Renal tubular acidosis during therapy for diabetic ketoacidosis

ROSE GIAMMARCO, MD; MARC B. GOLDSTEIN, MD, FRCP[C]; MITCHELL L. HALPERIN, MD, FRCP[C]; BOBBY J. STINEBAUGH, MD, FACP

Summary: A young woman presented with typical diabetic ketoacidosis. Five hours after insulin had been given hyperchloremic metabolic acidosis developed. This could not be attributed to gastrointestinal loss of bicarbonate, ingestion of HCl or carbonic anhydrase inhibitor, or the administered fluids and electrolytes. The combination of hyperchloremic metabolic acidosis and a urine pH of 5.6 during acidemia prompted specific studies that established the presence of disorders of renal acidification. A transient defect of hydrogen ion secretion in the distal nephron was suggested by the decrease in urine-blood Pco_2 gradient after administration of sodium bicarbonate. Proximal renal tubular acidosis was indicated by the reduced bicarbonate threshold that persisted for approximately 7 weeks.

Résumé: *Acidose tubulaire rénale durant un traitement pour acidocétose diabétique*

Une jeune femme présentait une acidocétose diabétique typique. Cinq heures après une injection d'insuline, se manifestait une acidose métabolique hyperchlorémique. Celle-ci ne pouvait être attribuée à une perte de bicarbonate par voie digestive, ni à l'ingestion de HCl ou d'un inhibiteur de l'anhydrase carbonique, ni à l'administration de liquides et d'électrolytes. L'association d'une acidose métabolique hyperchlorémique et d'un pH urinaire de 5.6 durant l'acidémie nous a incité à pratiquer des études spécifiques qui ont permis d'établir la présence de troubles de l'acidification rénale. L'administration de bicarbonate de sodium ayant déclenché une diminution du gradient de Pco_2 urine-sang, nous avons conclu qu'il s'agissait d'un défaut transitoire de la sécrétion des ions d'hydrogène dans le néphron distal. L'acidose rénale du tube proximal était indiquée par l'abaissement du seuil du bicarbonate qui a persisté durant près de 7 semaines.

From the renal division, department of medicine, St. Michael's Hospital, Toronto and Gorgas Hospital, CZ, USA

Reprint requests to: Dr. M.L. Halperin, Department of medicine, University of Toronto, Room 7363, Medical Sciences Building, Toronto, Ont. M5S 1A8

The mechanisms responsible for metabolic acidosis in patients with poorly controlled diabetes mellitus have been well documented.[1-5] In classic diabetic ketoacidosis, metabolic acidosis is produced by the accumulation in the blood of β-hydroxybutyric and acetoacetic acids and therefore there is an increase in concentration of unmeasured anions. After the initiation of therapy, however, hyperchloremia and a low serum bicarbonate concentration are frequently detected. This hyperchloremic acidosis is usually transient and has been attributed to sodium chloride administered intravenously to patients in whom the ketosis has been reversed by the administered insulin.[1-5]

We have recently studied a patient in whom hyperchloremic metabolic acidosis developed after insulin therapy for the typical unmeasured anion type of diabetic ketoacidosis. Specific studies established that the hyperchloremic acidosis was due to a defect at the proximal and probably also at the distal renal acidification sites. In this report we discuss the diagnosis, natural history and possible mechanisms of this disorder.

Methods

Values for serum sodium, potassium, chloride, creatinine and phosphorus, blood glucose and urea nitrogen, pH, P_aCO_2 and CO_2 content were determined as outlined in a previous communication.[16] Serum and urine ketones were detected by colour reaction of sodium nitroprusside reagent (Acetone Test [Denco]) and urine glucose (total reducing sugar) by colour reaction of bismuth oxychloride–sodium hydroxide reagent (Galatest [Denco]). Serum β–hydroxybutyrate was assayed spectrophotometrically on a blood perchloric acid filtrate.[17]

The urinary acidification studies with ammonium chloride were performed as described by Wrong and Davies.[18] Bicarbonate loading was achieved by the intravenous or oral administration of sodium bicarbonate, 1 to 2 meq/kg; the dose was selected to ensure that the urine pH exceeded that of the blood. In order to minimize the possibility that an admixture of alkaline and acid urines in the bladder would be studied, analyses were not performed until the urine pH exceeded the blood pH in two consecutive specimens. All samples were aspirated into a sealed glass syringe immediately after the urine had been voided, as previously described.[16] Venous blood was collected from an antecubital vein without the use of a tourniquet after the subject had remained recumbent for at least 10 minutes; forearm muscle contraction was minimized. On the two occasions that arterial blood samples were obtained the values were only minimally different from the venous values. The P_aCO_2 as determined by the Pco_2 electrode was checked by substitution in the Henderson-Hasselbalch equation; all values reported had less than a 10% deviation.

Case report

A 19-year-old white woman was admitted to hospital with the diagnosis of diabetic ketoacidosis. Diabetes mellitus had first been diagnosed 12 years earlier and she had been treated with diet and insulin since that time. Control of her disease had been excellent for the first 3 years. During the next 9 years, however, she required 15 hospital admissions for diabetic ketoacidosis, with an uneventful recovery on each occasion. She was being treated with 30 units of Lente Insulin per day and an 1800-calorie diabetic diet. On the day before admission she had a mild fever, muscle aches and nausea and had vomited once. Her urine had become strongly positive for glucose and ketones. The ketonuria persisted despite an increase in her insulin dose and therefore she was taken to hospital. She denied the intake of any additional medication and there had been no major modification of her management up to the present illness.

She was in some distress on admission. Respiration was deep and rapid (32/min). Acetone was not detected in her breath by the attending house officer. Her temperature was 37°C, pulse rate 88 beats/min, blood pressure 120/70 mm Hg, and there was no change in blood pressure with posture, hence clinical volume contraction was not detected. The extremities were warm and cyanosis was not present. She was moderately obese. The remainder of the physical examination did not reveal any abnormalities. Chest radiographs appeared normal.

Results of laboratory investigations are summarized in Table I. In addition, the initial urine specimen was strongly posi-

tive for sugar and ketones; there was no proteinuria and only a few leukocytes were detected in the urinary sediment. The blood sugar was greatly elevated (702 mg/dl) and an undiluted specimen was positive for serum ketones. Initially, therefore, the typical biochemical features of diabetic ketoacidosis were noted. The effects of insulin insufficiency are reflected by the blood sugar value of 702 mg/dl, the β-hydroxybutyrate value of 6 mmol/l (normal, < 0.5 mmol/l) and the severe metabolic acidosis (pH 7.20). The elevation of the concentration of ketoacid anions accounted for most of the increase in concentration of unmeasured anions.* Thus, she presented with a clinical picture characteristic of diabetic ketoacidosis.[1-6]

Specific therapy consisted of crystalline insulin, 30 units intravenously and 30 units subcutaneously. Over the first 5 hours of treatment 1.5 l of isotonic NaCl and 44 meq of sodium bicarbonate were administered. At the end of this period the metabolic lesion of diabetic ketoacidosis was largely reversed (blood sugar value, 121 mg/dl; serum β-hydroxybutyrate value, 0.6 mmol/l) but metabolic acidosis was still evident (pH 7.30) (Table I).

Five hours after insulin therapy was started the metabolic pattern had undergone a dramatic change (Table I). There was a striking decrease in the blood values of glucose, β-hydroxybutyrate and unmeasured anions. But despite the reversal of ketosis by therapy the blood bicarbonate value remained low and metabolic acidosis persisted: metabolic acidosis of the hyperchloremic or nonunmeasured anion type had emerged.

The changes in early acid-base balance noted during the first 5 days of the study are summarized in Table II. Metabolic acidosis (total CO_2, < 24 meq/l) recurred despite repeated administration of sodium bicarbonate; the bicarbonate was promptly excreted in the urine (urine pH, > 7.4) at a time when values for potassium and P_aCO_2 were not abnormal (day 3 onwards). This pattern was also observed in the ensuing 7 weeks (Fig. 1).

After her recovery the results of renal function studies were within normal limits: creatinine clearance was 156 ml/min and the intravenous pyelogram showed that the kidneys were slightly larger than expected and smooth in outline, with normal collecting systems. The urine was acidified to a pH of less than 5.30 during an ammonium chloride loading test.[18] Findings were normal on microscopic examination of the urine sediment on several occasions.

Discussion

The possible causes of hyperchloremic metabolic acidosis in diabetes mellitus are as follows:

1. Loss of β-hydroxybutyrate anion in the urine as the sodium or potassium salt. This would tend to restore to normal the elevated blood concentrations of unmeasured anions but would also result in loss of potential bicarbonate. Thus, the metabolic acidosis would convert from an unmeasured anion type to a hyperchloremic type.
2. Gastrointestinal loss of bicarbonate.
3. Ammonium chloride (HCl intake.
4. Sodium chloride administration to a patient with metabolic acidosis and extracellular fluid volume contraction. This would dilute the serum bicarbonate and contribute to the acidosis.
5. Renal causes:

(a) Carbonic anhydrase inhibitor intake.
(b) Renal tubular acidosis — proximal, distal or combined.

Neither gastrointestinal loss of bicarbonate nor ingestion of HCl or a carbonic anhydrase inhibitor was a factor in this case. Our patient received insufficient (1.5 l) isotonic NaCl to account for the decrease in concentration of unmeasured anions without concomitant elevation of bicarbonate concentration. Although the factors responsible for the initiation of the hyperchloremic acidosis cannot be delineated with certainty in this case, the subsequent course of events establishes that this acidosis was perpetuated by defects in the renal acidification mechanism. Although sufficient bicarbonate was administered to exceed her renal threshold (Fig. 1), the serum bicarbonate concentration remained low and metabolic acidosis persisted.

Table I—Data on admission and for first 5 hours of treatment

Variable	Time after admission (h) 0	5	15
Blood constituents			
Glucose (mg/dl)	702	121	212
BUN (mg/dl)	13	—	6
Na (meq/l)	128	138	136
K (meq/l)	5.7	3.4	5.1
Cl (meq/l)	91	110	107
Total CO_2 (meq/l)	11	13	15
Unmeasured anions* (meq/l)	26	15	14
β-hydroxybutyrate (mmol/l)	6	0.6	—
Blood gases			
pH	7.20	7.30	7.33
P_{aCO_2} (mm Hg)	26†	29	32
P_{aO_2} (mm Hg)	103	—	97
Treatment (cumulative values)			
Insulin (units)		60	
NaCl (l)		1.5	1.8
KCl (meq)			20
$NaHCO_3$ (meq)		44	
5% dextrose/water (l)			0.7

*Unmeasured anions: Na − (Cl + CO_2), normal range 13 ± 3 meq/l.
†Calculated from the determined pH and bicarbonate value. All other P_{CO_2} values were determined directly.

Table II—Acid-base data for days 1 to 5

Variable	Hospital day 1 Before* HCO_3^-	1 After (44)† HCO_3^-	3 Before HCO_3^-	3 After (220) HCO_3^-	5 Before HCO_3^-	5 After (132) HCO_3^-
Blood						
Na^+ (meq/l)	136	139	136	143	139	141
K^+ (meq/l)	5.1	4.3	4.2	3.6	4.7	3.8
Cl^- (meq/l)	107	101	101	103	102	100
Total CO_2 (meq/l)	15	22	20	25	22	26
Unmeasured anion (meq/l)	14	16	15	15	15	15
Blood gases						
pH	7.33	7.42	7.34	7.41	7.31	7.39
P_{aCO_2} (mm Hg)	32	31	36	42	42	45
Urine						
pH	5.70	7.60	5.80	7.82	5.90	7.75
P_{CO_2} (mm Hg)	40	49	34	61	40	84
Urine minus blood P_{CO_2} (mm Hg)	—	18	—	19	—	39

*Before sodim bicarbonate therapy, fasting am values.
†After sodium bicarbonate therapy, dosage in meq in parentheses, at peak serum bicarbonate value.

*Acetoacetate was not measured directly, but is approximately one third the β-hydroxybutyrate value at these concentrations in simple ketoacidosis.[19]

Inability to acidify the urine maximally in the presence of systemic acidosis is the generally accepted criterion for the diagnosis of distal renal tubular acidosis.[18] When this patient had systemic acidosis (pH = 7.30) the urine pH was 5.6 (Fig. 1). Urine pH, however, is not a reliable index of hydrogen ion secretion in the distal nephron in chronic metabolic acidosis. During the metabolic acidosis of fasting, urine pH decreases initially, then increases after 3 to 5 days despite a steadily increasing degree of ketoacidosis.[20] This increase in urine pH correlates with the increase in renal ammonium excretion observed in chronic metabolic acidosis of differing causes.[21] Thus, classic criteria that depend on urine pH for the diagnosis of distal renal tubular acidosis are not applicable during chronic metabolic acidosis.[18] However, Elkington *et al*[22] observed that the urine pH was usually lower than 5.6 in normal subjects who had metabolic acidosis for 3 to 5 days.

We proceeded, therefore, to evaluate hydrogen ion secretion in the distal nephron by determining the gradient between the urine P_{CO_2} and the arterial P_{CO_2} ($U\text{-}BP_{CO_2}$).[16] Carbonic acid is formed when hydrogen ions are secreted into the bicarbonate-rich fluid in the lumen of the distal nephron. Because of the absence of luminal carbonic anhydrase in this segment of the nephron, dehydration to carbon dioxide and water is delayed. Urinary carbon dioxide is derived from two major sources: hydrogen ions that are secreted in the distal nephron into alkaline urine, and urinary P_{CO_2} that equilibrates with the P_{CO_2} of the medullary parenchyma. This latter value is best reflected by the P_aCO_2. The presence of a decreased hydrogen ion secretion in the distal nephron in this patient on days 2 and 3 was suggested because her $U\text{-}BP_{CO_2}$ was lower then (18 and 19 mm Hg) than after the 5th hospital day (39 and 30 mm Hg). Distal acidification was normal on the 8th day, for the urine pH decreased to 5.2 during an ammonium chloride loading test[18] (Fig. 1). Thus, the decreased net hydrogen ion secretion in the distal nephron in this patient was transient. Factors commonly associated with distal renal tubular acidosis, such as a positive family history, hypokalemia, use of nephrotoxic drugs or heavy metals and dysproteinemias, were not evident.

If distal renal tubular acidosis were its sole cause, the hyperchloremic acidosis would have been corrected by the administration of sodium bicarbonate in a dosage of 2 to 3 meq/kg•day.[23-25] This was not the case, as can be appreciated from Fig. 1. Despite the repeated administration of bicarbonate in large quantities (132 meq) the serum bicarbonate value was consistently below normal limits. The very alkaline urine pH demonstrates that her bicarbonate threshold was exceeded and establishes the diagnosis of proximal renal tubular acidosis.[23-25]

Hypophosphatemia occurs after insulin treatment of diabetic ketoacidosis,[7,9,26-28] and in this patient the serum phosphorus value was low on day 2 (1.9 mg/dl). Recently, Gold *et al*[29] have shown that phosphate depletion can cause a defect in renal bicarbonate reabsorption (proximal renal tubular acidosis). Therefore, our patient was treated with sodium phosphate by mouth from the evening of day 2.† The serum phosphorus value returned to normal (3.9 mg/dl) on day 4 but the bicarbonate wasting continued, thus excluding phosphate depletion as the sole cause of her proximal renal tubular acidosis. Nor was there any evidence of generalized proximal tubular dysfunction, such as aminoaciduria, phosphaturia, uricosuria or glucosuria. The decrease in serum bicarbonate value occurred when the serum potassium value and P_aCO_2 were normal and also when there was no apparent expansion or contraction of the extracellular fluid volume (Table I and Fig. 1). In contrast to the rapid disappearance of her defect in hydrogen ion secretion in the distal nephron, the proximal renal tubular acidosis persisted long after she had recovered from her acute diabetic ketoacidosis (Fig. 1). Eventually, however, the proximal renal tubular acidosis also resolved, as demonstrated by the return of her renal bicarbonate threshold to normal by the 49th day (blood bicarbonate value was normal when bicarbonate therapy had been discontinued).

A review of the previous episodes of diabetic ketoacidosis in this patient revealed that hyperchloremic metabolic acidosis had occurred frequently during therapy. Specific studies for renal tubular acidosis, however, were not done on those occasions, and one can only speculate whether renal tubular acidosis was a frequent accompaniment of her diabetic ketoacidosis. Hyperchloremic metabolic acidosis is, however, a frequent finding during therapy for diabetic ketoacidosis. The frequency of renal tubular acidosis in this group of patients has yet to be ascertained.

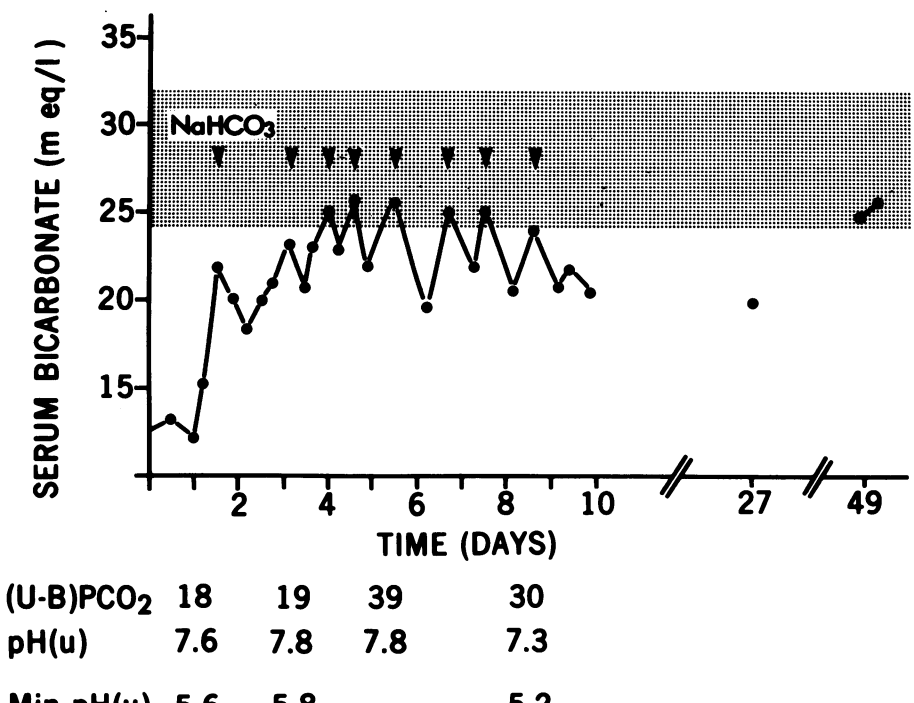

FIG. 1—Effect of bicarbonate administration on serum bicarbonate values, urine pH and urine-blood P_{CO_2} gradient.

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References

1. ATCHLEY DW, LOEB RF, RICHARDS DW JR, et al: On diabetic acidosis: a detailed study of electrolyte balances following the withdrawal and re-establishment of insulin therapy. *J Clin Invest* 12: 297, 1933
2. PETERS JP, KYDD DM, EISENMAN AJ, et al: The nature of diabetic acidosis. Ibid, p 377
3. KYDD DM: Salt and water in the treatment of diabetic acidosis. Ibid, p 1169
4. HARTMANN AF, ERGANIAN J: Treatment of diabetic acidosis. *J Pediatr* 31: 274, 1947
5. NABARRO JDN: in *On the Nature and Treat-*

†One tablet *tid*, each tablet containing NaH_2PO_4 1.936 g, $KHCO_3$ 315 mg, $NaHCO_3$ 350 mg.

ment of Diabetes, edited by LEIBEL BS, WRENSHALL GA, Amsterdam, Excerpta Med, 1965, pp 545-57
6. ZIMMET PZ, TAFT P, ENNIS GC, et al: Acid production in diabetic acidosis: a more rational approach to alkali replacement. *Br Med J* 3: 610, 1970
7. FRANKS M, BERRIS RF, KAPLAN NO, et al: Metabolic studies in diabetic acidosis. II. The effect of the administration of sodium phosphate. *Arch Intern Med* 81: 42, 1948
8. SUNDERMAN FW, AUSTIN JH, WILLIAMS P: Studies of serum electrolytes. VIII. The concentration of electrolytes and non-electrolytes in the serum following insulin administration in diabetic patients. *J Clin Invest* 11: 1261, 1932
9. TREVER RW, CLUFF LE: The problem of increasing azotemia during management of diabetic acidosis. *Am J Med* 24: 368, 1958
10. NABARRO JDN, SPENCER AG, STOWERS JM: Metabolic studies in severe diabetic ketosis. *Q J Med* 21: 225, 1952
11. EASTMAN MH, SMITH K, WILSON ML: The fluid and electrolyte therapy of severe diabetic acidosis and ketosis: a study of twenty-nine episodes. *Am J Med* 24: 376, 1958
12. SELDIN DW, TARAIL R: The metabolism of glucose and electrolytes in diabetic acidosis. *J Clin Invest* 29: 552, 1950
13. HARTMANN AF, DARROW DC: Chemical changes occurring in the body as the result of certain diseases. III. The composition of the plasma in severe diabetic acidosis and the changes taking place during recovery. *J Clin Invest* 6: 257, 1928
14. DANOWSKI TS, PETERS JH, RATHBUN JC, et al: Studies in diabetic acidosis and coma, with particular emphasis on the retention of administered potassium. *J Clin Invest* 28: 1, 1949
15. SPRAGUE RG, POWER MH: Electrolyte metabolism in diabetic acidosis. *JAMA* 151: 970, 1953
16. HALPERIN ML, GOLDSTEIN MB, HAIG A, et al: Studies on the pathogenesis of type 1 (distal) renal tubular acidosis as revealed by the urinary P_{CO_2} tensions. *J Clin Invest* 53: 669, 1974
17. MELLANBY J, WILLIAMSON DH: in *Methods of Enzymatic Analysis,* second ed, edited by BERGMEYER HU, New York, Acad Pr, 1965, pp 454-61
18. WRONG O, DAVIES HEF: The excretion of acid in renal disease. *Q J Med* 23: 259, 1959
19. HOCKADAY TDR, ALBERTI KGMM: Diabetic coma. *Clin Endocrinol Metab* 1: 751, 1972
20. SCHLOEDER FX, STINEBAUGH BJ: Defect of urinary acidification on fasting. *Metabolism* 15: 17, 1966
21. SCHLOEDER FX, STINEBAUGH BJ: Urinary ammonia content as a determinant of urinary pH during chronic metabolic acidosis. *J Clin Invest,* submitted for publication
22. ELKINGTON JR, HUTH EJ, WEBSTER GP JR, et al: The renal excretion of hydrogen in renal tubular acidosis. I. Quantitative assessment of response to ammonium chloride as an acid load. *Am J Med* 29: 554, 1960
23. SELDIN DW, WILSON JD: Renal tubular acidosis, in *Metabolic Basis of Inherited Disease,* third ed, edited by STANBURY JB, WYNGAARDEN JB, FREDRICKSON DS, New York, McGraw, 1972, p 1548
24. MORRIS RC JR: Renal tubular acidosis: mechanisms, classification and implications. *N Engl J Med* 281: 1405, 1969
25. RODRIGUEZ-SORIANO J, EDELMAN CM JR: Renal tubular acidosis. *Annu Rev Med* 20: 363, 1969
26. GUEST GM: Diabetic coma: metabolic derangements and principles for correction of therapy. *Am J Med* 7: 630, 1949
27. GUEST GM, RAPPOPORT S: Role of acid soluble phosphorus compounds in red blood cells in experimental rickets, renal insufficiency, pyloric obstruction, gastroenteritis, ammonium chloride acidosis, and diabetic acidosis. *Am J Dis Child* 58: 1072, 1939
28. BUTLER AM: Diabetic coma. *N Engl J Med* 243: 648, 1950
29. GOLD LW, MASSRY SG, ARIEFF AI, et al: Renal bicarbonate wasting during phosphate depletion: a possible cause of altered acid-base homeostasis in hyperparathyroidism. *J Clin Invest* 52: 2556, 1973

Postgraduate Courses

CORRESPONDENCE COURSE IN GENERAL SURGERY. Fifteen prepared weekly reading lists and weekly multiple-choice questionnaires to answer and submit for grading, March 1 - June 17, 1975. Registration closes March 15, 1975. Information: The Secretary, Postgraduate Board, The Montréal General Hospital, 1650 Cedar Ave., Montréal, Qué. H3G 1A4

NEUROLOGY IN A CLINICAL SETTING. University and Victoria Hospitals, London. March 5, 1975. Information: Assistant Dean, Continuing Education, Faculty of Medicine, University of Western Ontario, London, Ont. N6A 3K7

DIALOGUE IN DIAGNOSIS — VALUE AND RELIABILITY OF SOME ENDOSCOPIC, NUCLEAR, RADIOLOGIC AND ULTRASOUND TECHNIQUES. McMaster University Medical Centre, Hamilton. March 5, 1975. Information: Dr. W. P. Cockshott, Chairman, Dept. of Radiology, McMaster University Medical Centre, 1200 Main St. W., Hamilton, Ont. L8S 4J9

FAMILY THERAPY MINI WORKSHOP. London Psychiatric Hospital, London, Ont. March 6, 1975. Information: Assistant Dean, Continuing Education, Faculty of Medicine, The University of Western Ontario, London, Ont. N6A 3K7

LA PSYCHIATRIE DU PRATICIEN. Hôpital Saint-Luc, Montréal. Le 8 mars 1975. Renseignements: Directeur du Service d'éducation médicale continue, Université de Montréal, C.P. 6207, Succursale A, Montréal, Qué. H3C 3T7

OPHTHALMOLOGY AND ENT. Health Sciences Bldg., University of Saskatchewan, Saskatoon. March 13-15, 1975. Information: Mrs. M. P. Sarich, Continuing Medical Education, 408 Ellis Hall, University of Saskatchewan, Saskatoon, Sask. S7N 0W8

REVIEW '75. 12th annual clinical days. Royal Alexandra Hospital, Edmonton. Mar. 13 and 14, 1975. Information: Renée Cohen, Secretary, Clinical days committee, Room 1417, Royal Alexandra Hospital, Edmonton, Alta. T5H 3V9

ANESTHESIA FOR FAMILY PHYSICIANS. St. Michael's Hospital Auditorium, Toronto. March 15, 1975. Information: Ontario Medical Foundation, 242 St. George St., Toronto, Ont. M5R 2P4

MONTREAL NEURO-OPHTHALMOLOGY CONFERENCE. Queen Elizabeth Hotel, Montréal. March 17-18, 1975. Information: The Secretary, Postgraduate Board, Royal Victoria Hospital, 687 Pine Ave. W., Montréal, Qué. H3A 1A1

SEVENTH ANNUAL POSTGRADUATE COURSE IN DRUG THERAPY. The Montréal General Hospital and McGill University. March 20-21, 1975. Information: Dr. R. I. Ogilvie, Division of Clinical Pharmacology, The Montréal General Hospital, 1650 Cedar Ave., Montréal, Qué. H3G 1A4

HYPERTENSION ET CONDITIONS ASSOCIÉES. Institut des Recherches Cliniques, Montréal. Le 22 mars 1975. Renseignements: Directeur du Service d'éducation médicale continue, Université de Montréal, C.P. 6207, Succursale A, Montréal, Qué. H3C 3T7

BASIC AND ADVANCED WORKSHOP — CLINICAL HYPNOSIS. St. Paul's Hospital, Saskatoon. March 22-23, 1975. Information: Dr. K. S. Thakur, 102 Medical Arts Bldg., Saskatoon, Sask. S7K 3H3

ANTIBIOTICS IN CHILDREN. Main Lecture Theatre, Women's College Hospital, Toronto. March 26, 1975. Information: Ontario Medical Foundation, 242 St. George St., Toronto, Ont. M5R 2P4

SECOND ANNUAL DAY IN CLINICAL NEUROSCIENCES. McMaster University Medical Centre, Hamilton. April 2, 1975. For family physicians and internists. Information: Dr. Andrew Talalla, Dept. of Surgery, McMaster University Medical Centre, 1200 Main St. W., Hamilton, Ont. L8S 4J9

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

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

THERAPEUTICS. Saskatoon. Originally scheduled for April 10-12, 1975. Cancelled indefinitely.

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

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

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

REFRESHER COURSE. Spring session. Royal Victoria Hospital and Montreal Children's Hospital. Apr. 21-25, 1975. Information: Secretary, Postgraduate board, RVH, 687 Pine Ave. W, Montréal, Qué. H3A 1A1

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

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

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

CHEST DISEASES. Clinical day. University Hospital, London, Ont. May 7, 1975. Information: Assistant Dean, Continuing Education, Faculty of Medicine, The University of Western Ontario, London, Ont. N6A 3K7

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

CPRI SYMPOSIUM. Children's Psychiatric Research Institute, London, Ont. May 14, 1975. Information: Assistant Dean, Continuing Education, Faculty of Medicine, The University of Western Ontario, London, Ont. N6A 3K7

ENDOCRINOLOGIE PÉDIATRIQUE. Holiday Inn, Montréal (centre ville). Les 15-16 mai 1975. Renseignements: Directeur du Service d'éducation médicale continue, Université de Montréal, C.P. 6207, Succursale A, Montréal, Qué. H3C 3T7