Review of yellow cards (1986): report to the Committee on the Safety of Medicines

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1 In 1986 the CSM received 15,527 yellow cards. This was the highest number received in any one year since the scheme started in 1964. Much of the increase was due to the use by doctors of the yellow cards now included in the British National Formulary and NHS prescription pads.

2 The overall profile of reports of serious reaction, in 1986, was broadly similar to that of the previous years. The most commonly reported serious suspected adverse reactions involved the gastro-intestinal tract (801 reports), the skin (539 reports), the central nervous system (535 reports), and the blood (505 reports).

3 Of the drugs introduced between 1984 and 1986 appreciable numbers of reports of serious reactions were received in association with the use of diltiazem (33 reports), mitozantrone (30 reports), enalapril (173 reports) and etodolac (27 reports).

Keywords yellow cards Committee on Safety of Medicines adverse reactions

Introduction

The Committee on the Safety of Medicines (CSM) has a statutory obligation to promote the collection and investigation of information relating to adverse drug reactions. In discharging this responsibility the Committee relies, to a substantial extent, on spontaneous reports of suspected adverse reactions made by doctors and dentists either directly (using a 'yellow-card') or indirectly via pharmaceutical companies. The advantages and limitations of the yellow card scheme have been recently reviewed (Mann, 1987; Rawlins, 1988a, 1988b).

The CSM's Adverse Reaction Register now comprises over 200,000 individual reports of suspected drug toxicity and this paper analyses those accruing during 1986. The Committee has special arrangements for the close monitoring of new products (new active substances and novel dosage forms) during the 3 years following their introduction to the UK market: these include a request to doctors to report all suspected reactions

(irrespective of severity), and monthly scrutiny of reports by the Committee's Adverse Reaction Group (ARGOS). The paper therefore also describes, in detail, adverse reaction reports involving new drugs introduced between 1984 and 1986. A summary was recently published in the British Medical Journal (Committee on the Safety of Medicines, 1988).

Methods

All reports received by the CSM are assessed by its staff, and the relevant details coded before entry on to the Committee's computerised Adverse Reaction Register. The assessment includes identification of both the drug most likely to have caused the reaction (the 'suspect' drug), and the 'most important reaction' (MIREA) if the report contains more than one drug or reaction (respectively). Full details of

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the management of the yellow card system have recently been described (Mann, 1987). The Committee's Register was searched to identify all 'serious' (Appendix A) reactions (MIREA), together with their associated 'suspect' drugs, which were reported in 1986. The Committee defines as 'serious' those reactions which are (potentially) fatal, life-threatening, disabling, incapacitating; or which are likely to result in admission to hospital. Obviously adverse reactions not included in Appendix A may, in individual patients, cause distress and concern and there is an inevitable degree of subjectivity in judging which reactions should be included. During the year the Committee revised its case definition of 'severe' reactions and additions are indicated in (Appendix A): in order to produce annual data for 1986 which were comparable with those of previous years, the number of reports of 'serious' reactions reported between 1982 and 1985 were re-analysed using current criteria.

Reports of reactions to new products, introduced between 1984 and 1986, were collated prospectively and include those accruing between the date of first marketing and the end of 1986.

The computer record of the yellow card reports is constantly updated. Reports of suspected adverse drug reactions sometimes reach the CSM with considerable delays. Occasionally the data have to be amended after receiving new, pertinent data, such as the results of post-mortem examination or Coroners' reports. The figures for 1986 are therefore correct at the time of writing, but they are not necessarily the final numbers.

Results and discussion

The number of reports (15, 527) of suspected adverse drug reactions, received by the CSM during 1986 was substantially greater than in any previous year (Table 1). We attribute this largely to the increased availability of reporting forms interleaved into NHS (FP10) prescription pads

(1,383 reports) and into the British National Formulary (1,874 reports). Doctors and dentists seem to find these convenient and accessible, and we are grateful to all members of the medical and dental professions who have reported suspected adverse drug reactions to the Committee. It is apparent that the recent overall increase in reporting rates has not been confined to less serious reactions (Table 1), but has involved similar proportions of serious reactions to previous years.

Table 2 Serious suspected adverse reactions (MIREA) reported during 1986

<i>Organ/System</i>	
Skin (total)	539
Angioedema	213
Erythema multiforme	131
Exofoliation	81
Stevens Johnson	50
Central nervous system (total)	535
Convulsions	162
Neuropathy	60
Neuroleptic malignant syndrome	34
Autonomic nervous system (total)	269
Psychiatric (total)	271
Hallucinations	102
Depression	90
Gastrointestinal (total)	801
Haemorrhage	575
Perforation	119
Colitis (including pseudomembranous colitis)	46
Liver (total)	437
Cardiovascular system (total)	246
Arrhythmias	146
Hypertension	113
Pulmonary (total)	328
Asthma	184
Allergic or fibrosing alveolitis	31
Blood (total)	505
Agranulocytosis, Granulocytopenia, Leucopenia	188
Thrombocytopenia	122
Aplastic anaemia	86
Urinary	142
Anaphylactic	232
Other Organ/System	464
Total serious MIREA	4769

Table 1 Suspected adverse reaction reports received by CSM 1982-1986

<i>Year</i>	<i>Total reports</i>	<i>Serious reports*</i>	<i>(%)</i>
1982	10,922	3,128	(29)
1983	12,689	3,851	(30)
1984	12,163	4,131	(34)
1985	12,652	4,234	(33)
1986	15,527	4,769	(31)

* the number of serious reactions have been adjusted using the current definition of serious adverse reaction

Serious reactions

The Committee asks doctors and dentists to report all suspected serious adverse effects irrespective of the age of the drug or the notoriety of the reaction. Serious suspected reactions reported during 1986 are shown in Table 2.

Skin reactions

Angioedema (213 reports) was most commonly associated with non-steroidal anti-inflammatory drugs (NSAIDs) (71 reports), with antimicrobial agents (24 reports), and with angiotensin-converting enzyme inhibitors (21 reports). An analysis of the latter has recently been published (Wood *et al.*, 1987). Erythema multiforme (131 reports) and Stevens-Johnson syndrome (50 reports) were also attributed to the use of NSAIDs (69 and 16 reports respectively), and antimicrobial agents (19 and 21 respectively). Fenbufen was incriminated in 50 reports of erythema multiforme and 10 of Stevens Johnson syndrome. Exfoliative eruptions (81 reports) were particularly associated with patients receiving allopurinol (11 reports) and carbamazepine (eight reports).

Central nervous system

The wide range of drugs suspected of causing, or aggravating, convulsions (162 reports) included 41 reports with vaccines, 15 with cyclosporin A, and 14 with antidepressants. Products most often reported in association with neuropathies included amiodarone (seven reports) and calcium-channel blockers (five nifedipine, two diltiazem). Thirty-four reports of the neuroleptic malignant syndrome (Committee on the Safety of Medicines, 1986) were received, and were most commonly associated with haloperidol (10 reports) and chlorpromazine (seven reports).

Psychiatric reactions

Hallucinations (102 reports) and depression (90 reports) were described following the administration of a range of products. Reports of hallucinations with β -adrenoceptor blockers (nine reports), opiates (eight reports) and antidepressants (seven reports) are perhaps to be expected. More surprising, however, were the six reports of hallucinations in patients receiving calcium-channel blockers (five with nifedipine, one with diltiazem).

Gastrointestinal reactions

Of the 801 reports of gastrointestinal bleeding, or perforation, all but 37 involved NSAIDs thus emphasising the apparent toxicity of this therapeutic class. Reports of colitis (including pseudomembranous colitis) primarily concerned broad-spectrum penicillins (11 reports), cephalosporins (seven reports) and NSAIDs (eight reports).

Hepatic reactions

Manifestations of hepatotoxicity (including hepatic failure, hepatic necrosis, hepatitis or jaundice) were described (437 reports) following the administration of many different products. Those most often incriminated were halothane (16 reports), diclofenac (13 reports), fusidate (11 reports), amiodarone (eight reports) and cotrimoxazole (eight reports). By contrast, there was only one (each) report of hepatotoxicity ascribed to enthane and piroxicam, and none to isoflurane. The Committee reviewed its experience of halothane hepatotoxicity during the year (Committee on the Safety of Medicines, 1986).

Cardiovascular reactions

The Committee received a substantial number (246 reports) of suspected serious adverse cardiovascular reactions (Table 2). The 146 reports describing arrhythmias (ranging from sinus tachycardia to ventricular fibrillation and sudden death), involved drugs of many therapeutic classes. Such reports are particularly difficult to evaluate, but 11 implicated calcium-channel blockers, eight concerned sympathomimetic agents, and nine involved antiarrhythmic drugs. The latter may reflect an increasing interest in the arrhythmogenic potential of antiarrhythmic drugs. Thromboembolism (95 reports) was associated in 26 reports with oestrogen-containing products: of these, 22 concerned combined oral contraceptive preparations. Twenty of 113 reports of hypotension were attributed to treatment with angiotensin converting-enzyme inhibitors (15 with enalapril and five with captopril).

Pulmonary reactions

Asthma (184 reports), or exacerbations of asthma, was reported most frequently in patients receiving NSAIDs (33 reports), desensitising vaccines (16 reports), and β -adrenoceptor blockers (nine reports). Alveolitis or pulmonary fibrosis was

particularly associated with amiodarone (nine reports) and nitrofurantoin (six reports).

Blood dyscrasias

The Committee continues to receive reports of blood dyscrasias associated with drug therapy. Table 3 shows the therapeutic groups, and individual drugs, that predominate. NSAIDs, mianserin and co-trimoxazole were especially implicated in the development of both red and white cell dyscrasias. The elderly appear to be particularly vulnerable to haematological toxicity with both the latter drugs (Committee on the Safety of Medicines, 1983, 1985). The association between thrombocytopenia and the use of thiazide diuretics, though rare, is widely recognised.

Renal toxicity

Nephrotoxicity has most often been described in patients receiving, ACE inhibitors (29 enalapril, nine captopril), antibiotics (18 reports) and NSAIDs (four reports).

Anaphylaxis

Desensitising vaccines (30 reports), muscle relaxants and intravenous anaesthetic agents (18

and nine reports respectively), and radiological contrast media (16 reports) have been most often described in association with anaphylaxis and anaphylactoid reactions. The Chairman of the Committee on Safety of Medicines wrote to all doctors, in September 1986, advising that desensitising vaccines should only be given where facilities for cardio-respiratory resuscitation were available, and that patients should be observed for 2 h after injection.

Reactions to newer drugs

The Committee asks doctors and dentists to report *all* suspected adverse reactions, whether mild or serious, *with new products* (marked with an inverted black triangle in the British National Formulary, the Data-Sheet Compendium and MIMS). Tables 4, 5 and 6 show the numbers of reports (total, serious and deaths) to new chemical entities introduced between 1984 and 1986 (respectively).

Of the new drugs introduced in 1984, appreciable numbers of adverse drug reaction reports have been received for diltiazem and mitozantrone. Those occurring in association with mitozantrone, a cytotoxic agent, were predominantly of blood dyscrasias and are typical of compounds of this class. The neurological and

Table 3 Therapeutic groups and drugs most frequently associated with reports on blood dyscrasias (1986)*

	<i>Aplastic anaemia marrow hypoplasia</i>	<i>Agranulo- cytosis granulo- cytopenia</i>	<i>Thrombocytopenia</i>
Non steroidal anti-inflammatory drugs	7	31	10
Antidepressants	9	34	4
– mianserin	9	32	6
All antimicrobials	24	28	18
– cotrimoxazole	12	12	10
– trimethoprim	8	5	2
– amodiaquine	1	11	1
All anticonvulsants	7	8	7
– sodium valproate	4	5	2
Diuretics	3	2	15
– thiazide-containing	2	1	10
ACE inhibitors	1	6	6
– captopril	1	4	3
– enalapril	0	2	3
Carbimazole	1	8	0
Sulphasalazine	3	9	3

* Some patients had more than one reaction.

Table 4 Suspected adverse reactions to drugs first marketed in 1984

<i>Approved name</i>	<i>Brand name</i>	<i>Date of marketing</i>	<i>Total ADR</i>	<i>Serious (Deaths)</i>
Piretanide	Arelix	Feb 1984	38	4(0)
Dipivefrin	Propine	Mar 1984	7	0(0)
Inosine pranobex	Imununovir	Apr 1984	38	5(1)
Isoflurane	Aerrane Forane	May 1984	5	5(0)
Amsacrine	Amsidine	Jun 1984	4	4(1)
Diltiazem	Tildiem	Jun 1984	183	33(2)
Mitozantrone	Novantrone	Jun 1984	41	30(7)
Betaxolol	Kerlone	Sep 1984	7	0(0)
Norethisterone oenanthate	Noristerat	Nov 1984	4	0(0)
Terlipressin	Glypressin	Dec 1984	0	0(0)

Table 5 Suspected adverse reaction to drugs first marketed in 1985

<i>Approved name</i>	<i>Brand name</i>	<i>Date of marketing</i>	<i>Total ADR</i>	<i>Serious (Death)</i>
Epirubicin	Pharmorubicin	Feb 1985	4	3(2)
Enalapril	Innovace	Apr 1985	696	173(29)
Sulconazole	Exelderm	Apr 1985	12	1(0)
Mupirocin	Bactroban	Jun 1985	15	1(0)
Mesalazine	Asacol	Jul 1985	73	7(0)
Gemeprost	Cervagem	Aug 1985	1	0(0)
Inactivated lactobacillus	Gyntren	Nov 1985	2	0(0)
Somatrem	Somatonorm	Dec 1985	1	0(0)

psychiatric reactions in patients receiving diltiazem, a calcium-channel blocker, are mentioned above. This product has also been implicated in reports of adverse cardiovascular (11 reports), dermatological (six reports), and pulmonary (six reports) reactions. The reports of adverse cardiovascular effects mainly described worsening of angina or chest pain, and the pulmonary reactions were of dyspnoea. The absence of reports of hepatotoxicity with isoflurane contrasts with the continued reporting of liver damage with halothane mentioned above.

Although it has been extensively prescribed, the substantial numbers of reports of suspected adverse reactions to enalapril remains a cause

for concern. Severe reactions with this compound predominantly involved the skin (25 reports), the kidney (57 reports), and the cardiovascular system (32 reports). Comparisons with the only other licensed ACE inhibitor, captopril, are difficult because the two products have been available for different periods of time, and because they were introduced with differing indications. It is not yet clear to what extent the revised prescribing advice given by the manufacturer of enalapril, during 1987, has influenced the incidence of its adverse reactions. Reports currently being received, however, suggest that the ACE inhibitors are being used in a way that does not adequately conform to the relevant

Table 6 Suspected adverse reactions to drugs first marketed during 1986

<i>Approved name</i>	<i>Brand name</i>	<i>Date of marketing</i>	<i>Total ADR</i>	<i>Serious (Death)</i>
Etodolac	Lodine Ramodan	Jan 86 Mar 86	169	27(1)
Alclometasone	Modrasone	May 86	0	0(0)
Carboplatin	Paraplatin	May 86	1	1(0)
Carteolol (eye drops)	Teoptic	May 86	1	0(0)
Buserelin	Suprefact	Jun 86	1	0(0)
Propofol	Diprivan	Jun 86	24	6(0)
Terodiline	Terolin	Jul 86	12	2(0)
Metipranolol (eye drops)	Glauline	Aug 86	1	0(0)
Digoxin – specific antibody	Digibind	Sep 86	0	0(0)
Nicardipine	Cardene	Sep 86	5	2(0)
Gemfibrozil	Lopid	Oct 86	0	0(0)
Nedocromil	Tilade	Oct 86	5	0(0)
Betaxolol (eye drops)	Betoptic	Nov 86	0	0(0)
Aztreonam	Azactan	Dec 86	0	0(0)
Ticarcillin and clavulanic acid	Timentin	Dec 86	0	0(0)

Data Sheets and the guidance of either the CSM or the manufacturer. The reactions reported in patients receiving mesalazine (a formulation of 5-aminosalicylate for the management of ulcerative colitis) included three cases of leucopenia or granulocytopenia.

It is too early to draw firm conclusions about the adverse reaction profiles of drugs introduced during 1986. The serious adverse effects associated with etodolac (27 reports) include, however, gastrointestinal reactions (11 reports), skin reactions (four reports) and pulmonary reactions (four cases). At this stage, the toxicity of this particular NSAID cannot be distinguished from other members of the class that are currently available on prescription.

The reports of less serious reactions revealed, with few exceptions, typical patterns of toxicity. Skin rashes predominated in less serious adverse reaction reports concerned pirtanide, inosine pranobex and mesalazine. Reports associated with diltiazem included both rashes (erythematous, maculo-papular and urticaria) and headache. Milder reactions reported with

etodolac were primarily gastro-intestinal (nausea, vomiting, dyspepsia and diarrhoea). Reports of coughing were particularly striking amongst the less severe reactions associated with enalapril.

Conclusion

As in previous years, the yellow card system continues to make an important contribution to the safety assessment of marketed drugs. It relies on the dedication, energy and enthusiasm of a relatively small number of doctors and dentists, and the Committee will be grateful to them for their assistance. Adverse reactions, however, are still grossly under-reported (Rawlins, 1988a) and the CSM asks *all* doctors and dentists for their help in ensuring that problems with both new and established drugs are brought to its attention.

We are grateful to the Committee on the Safety of Medicines for permission to publish data from the Adverse Reactions Register.

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(Received 22 January 1988,
accepted 3 August 1988)

Appendix A CSM serious adverse drug reactions list. Reactions not included prior to July 1986 market with (*)

Abdominal wall dysgenesis	*	Aortic coarctation	*
Abnormal twins	*	Aortic stenosis	
Abortion		Apnoea	
Abortion missed		Apnoea neonatal	
Abortion septic		Arrhythmia	
Absent digits	*	Arrhythmia atrial	
Acidosis		Arrhythmia nodal	
Acidosis lactic		Arrhythmia ventricular	
Adams Stokes syndrome		Arteritis	
Adrenal hypercorticism		Artery malformation	*
Adrenal insufficiency		Arthritis rheumatoid	*
Adrenogenital syndrome congenital	*	Arthropathy	*
Agranulocytosis		Aseptic bone necrosis	
Airways obstruction		Asphyxia	
Allergic reaction		Asphyxia neonatal	
Alveolitis allergic		Asthma	
Alveolitis fibrosing		Asthma aggravated	
Amblyopia		Atrial septal defect	*
Anaemia aplastic	*	AV block	*
Anaemia haemolytic		Biliary atresia	*
Anaemia haemolytic DCN		Bladder abnormality congenital	*
Anaemia haemolytic DCP		Bladder calculus	*
Anaemia haemolytic G6PD		Bladder carcinoma	*
Anaemia haemolytic ICP		Bleeding time increased	
Anaemia hypoplastic		Blindness	
Anaemia sideroblastic	*	Blindness congenital	*
Anaphylactoid reaction		Bone necrosis	
Anaphylaxis		Bradypnoea	
Anencephaly	*	Brain damage congenital	*
Aneurysm ruptured		Brain malformation	*
Angina pectoris		Breast neoplasm female	*
Angina pectoris aggravated		Breast neoplasm male	*
Angioedema		Breast neoplasm malignant female	*
Anorexia nervosa		Bronchospasm	
Ante-partum haemorrhage		Budd chiari syndrome	
Anuria		Bullous eruption	*
Anus imperforate	*	Cardiac arrest	

Cardiac arrest neonatal		Diabetes insipidus	*
Cardiac failure		Disseminated intravascular coagul	
Cardiac failure left		Diverticular perforation	
Cardiac failure right		Driving ability impaired	*
Cardio respiratory depression		Drug dependence	*
Cardiomyopathy		Ductus arteriosus pat.	*
Cataract		Duodenal ulcer haemorrhagic	
Cataract congenital	*	Duodenal ulcer haemper	
Cataract subcapsular	*	Duodenal ulcer perforated	
Catatonic reaction	*	Dyskinesia tardive	
Cerebral atrophy	*	Dyspnoea	
Cerebral haemorrhage		Eclampsia	
Cerebral haemorrhage neonatal		Embolism amniotic	
Cerebral irritation		Embolism arterial	
Cerebrovascular accident		Embolism blood clot	*
Cervix carcinoma	*	Embolism cerebral	
Chest pain		Embolism limb	
Chest pain precordial		Embolism mesenteric	
Chest pain substernal		Embolism pulmonary	
Cheyne-Stokes breathing		Encephalomyelitis	
Chronic renal failure aggravated		Encephalopathy	
Circulatory depression		Encephalopathy hypertensive	*
Circulatory failure		Encephalopathy neonatal	
Circulatory failure neonatal		Endocardial fibrosis	
Cirrhosis biliary		Epidermal necrolysis	
Cleft palate	*	Epilepsy aggravated	
Clubfoot	*	Erythema exudativum	*
Coagulation disorder		Erythema multiforme	
Coagulation disorder neonatal		Erythroblastopenia	
Coagulation time increased		Fibrillation atrial	
Colitis		Fibrillation cardiac	
Colitis pseudomembranous		Fibrillation ventricular	
Colitis ulcerative		Foetal distress	
Coma		Fracture pathological	
Coma diabetic		Gangrene	
Coma hepatic		Gangrene neonatal	
Congenital dislocation of the hip		Gastric carcinoma	
Convulsions		Gastric dilatation	
Convulsions aggravated		Gastric perforation	
Convulsions grand mal		Gastric ulcer haemorrhagic	
Convulsions local		Gastric ulcer haemper	
Convulsions neonatal		Gastric ulcer perforated	
Corneal opacity		Gastritis haemorrhagic	
Corneal ulceration		GI haemorrhage	*
Cot death	*	GI malformation	*
Cyanosis		Glaucoma	
Cyanosis neonatal		Glomerulonephritis	
Deafness		Goitre	*
Deafness congenital	*	Gonadal dysgenesis	*
Deafness nerve		Goodpasture syndrome	
Death foetal	*	Graft rejection	
Dementia	*	Granulocytopenia	
Depression	*	Grey baby syndrome	
Depression psychotic	*	Guillain Barre syndrome	
Depression worsened	*	Haematemesis	
Dermatitis exfoliative		Haemoglobinuria	
Dermatomyositis	*	Haemolysis	
Diabetes hyperosmolar non-ketotic		Haemoperitoneum	

Haemorrhage accidental		Infection aggravated	
Haemorrhage ocular		Infection bacterial	
Haemorrhage rectal		Infection fungal	
Hallucination	*	Infection viral	
Hare lip	*	Infertility female	*
Heart block		Infertility male	*
Heart malformation	*	Influenza-like syndrome	*
Hemianopia		Injection site necrosis	
Hemiparesis		Intestinal gangrene	
Hemiplegia		Intestinal ischaemia	*
Hepatic adenoma		Intestinal malformation	*
Hepatic cirrhosis		Intestinal obstruction	
Hepatic failure		Intestinal perforation	
Hepatic function abnormal		Intestinal pseudo obstruction	
Hepatic necrosis		Intestinal stenosis	
Hepatic neoplasm malignant		Intestinal ulceration	
Hepatitis		Intestinal ulceration perforated	
Hepatitis cholestatic		Intracranial pressure increased	
Hepatocellular damage		Iridocyclitis	
Hepatocellular damage neonatal		Iritis	
Hepatoma		Jaundice	
Hepatomegaly		Jaundice cholestatic	
Hepatosplenomegaly		Jaundice neonatal	
Hepatosplenomegaly neonatal		Keratitis	
Hermaphrodite	*	Keratoconjunctivitis	
Herxheimer reaction		Laryngismus	
Hydrocephalus		Larynx oedema	
Hypercalcaemia		LE rash	
Hyperkalaemia		LE syndrome	
Hyperpyrexia		Leucopenia	
Hyperpyrexia malignant		Leukaemia	*
Hypertension		Leukaemia acute	*
Hypertension aggravated		Leukaemia lymphocytic	*
Hypertension intracranial		Leukaemia monocytic	*
Hypertension portal		Leukaemia myeloid	*
Hypertension pulmonary		Leukaemia neonatal	*
Hypertension rebound		Liver fatty	
Hyperthyroidism		Lymphoma-like disorder	*
Hyperuricaemic nephropathy		Malformations multiple	*
Hypoadrenocorticism		Manic reaction	*
Hypocalcaemia		Marrow aplasia	
Hypoglycaemia		Marrow depression	
Hypoglycaemic reaction		Marrow hypoplasia	
Hypokalaemia		Megacolon toxic	
Hyponatraemia		Melaena	
Hypotension		Meningitis	*
Hypotension postural		Microcephaly	*
Hypothermia		Micrognathia	*
Hypothyroidism		Microphthalmia	*
Hypothyroidism congenital		Mongolism	*
Hypoventilation		Mono neuritis multiplex	
Hypoxia		Monoplegia	
Ileus		Motor neurone disease	*
Ileus paralytic		Multiple sclerosis	*
Ileus paralytic neonatal		Mutagenic effect female	*
Increased intraocular tension		Mutagenic effect male	*
Infantile spasms		Myasthenia	
Infarction renal		Myasthenia gravis	

Myasthenia gravis aggravated		Phlebitis deep	
Myelitis		Phocomelia	*
Myelofibrosis	*	Pituitary disorder	
Myelopathy		Pituitary malfunction	
Myeloproliferative disorder	*	Pleural effusion	
Myocardial infarction		Pleural fibrosis	
Myocardial ischaemia		Pneumonia eosinophilic	
Myocarditis		Pneumonitis	
Myxoedema		Polands syndrome	*
Neonatal coagulopathy		Polyarteritis nodosa	
Nephritis		Polyneuropathy	
Nephritis interstitial		Porphyria	
Nephropathy toxic		Pregnancy ectopic	
Nephrosis		Pregnancy toxemia	
Neuritis		Priapism	
Neuritis bulbar		Prothrombin decreased	
Neuritis cranial		Psychosis	*
Neuritis motor		Pulmonary fibrosis	
Neuritis sensory		Pulmonary haemorrhage	
Neuroleptic malignant syndrome		Pulmonary infarction	
Neuropathy		Pulmonary oedema	
Ocular haemorrhage		Pulmonic stenosis congenital	
Oculomotor nerve paralysis		Purpura thrombopenic thrombotic	
Oesophageal atresia	*	Pyometra	
Oesophageal carcinoma	*	Quadriplegia	
Oesophageal rupture		Rectal atresia	*
Oesophageal stricture		Rectal carcinoma	*
Oesophagus ulceration		Renal agenesis	*
Oesophagus ulceration haemorrhage		Renal calculus	*
Oligospermia		Renal cortical necrosis	
Oliguria		Renal dysgenesis	
Optic atrophy		Renal failure	
Optic neuritis		Renal papillary necrosis	
Osteomalacia		Renal tubular necrosis	
Osteonecrosis		Resp distress syndrome neonatal	
Ototoxicity		Resp tract haemorrhage neonatal	
Ovarian cyst malignant	*	Respiratory arrest	
Pancreatitis		Respiratory depression	
Pancytopenia		Respiratory depression neonatal	
Papilloedema		Respiratory insufficiency	
Paralysis flaccid		Respiratory obstruction unspec.	
Paralysis spastic		Retinal detachment	*
Paranoid reaction	*	Retinal disorder	
Paraplegia		Retinal haemorrhage	
Paresis		Retinal vein thrombosis	
Pelvic inflammatory disease		Retinitis	
Peptic ulcer haemorrhagic		Retinopathy	
Peptic ulcer haemper		Retrobulbar neuritis	
Peptic ulcer perforated		Retroperitoneal fibrosis	
Pericardial effusion		Reyes syndrome	
Pericarditis		Rupture of uterus	
Peripheral gangrene		Salpingitis	
Peripheral ischaemia		Sarcoidosis	*
Peritoneal fibrosis diffuse		Sarcoma	*
Peritonitis		Schizophrenic reaction	*
Peritonitis hyperplastic		Scleroderma	*
Peritonitis sclerosing		Screaming	
Phlebitis		Sepsis	

Sepsis neonatal		Thrombophlebitis retinal vein	
Sepsis secondary		Thrombophlebitis vena cava	
Septicaemia		Thrombosis	
Serum sickness		Thrombosis arterial	
Skeletal malformation	*	Thrombosis arterial arm	
Skin exfoliation	*	Thrombosis arterial leg	
Skin necrosis		Thrombosis carotid	
Spina bifida	*	Thrombosis cerebral	
Status asthmaticus		Thrombosis cerebral arterial	
Stevens Johnson syndrome		Thrombosis coronary	
Stillbirth		Thrombosis mesenteric vessel	
Stomatitis necrotizing		Thrombosis pulmonary	
Stridor		Thrombosis retinal artery	
Subarachnoid haemorrhage		Thyroid carcinoma	*
Sudden death filed	*	Thyrotoxicosis	
Sudden death unexplained	*	Tracheo-oesophageal fistula	*
Suicide attempt	*	Transposition of great vessels	*
Syncope		Twins conjoined	*
Tachycardia		Unconsciousness	
Tachycardia paroxysmal	*	Upper motor neurone lesion	*
Tachycardia supraventricular		Uraemia	
Tachycardia ventricular		Ureteric calculus	*
Teratoma		Urinary retention	*
Tetany	*	Urinary tract malformation	*
Thrombocytopenia		Uterine carcinoma	*
Thrombocytopenia neonatal		Uterine haemorrhage	
Thromboembolism		Uterine perforation	
Thrombophlebitis		Uterine spasm	
Thrombophlebitis arm		Uveitis	
Thrombophlebitis arm deep		Vascular malformation peripheral	*
Thrombophlebitis cerebral vein		Vasculitis	
Thrombophlebitis deep		Vasculitis allergic	
Thrombophlebitis leg		Water intoxication	
Thrombophlebitis leg deep		White attacks	
Thrombophlebitis mesenteric vein		Withdrawal convulsions	
Thrombophlebitis multiple		Withdrawal syndrome	*
Thrombophlebitis multiple deep		Withdrawal syndrome neonatal	*
Thrombophlebitis neonatal		Xerophthalmia	
Thrombophlebitis pelvic vein			