serum potassium was 4.45 mEq/litre, and this rose steadily thereafter to 5.1 mEq/litre one week later. His urinary potassium excretion likewise fell to 25 mEq/24 hours with restoration of the pH to normal.

The possibility of a primary hyperaldosteronism (Conn's syndrome) was considered, but the fall in the urinary potassium output with the progressive rise in serum potassium tended to be against this; also the fact that the specific gravity of his urine, while originally 1010, rose after repletion to 1015 and 1020. Familial periodic paralysis was likewise considered, but did not seem likely from the history. The low calcium levels may be associated with increased calcium excretion, which, while not estimated in this case, has been reported to occur in patients on carbenoxolone therapy and may be influenced by the accompanying sodium retention.

It is felt that this case is of interest in two ways: (a) The fact that a dangerous degree of hypokalaemia occurred in a patient taking this drug for a period within the prescribed time and not in excessive dosage and not in association with diuretics; and (b) that the hypokalaemia induced was initially refractory to replacement therapy even in large amounts. Whether or not this was due to carbenoxolone lying in quantities in an atonic bowel is open to conjecture. Although the other possible diagnoses have been mentioned and perhaps may still have to be borne in mind, it would seem most likely that this man's hypokalaemia was Duogastrone-induced, since he is now well and maintains his serum potassium within normal levels.—We are, etc.,

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Dangers of Perchlorethylene

SIR,—There has been recent public interest¹ in the possible dangers associated with the use of perchlorethylene in coin-operated dry cleaning machines. It was therefore felt appropriate to report the following case.

A 68-year-old man worked a few hours a day maintaining a launderette. On 5 January 1969 a container of perchlorethylene spilt over him, soaking his clothes. He was anaesthetized by the material, and lay unconscious for half an hour before being found. He was resuscitated in the casualty department of the local hospital. He was noted to have erythema and blistering amounting to 30% of his surface area, involving his neck, shoulders, left side of his chest and abdomen, left thigh, and perineum. As these were in the nature of chemical burns he was transferred to the burns centre. His appearance on admission was of a 30% superficial burn, and he was therefore treated with intravenous plasma, and antibiotics were commenced. The areas were exposed; the blisters were not deroofed, as they were very small. Five days later the erythema had subsided considerably and the blistering had gone; there was no cracking of the skin.

The patient was discharged and has been followed up by his general practitioner, Dr. G. R. C. Fisher, who reports that his burns have healed very well, apart from some dryness and irritation. There is slight staining of the skin on the areas injured.

This case illustrates the two effects of perchlorethylene, which has anaesthetic properties and on prolonged contact can produce "defatting" of the skin. The damaged skin is likely to crack and thereby become infected. Perchlorethylene, however, is far less dangerous than carbon tetrachloride.—I am, etc.,

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REFERENCE

- ¹ *The Guardian*, 28 March 1969.

Lymphoblastic Leukaemia

SIR,—The interesting paper by Dr. H. C. Laurie¹ demonstrating that strong periodic-acid-Schiff (P.A.S.) reactivity in the primitive cells of lymphoblastic leukaemia is inversely related to the progression of the disease has prompted us to review our experience with a large series of patients diagnosed and treated at the Clinical Center, National Cancer Institute, National Institutes of Health.

Bone marrow "squash" smears from 44 patients with acute lymphocytic leukaemia were evaluated prior to initial therapy. The mean age was 6 years. The term acute lymphocytic leukaemia encompassed all leukaemic "blasts" that showed any degree of lymphoid differentiation, and undoubtedly included many cases that are referred to as "acute stem cell" leukaemia by others.² A P.A.S. scoring system similar to that proposed by Quaglino and Hayhoe³ was used. The leukaemic blast cells were graded from 0 to 3+, and arbitrarily scores above 100 were considered elevated. In those cases with elevated scores (61% of group, or 27 patients) 2 and 3+ reactive cells constituted 57 to 96% of the P.A.S.-positive cells. In the group with scores between 50 and 100 (four cases) 23% of the positive cells were 2 and 3+, and in the lowest group (13 cases) 7% of the cells were 2+ or 3+.

Laurie reported that his patients could be readily divided into a group with less than 40% P.A.S.-negative blast cells and a group with greater than 55% P.A.S.-negative blast cells. The median survival in the former group was 25 months but only 11½ months in the latter. Analysing our data, a natural division was found with greater or less than 50% P.A.S.-negative blast cells. The median survival of both groups, 16 and 18 cases respectively, using life table methods, was 37.5 months for the weak P.A.S.-positive group and 33 months for the strong P.A.S.-positive group; not statistically significant. Another minor subdivision was created with a group having 75% or more P.A.S.-negative blasts (nine cases) and the other group 25% or less P.A.S.-negative blasts, 34 cases. The median survival of both groups was identical, namely 36 months. In all of the four groups there were at least two or more patients living and well a minimum of 3½ years from initiation of therapy.

Therefore, although our studies confirm the presence of significant amounts of P.A.S.-positive material in the cytoplasm of leukaemic lymphoblasts from the majority of patients with acute lymphocytic leukaemia, the data do not support the usefulness of the P.A.S. reaction in predicting individual patient remission or survival.

These two studies also differ in their chemotherapeutic programmes. The patients studied by Laurie were treated initially with prednisone and 6-mercaptopurine or vincristine.⁴ Then, after remission induction, cyclical therapy with 6-mercaptopurine, methotrexate, and cyclophosphamide was administered sequentially. Some of our patients were initially treated with a combination of four drugs (vincristine, prednisone, methotrexate, and 6-mercaptopurine), or "VAMP." Twenty-four received an intensification of this programme, including monthly "pulses" for one year.⁵ It might be appropriate to point out that neither initial duration of symptoms nor leucocyte counts correlated with the duration of the first remission. Though the remission duration periods are approximately the same for both groups (60–65 weeks), there is a longer survival in our series. Whether this is due to a greater reduction in leukaemic cells or a change in the kinetic behaviour of the cells is unclear. This additional period of prolongation of life in these children, however, may offset and conceal any difference that may have been detected by the P.A.S. method.—We are, etc.,

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- ⁴ Willoughby, M. L. N., and Laurie, H. C., *Archives of Disease in Childhood*, 1968, 43, 187.
- ⁵ Henderson, E. S., *Cancer Research*, 1967, 27, 2570.

Management of Acute Salicylate Poisoning

SIR,—We were very interested to read the valuable contribution by Drs. A. G. Morgan and A. Polak (4 January, p. 16), and the ensuing correspondence (18 January, p. 185; 1 February, p. 315; 8 February, p. 383; and 17 March, p. 577). As we have several years' experience of the treatment of salicylate poisoning, including the use of acetazolamide, we should like to make certain comments.

It is generally agreed that the renal excretion of salicylate depends partly on urine flow rate and partly on the alkalinity of the urine, but the relative importance of the two factors does not appear to have been worked out. We have therefore analysed our own records and also those which Dr. Morgan has kindly supplied to us and have calculated the crude clearance of salicylate (deriving free salicylate levels in plasma from total salicylate levels using the data of Moran and Walker).¹ We then attempted to determine the separate effects of flow rate and alkalinity on the clearance.

The results are summarized in the Table and indicate that, to get the best clearance, (1) if relying mainly on alkalinity the urine flow should be at least 3 ml./min. and, except at high flow rates, the urine pH should be greater than 7.5; (2) if relying mainly on

flow rate without alkalization the flow rate should be at least 12 ml./min; and (3) if the urine is weakly alkaline a flow rate of over 9 ml./min. is still required. If the case is not very severe—for example, peak plasma salicylate level not exceeding 80 mg./100 ml.—it is probably immaterial whether one adopts simple diuretic therapy, or alkalization, or both, provided that the treatment is vigorous. However, in very severe cases it is desirable to remove salicylate from the body at the maximum possible rate, and this means combining very high flow rates with high urine alkalinity.

Mean Salicylate Clearance* in ml. per Minute
Classified According to Urine Flow Rate
and Urine pH

Urine Flow Rate ml./min.	<6.0	6.0-6.5	6.5-7.0	7.0-7.5	>7.5
0-3	21 (6)	19 (1)	38 (3)	29 (6)	57 (25)
3-6	13 (2)	24 (1)	35 (3)	62 (8)	85 (50)
6-9	—	30 (3)	32 (3)	57 (11)	86 (32)
9-12	13 (1)	67 (1)	47 (3)	101 (13)	93 (18)
>12	—	—	74 (3)	84 (3)	125 (5)

* Figures in parenthesis indicate the number of clearance periods.

Until recently the regimen which we have recommended has been as follows: 500 mg. of acetazolamide is given intramuscularly at the start of the treatment, and at the same time a drip is set up starting with one litre of 5% dextrose containing 150 mEq/l. of sodium lactate or bicarbonate given in the first hour, followed by one litre of 5% dextrose containing 75 mEq/l. of sodium lactate or bicarbonate every two hours until the plasma salicylate level is below 50% of its highest recorded concentration. Alkaline urine, whether produced by acetazolamide or by alkalinizing solutions, always has a high potassium content, and therefore, as soon as an alkaline diuresis has started, potassium citrate is added to the infusion to a concentration of 50 mEq/l. This dose is continued only if the rate of urine output keeps pace with the rate of intravenous infusion.

The use of alkalis is controversial; it is said to be unnecessary, because the patient is usually already alkalotic as a result of hyperventilation, and because further alkali may produce an alkalosis severe enough to produce tetany. In our view these arguments carry little weight. Firstly, although the patient may have respiratory alkalosis on admission, the urine is nearly always acid, and, if it is not alkalized, excretion of salicylates will be poor unless a very high urine flow rate is achieved. Secondly, we have never seen tetany as a result of alkali treatment, with or without acetazolamide, though this may be because all our patients have been adults. The use of acetazolamide has two advantages. In the first place it produces a rapid alkaline diuresis. In the second place, by lowering the renal threshold for bicarbonate, acetazolamide permits the maintenance of a strongly alkaline urine with a minimal degree of systemic alkalosis, so that the risk of tetany is minimized. We have never seen ill effects which we considered attributable to this drug.

The need to dialyse these patients clearly depends on the efficacy of alkaline diuretic therapy. In very severe cases we advocate a trial of immediate treatment with acetazolamide together with an infusion starting with 1 litre of sodium bicarbonate solution (150 mEq/l.) and containing mannitol (50-100 g.), given in 30-45 min. The patient should be catheterized, and a decision to dialyse made only if an alkaline diuresis is not present at the end of the first hour. The use of mannitol will help to produce a brisk diuresis, and at this total dosage is unlikely to cause the

complications which Morgan *et al.*² have described.

Thereafter treatment should be continued on the lines recommended by Drs. Morgan and Polak or on our own similar regimen.—We are, etc.,

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Trichomonas and Haematospermia

SIR,—It does not seem to be widely known that *Trichomonas vaginalis* can be a cause of haematospermia, although it is recognized as a common cause of male urethritis. The diagnosis is made by staining a slide of the semen by Papanicolaou's method, when the parasites show as distinctly as they do in cervical smears.

In this laboratory Papanicolaou stains of the seminal fluid are done as part of the routine investigation of infertility. *Trichomonas* are sometimes found in males who have no symptoms of infestation. It has not proved possible to confirm the diagnosis by culture, although the parasite can usually be found in the wife by examination of a wet preparation and culture of the vaginal discharge, or by examination of the cervical smear, as indicated above.

Fortunately, metronidazole given to both partners has cured the condition effectively, though it may be necessary to give a second course.—I am, etc.,

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Chemotherapy in Drug-induced Leucopenia

SIR,—We wish to draw attention to the possibility of using combinations of sulphamethoxazole and trimethoprim (Septrin, Bactrim) as prophylactic chemotherapy in patients at special risk of developing bacterial infection due to drug-induced depression of the bone marrow. Three patients recently admitted to the Whittington Hospital illustrate the application of this measure.

A 77-year-old woman was admitted with an inoperable carcinoma of the left breast. The right subclavian artery was cannulated and methotrexate was injected intra-arterially in divided doses over six days. The patient became febrile and developed an erythematous rash, stomatitis, and acute bronchitis. These responded to antihistamines and intramuscular penicillin. At the commencement of treatment the total white cell count was 11,100/cu. mm., of which 81% were neutrophils, but by the eighth day the white cell count had fallen to 150/cu. mm., of which only 12% were neutrophils. Prophylactic treatment was commenced with tablets containing a combination of sulphamethoxazole 400 mg. and trimethoprim 80 mg. (Septrin), two tablets twice a day. The patient

remained febrile, with a temperature of up to 39° C., but there was no clinical or bacteriological evidence of infection. She became progressively more ill and died three days later.

A post-mortem examination (Dr. P. C. Meyer) showed spread of the carcinoma of the breast to the lymphatics of the lungs, necrotic ulceration of the mucosa of the pelvic colon, and hypoplastic bone marrow with suppression of the granulocytic series beyond the myeloblastic phase. There was no macroscopic or microscopic evidence of bacterial infection in the lungs or elsewhere.

A 63-year-old woman was admitted with a large, progressively ulcerating carcinoma of the left breast, attached to the underlying tissues. The left subclavian artery was cannulated, and in the course of the following three weeks intra-arterial methotrexate was given in divided doses. She was also given leucovorin intramuscularly. The patient remained well until a week after cessation of the methotrexate therapy, when she became drowsy and pale and developed melaena. The white cell count fell to 300/cu. mm., of which only 6% were neutrophils. She was transfused and given prophylactic treatment with tablets containing a combination of sulphamethoxazole 400 mg. and trimethoprim 80 mg. (Septrin), two tablets twice a day. By four days later the white cell count had returned to normal, but the prophylactic chemotherapy was continued. The patient remained afebrile until a few hours before death, which occurred three weeks after discontinuing the methotrexate, after a progressively downhill clinical course. At no stage was there any clinical, bacteriological, or radiological evidence of bacterial infection. Permission for post-mortem examination was not obtained.

A 65-year-old woman with an inoperable carcinoma of the right breast had her right subclavian artery cannulated and methotrexate infused intra-arterially on alternate days. After 20 days of treatment she developed gingivitis and stomatitis, and prophylactic chemotherapy was commenced two days later, when it was found that the white cell count had fallen from normal levels to 3,600 cu. mm., of which only 22% were neutrophils. Very low neutrophil counts were maintained for 11 days, and prophylactic cover was maintained for this period. No evidence of bacterial infection was found clinically, radiologically, or bacteriologically throughout this period, and the patient remained afebrile. As a result of the methotrexate infusion the breast tumour decreased in size and was subsequently considered operable. A modified radical mastectomy has since been performed and the patient continues to maintain good progress.

The noteworthy feature of these case histories is the absence of any form of bacterial infection, even terminally, in three patients, who because of severe drug-induced agranulocytosis were specially susceptible to such infection. We were encouraged to use a combination of sulphamethoxazole and trimethoprim for these patients because of the remarkable success of this form of prophylaxis in another group of patients at special risk of infection, those with leukaemia and very low neutrophil counts.¹ Combinations of sulphamethoxazole and trimethoprim are highly suitable for prophylaxis because of their very wide spectrum of antimicrobial effectiveness, their low toxicity, and their acceptability to the patient.—We are, etc.,

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