted to simple remedies such as eyedrops, cough syrups, and tinctures of camphor and ginger. In 1958, during the Great Leap Forward, great changes took place. The factory began to produce synthetic chemicals such as chloramphenicol, and drugs were prepared from bile acids. Streptomycin production was begun also. Since the Great Leap Forward, all raw materials were available from within China.

After the Cultural Revolution, further expansion took place. The factory began to produce chloromycetin, streptomycin, dihydrostreptomycin, and kanamycin, as well as phenobarbitone and other medicinal products. The volume of production exceeds 500 tons of antibiotics annually, and the factory employs 1,600 people. The factory meets all domestic requirements and has material for export.

Our hosts at the factory were



Chin Po-ch'eng
Chairman
Revolutionary Committee

Lin Chün-ch'ao
Member
Revolutionary Committee

張玉妹 (女) Chang Yü-mei
Technician

丁珠娟 (女) Ting Chu-chüan
Technician

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