to damage by cytotoxic drugs. A study of childhood-cancer survivors, however, showed no evidence of a raised rate of spontaneous abortions or malformations in the progeny of men after treatment with various cytotoxic agents.[1] On the other hand, a recent report has described two cases of severe malformations after chemotherapy for acute myelogenous leukaemia in two men.[2]

In our case the lack of malformations in the child born after the second pregnancy is noteworthy as the father had been treated with MTX and 6-MP at the time of conception for over one and a half years. Both drugs are known to carry a definite teratogenic risk in the mother.[2] In view of the considerable rate of spontaneous abortions in the general population, it is not possible to decide whether the previous abortion was due to a mutagenic effect of the chemotherapy, was otherwise related to the malignancy, or was purely coincidental.

The improvements in chemotherapy have led to increasing numbers of young long-time survivors of malignant disease. These patients often seek information about the risk to the fetus in case of a pregnancy. To obtain data for better counselling more reports about the outcome of such pregnancies are needed.

We thank Dr M Metaxas, Blutspendezentrum des Schweizerischen Roten Kreuz, Zürich, for testing the affiliation and Prof W Schmid, Universitäts-Kinderklinik, Zürich, for the chromosomal analysis.

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Empyema due to splenic abscess in typhoid fever

Typhoid fever is one of the commonest infectious diseases seen at our hospital, where naturally we encounter many of the classical complications. We report here a patient with typhoid fever who developed a rare complication: splenic abscess and empyema due to *Salmonella typhi*.

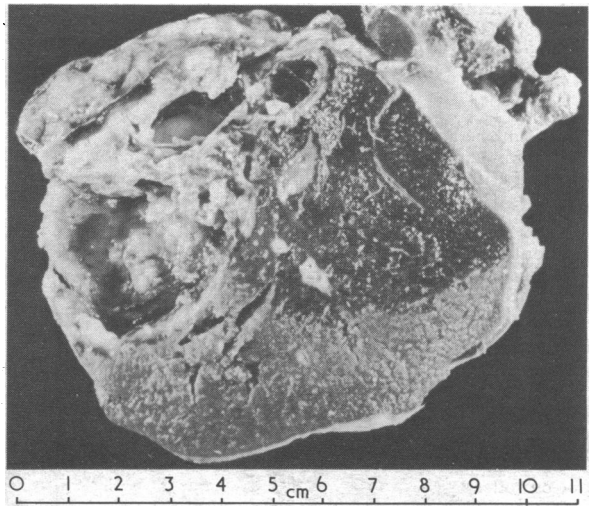
Case report

A 13-year-old girl was admitted to our hospital with two weeks' history of fever. Examination showed that she had a soft, slightly enlarged spleen. Investigations disclosed: haemoglobin 11 g/dl; white cell count $6{\cdot}1 \times 10^9$/l, with no eosinophils; ESR 40 mm 1 hour; chest *x*-ray film was normal.

The result of blood culture was negative. Agglutinins against the somatic (0) and flagellar antigens of *S typhi* were 1/80 and 1/640, respectively. Typhoid fever was diagnosed and she was started on chloramphenicol, 2 g daily. The girl was discharged on the tenth day symptom-free, but four days later fever returned and she complained of left pleuritic pain. The chest *x*-ray film showed appearances consistent with a left pleural effusion, and this was confirmed on thoracocentesis: the fluid was purulent and on culture grew *S typhi*. A splenic scintiscan disclosed a defect in the upper lobe of the spleen. Findings in an arteriogram was compatible with an abscess. After several pleural taps and further antibiotic treatment (24 g of chloramphenicol) she underwent splenectomy and the diagnosis of splenic abscess was confirmed. No organisms were grown from the pus from the abscess on culture. Her postoperative course was uneventful.

Discussion

A rare complication of typhoid is suppurative cysts of the ovary,[1] while abscesses of the spleen have been reported in patients with haemolytic disorders.[2] Other infective foci[3 4] of salmonellosis include



Specimen obtained at splenectomy showing an abscess in the upper lobe of the spleen.

osteomyelitis, mycotic aneurysms, meningitis, postgastrectomy enteritis, pneumonitis, and salmonella "appendicitis." The organisms most frequently implicated in these cases have been *S typhimurium* and *S chloeraesuis*. We believe that the development of an empyema due to a typhoid splenic abscess in a previously healthy patient is an extremely unusual complication of the disease. The present-day rarity of typhoid splenic abscess itself is confirmed by a recent review,[5] which states that no case has been reported since 1940.

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Aide-mémoire for preparing clinical trial protocols

The list below may serve as an aide-mémoire for those planning clinical trials. It assumes some basic knowledge of clinical trial methodology, but a few of the headings are amplified in footnotes. Further information is available in textbooks such as *Principles and Practice of Clinical Trials*.[1]

Aide-mémoire

1.0 Description and rationale
1.1 Short title
1.2 Descriptive title
1.3 Trial number (serial number and date of revision; insert "draft" until finalised)
1.4 Contact and phone number
1.5 Aim of trial: questions to be answered
1.6 Reasons for doing it

2.0 Entry and exclusion criteria
2.1 Name of clinical disorder
2.2 Definition and limits of disorder
2.3 Age range
2.4 Gender
2.5 Race
2.6 Present therapy
2.7 Previous therapy
2.8 Other criteria

3.0 Recruitment
3.1 Population from which sample drawn
3.2 Method of sampling
3.3 Referral sources and procedure

4.0 Screening test for admission/retention
4.1 First visit
4.2 Repeat visits

5.0 Personnel and roles; titles and locations
5.1 Clinicians
5.2 Controller
5.3 Pharmacist
5.4 Nursing staff
5.5 Manufacturer
5.6 Statistician
5.7 Other contributors, such as clinical pathologists
5.8 Secretary
5.9 Personnel substitutions

6.0 Clinic(s)
6.1 Addresses, telephones

Trial observations: therapeutic and adverse effects
7.1 Symptoms
7.2 Signs : validation of observations
7.3 Other measured variables, including toxicity
7.4 Tablet return or other compliance observations
7.5 Patient preferences/treatment identification*
7.6 Physician preferences/treatment identification*
7.7 Other

8.0 Trial design
8.1 Within or between groups
8.2 Crossover, block, sequential, etc
8.3 Blindness: open, single, double: need for independent assessor
8.4 Treatment periods: number, duration, run-in, washouts
8.5 Is pilot trial needed?

9.0 Treatment allocation
9.1 Stratification/minimisation†
9.2 Allocation procedure: randomised, Latin square, other
9.3 Form and location of treatment code

10.0 Drugs
10.1 Test and comparative
10.2 Dosage form
10.3 Specification and source
10.4 Assurance of comparability, bioavailability
10.5 Quality control, stability
10.6 Packaging and labelling
10.7 Storage and dispensing

11.0 Dosage
11.1 Fixed: one or more dose levels
11.2 Variable: adjustments, limits
11.3 What concurrent treatment permitted or forbidden?

12.0 Statistical design
12.1 Hypotheses under test
12.2 Tails of comparison
12.3 Sample estimates of parameters‡
12.4 Probability criteria α, β, θ§
12.5 Tests to be used
12.6 Handling of dropouts: replacement or not
12.7 Action in cases of adverse drug reactions, treatment failure, loss from trial or incomplete records
12.8 Probable numbers required
12.9 Data handling and computer link
12.10 Stopping rules

*Can the patient or doctor identify the treatment?
†Minimisation: a new method of assigning patients to treatment and control groups.[2]
‡Forecast estimate of variances and means of groups being compared.
§See Good.[1]

13.0 Agreement and consent
13.1 Patients and volunteers
13.2 Service departments
13.3 General Practitioner, industrial medical officer
13.4 Ethics committees
13.5 Committee on Safety of Medicines clinical trial certificate
13.6 Confidentiality, disclosure of information
13.7 Publication

14.0 Documentation required
14.1 Background supporting literature
14.2 Protocol
14.3 Record form
14.4 Treatment allocation procedure
14.5 Labelling
14.6 Consent forms
14.7 Instructions to all collaborators
14.8 Emergency code-breaking procedure
14.9 Warning notice of trial participation for case notes
14.10 Flow sheet

15.0 Other planning matters
15.1 Availability of resources: staff and equipment
15.2 Finance: payments and other expenditure, income
15.3 Foreseen constraints
15.4 Target dates
15.5 Post-trial drug supply and follow-up

Comment

This list was elaborated from a much simpler one that has been used for some time in this department. The revision reflects the increasing sophistication of trial techniques and the extension of legal and ethical obligations. We are indebted to several colleagues for their help (which, somewhat to our dismay, almost always resulted in the inclusion of additional items rather than in deletions or simplification).

Not every heading will apply in every case, but they all deserve consideration, and their omission from the protocol should be deliberate and not through neglect. It would be virtually impossible for anyone to remember so many points in systematic and logical sequence and, since many of them interrelate, it may be necessary to go through them several times in order to achieve the optimum balance. The wording of the final protocol will obviously not slavishly adhere to the headings as set out and should be as simple as possible.

We have provided this list so that others may send us their comments. We would be particularly grateful to hear from those who put the list to practical test. On the basis of such experience we hope to refine it further.

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The list was compiled by present and past members of the unit.

Isoimmunisation after narcotic addiction

Injection of small volumes of red cells is a technique used for boosting blood group antibodies in programmes designed for the production of anti-D. Gunson *et al*[1] showed that high titres of anti-Rhesus antibodies could be induced in Rhesus-negative male volunteers by repeated injections of Rhesus-positive red cells. It was later shown[2] that this could be accomplished by volumes as small as 0·01 ml of red cells. We report a case of the production of isoantibodies