A clinical look at the problem of drugs in pregnancy and their effect on the fetus

SUMNER J. YAFFE,* MD

Summary: The first annual W. E. Upjohn Lecture concerned itself with the interrelationship between administration of drugs to the pregnant woman and fetal outcome. The epidemiology of drug intake (both prescibed and self-administered drugs) during pregnancy is reviewed, using data derived from several surveys conducted both in the United States and in Scotland. The complexities of establishing a causal relationship between drug intake during pregnancy and effects upon the fetus are considered. Special emphasis is given to the adverse effects of aspirin and cigarette smoking. The shortage of data is critical and the need for further research is stressed.

Résumé: *Considération clinique sur le problème des médicaments pris durant la grossesse et leur effet sur le fétus*

La première conférence annuelle W. E. Upjohn s'intéressait à la relation existant entre l'administration de médicaments à la femme enceinte et leur effet sur le fétus. On y a passé en revue l'épidémiologie de la question des médicaments pris pendant la grossesse (tant ceux obtenus par ordonnance que les autres), utilisant à cet effet les renseignements provenant de plusieurs enquêtes, américaines et écossaises. On a admis qu'il s'agissait d'un problème complexe, rendant difficile l'établissement d'une relation de cause à effet. On y a souligné particulièrement les effets nocifs de l'aspirine et de l'usage de la cigarette. La pénurie de données sur le sujet atteint un point critique qui exigera de nouvelles recherches.

Drugs are an inescapable element in the environment of 20th-century man (and woman) and are likely to remain so in the foreseeable future. Contact with drugs begins before birth for our species in most advanced countries and the degree and variety of contact appear to be increasing. Up to now drugs have been used during pregnancy mainly to treat maternal disease. Under these circumstances it is evident that the fetus will also function as a drug recipient. Consequently, it is not surprising that such endeavours often produce unexpected and occasionally tragic results in the developing fetus for whom the drug was not intended in the first place.

Before 1961 most reports of drug effects on the fetus were concerned with the perinatal period, particularly with the effect of narcotics and analgesics on the fetus at the time of delivery. Thalidomide changed that and, if any positive action was derived from that disaster, it was that attention was focused on the possibility that other drugs less teratogenic than thalidomide had not yet been recognized as such. Until the thalidomide catastrophe there was not a great deal of interest in the subject and hence there had been little clinical research into the problem. We now know that any drug or chemical substance administered to the mother is able to penetrate the placenta to some extent unless it is destroyed or altered during passage. Placental transport of maternal substances to the fetus and of fetal substances to the mother is established at about the 5th week of embryonic life. Foreign substances cross the placenta, primarily by simple passive diffusion, to establish an equilibrium between the maternal and fetal blood, with the rate of passage primarily dependent upon the concentration gradient. The "placental barrier" is a myth and the use of this term should be discontinued.

Hence, administration of a drug to a pregnant woman presents a unique problem to the physician: not only must he consider maternal pharmacologic mechanisms, but also he must be constantly aware of the fetus as a potential recipient of the drug. When malformations observed in an infant at birth are apparently the result of drug administration during the first trimester the drug is considered to be a teratogen.

Drugs in early pregnancy

Experiments with laboratory animals have yielded considerable information regarding embryopathic effects of drugs but unfortunately these experimental findings cannot be extrapolated from species to species or even from strain to strain within the same species, much less from animals to man. For example, ordinary animal tests for teratogenicity would not have incriminated thalidomide (except in the rabbit) but would have incriminated aspirin, which is not known to be a human teratogen. It is also apparent that a single teratogen can produce a variety of malformations and conversely the same malformations can be caused by a variety of teratogens. Hence, because of

Presented at the 107th annual meeting of The Canadian Medical Association, June 28, 1974 as the first annual W. E. Upjohn Lecture

*Professor of pediatrics, State University of New York at Buffalo and Children's Hospital of Buffalo

Reprint requests to: Dr. Sumner J. Yaffe, Children's Hospital, Division of pharmacology, 219 Bryant St., Buffalo, NY 14222, USA

the lack of specificity of both cause and effect, it is difficult to establish in man a relationship between events during pregnancy and malformations manifested after birth. It has been said that the teratogenic nature of thalidomide was recognized only because the drug produced a rare and rather specific combination of defects. If it had produced a more common type of defect, such as cleft palate or harelip, it probably would not have been suspected. It may well be that drug and chemical contacts during early intrauterine life are responsible for the defects in a number of all malformed infants.

The difficulties of ascertaining the relationship between drug administration and congenital malformations are compounded also by the fact that people in the Western world are unaware of their own drug and chemical exposures. Yet this would seem to be a first requirement in studying this problem.

Studies on drug use during pregnancy

Recently several investigators have tried to assess the number of drugs ingested by women during pregnancy.[1,2] From Table I the similarity in prevalence of consumption of various drugs during pregnancy between Scotland and the United States is quite apparent but there are some differences that reflect regional practice habits. In the Texas study the mean number of drugs consumed by the 156 women followed was 10.3;[1] in Scotland 97% of 911 mothers were prescribed drugs during pregnancy.[2] A third study, reported from California shortly after the thalidomide tragedy, demonstrated that drug consumption during pregnancy had not decreased.[3]

Table I—Prevalence of drug consumption during pregnancy

Drug type	Study area	
	Scotland (%)	Texas (%)
Analgesic	63	64
Antihistamine	7	52
Diuretic	18	57
Antibiotic	16	41
Antacid	34	35
Sedative	28	24
Antiemetic	16	36
Iron	82	41

Preliminary analysis of the prospective collaborative study of 50 000 pregnancies conducted by the National Institutes of Health in the United States reveals that 900 pharmacologic compounds were used by mothers during pregnancy.[4] Table II lists the different drugs used during different stages of pregnancy. During early pregnancy bronchodilators and antihistamines are employed to control bronchospasm, a symptom more prominent at that time than in later pregnancy. The analgesics and barbiturates used in late pregnancy are most often prescribed for headaches and functional and emotional disturbances. Dyspeptic symptoms, treated with antacids, occur predominantly later in pregnancy, as does edema.

The duration of consumption of drugs during pregnancy and the timing of drug administration are important if one is to ascertain clinical effects upon the fetus. In the Scottish study two of every three mothers took aspirin in full dosage for 6 weeks during pregnancy. Barbiturates were the next most widely used single drug in terms of doses consumed per pregnancy. In fact the Scottish study demonstrated that every mother consumed one drug in normal daily dosage throughout 60% of her pregnancy.

Teratogenic drugs

Table III lists those drugs that have been classified as possibly teratogenic; that is, those that possibly will essentially affect the embryo during the first 3 months of pregnancy. The list is very short because no drug used in therapy has shown the same teratogenic potency as thalidomide. It should be emphasized again that it was only after nearly 4 years of extensive use that the profound teratogenic effects of that drug were recognized. Recognition was also made easier because the limb deficiencies that thalidomide caused were otherwise very rare abnormalities.

The powerful folic acid antagonists aminopterin and methotrexate are also abortifacients. If they fail as such, the liveborn infant who has been subject to their influence is very likely to be severely malformed. Given early in pregnancy, synthetic progestogens and androgens can cause masculinization of the female fetus. Progestational agents given in large doses over prolonged periods of time, usually in the treatment of threatened abortion, account for the majority of cases, but the incidence of masculinization under these circumstances is probably less than 1%. A very delayed effect of diethylstilbestrol has been the occurrence of carcinoma of the vagina in female offspring 20 years after their mothers had received this drug during pregnancy.[5]

The remaining drugs on the list have been implicated in several case reports as responsible for the production of congenital malformations. With the exception of the powerful folic acid antagonists (in prolonged use) and thalidomide, for most of the drugs listed the evidence suggests no more than a slight increase in the risk of teratogenicity; the great majority of children born to mothers taking these drugs will be normal.

Drugs affecting fetal and neonatal function

Table IV is only a partial listing of drugs that have been identified as affecting the functioning of the fetus, usually late in pregnancy or at the time of delivery. The narcotics, inhalational and local anesthetics, and barbiturates in large doses may depress the fetus's central nervous system so that respiration is not adequately established. Addiction of the mother to morphine, heroin or alcohol may result in withdrawal symptoms such as hyperirritability, vomiting and shrill cry in the baby after delivery. Diazepam administered to the mother may result in hypothermia and hypotonia in the infant. Atropine may exert a sympathomimetic effect. Succinylcholine may result in a temporary ileus. Reserpine may cause nasal congestion associated with

Table II—Drugs used during pregnancy

In early pregnancy	In late pregnancy	Throughout pregnancy
Antiemetics	Antacids	Antibiotics
Antihistamines	Analgesics	Cough medicines
Appetite suppressants	Barbiturates	Iron
Bronchodilators	Diuretics	Tranquillizers
Hormones	Hypnotics	
	Sulfonamides	
	Vitamins	

Table III—Possibly teratogenic drugs

Aminopterin	Aspirin
Methotrexate	Phenytoin
Progestogens	Dexamphetamine
Estrogens	Antacids
Androgens	Nicotinamide
Barbiturates	Iron
	Thalidomide

Table IV—Drugs affecting fetal and neonatal function

Morphine	Tetracyclines
Heroin	Streptomycin
Meperidine	Thiazide diuretics
Inhalation anesthetics	Warfarin
Local anesthetics	Dicumarol
Alcohol	Diphenylhydantoin
Barbiturates	Antithyroid drugs
Diazepam	Nitrofurantoin
Atropine	Chlorpropamide
Succinylcholine	Vitamin K
Reserpine	Smoking

excessive mucus production, lethargy and bradycardia.

Local anesthetics

Local anesthetics are the most widely used anesthetic agents in obstetrics. Their popularity can be attributed in part to the widespread belief that they have few depressant effects on the fetus and newborn. Shnider and Way,[6] however, have shown that lidocaine does cross the placenta and may cause CNS depression in the newborn. They determined the concentration of lidocaine in maternal arterial and fetal umbilical vein blood at the time of delivery, after multiple paracervical and pudendal injections of the anesthetic at varying times before delivery. The concentration in maternal blood tended to be higher than that in fetal blood, but more important was the actual concentration in fetal blood; CNS depression was observed in only 4 of the 23 infants in this series, each of whom had a blood lidocaine concentration of more than 2.5 μg/ml. It is also important to realize that any route of administration (caudal or lumbar, epidural, continuous epidural or paracervical block) will allow sufficient anesthetic agent to cross the placenta.

Teramo and Rajamäki[7] in Helsinki obtained frequent measurements of the concentration of mepivacaine in maternal and fetal blood and found that an equilibrium was established. They found, from serial measurements of acid-base balance, that paracervical blockade with amide-type local anesthetics tends to produce fetal bradycardia and acidosis. Although these changes are usually transient, perhaps we should take another look at the use of these drugs as routine anesthetic agents during labour.

Obstetric analgesics

The goal in obstetric analgesia is to provide pain relief for the mother without affecting the fetus or the delivery process. Meperidine, a synthetic substitute for opiates, has been hailed by many as the safest non-narcotic strong analgesic for both mother and infant. Nevertheless, a demonstrable depression of neonatal respiration and oxygen saturation has been noted. Both the time interval before the infant sustains his own respiration and the Apgar score appear to be related to the administration of the drug and more particularly with the time of administration. The peak depressive effect appears when the drug is administered 2 to 3 hours before birth. This delayed effect can be explained by the slow rate of passage of meperidine, not only across the placenta but also across the blood-brain barrier of the fetus.

It has been assumed from clinical observation that depression of the newborn from maternal meperidine is self-limited and of several hours' duration. This conclusion is based on the misapprehension that infant functioning can be adequately evaluated by such gross indices as respiratory function, muscle tone and motor activity. The use of more sophisticated measures of infant psychophysiologic functioning indicates that effects of the analgesic may be detected up to 30 days after delivery. The ability to respond to stimuli and the learned inhibition of response were significantly decreased in treated infants. The duration of these effects and their ultimate consequence for the child are not clear at present.

Aspirin

Aspirin is generally used freely throughout pregnancy. Although the activity of the mechanisms for its metabolism (glucuronide formation and coupling with glycine) is low in the fetus and newborn, and high concentrations of unaltered salicylate are found in cord blood immediately after delivery, overt toxic effects on the fetus and newborn have rarely been noted. This is perhaps related to the difficulties of surveillance of drug ingestion during pregnancy and also to the limited scope of our observation of adverse effects — two factors of tremendous importance.

Recently, a prospective study has been reported in which accurate prenatal drug histories were obtained in 42 pregnant women during the last 2 months of gestation and compared with clinical and laboratory studies performed post partum.[8] In 14 newborn infants whose mothers had taken more than 5 grains of aspirin during the week before delivery, there was significant evidence of platelet dysfunction and diminished factor XII (Hageman factor) in the cord blood. There was a significant difference between mean factor XII activity in the drug group (46%) and that in the control group (62%). A direct correlation was also observed between factor XII activity and the interval between the last ingestion of aspirin and birth. These findings occurred after ordinary doses of aspirin had been ingested by the mother as long as 2 weeks before delivery. There was a significant lack of platelet aggregation in both newborn and mother when aspirin had been ingested and this was also related to the time of administration of aspirin; no such lack was detected when the aspirin had been ingested more than 2 weeks before delivery. Diminished factor XII activity is of uncertain clinical importance since bleeding in patients with a Hageman trait is unusual. Aspirin-induced platelet dysfunction, however, may have clinical relevance, particularly during difficult traumatic deliveries. Hemorrhagic phenomena in this series were noted at birth in 3 of the 14 aspirin-exposed newborn. One newborn had transient gastrointestinal tract bleeding (guaiac-positive stools), another had a cephalohematoma and the third had bilateral periorbital purpura. The bleeding in each case resolved spontaneously without residual morbidity. It would appear prudent to avoid aspirin during the week before delivery until the clinical significance of these findings is further evaluated.

As far as drug surveillance during pregnancy is concerned, aspirin also affords another excellent illustrative example. In a series of 272 consecutively delivered infants at the University of Alabama Medical Center in Birmingham, Palmisano and Cassady[9] determined the concentration of salicylate in cord serum. After delivery several women were asked whether or not they had taken aspirin before labor and delivery. The answer was uniformly negative, yet 9.5% of the infants had significant concentrations of salicylate (> 1 mg/dl) in cord blood. When the investigators rephrased their question and asked about the intake of specific proprietary products the truth came out. This points out the difficulties one encounters in eliciting an obstetric drug history. It has been suggested that, instead of asking about the ingestion of certain drugs by generic name, terms be employed that the pregnant woman will understand, for example "pain medication" for headache and arthritis, "heart medicine", "water pills" for diuretics, "blood pressure medicine" for antihypertensives and "blood thinner" for anticoagulants.

Smoking

It is now universally agreed that cigarette smoking during pregnancy affects fetal development. Many investigators have demonstrated that smokers produce smaller babies, have a greater incidence of premature delivery and an increased incidence of abortion, stillbirth and neonatal death. Opinions vary as to the exact meaning of these observations and doubts have been cast on their validity because of inevitable differences of social class and background. However, these factors have been taken into consideration in prospective studies and it is quite evident that the clinical findings can be justifiably attributed to the smoking. Furthermore, there are a number of animal experiments that have indicated nicotine to be the principal toxic product in tobacco.[10] Unfortunately, the

doses that have to be employed are much greater than those attained during smoking in man. Nicotine's action in this instance is probably via its effect on blood supply to the fetus.

More recent studies have correlated the smoking habits of a group of pregnant women with the level of carboxyhemoglobin in the circulating blood.[11] Furthermore, when simultaneous estimates of maternal and fetal carboxyhemoglobin levels were made at delivery the fetal levels were on the average 1.8 times higher than the respective maternal level. Carboxyhemoglobin is a stable compound formed when carbon monoxide combines with a portion of hemoglobin. The total oxygen-carrying capacity of both maternal and fetal blood is thereby reduced. In addition, the oxygen dissociation of the remaining active oxyhemoglobin is impaired by the presence of carbon monoxide, so that less oxygen is available to the tissues. Fetal blood normally requires a tissue oxygen tension of about 18 mm Hg to provide an oxygen saturation of 35%, whereas blood containing carboxyhemoglobin requires a much lower tension to deliver a similar quantity of oxygen to the tissues. Also, maternal arterial oxygen tension is reduced by a direct effect of carbon monoxide on the pulmonary vasculature. These factors must certainly contribute to the low birth weight and other reported consequences of smoking during pregnancy.

The dilemma

What is the solution to the dilemma the physician faces? How can he advise his pregnant patient as to whether any particular drug is likely to be dangerous to her fetus? Certainly animal tests are not predictive and cannot protect the patient, particularly in a society that consumes medication en masse upon the insistence of the TV screen rather than upon physician prescription. Labels on medicines warning the doctor and his patient that the enclosed pills are "not to be taken during pregnancy" will do no good. The chief source of protection lies in an understanding by the obstetrician of his role as the pediatrician of the fetus. In this situation he must lead the crusade for a widespread acceptance of a sensible attitude towards drug consumption during pregnancy. This period can be rendered safe only by practising therapeutic nihilism for all women between the ages of 14 and 40. In view of the fact that most people in our contemporary society (as well as their physicians) seem to regard life as a drug-deficient disease, to be cured or even endured only with the aid of innumerable medica-

tions, this will be a slow and difficult crusade. We must also keep in mind that with the advent of intrauterine diagnosis the need for prescription of drugs to the pregnant woman for the treatment of her fetus is already at hand. We must acquire sufficient data from human studies to make fetal therapeutics as founded upon fact as is therapeutics in the adult organism. This requires more research into, and a greater understanding of, the disposition of drugs within the maternal–fetal–placental unit and the effects of drugs upon the fetus. Furthermore, this information can be gained only from studies in pregnant women and at this time the social and political climate is decidedly against fetal research.

It has been estimated[12] that 75. to 85% of all therapeutic agents are not approved for use in infants, children and pregnant women because conclusive evidence of their safety and efficacy in this population is not available, but many are administered in ignorance with potential hazard to the patient. Resolution of this vexing problem will be achieved only if fundamental and clinical investigative activities in the area of obstetric and pediatric pharmacology are expanded in many directions.

References

1. HILL RM: Drugs ingested by pregnant women. *Clin Pharmacol Ther* 14: 654, 1973
2. FORFAR JO, NELSON MM: Epidemiology of drugs taken by pregnant women: drugs that may effect the fetus adversely. Ibid, p 632
3. YERUSHALMY J, MILKOVICH L: Evaluation of the teratogenic effect of meclazine in man. *Am J Obstet Gynecol* 93: 553, 1965
4. SLONE D, HEINONEN OP, MONSON RR, et al: Maternal drug exposure and fetal abnormalities. *Clin Pharmacol Ther* 14: 648, 1973
5. HERBST AL, ULFELDER H, POSKANZER DC: Adenocarcinoma of the vagina: association of maternal stilbesterol therapy with tumor appearance in young women. *N Engl J Med* 284: 878, 1971
6. SHNIDER SM, WAY EL: Plasma levels of lidocaine (Xylocaine®) in mother and newborn following obstetrical conduction anesthesia. *Anesthesiology* 29: 951, 1968
7. TERAMO K, RAJAMÄKI A: Foetal and maternal plasma levels of mepivacaine and foetal acid-base balance and heart rate after paracervical block during labour. *Br J Anaesth* 43: 300, 1971
8. BLEYER WA, BRECKENRIDGE RT: Studies on the detection of adverse reactions in the newborn. *JAMA* 213: 2049, 1970
9. PALMISANO PA, CASSADY G: Salicylate exposure in the perinate. *JAMA* 209: 556, 1969
10. BECKER RF, LITTLE CRD, KING JE: Experimental studies on nicotine absorption in rats during pregnancy. *Am J Obstet Gynecol* 100: 957, 1968
11. COLE PV, HAWKINS LH, ROBERTS D: Smoking during pregnancy and its effects on the fetus. *J Obstet Gynaecol Br Commonw* 79: 782, 1972
12. EDWARDS CC JR (Commissioner of the FDA): Address to the 1972 annual meeting of the American Academy of Pediatrics, New York, NY

Postgraduate Courses

ORTHOPEDIC SURGERY. Clinical seminar. Westminster Hospital, London. Apr. 2, 1975. Information: Assistant dean, Continuing education, Faculty of medicine, University of Western Ontario, London, Ont. N6A 3K7

ESTHETIC PLASTIC SURGERY. The Wellesley Hospital, Toronto. April 4-5, 1975. Information: The Director, Division of Postgraduate Medical Education, University of Toronto, Toronto, Ont. M5S 1A8

CLINICAL PHARMACOLOGY OF ANTIMICROBIAL AGENTS. Toronto Western Hospital. April 5, 1975. Information: The Director, Division of Postgraduate Medical Education, University of Toronto, Toronto, Ont. M5S 1A8

GYNECOLOGIC ENDOSCOPY. Christmas Seal Auditorium, 10th Ave. and Willow St., Vancouver. Apr. 7-8, 1975. Information: Division of continuing education in the health sciences, P.A. Woodward Instructional Resources Centre, University of British Columbia, Vancouver, BC V6T 1W5

MEDICAL RECORD KEEPING. Victoria Hospital, London. April 9, 1975. Information: Assistant Dean, Continuing Education, Faculty of Medicine, University of Western Ontario, London, Ont. N6A 3K7

DERMATOLOGY CLINICAL DAY. Royal Victoria Hospital, Montréal. Apr. 9, 1975. Information: Secretary, Postgraduate board, RVH, 687 Pine Ave. W, Montréal, Qué. H3A 1A1

PEDIATRIC OPHTHALMOLOGY. The Hospital for Sick Children, Toronto. April 10-11, 1975. Information: Dr. Clement McCulloch, Dept. of Ophthalmology, University of Toronto, 1 Spadina Cres., Toronto, Ont. M5S 2J5

REFRESHER COURSE FOR PRACTISING OPHTHALMOLOGISTS. University of Toronto. April 10-11, 1975. Information: The Director, Division of Postgraduate Medical Education, University of Toronto, Toronto, Ont. M5S 1A8

TRAUMA TO THE UPPER LIMB. Four Seasons Sheraton Hotel, Toronto. April 10-12, 1975. Information: The Director, Division of Postgraduate Medical Education, University of Toronto, Toronto, Ont. M5S 1A8

FETAL MONITORING WORKSHOP. McMaster University Medical Centre, Hamilton. April 11-12, 1975. Information: Dr. S. B. Effer, Associate Professor, Dept. of Obstetrics & Gynecology, McMaster University Medical Centre, 1200 Main St. W., Hamilton, Ont. L8S 4J9

EIGHTH ANNUAL SPRING SEMINAR. Ontario chapter of the College of Family Physicians of Canada in cooperation with the Ontario Medical Association section on general practice. Inn on the Park, Toronto. Apr. 12, 1975. Topics: methods of remuneration; problem-oriented records; efficient use of ancillary personnel. Information: Dr. M.H. Humphrys, Chairman, Professional and public policy committee, CFPC, Ontario chapter, 30 Church St. N, St. Marys, Ont. N0M 2V0

ANESTHESIA FOR FAMILY PHYSICIANS. University of Toronto. April 14-18, 1975. Information: The Director, Division of Postgraduate Medical Education, University of Toronto, Toronto, Ont. M5S 1A8

ACUTE AND CHRONIC POISONING. Downtowner Hotel, Owen Sound, Ont. Apr. 16, 1975. Sponsors: Ontario Medical Foundation and College of Family Physicians of Canada, Ontario chapter. Information: Dr. J.I. Leeson, Box 88, Wiarton, Ont. N0H 2T0

TRANSSEXUALITE. Les implications médicales, psychologiques et juridiques. Auditorium de la Banque Royale, 1 Place Ville Marie, Montréal. Le 18 avril 1975. Ce colloque s'adresse exclusivement au monde médical. Renseignements: Secrétariat du colloque, Département de sexologie, CP 8888, Montréal 101, Qué.

GYNECOLOGIC ENDOCRINOLOGY. Montreal General Hospital. Apr. 17-18, 1975. Information: Secretary, Postgraduate board, MGH, 1650 Cadar Ave., Montréal, Qué. H3G 1A4

JOURNÉES CHIRURGICALES DE L'HÔTEL-DIEU. Hôtel-Dieu de Montréal. Les 18-19 avril 1975. Renseignements: Directeur du Service d'éducation médicale continue, Université de Montréal, C.P. 6207, Succursale A, Montréal, Qué. H3C 3T7

CLINICAL, THERAPEUTIC AND INTERPRETATIVE ASPECTS OF HEMOPHILIA AND HEMOSTASIS. Medical Sciences Bldg., Rm 1747, UWO campus, London. April 18, 1975. Information: Assistant Dean, Continuing Education, Faculty of Medicine, University of Western Ontario, London, Ont. N6A 3K7

MALADIES INFECTIEUSES ET ANTIBIOTIQUES. Hôpital Saint-Luc, Montréal. Le 19 avril 1975. Renseignements: Directeur du Service d'éducation médicale continue, Université de Montréal, C.P. 6207, Succursale A, Montréal, Qué. H3C 3T7

25TH ANNUAL REFRESHER COURSE FOR FAMILY PHYSICIANS. Spring session (repetition of Fall 1974 program). Royal Victoria Hospital, Montréal. April 21-25, 1975. Information: The Secretary, Postgraduate board, Royal Victoria Hospital, 687 Pine Ave. W, Montréal, Qué. H3A 1A1

24TH ANNUAL REFRESHER COURSE FOR FAMILY PRACTITIONERS. Ottawa Civic Hospital. April 23-25, 1975. Information: Department of medical education, Ottawa Civic Hospital, 1053 Carling Ave., Ottawa, Ont. K1Y 4E9

CURRENT TRENDS IN THE TREATMENT OF INFECTIOUS DISEASE. St. Joseph's Hospital, London, Ont. April 23, 1975. Information: Assistant Dean, Continuing Education, Faculty of Medicine, The University of Western Ontario, London, Ont. N6A 3K7

ANTIBIOTICS IN PERSPECTIVE. Caswell Hotel, Sudbury, Ont. Apr. 23, 1975. Information: Ontario Medical Foundation, 242 St. George St., Toronto, Ont. M5R 2P4

COLPOSCOPY AND EARLY CERVICAL NEOPLASIA. Ewart Angus Theatre, McMaster University Medical Centre, Hamilton. Apr. 24-26, 1975. Information: Ms. Lorraine Putnins, Conference Coordinator, Conference Office, Rm. 3H8, McMaster University Health Sciences Centre, 1200 Main St. W, Hamilton, Ont. L8S 4J9

OFFICE TREATMENT IN FAMILY PRACTICE, 1975. 20th annual clinical day. Toronto East General and Orthopaedic Hospital. Apr. 25, 1975. Information: Dr. J.R. Topp, Suite 301, 20 Wynford Dr., Don Mills, Ont.

ORIENTATION WORKSHOP. For practice-eligible candidates taking 1975 certification examination of the College of Family Physicians of Canada. McMaster University Medical Centre, Hamilton. Apr. 25-26, 1975. Information: Dr. J.C. Reid, Associate professor, Department of family medicine, McMaster University Clinic, Henderson General Hospital, Concession St., Hamilton, Ont. L8V 1C3

DROGUES, ALCOOL ET AUTRES TOXICOMANIES. Hôtel Bonaventure, Montréal. Le 26 avril 1975. Renseignements: Directeur du Service d'éducation médicale continue, Université de Montréal, C.P. 6207. Succursale A, Montréal, Qué. H3C 3T7

CREATIVE SEXUALITY. Study seminar on sex counselling with Drs. Noam and Beryl Chernick. Westbury Hotel, Toronto. Apr. 30–May 2, 1975. Information: Creative Sexuality, Suite 400, 73 Richmond St. W, Toronto, Ont. M5H 2A1

EMERGENCY MEDICINE. Oshawa General Hospital, Oshawa, Ont. Apr. 30, 1975. Information: Ontario Medical Foundation, 242 St. George St., Toronto, Ont. M5R 2P4

OPHTHALMOLOGY SPRING CLINICAL DAY. University Hospital, London, Ont. May 2, 1975. Information: Assistant Dean, Continuing Education, Faculty of Medicine, The University of Western Ontario, London, Ont. N6A 3K7

ASSESSMENT AND MANAGEMENT OF THYROID FUNCTION. Bristol Place Hotel, Toronto. May 2, 1975. Sponsored by the faculty of medicine of the University of Toronto, The Canadian Society of Endocrinology and Metabolism and The Canadian Society of Clinical Chemists. Information: Ames Educational Institute, 77 Belfield Rd., Rexdale, Ont. M9W 1G6

CARDIOLOGIE EN PRATIQUE GÉNÉRALE. Institut de Cardiologie de Montréal. Les 8-10 mai 1975. Renseignements: Directeur du Service d'éducation médicale continue, Université de Montréal, C.P. 6207, Succursale A, Montréal, Qué. H3C 3T7

RECENT ADVANCES IN PSYCHIATRY. Banff Springs Hotel, Banff, Alta. May 12-14, 1975. Information: Director, Division of continuing medical education, University of Alberta, Edmonton, Alta. T6G 2G3

18th ANNUAL POSTGRADUATE COURSE IN MEDICAL TECHNOLOGY. Royal Inland Hospital, Kamloops. May 12-16, 1975. Information: Dr. Glenn M. Martin, Director, Postgraduate course in medical technology, Royal Inland Hospital, 311 Columbia St. Kamloops, BC V6A 2R7

REFRESHER COURSE IN FAMILY PRACTICE. Sunnybrook Medical Centre, Toronto. May 12-30, 1975. Lectures and in-office experience. Information: Dr. J.K. Ross, Chairman, Refresher course, Sunnybrook Medical Centre, 2075 Bayview Ave., Suite 1001, Toronto, Ont. M4N 3M5

CHEST DISEASES. Clinical day. University Hospital, London, Ont. May 14, 1975. Information: Assistant Dean, Continuing Education, Faculty of Medicine, The University of Western Ontario, London, Ont. N6A 3K7

ANESTHETIC EMERGENCIES. Civic Hospital Auditorium, North Bay, Ont. May 14, 1975. Information: Ontario Medical Foundation, 242 St. George St., Toronto, Ont. M5R 2P4

continued on page 740