

# BRITISH MEDICAL JOURNAL

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SATURDAY 14 APRIL 1984

## LEADING ARTICLES

Benzodiazepines on trial	P J TYRER	1101
Protecting confidentiality	J D J HAVARD	1102
The sweet road to gall stones	K W HEATON	1103

## CLINICAL RESEARCH • PAPERS AND SHORT REPORTS • PRACTICE OBSERVED

Treatment of prolactinomas with megavoltage radiotherapy		
A GROSSMAN, B L COHEN, M CHARLESWORTH, P N PLOWMAN, LESLEY H REES, J A H WASS, A E JONES, G M BESSER		1105
Effect of electroconvulsive therapy on serum myelin basic protein immunoreactivity	N R HOYLE, R T C PRATT, D G T THOMAS	1110
Carcinoid tumour secreting dopa	B K SHARMA, B J SMITS, R ROBINSON, SYLVIA BURNS, E N TROUNSON	1111
Diet, alcohol, and relative weight in gall stone disease: a case-control study	R K R SCRAGG, A J MCMICHAEL, P A BAGHURST	1113
Negative selection of patients for dialysis and transplantation in the United Kingdom		
S CHALLAH, A J WING, R BAUER, R W MORRIS, S A SCHROEDER		1119
"Transferable deaths": their epidemiological importance	A FLEISSIG, K A M GRANT	1123
Eosinophilic leukaemia presenting with intolerance of alcohol	G E PACKE, N H STENTIFORD, S G N RICHARDSON	1123
Unilateral myopathy: an unusual presentation of thyrotoxicosis	M H LABIB, R F BING	1124
Paralysis of phrenic nerve due to enlargement of left atrium	W L MORRISON, S B COGHILL, R N JOHNSTON	1125
Interaction between oral contraceptives and griseofulvin	C P H VAN DIJKE, J C P WEBER	1125
Fears aroused in patients by migraine	J N BLAU	1126
Death certification in general practice: review of records	D A BLACK, S J JACHUCK	1127
Generic alternatives in general practice	ROBERT J ANDERSON, PHILIP M REILLY	1129
Interesting GPs of the Past: Archibald Cleland: c1700-71	ROGER ROLLS	1132

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## MEDICAL PRACTICE

Benzodiazepine withdrawal: an unfinished story	HEATHER ASHTON	1135
Green College Lectures: 1984: Medicine in the Third World	J K G WEBB	1141
From chlorpromazine to NMR scans	JOHN CRAMMER	1144
Lesson of the Week: Association of hyperglycaemia with hyponatraemia	EWAN WALTERS, LAVINIA HALLAM	1146
Clinical Algorithms: Sensory disturbances	DAVID I SHEPHERD	1147
Any Questions		1145
Medicine and Books		1150
Personal View	MARGARET MCKIDDIE	1154

PROCUREMENT SECTION

CURRENT SERIAL RECORDS

CORRESPONDENCE—List of Contents	1155
---------------------------------	------

OBITUARY	1169
----------	------

## NEWS AND NOTES

Views	1165
Medical News	1166
BMA Notices	1167
One Man's Burden	MICHAEL O'DONNELL 1168

## SUPPLEMENT

The Week	1171
General practice: consultation not confrontation	
WILLIAM RUSSELL	1172
Junior members forum: Towards compassionate care for the aged	1173
MASC criticises UGC's strategy	1174
From the JCC: Data protection and manpower	1175

## CORRESPONDENCE

<b>Postmarketing surveillance of adverse reactions to drugs</b> W H W Inman, FRCP; E S Snell, FRCP... 1155	<b>Paramedics in the United Kingdom?</b> B Robertson, MRCS... 1159	<b>BMA seeks work permits for overseas medical graduates</b> M A Wilson, FRCP... 1163
<b>Disgruntlement with the CSM</b> A J Fogarty, MRCP... 1156	<b>Assessment of a general practitioner accident service</b> P P Silverston, BA... 1160	<b>Industrial injury benefits</b> W G A Riddle, MB... 1163
<b>Hypertension in general practice</b> M S Lawrence, FRCP; J Hospedales, MB; I G V James, MB... 1156	<b>Pharmacy: an inquiry into its contribution to patient care</b> A M Martin, MRCP, and others; P A Pannett, MPS... 1160	<b>Preregistration house officer posts: new arrangements</b> E D Acheson, FRCP... 1163
<b>Thyroid hormone concentrations after exogenous thyroxine</b> E Soppi, MD, and others... 1157	<b>Gynaecomastia in cystic fibrosis</b> E W Russi, MD; Jean Ginsburg, DM... 1160	<b>Points Leprosy masked by steroids (H Baker) ... 1163</b>
<b>Misleading laboratory findings</b> P B S Fowler, FRCP... 1157	<b>Raised serum urate concentration as risk factor for premature mortality in middle aged men</b> H Takkunen, MD, and others... 1161	<b>Who coined the term accident neurosis? (M Tyndel and F Tyndel); Treatment of the restless legs syndrome (T B Pulvertaft); Quality control of laboratory tests in diabetes (B Thalayasingam); Oral contraceptives and otosclerosis (C R Kay and Sally J Wingrave); The rise and fall of surgery for the "floating" kidney (Lilly H Zondek and T Zondek); Deceivers (J W Koten); Risk of giving intravenous aminophylline to acutely ill patients receiving maintenance treatment with theophylline (C S Munro and K Prowse); Diagnosis of encephalitozoonosis in man by serological tests (Jane M Wilson)... 1164</b>
<b>Sexually transmitted diseases in pregnancy</b> Janina M Harvey, MRCOG; M W Adler, MD; I Anne Tait, MD... 1158	<b>Gastroenteritis in infancy</b> D Isaacs, MD, and others; D F M Thomas, FRCS, and others... 1161	
<b>Boxers' brains</b> A T Irvine, MRCP... 1158	<b>Acute stridor in the preschool child</b> J Couriel, MRCP; P J Robb, MB, and P D M Ellis, FRCS... 1162	
<b>Unfairness in oral exams</b> H Didier, MRCOG... 1158	<b>Patient information booklets</b> C A A Kilmister; D Murray, MRCP; D N Matthews... 1162	
<b>Urinary tract infection in children</b> N R C Robertson, FRCP; R J Hallett, FRCP; D W Pilling, FRCP... 1159		

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*Correspondents should present their references in the Vancouver style (see examples in these columns). In particular, the names and initials of all authors must be given unless there are more than six, when only the first three should be given, followed by et al; and the first and last page numbers of articles and chapters should be included.*

## Postmarketing surveillance of adverse reactions to drugs

SIR,—Professor Michael D Rawlins reviews a number of postmarketing studies, among them prescription event monitoring run by the Drug Surveillance Research Unit at Southampton University in collaboration with the Prescription Pricing Authority (24 March, p 879). Only two of our eight studies are mentioned, which hardly does justice to the magnificent response by general practitioners in England, about three quarters of whom have actively participated (table).

Prescription event monitoring is the second national scheme to have been established since the thalidomide disaster. The green forms used are complementary to the yellow cards. Only a small proportion of the events that are recorded are adverse reactions, but the green

forms allow their incidence to be measured and provide invaluable information about beneficial as well as harmful effects of treatment. The average monthly input of green forms is about the same as the annual input of yellow cards, and about 700 doctors have participated in follow up studies.

Prescription event monitoring has been developed to the stage where we expect to study routinely most new drugs introduced into general practice as soon as their sales are sufficient to produce cohorts of at least 10 000 patients. Delays in detecting rare side effects of new drugs relate as much to their slow market penetration as to difficulties with current monitoring methods.

We are faced with a dilemma familiar to the Committee on Safety of Medicines. All too often stories about problems in drug safety reach patients through the media before their doctors have had an opportunity to study the evidence. Six successive drug withdrawals from general practice (benoxaprofen, zomepirac, zimeldine, indomethacin (as Osmosin), indoprofen, and phenylbutazone) have received wide publicity before the committee could communicate with the profession. Many doctors have reported on the harm this does. For example, the sudden withdrawal of zomepirac was particularly distressing for 400 patients in our series who had metastatic cancer. We regard general practitioners as

coworkers and will ensure that they are the first to hear of our preliminary results through *PEM NEWS* rather than through the media. We also hope to publish more detailed reports, but we do not wish to delay communication to prescribers until the lengthy process of validation and analysis has been completed.

Prescribers need more details of the case investigations that must have preceded certain licensing decisions. This was particularly important with benoxaprofen. Professor Rawlins refers to our survey of 24 000 patients, which covered about 5% of all patients who had been treated with the drug. We have encountered three cases of "Opren jaundice" reported to the Committee on Safety of Medicines on yellow cards and to the unit on green forms. Two of these died from carcinoma of the pancreas, and one of the latter was in the process of litigation against the manufacturers. The results from both national studies were similar. Both signalled jaundice as a problem, but both have suggested that hepatorenal toxicity was very rare—certainly occurring in less than one in 10 000 patients and probably considerably less. The results of these two studies are quite out of line with the experience of Taggart, who reported that all six of the only six patients he had treated with benoxaprofen had died.<sup>1</sup>

As Professor Rawlins points out, control populations of comparable age, sex, and

*Number and percentage of green forms returned between February 1982 and February 1984.*

Drug	Green forms returned
Opren (benoxaprofen)	17 079 (57)
Lederfen (fenbufen)	6 989 (56)
Three antibiotics	9 246 (76)
Zantac (ranitidine)	10 866 (60)
Zomax (zomepirac)	11 074 (60)
Cetiprin (emepromium bromide)	15 920 (65)
Osmosin (indomethacin)	13 132 (60)
Feldene (piroxicam)	14 305 (69)
All	98 611 (63)