CONDENSED REPORT

Acute leukaemia after busulphan

H STOTT, WALLACE FOX, D J GIRLING, R J STEPHENS, D A G GALTON

British Medical Journal, 1977, **2**, 1513-1517

Summary

During a double-blind study of two years' cytotoxic chemotherapy with busulphan or cyclophosphamide in patients who had had resection of carcinoma of the bronchus the long-term effects of these two drugs were also studied. Four of the 243 patients treated with busulphan developed leukaemia compared with none of the 234 treated with cyclophosphamide and none of the 249 on placebo. None of these four patients received radiotherapy or other cytotoxic chemotherapy before leukaemia was diagnosed, and all four were among the 19 patients who developed pancytopenia while taking busulphan, five to eight years before leukaemia became clinically apparent.

These findings suggest that busulphan is leukaemogenic, though its mode of action is uncertain.

Introduction

Acute leukaemia has been reported after the long-term administration of melphalan in patients with multiple myeloma[1-3] and also after the use of other cytotoxic drugs for treating carcinoma.[1-7]

A large-scale double-blind investigation of over 700 patients was undertaken by a Medical Research Council working party in 1965 to discover whether busulphan and cyclophosphamide delayed or even prevented the recurrence of bronchial carcinoma after the surgical removal of all visible intrathoracic growth. This presented an opportunity to study the long-term effects of these two cytotoxic drugs, particularly the likelihood of their inducing leukaemia.

Patients and methods

There were 726 patients with bronchial carcinoma in the study, all of whom had had all visible intrathoracic growth resected.[8] Immediately after operation the patients were allocated at random to receive daily treatment with busulphan, cyclophosphamide, or placebo. The tablets were indistinguishable, and the study was conducted double-blind throughout the two years of treatment and the subsequent follow-up, neither the patient nor the doctor in charge knowing which agent had been allocated. For the first 10 days of treatment all patients received eight tablets once a day (one tablet of busulphan was equivalent to 0·5 mg and one of cyclophosphamide to 25 mg). Thereafter they received six tablets daily as maintenance chemotherapy. Because of an unexpectedly high incidence of toxicity from the cytotoxic drugs, however, this dose was halved about 11 months after the start of the study to three tablets daily for all three regimens. Altogether 243 patients received busulphan (B series), 234 received cyclophosphamide (C series), and 249 received placebo (P series).

Total leucocyte and platelet counts and haemoglobin concentrations were estimated every month during the first two years and subsequently only when requested by the doctor. The maintenance dose was controlled monthly by the doctor from the results of regular monthly blood investigations and the dose was reduced when haematological toxicity was suspected, particularly thrombocytopenia (defined as a fall in the platelet count below 100×10^9/l), leucopenia (a fall in the total leucocyte count below $3{\cdot}0 \times 10^9$/l), or anaemia (a fall in the haemoglobin concentration below 9 g/dl). If all three occurred the condition was defined as pancytopenia. These definitions have also been used in this report.

Each patient's general condition was reported on by the doctor every month during the first three years, then every three months to five years, and yearly thereafter.

Results

INCIDENCE OF LEUKAEMIA

No patient in any series developed leukaemia in the first five years after the start of treatment. By nine years, however, three cases of myelomonocytic leukaemia (in the 62nd, 63rd, and 64th months) and one case of erythroleukaemia (in the 97th month) had been diagnosed, all from among the 69 patients who received busulphan and who were still alive at five years (an incidence of 5·8%). None of the 63 five-year survivors who received cyclophosphamide or the 85 who received placebo developed leukaemia.

PATIENTS WITH LEUKAEMIA

The details of the four patients who developed leukaemia are shown in figs 1 to 4. The main morphological findings (reported by D A G G) are set out below.*

Case 1—At 10 months the marrow was cellular with active normoblastic and macronormoblastic erythropoiesis; the megakaryocytes were scanty and most were small forms. At 64 months a marrow biopsy showed that the haemopoietic tissue was almost replaced by poorly differentiated cells including immature granulocytes, an appearance consistent with a diagnosis of acute myelomonocytic leukaemia.

Case 2—At 64 months blood films showed morphological abnormalities in the platelets, granulocytes, and red cells; there was an absolute monocytosis of up to $6{\cdot}5 \times 10^9$/l, basophilia of up to $1{\cdot}7 \times 10^9$/l, and neutrophilia with a high proportion of unsegmented forms. Megakaryocyte fragments, undifferentiated blast cells (up to $2{\cdot}1 \times 10^9$/l), promyelocytes, myelocytes, and normoblasts were present. The bone marrow was hypercellular and showed an excess of promyelocytes, myelocytes, and blast cells. The neutrophil alkaline phosphatase score was normal (70). Karyotype analysis was not carried out, but the morphological features suggested an atypical chronic myelomonocytic leukaemia in transformation rather than chronic granulocytic leukaemia in transformation.

Case 3—The histological picture of the marrow after death was that of a monocytic or myelomonocytic variant of acute myeloid leukaemia with destruction of the normal pattern of haemopoiesis and heavy infiltration of the marrow with abnormal monocytic cells.

Case 4—The marrow at 32 months showed relative erythroid hyperplasia and gross dyserythropoiesis; most megakaryocytes had small single or multiple nuclei (up to 6). Erythroblast abnormalities included multinuclearity at all stages (2 or 3, occasionally 4 or 5 nuclei), multilobed nuclei, irregular

*Copies of detailed case histories can be obtained from HS.

Medical Research Council Tuberculosis and Chest Diseases Unit, Brompton Hospital, London SW3 6HP

H STOTT, MD, FRCP, member of scientific staff
WALLACE FOX, MD, FRCP, director
D J GIRLING, MA, MRCP, member of scientific staff
R J STEPHENS, statistical assistant

Medical Research Council Leukaemia Unit, Royal Postgraduate Medical School, Hammersmith Hospital, London W12 0HS

D A G GALTON, MD, FRCP, honorary director

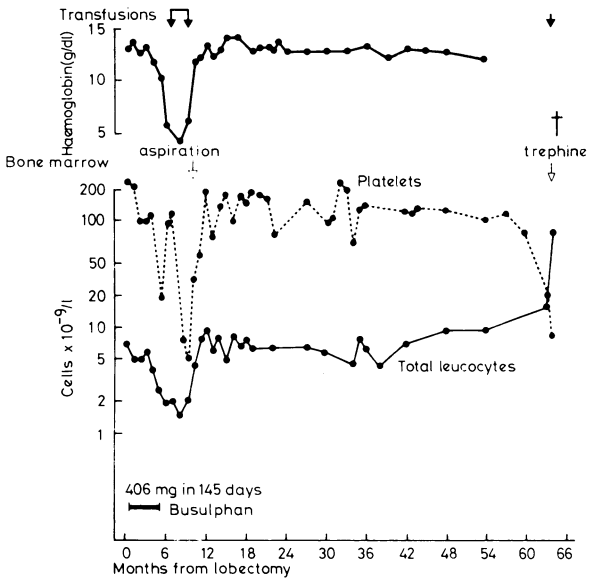


FIG 1—*Case 1.* Haemoglobin concentration and platelet and leucocyte counts of 68-year-old man during 66 months after lobectomy. Period of busulphan administration and times of bone-marrow samples and blood transfusions are also shown.

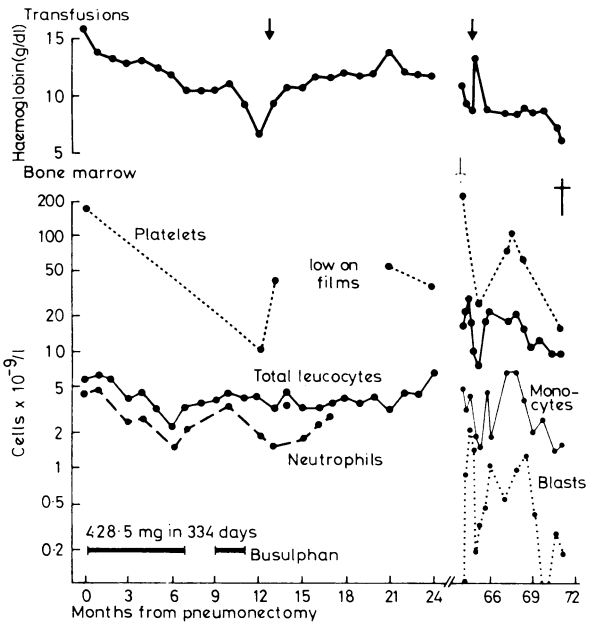


FIG 2—*Case 2.* Haemoglobin concentration and platelet and leucocyte counts of 57-year-old woman during first two years after pneumonectomy and during last seven months of life, for which monocyte and blast-cell counts are shown. Periods of busulphan administration and times of bone marrow and blood transfusions are also shown.

chromatin fragments, macrocytosis, polychromasia, Howell-Jolly bodies, and megaloblastic features. A few undifferentiated blast cells were present. At 97 months the sternal marrow showed hypercellular fragments and trails. There were few megakaryocytes, some showing the same abnormalities as seen previously. The other abnormalities of the previous marrow sample were now grossly exaggerated. The picture was that of acute erythroleukaemia.

LEUKAEMIA RELATED TO HAEMATOLOGICAL TOXICITY IN THE THREE SERIES

All the patients with leukaemia were among the 19 patients who developed pancytopenia during busulphan chemotherapy (table I). Ten of these patients survived to two years and eight to five years (table II), and four of the latter developed leukaemia. The only other case of pancytopenia in the entire study was a patient on cyclophosphamide who died in the sixth month with multiple spinal metastases from the original bronchial carcinoma.

So far no other case of leukaemia has been reported among the survivors at five years. Table II shows the nine-year survival according to haematological toxicity in the first two years.

LEUKAEMIA RELATED TO DOSAGE OF DRUG

Busulphan—Given that the patients in series B took their busulphan regularly, the eight pancytopenic patients surviving at five years would have received a mean total dose of 514 mg administered over a mean of 352 days. Of these, the four patients who developed leukaemia received a mean of 486 mg over 453 days, an average daily dose of 1·1 mg; for the four who did not develop leukaemia the mean dose of

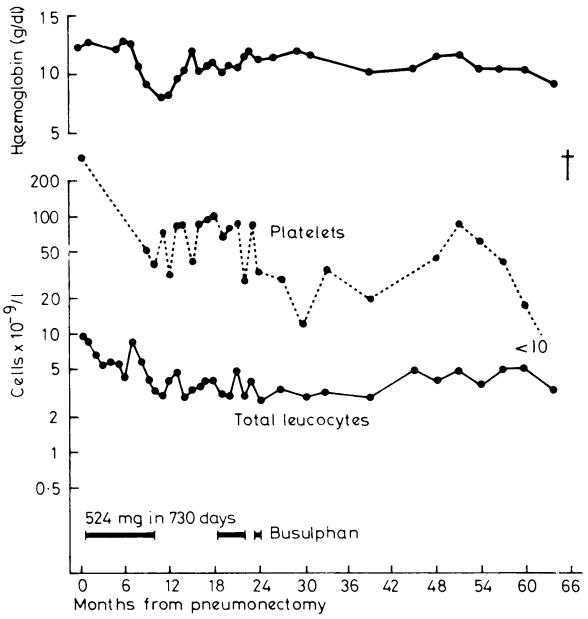


FIG 3—*Case 3.* Haemoglobin concentration and platelet and leucocyte counts of 60-year-old man during 66 months after pneumonectomy. Periods of busulphan administration are shown.

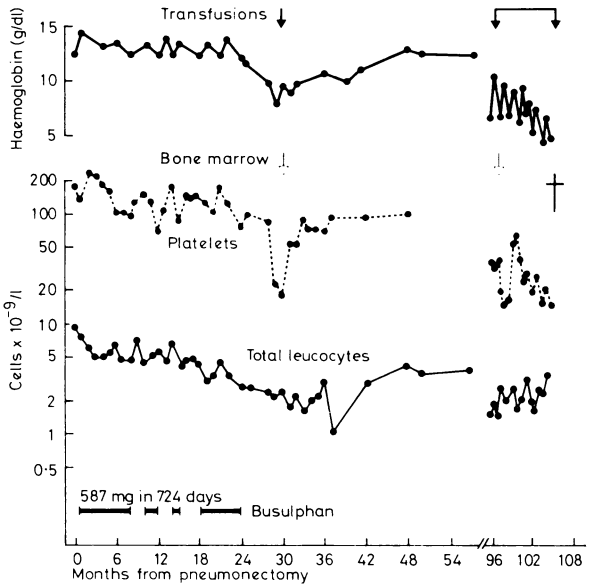


FIG 4—*Case 4.* Haemoglobin concentration and platelet and leucocyte counts of 55-year-old man during first 56 months after pneumonectomy and last 8 months of life. Periods of busulphan administration and times of bone-marrow aspirations and blood transfusions are also shown.

TABLE I—*Outcome in 19 patients with busulphan-induced pancytopenia*

Status at 9 years	No of patients	Duration of survival after resection (months)
Dead from:		
Recurrence of carcinoma	7	8, 10, 14, 19, 21, 22, 45
Aplastic anaemia:		
No evidence of recurrence of carcinoma	3	9, 10, 32
Clinical evidence of recurrence of carcinoma	1	16
Leukaemia, no evidence of recurrence of carcinoma	4	66, 66, 71, 105
Alive:		
No evidence of recurrence of carcinoma	4	

546 mg was similar, although it was administered over only 250 days, giving an average daily dose of 2·2 mg. The latter four patients had a shorter period of administration because treatment was terminated after the first episode of pancytopenia, whereas in three of the four patients who later developed leukaemia the drug was restarted at least once again during the first two years. The other five-year survivors who suffered haematological toxicity during treatment had broadly similar doses and periods of administration to the leukaemic patients (table III). The four survivors who suffered no toxicity received on average a higher dosage of busulphan—804 mg—because, unlike the others, their busulphan treatment was neither interrupted nor terminated because of toxicity.

Cyclophosphamide—The mean total dose of cyclophosphamide received by the 63 five-year survivors was 43 g and the mean daily dose 70 mg; the corresponding doses for the two-year survivors were similar. Eleven (17%) of the 63 five-year survivors received a mean total dose of 30 g or less, 51 (81%) received 31-60 g, and one (2%) received more than 60 g; the corresponding proportions for the 113 two-year survivors were similar (16%, 81%, and 4% respectively).

Further detailed analyses of the mean doses received by the two-year survivors in the busulphan and cyclophosphamide series showed similar figures.

RADIOTHERAPY AND OTHER CYTOTOXIC CHEMOTHERAPY

None of the four patients who developed leukaemia received extra treatment with radiotherapy or any other cytotoxic chemotherapy before leukaemia was diagnosed. Only one of the patients with pancytopenia received radiotherapy and none was given cytotoxic chemotherapy other than that allocated. Nevertheless, 36 (15%) of the original 243 patients in series B, 28 (12%) of the 234 in series C, and 44 (18%) of the 249 in series P received radiotherapy or extra chemotherapy with cytotoxic drugs, or both (table IV). The extra treatment was given within six months of death in most cases (in 26 B, 23 C, and 31 P patients). There was no suggestion that the radiotherapy or other cytotoxic chemotherapy was related to haematological toxicity.

OCCURRENCE OF FRESH PRIMARY CANCERS

As well as the four patients with leukaemia, 19 others (6B, 5C, 8P) developed at least one other primary malignant neoplasm in addition to the original bronchial carcinoma. In 16 only one other site was affected: eight patients (3 B, 2 C, 3 P) developed tumours in the gastrointestinal tract; five (2 C, 3 P) developed tumours in the genito-urinary tract; and one (in series C) developed a tumour in the opposite lung with different histology; the remaining two patients (1 B, 1 P) had epitheliomas. One patient (in series B) had primary cancers of the caecum and pelvic colon, another (in series B) cancers of the bladder and opposite lung with different histology, and a third (in series P) cancers of the colon and prostate.

TABLE III—*Total doses of busulphan and periods of administration according to haematological toxicity in patients surviving at five years*

	No of patients	Average total dose (mg)	Average period of treatment (days)	Average daily dose (mg)
Thrombocytopenia and leucopenia	12	555	464	1·2
Thrombocytopenia and anaemia	3	415	305	1·4
Thrombocytopenia only	42	555	500	1·1

Discussion

The MRC working party study was particularly suitable for assessing the long-term effects of chemotherapy with busulphan and cyclophosphamide because the drugs were prescribed for two years as the only treatment other than the surgical resection and only a few patients ever received radiotherapy or other cytotoxic drugs, most of them within six months of death. The study covered over 700 patients (none of whom has so far been lost from observation), and about a third survived for five years or longer. There was no bias in interpreting the findings because the chemotherapy was allocated at random. An untreated control group of patients was included, and the study was conducted double-blind not only during the two years of allocated chemotherapy but also during follow-up. Finally, detailed clinical and haematological information on each patient was available throughout the whole period. The occurrence of four cases of acute leukaemia among the 243 patients who had received busulphan and generally no other cytotoxic drugs or radiotherapy compared with none among the 234 patients treated with cyclophosphamide or the 249 patients on placebo suggests that busulphan is leukaemogenic.

The nature of busulphan's leukaemogenic action is uncertain. All four cases of leukaemia occurred among the 19 patients who became pancytopenic during busulphan treatment. No case has so far occurred among the many patients, in all treatment groups, who had less severe marrow depression. In the busulphan-treated patients marrow depression continued for months and sometimes years after stopping the drug.[9] The three patients with myelomonocytic leukaemia developed clinically evident disease five to six years after the start of busulphan chemotherapy, while erythroleukaemia did not develop in the fourth patient until eight years after the start of treatment. During most of this intervening period the patients were clinically well and fully active, but three had periodic blood tests and these showed consistently or sporadically low platelet counts, indicating residual marrow damage, and the patient with

TABLE II—*Survival up to nine years according to haematological toxicity in first two years*

Haematological toxicity in first 2 years	Busulphan series				Cyclophosphamide series				Placebo series			
	No of patients	Patients surviving at (years):			No of patients	Patients surviving at (years):			No of patients	Patients surviving at (years):		
		2	5	9		2	5	9		2	5	9
Pancytopenia	19	10	8	4	1	0	0	0	0			
Thrombocytopenia and leucopenia	34	24	12	9	6	3	1	1	0			
Thrombocytopenia and anaemia	17	6	3	1	5	3	1	1	1	0	0	0
Leucopenia and anaemia	0				1	0	0	0	1	0	0	0
Thrombocytopenia only	103	64	42	25	36	23	13	9	35	29	20	15
Leucopenia only	3	0	0	0	29	14	11	7	4	2	0	0
Anaemia only	3	0	0	0	8	1	0	0	8	2	1	1
No toxicity	64	12	4	3	148	69	37	20	200	91	64	49
Total	243	116	69	42	234	113	63	38	249	124	85	65

TABLE IV—*Radiotherapy and other cytotoxic chemotherapy received by patients*

Haematological toxicity in the first 2 years	Busulphan patients receiving:			Cyclophosphamide patients receiving:			Placebo patients receiving:		
	Radiotherapy	Other cytotoxic chemotherapy	Both	Radiotherapy	Other cytotoxic chemotherapy	Both	Radiotherapy	Other cytotoxic chemotherapy	Both
Pancytopenia	1	0	0	0	0	0	0	0	0
Thrombocytopenia and leucopenia	3	1	0	2	0	0	0	0	0
Thrombocytopenia and anaemia	4	1	1	0	0	0	1	0	0
Leucopenia and anaemia	0	0	0	0	0	0	1	0	0
Thrombocytopenia only	12	2	3	7	0	0	3	0	1
Leucopenia only	0	0	0	4	0	1	1	2	0
Anaemia only	0	0	0	1	0	0	1	0	0
No toxicity	7	0	1	13	0	0	27	5	2
Total	27	4	5	27	0	1	34	7	3
Total patients admitted	243			234			249		

erythroleukaemia had typical marrow changes two and a half years after starting treatment with busulphan and more than six years before there was clinical evidence of disease. Busulphan also causes prolonged hypoplasia in mice[10] and rats,[11] and if it can induce a permanent genetic change in the stem cell[12] the attempts of a hypoplastic marrow to repair itself might lead to the emergence and proliferation of an abnormal clone of cells.[13 14]

A hypothesis of a direct leukaemogenic effect of busulphan must explain the restriction of leukaemia to patients who experienced prolonged pancytopenia even though the patients who did not experience pancytopenia received similar or even larger total doses of busulphan. This suggests a non-specific effect of the drug, its role being no more than that of a marrow-destructive agent. That potentially malignant cell clones can emerge in marrow stem cells generating from a hypoplastic state, however induced, is suggested by the variety of causes of prolonged hypoplasia that has been followed, usually several years after apparent recovery, by the development of acute myeloid leukaemia. These include ionising radiation,[15–17] benzene,[18–20] chloramphenicol,[21] and phenylbutazone,[22 23] and the same sequence has occurred in idiopathic aplastic anaemia.[24 25] The peak incidence of leukaemia was between five and nine years, but some cases occurred within five years and later than 15 years. A specific leukaemogenic effect of busulphan would, however, have to be invoked if it could be shown that the incidence of leukaemia in patients who recover from busulphan-induced bone-marrow hypoplasia is higher than that in patients with hypoplasia from other causes. Four cases of leukaemia occurred among the eight pancytopenic patients who survived five years, which seems to be a high proportion; the incidence among patients with aplastic anaemia who survived beyond three years and who developed a clone of paroxysmal-nocturnal-haemoglobinuria cells was only 10% (S M Lewis, personal communication), but no reliable figures are available for the incidence of leukaemia in patients who have recovered from hypoplastic anaemia.

Alternative explanations for busulphan's leukaemogenic action cannot altogether be discounted. The immunosuppressive action of the drug may induce leukaemia. No specific tests were done to assess immunological competence in this study. But it is lymphomas rather than acute leukaemias that are more common after immunosuppression for transplantation. If lung cancer itself predisposes to leukaemia while busulphan and busulphan-induced pancytopenia do not, the distribution of the leukaemic cases in the three series should have been similar. But all four cases occurred in the busulphan series; the probability of this occurring by chance is 1 in 27, and the likelihood of all the cases occurring among the 19 pancytopenic patients in the busulphan series is as small as 1 in 50 000. A further possibility is that busulphan activates a leukaemogenic virus or releases one from immunological control.

Although no case of leukaemia has so far occurred among the patients treated with cyclophosphamide in this study, the disease may follow the treatment of malignant neoplasms with this drug.[1 3 7 26] In some cases marrow hypoplasia occurred, but most of these patients had also received other cytotoxic drugs or radiotherapy. Nevertheless, cyclophosphamide given in larger doses and for longer periods than in this study has caused acute leukaemia in patients with non-malignant disease who received no other radiotherapy or cytotoxic treatment and who did not in general develop marrow hypoplasia.[27–29] The malignant change may have resulted from the immunosuppressive effect of the drug, allowing either the emergence and multiplication of a malignant clone of cells or the escape of a leukaemogenic virus from immunological control. But the same argument against this hypothesis applies as was stated above in the case of busulphan—namely that there is a lack of association between leukaemia and other immunodeficiency states, whether these are idiopathic or drug-induced.

The nature of the leukaemogenic action of cyclophosphamide may or may not be the same as that of busulphan. The absence of leukaemia in the cyclophosphamide series of the present study may merely reflect the absence of any case of pancytopenia among the five-year survivors. Alternatively, the association of leukaemia with prolonged exposure to cyclophosphamide without the occurrence of marrow hypoplasia may indicate a different, and possibly more specific, leukaemogenic mechanism for this drug. Cyclophosphamide, like melphalan[1–3] and chlorambucil[30] but unlike busulphan, might have a mutagenic effect that confers a risk of malignant transformation even in the absence of growth-impeding damage to the stem cells.

All the surviving patients in the study have now been followed up for at least nine years and are being clinically examined each year. More recently, regular haematological examinations have been performed to identify abnormal cell lines that might indicate the persistence of abnormal, but not necessarily malignant, clones. The results will be reported later.

The physicians, pathologists, and surgeons who collaborated in this study were listed in an earlier report (MRC Working Party, 1971). Their co-operation is again acknowledged and appreciated. We are particularly grateful to Drs H C Calvey, W P U Kennedy, and J Q Matthias, and the late Dr E G Sita Lumsden for providing particulars of the terminal illness of the four leukaemia patients; to Drs J W Nicholas and Jeanne Reeve, who provided the pathological and biopsy specimens; to Dr Irvine Lampert, who participated in the histological examinations of the specimens in case 3; and to Mrs Louise Perks for drawing figures 1-4.

Requests for reprints should be addressed to Dr H Stott, MRC Tuberculosis and Chest Diseases Unit, Brompton Hospital, Fulham Road, London SW3 6HP, who will also supply copies of the detailed case histories, or to Professor D A G Galton, MRC Leukaemia Unit, Royal Postgraduate Medical School, Du Cane Road, London W12 0HS.

References

[1] Andersen, E, and Videbaek, A, *Scandinavian Journal of Haematology*, 1970, **7**, 201.

[2] Kyle, R A, Pierre, R V, and Bayrd, E D, *New England Journal of Medicine*, 1970, **283**, 1121.

[3] Karchmer, R K, *et al*, *Cancer*, 1974, **33**, 1103.
[4] Allan, W S A, *Lancet*, 1970, **2**, 775.
[5] Garfield, D H, *ibid*, p 1037.
[6] Kaslow, R A, Wisch, N, and Glass, J L, *Journal of the American Medical Association*, 1972, **219**, 75.
[7] Davis, H L, *et al*, *Cancer*, 1973, **31**, 543.
[8] Medical Research Council Working Party, *British Medical Journal*, 1971, **2**, 421.
[9] Stott, H, *et al*, *British Journal of Cancer*, 1976, **34**, 167.
[10] Morley, A, Trainor, K, and Blake, J, *Blood*, 1975, **45**, 681.
[11] Elson, L A, Galton, D A G, and Till, M, *British Journal of Haematology*, 1958, **4**, 355.
[12] Geary, C G, *Lancet*, 1976, **2**, 862.
[13] Dameshek, W, *Blood*, 1967, **30**, 251.
[14] Weiden, P L, *et al*, *Blood*, 1973, **42**, 571.
[15] Court Brown, W M, *British Medical Bulletin*, 1958, **14**, 168.
[16] Court Brown, W M, and Doll, R, *British Medical Journal*, 1965, **2**, 1327.
[17] Ishimaru, T, *et al*, *Radiation Research*, 1966, **45**, 216.
[18] De Gowin, R L, *Journal of the American Medical Association*, 1963, **185**, 748.
[19] Vigliani, E C, and Saita, G, *New England Journal of Medicine*, 1964, **271**, 872.
[20] Cronkite, E P, *Archives of Environmental Health*, 1961, **3**, 297.
[21] Cohen, T, and Creger, W P, *American Journal of Medicine*, 1967, **43**, 762.
[22] Bean, R H D, *British Medical Journal*, 1960, **2**, 1552.
[23] Woodliff, H J, and Dougan, L, *British Medical Journal*, 1964, **1**, 744.
[24] Delamore, I W, and Geary, C G, *British Medical Journal*, 1971, **2**, 743.
[25] Lewis, S M, in *Blood and its Disorders*, ed R M Hardisty and D J Weatherall, p 113. Oxford, Blackwell, 1974.
[26] Smit, C G S, and Meyler, L, *Lancet*, 1970, **2**, 671.
[27] Roberts, M M, and Bell, R, *Lancet*, 1976, **2**, 768.
[28] Tchernia, G, *et al*, *Blood Cells*, 1976, **2**, 67.
[29] Chang, J, and Geary, C G, *Lancet*, 1977, **1**, 97.
[30] Catovsky, D, and Galton, D A G, *Lancet*, 1971, **1**, 478.

(*Accepted 21 September 1977*)

SIDE EFFECTS OF DRUGS

Renal papillary necrosis after aspirin and alclofenac

Renal papillary necrosis (RPN) is well known to be associated with long-term analgesic consumption, the most common preparations implicated being aspirin, phenacetin, and caffeine mixtures.[1] There are reported cases of RPN from aspirin usage alone, but most epidemiological studies implicate phenacetin as the toxic component.[2] Combined analgesic preparations may be more toxic to the kidney, as one drug may alter the renal tissue response to the other drug.[3] We report a case of radiologically confirmed RPN after the use of aspirin and alclofenac, a combination which has not been implicated in the aetiology of analgesic nephropathy.

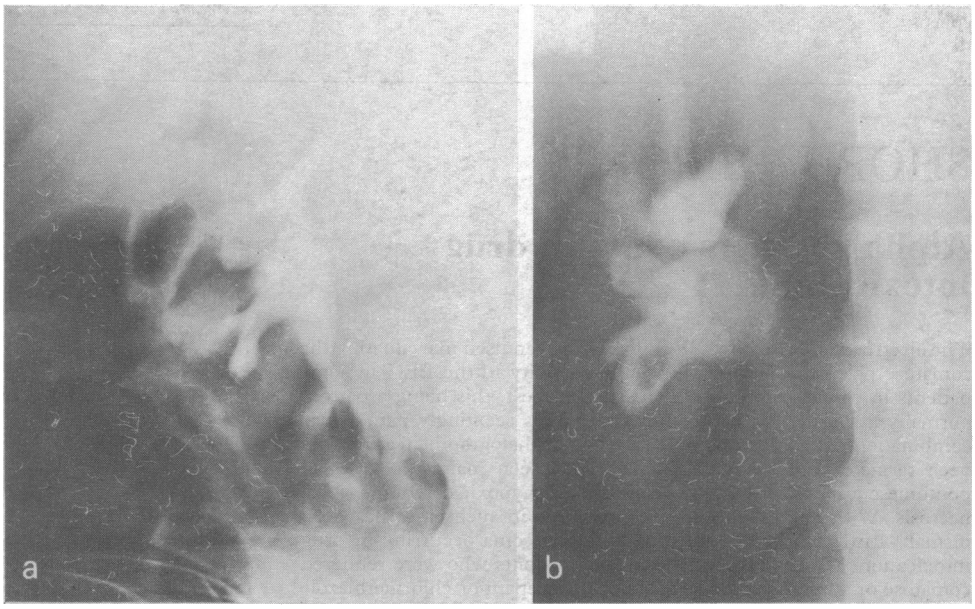
Case report

A 65-year-old woman had a 20-year history of seronegative rheumatoid arthritis affecting small and large joints. In 1961 she had an arthrodesis of the left knee, and in 1969 a total replacement of the left hip. Joint pain had been treated at various times with paracetamol, indomethacin, and aspirin. In 1970 she developed iron-deficiency anaemia and platelet dysfunction associated with bruising and splenomegaly. No definitive diagnosis was made but the anaemia was thought to be caused by indomethacin. An intravenous urogram (IVU) showed nothing apparently abnormal (see figure). Indomethacin treatment was stopped and Levius (a microencapsulated aspirin compound) prescribed, together with iron and folic acid supplements. Levius was withdrawn in 1973 because of persistent anaemia and bleeding tendency, and was replaced by alclofenac (Prinalgin).

In 1975 she was admitted with a history of macroscopic haematuria, bruising, and malaise. By this time she had developed appreciable splenomegaly, severe anaemia, and thrombocytopenia. Investigations confirmed myelosclerosis. A second IVU (see figure) showed classical papillary necrosis, and although the IVU in 1970 had not completely excluded analgesic nephropathy, proteinuria and haematuria at that time were absent, and renal function had been normal. Cytoscopy in 1975 showed nothing remarkable. At this stage alclofenac treatment was discontinued. Apart from an asymptomatic urinary tract infection at the time of admission, there was no evidence of previous infections. From 1971 to 1973 the intake of aspirin totalled 1·5 kg, and between 1973 and 1975 that of alclofenac was 2·2 kg.

Comment

Although phenacetin has been considered to be the major drug causing RPN, experiments on rats have implicated aspirin as a primary cause.[4] Yet analgesic neuropathy was not associated with long-term use of high doses of aspirin in patients with rheumatoid arthritis.[5] Alclofenac (4-allyloxy-3-chlorophenylacetic acid) is a non-steroid compound, not hitherto implicated in this syndrome. Our patient was on this drug alone for two years before clinical and radiological diagnosis of RPN. There is therefore strong circumstantial evidence linking alclofenac (perhaps in combination with aspirin) to the development of papillary necrosis. The patient also suffered from a myeloproliferative disorder, which does not in itself give rise to RPN.



Intravenous urograms (showing right kidney only) in patients who developed renal papillary necrosis (RPN). Picture (a) taken in 1970: kidney reported as normal. Picture (b) taken in 1975: collecting system is deformed with dilatation and clubbing of the calices. "Ring shadows" surrounded by contrast medium are present in right lower and middle calices, changes typical of RPN.