primary reason was removed. However, we also found that we were picking up other conditions and were beginning to ask questions about their prevalence in the population and whether they could be treated.

DR. FRANKLIN: You are discovering the extent of the problems and whether they are preventable; you must know what you are dealing with before you can begin treatment.

CHAIRMAN: Aren't we back at the greater good concept?

DR. PORTER: The greater good concept is secondary, surely; when these tests are done on babies in my practice I've never been conscious of the slightest difficulty or anxiety, but perhaps I haven't been looking.

DR. RAINE: There is a lot of anxiety, generated particularly by an occasional midwife, who says: "oh it's just a test to see if your baby is mentally handicapped." You couldn't conceive of a worse presentation than this. We tried in the early stages to have a lot of publicity—talks, newspaper articles, and television programmes—but we've got a bit lax about this.

DR. PORTER: But surely the individual paediatrician needs to know whether a child has an inborn error of metabolism?

DR. RAINE: Yes.

DR. PORTER: Therefore this test is for the welfare of that child and not an experiment. The greater good for society is secondary, and so no ethical questions arise.

DR. FRANKLIN: But you can't always treat what you discover.

DR. RAINE: We found that histidinaemia and prolinaemia were as common as phenylketonuria—that was new knowledge. There's probably a good case for treating histidinaemia, and so we did, but nobody knows about prolinaemia, so we decided not to treat these babies, but are following them up.

DR. FRANKLIN: What is your incidence of phenylketonuria?

DR. RAINE: One in ten thousand.

DR. FRANKLIN: So there are 9,999 babies having pricks for the sake of one.

CHAIRMAN: Shall we ever get to the point where a venepuncture for research on a normal child is accepted as right?

DR. FRANKLIN: I'm not sure that they are considered to be wrong; but you need to defend your position clearly if you do one—and that's as it should be.

DR. PORTER: At present they are regarded as wrong mainly because of what I regard as wrong advice to the M.R.C.

DR. RAINE: We also need to think carefully before we bring the child to the hospital for an unnecessary visit. A lot of our effort goes into managing the child with a metabolic disease at home.

DR. PORTER: This emphasizes that a lot more research should be done where these difficulties are much less—in general practice.

CHAIRMAN: I think that is the subject of another discussion.

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General Practice Observed

Iatrogenic Disease in General Practice: Its Incidence and Effects

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Summary

A year's survey of iatrogenic disease in general practice showed that one consultation in every 40 was the result of iatrogenic disease. Iatrogenic disease may affect the doctor/patient relationship, often leading the doctor to feel guilty or the patient to become aggressive.

Introduction

Reports and discussion of the adverse effects of medical treatment form a substantial part of both lay and medical literature. Remarkably little is known, however, of its incidence in the community, the reports published by the Committee on Safety of Medicines probably indicating only the tip of the iceberg. Several surveys have dealt with the incidence in hospital practice. Hurwitz and Wade¹ observed

1,268 hospital inpatients, and drug reactions were found in 10.2% of all patients receiving drug therapy (digitalis, ampicillin, and bronchodilators particularly). In medical wards the incidence was 16.4%. Surveys in other hospitals showed considerable variation in incidence, probably because of different methods of reporting the side effects. Hurwitz² found that 2.9% of 1,268 patients in hospital were admitted because of adverse reactions to drugs given for therapeutic reasons (digoxin, antibiotics, corticosteroids, anticoagulants, analgesics, and tranquillizers were the commonest offenders). A further 2.1% of the patients were admitted with self-poisoning.

This survey attempts to estimate the prevalence of iatrogenic disease in general practice and draws attention to the effects on the doctor/patient relationship.

Method

The practice under study consists of 6,200 patients and is mixed rural and industrial on the edge of the South Yorkshire coalfield. Patients move freely among the three partners, whose prescribing habits are similar. Comparison between the prescribing habits of the practice and the national pattern is shown in fig. 1, where the figures are taken from a sample

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FIG. 1—Comparison between prescribing habits of the study practice and national pattern, showing breakdown of prescribed items into therapeutic categories expressed as percentage of whole.

month during the survey. In a further sample month (June) the number of prescriptions per person issued by the practice was 0.408 compared with an area average of 0.442 and a national average of 0.438.

The definition of iatrogenic disease applied during this survey was that of Cluff *et al.*³ "Any adverse reaction to medication undesired or unintended by the physician." Any consultation which occurred as a direct result of iatrogenic disease was regarded as an "iatrogenic consultation." Such consultations were recorded by one partner in his own consultations from 1 January to 31 December 1971.

Results

The total number of consultations during the survey was 9,315. Of these, a total of 239 (2.6%) were thought to be the result of the ill effects of medical or surgical treatment. Some iatrogenic incidents accounted for several consultations—for example, the control of hypothyroidism after partial thyroidectomy accounted for six consultations by the same patient in the course of the survey.

SEX

Of all consultations, 53% were with females, but in iatrogenic consultations females outnumbered males in the ratio of 2 to 1 (fig. 2). The contraceptive pill accounted for 14% of all iatrogenic consultations, and if we exclude these figures the male : female ratio is 1 : 1.6.

FIG. 2—Sex ratio of iatrogenic consultations in the practice in 1971. Hatched area shows percentage related to contraceptive pill.

AGE

In the first year of life there were 10 iatrogenic consultations

of which 8 were related to antibiotics. The incidence of iatrogenic disease was found to be low after the first year of life for the next 10 years and thereafter gradually increased to a maximum at 21-39 years and then fell and remained constant thereafter (fig. 3). The earliest age at which a sensitivity reaction was recorded was 10 years—urticaria secondary to oral penicillin. Drug sensitivity reactions were noted in all age groups thereafter.

FIG. 3—Incidence of iatrogenic disease in developmental age groups. Percentage of all consultations in age groups concerned.

TYPE OF TREATMENT

Prophylaxis.—Thirty-three iatrogenic consultations (14%) were related to the contraceptive pill (fig. 4). All the eight consultations in the under 20 age group taking the pill resulted from irregular menstrual bleeding, either "spotting" or amenorrhoea after stopping the pill. The remaining 25 consultations (in the over 20 age group) were: vaginal discharge in 10 patients (six proved candidiasis); hypertension and/or headache in eight patients; irregularities of menstruation in two, and weight gain in a further two. Twelve iatrogenic consultations (5%) resulted from reactions to immunization and vaccination procedures. These included 11 local reactions—triple immunization (5), B.C.G. vaccinations (2), adsorbed tetanus toxoid (2), and T.A.B. immunization (2). There was one general reaction to cholera vaccination. One consultation was the result of severe pelvic cramps after the insertion of a coil.

FIG. 4—Prevalence of iatrogenic disease in treatment groups as a percentage of the whole.

Ill Effects of Antibiotic Therapy in Patients Under Study

Antibiotics	Gastrointestinal Disorder	Candida	Sensitivity Eruption	Others
Ampicillin ..	3	12	5	0
Co-trimoxazole ..	1	2	5	1
Tetracyclines ..	10	2	2	1
Penicillin ..	0	0	3	0
Erythromycin ..	1	2	0	0
Sulphas ..	0	0	1	1
Total ..	15	18	16	3

Antibiotics—The ill effects of antibiotic therapy resulted in 52 consultations (21.7%) (fig. 4, table). Those reactions classed as gastrointestinal excluded any in which *Candida albicans* was detected microscopically from either the mouth, perianal region, or the vagina. Two of the sensitivity reactions to ampicillin occurred in infectious mononucleosis (blood film and Paul-Bunnell test positive). One patient in chronic renal failure suffered an exacerbation of her disorder when given oxytetracycline for her chronic bronchitis.

Cardiovascular Therapy—There were 19 iatrogenic consultations relating to the ill effects of drugs used in the treatment of cardiovascular disease (8%) (fig. 4). Only two incidents related to the over-dosage of digoxin were recorded but there was one local reaction to intravenous administration of the drug. Two consultations were the results of severe headache after taking glyceryl trinitrate. Ill effects of the Rauwiloid derivatives resulted in eight consultations, six because of depression. Withdrawal of the drug resulted in improvement in all but one patient, who required antidepressive therapy. Four consultations resulted from the ill effect of thiazide diuretics. On two occasions gout was confirmed biochemically and parasthesia of the arms and legs accounted for another incident. One case of hypokalaemia was confirmed biochemically (in a patient also on cortisone replacement therapy).

Local Applications—Eighteen iatrogenic consultations (7.5%) resulted from the ill effects of local applications (fig. 4). Locally applied fluorinated steroids resulted in three consultations because of telangiectasia of the face. A further consultation followed prolonged application of local steroid to the hands and arms resulting in severe atrophy of the skin with ecchymoses. In addition to direct ill effects of these ointments they were thought to be responsible for altering the clinical picture in three cases of tinea (confirmed microscopically) and in one case of impetigo. Exogenous dermatitis was seen at nine consultations. A variety of applications was incriminated, including Elastoplast (3), iodoform derivatives (2), local antibiotics (2), and unidentified ointments (2).

Central Nervous System Therapy—Twenty-three iatrogenic consultations (10%) were related to drugs affecting the central nervous system. On seven occasions tricyclic antidepressants were the cause. Acute glaucoma complicated therapy with amitriptyline twice and surgery was required on both occasions. Other ill effects of tricyclic antidepressants which resulted in iatrogenic consultations included dizziness, dry mouth, difficulties with micturition and photosensitivity. Two patients developed dyskinesia in conjunction with fluphenazine decanoate (Modectate) and trifluoperazine, (Stelazine). There was one case of intrahepatic biliary obstruction after chlorpromazine (Largactil), which cleared after withdrawing the drug. Severe gastrointestinal bleeding (requiring transfusion) after aspirin was recorded on one occasion. Acne vulgaris complicated anticonvulsant therapy (phenytoin) in two patients. Addiction was noted on three occasions, two related to barbiturates and one to diazepam.

Corticosteroids—Three patients on systemic corticosteroids suffered ill effects of therapy necessitating a total of 12 consultations. One suffered osteoporosis with some vertebral collapse, another had unacceptable facial changes in addition to hypertension and osteoporosis. The third, on triamcinolone for 12 years for what eventually proved to be gout, developed a severe facial herpes simplex with considerable secondary infection.

Surgery—Forty-five consultations were the result of ill-effects of surgical procedures (19%) (fig. 4). The most common ill effect of surgery was a keloid scar (seven consultations after thoracotomy (1), thyroidectomy (4), and laparotomy (2)). There was a death after a "cold" cholecystectomy in an otherwise healthy man and a severe postpartum

haemorrhage requiring the flying squad after probable mismanagement of the third stage of labour. Control of surgery-induced hypothyroidism accounted for eight iatrogenic consultations (two patients). Otitis externa followed ear syringing in four patients (six consultations). Surgical treatment for duodenal ulcer resulted in one case of macrocytic anaemia (after emergency gastrectomy); both the serum B₁₂ and folate levels were low. There was one case of post-gastrectomy syndrome after a "cold" gastrectomy and one case of "blind loop" syndrome after a gastroenterostomy. These cases accounted for eight iatrogenic consultations. Minor surgical procedures in the practice resulted in four iatrogenic consultations—corn formation (2), secondary bleeding, and secondary infection, all after curettage of plantar warts. Attempted manipulation of the neck in a patient with acute torticollis resulted in collapse, presumably due to carotid sinus compression. Dental procedures resulted in only one iatrogenic consultation as a result of bleeding from the socket after extraction.

Miscellaneous Procedures and treatments which resulted in ill effects included four for secondary infection after post-radiation fibrosis in a case of Hodgkin's disease. Radiotherapy was also the cause of a severe reaction in the mouth and throat in a case of pharyngeal carcinoma resulting in two consultations. A fracture of the head of the radius was not diagnosed but treated with physiotherapy, and although it healed, alignment was not good and resultant problems in the elbow joint resulted in two consultations. A painful nodule of the buttock after intramuscular injections of iron dextran necessitated two consultations.

Discussion

One of the problems encountered in a survey of this kind is the difficulty of defining and measuring certain ill effects of medical treatment. For instance, on only three occasions was addiction noted, yet many repeat prescriptions were issued—many for tranquillizers or sedatives. Is this iatrogenic disease? Balint *et al.*⁴ explored the problem of the repeat prescription and implied that the doctor usually accedes readily to this regimen and may indeed resist change. One item of every five prescribed in our practice during a sample month was for a sedative, tranquillizer, or antidepressant (fig. 1).

Any investigation of the incidence of iatrogenic disease is affected by the "non-drug" reaction. Reidenberg and Lowenthal⁵ described the incidence of symptoms in a healthy population on no medication and Green⁶ studied the occurrence of symptoms after administration of a placebo. A control group would be necessary to exclude such "non-drug" reactions from a survey like this.

In the present survey the most striking area of "non-drug" reactions was probably experienced in relation to the contraceptive pill. Widespread publicity of any ill effect, real or implied, of this form of medication sensitizes both the patient and the doctor so that any symptom experienced by the patient while taking the pill is attributed to it.

The incidence of reactions in the aged (60+) was no higher than in other adult age groups. Hurwitz and Wade¹ found or implied an increased incidence in the older people. However, the side effects of medical treatment noted in the older age group were, in this survey, less likely to be confused with the "non-drug" reaction and many were observed objectively.

The ill effects of drugs used in the management of disease of the cardiovascular system although well-publicized were comparatively uncommon in this survey. Digoxin over-dosage was noted only twice. It is usual in our practice to give potassium supplements with diuretic therapy either separately or in a combined tablet. Only one case of potassium

depletion was proved biochemically but less obvious degrees of the condition are difficult to prove and may have been under-diagnosed in this review. Rauwiloid derivatives are still widely used in the practice as hypotensives. Six consultations resulting from depression during such therapy make one wonder whether their place should not be taken by, for example, chlorthalidone in the management of mild hypertension.

The ill effects of long-term, locally-applied potent corticosteroids are well described but still occur regularly. Many patients originally given these for psoriasis and long-standing eczema are "repeat prescription" patients and obtain their supplies in the practice without being seen regularly by the doctor. The consequent atrophy and telangiectasia of the skin which was noted on four occasions in our survey are probably the result of such long-term therapy. Unfortunately, patients are loath to stop application because of the rebound phenomenon that often occurs. Moreover, local steroid therapy may become a panacea for all skin ills for they almost always relieve irritation (if only temporarily) no matter what the underlying cause.

The association of the tricyclic antidepressants and acute glaucoma has not been described though they are known to be contraindicated in chronic glaucoma. The relationship would not have been noted in this survey except that the two incidents involved occurred within a fortnight of each other and in identical circumstances.

Throughout the duration of this survey one gained the impression that a patient who had suffered one iatrogenic incident was more likely to suffer another. This impression of the recurrence of iatrogenic disease is substantiated by Norman and Cluff⁷ and Hurwitz.⁸ The incidence of recurrence was not specifically measured in this survey.

The effect on the doctor/patient relationship of iatrogenic disease is of some interest. When the treatment which he recommended caused ill effects of which the patient complained the doctor usually felt guilt and this manifested itself as either anger, usually towards the patient, or over activity in care. The patient reacted in two ways. (1) Resentful, "Experimenting on me," "Doesn't know his job." In an aggressive patient this resentment resulted in anger at the doctor but in the "poor me" patient it resulted in further regression into his illness. (2) Contrarily, the ill effects of treatment, although uncomfortable, were appreciated by some patients—for example, an antibiotic "bringing it out through the bowels."

Nevertheless, when both the doctor and the patient reacted aggressively to each other the doctor/patient relationship was considerably strained, though it never became untenable. An iatrogenic incident sometimes affected further consultations. The recurrence of iatrogenic disease in the same patient occasionally brought the doctor to regard such patients as "awkward" or "neurotic." The patient, dependent on his type and the nature of the side effects he had suffered reacted in one of three ways. He sometimes had great regard for his doctor, "He was marvellous when I had that rash"; sometimes he punished his doctor—for example, by demanding a visit instead of attending the surgery, the request for a visit often being late—or sometimes he no longer trusted his doctor and demanded early referral. In the course of this survey no patient left the list because of ill effects of medical treatment.

The following case history may exemplify all the problems of iatrogenic disease in general practice.

A 23-year-old married woman was an "ideal" patient. Shortly after becoming pregnant she developed acute cystitis which was treated with sulphamethizole. Seven days later she developed a generalized irritating maculopapular eruption. She was reassured, the drug was stopped, and she was given promethazine hydrochloride to relieve the irritation. Within 10 to 12 days she felt quite well, the eruption had subsided, and she went sunbathing. Within a few hours she developed an acute photosensitization which resulted in some blistering of her face, arms, and feet. This may have been due to either the promethazine or the sulphamethizole. Four months later on in the pregnancy she was noted to have an iron-deficiency anaemia. She was given intramuscular iron (iron dextran) and developed an acutely tender nodule in the right buttock. She was concerned at the possibility of developing a sarcoma in that site. Her confinement proceeded normally. When the child was four months old he developed an acute respiratory tract infection, which responded well to ampicillin. Within four days treatment had to be discontinued because of severe diarrhoea and obvious candidiasis of the mouth and buttocks.

Her requests for visits are now usually late and there have been several calls "off the street." Consultations are conducted in an atmosphere of suspicion, mistrust, and a mild degree of aggression on the patient's side and hesitation from the doctor's side.

PREVENTION

In an effort to prevent iatrogenic disease, various measures are taken in the practice. All records are labelled when a sensitivity reaction occurs (both the envelope and current continuation card). Moreover, each patient suffering a sensitivity reaction is issued with a card (which fits into the plastic envelope provided for the steroid card), brightly coloured and stating the drug to which the patient is sensitive. All referral letters to hospital include details of current therapy and any drug sensitivities are underlined in red. During the survey no single letter from hospital included details of sensitivity reactions noted in hospital though two patients stated that they had suffered drug reactions during their stay as inpatients.

The repeat prescription card is not yet used in our practice. No doubt it does prevent confusion in therapy and is useful when the patient is away from home. As noted above, however, there are reservations about increasing the ease of obtaining long-term therapy without regular consultation with the doctor.

Of the iatrogenic consultations noted in the survey, 18 incidents were reported to the Committee on Safety of Medicines. This is a considerably higher referral rate than average as reported by Wade,⁹ "During the five and a half years to October 1969 4,527 general practitioners, about 1 in every 5 in the country, sent a total of 10,011 reports to the Registrar."

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