that, despite these differences, the biological response of the bronchial epithelium to both was similar if assessed by goblet cell increase.

This similarity is in striking contrast to the difference in mitotic counts produced at higher doses. Daily exposure to smoke from more than 30 cigarettes produced so many mitoses that goblet cell counts as here described were not possible: there was no such excess from exposure to cigar smoke (Lamb, 1967 ; Passey and Blackmore, 1967). It has been shown, using sulphur dioxide as the irritant, that the alteration in goblet cell number does not parallel the severity of epithelial damage as measured by the mitotic count (Lamb and Reid, 1968).

Loss of weight or failure to gain weight is usual in experimental animals exposed to tobacco smoke. This loss of weight is not usually attributable to the severity of pulmonary damage, and Elson and Passey (1963) produced evidence to suggest that the nicotine present in the tobacco smoke is the main cause of loss of weight.

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Medical Memoranda

Treatment of Severe Salicylate Poisoning by Forced Alkaline Diuresis

Treatment of adult salicylate poisoning by forced alkaline diuresis is now well established. The case reported here illustrates the effectiveness of this form of treatment in very severe intoxication. The relative importance of diuresis and alkalinization in elimination of salicylate from the body is discussed.

CASE REPORT SUMMARY

A man aged 36 was admitted in coma to the London Hospital approximately one and a half hours after taking 300 0.3-g. aspirin tablets (90-g. of salicylate). Following immediate administration of 150 mEq of sodium bicarbonate his standard bicarbonate was still only 18 mEq/l. Further intravenous therapy consisted of rapid infusion, in rotation, of sodium bicarbonate, normal saline, and 5% dextrose. During the first 12 hours 14 litres of fluid were administered and urine output was 10.3 litres ; 190 g. of mannitol in solution was given to counter fluid retention.

Repeated estimations were made of blood salicylate, serum potassium, arterial pH, standard bicarbonate, and $PaCO_2$. Urine pH and salicylate concentrations were measured hourly.

Fig. 1 shows the rise in arterial and urine pH and the rapid fall in blood salicylate level from 138 to 15 mg./100 ml. during the first 12 hours. Over the second 12-hour period intravenous fluids were administered at a much reduced rate. During the first period serum potassium fell to 2.8 mEq/l. despite administration of 230 mEq of potassium as intravenous potassium chloride. Preparations were made for haemodialysis, but this proved unnecessary.

DISCUSSION

Severe aspirin poisoning can be treated either by haemodialysis or by forced alkaline diuresis. Haemodialysis is an effective method of treatment and is of especial value in the circumstances of cardiovascular collapse or renal failure. It may be required if the blood salicylate continues to rise despite

other treatment. The reports reviewed by Beveridge et al. (1964) show that 3 to 9 g. of salicylate may be removed during two to six hours of haemodialysis, resulting in a significant fall in blood level. The majority of patients in this review had high levels of salicylate (51 to 115 mg./100 ml.) and had taken the drug more than 12 hours before treatment was instituted. The present case shows that forced diuresis can result in excretion rates in excess of the above values. Moreover, haemodialysis requires special staff and apparatus which takes two to three hours to prepare.

Forced alkaline diuresis has the advantage that it is simple to carry out if carefully controlled, and may be started immediately the diagnosis is made. By giving a water load the dehydration commonly present in salicylate poisoning due
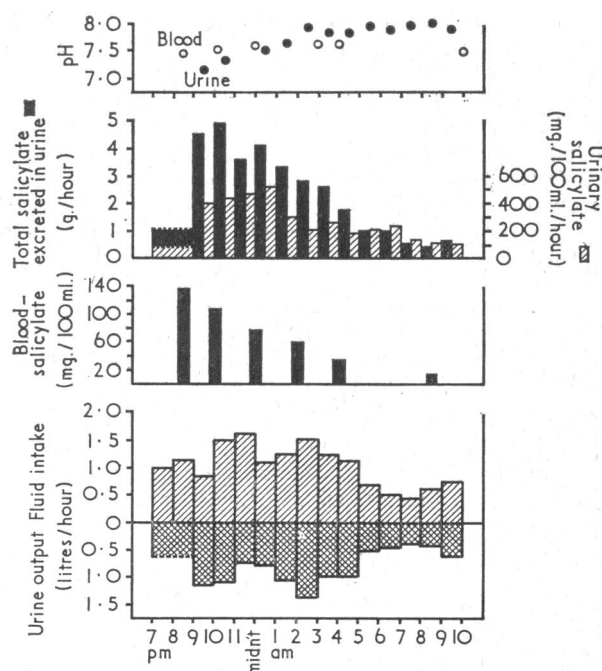

FIG. 1.—Biochemical observations during treatment.

to overbreathing and sweating is corrected. Moreover, meta-bolic acidosis, if present, is reversed by alkalinization.

In Fig. 1 the concentration of salicylate in the hourly urine collection and the total excreted per hour are plotted. The urinary pH is also shown. In the first eight hours 21.5 g. of salicylate was eliminated and a further 12.5 g. over the next 14 hours. The blood salicylate level declined with a half-time of 5.6 hours, which compares with the mean half-time of 7.5 hours in the series of Cumming et al. (1964).

The place of potassium replacement in this form of treatment requires special mention. Cumming et al. (1964) suggest that potassium loss during forced alkaline diuresis is unimportant.
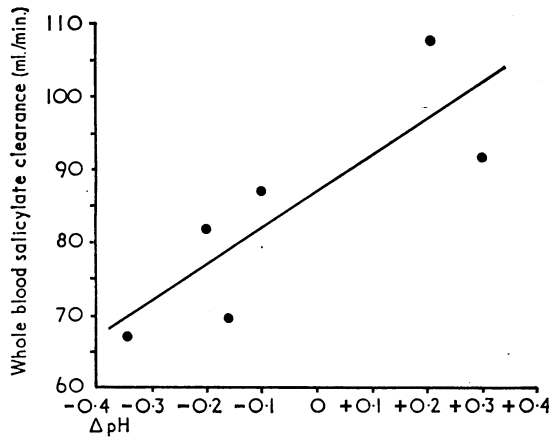
excretion of urine is shown in Figs. 2 and 3. There is no apparent relation of clearance to urinary volume but a signifi-cant positive linear regression is shown with $\triangle p$H.

If it is assumed that errors in the estimation of pH owing to delayed dehydration of carbonic acid in the gross urinary passages (Reid and Hills, 1965) and to the multiple puncture technique of obtaining arterial blood are small, it may be seen from Fig. 2 that a change in $\triangle p$H from -0.34 to $+0.3$ increases the salicylate clearance by a factor of about 1.5. The mean half-time of disappearance of salicylate in untreated cases is 22 hours (Cumming et al., 1964). In this patient it was 5.6 hours—that is, clearance is about four times as rapid. Thus

FIG. 2.—Relation of salicylate clearance to difference between arterial and urinary pH ($\triangle$ pH). The regression line may be represented as clearance $= 86.6 + 49.9 \triangle p$H. The regression coefficient is significantly different from zero ($0.05 > P > 0.02$). FIG. 3.—Relation of salicylate clearance to urine volume.
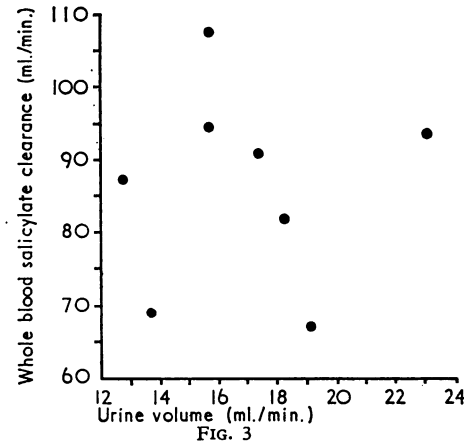
In this case, despite the administration of 230 mEq of potas-sium in the first 12 hours, the serum potassium fell to 2.8 mEq/l., indicating that careful attention must be paid to the prevention of hypokalaemia.

DIURESIS AND ALKALINIZATION

We have attempted to assess from the data in this case the relative importance of diuresis and alkalinization in the removal of salicylate from the body. The rate of urinary excretion of salicylate is dependent on three processes—glomerular filtration, tubular secretion, and non-ionic diffusion (Weiner and Mudge, 1964). The ratio of urinary to plasma ultrafilterable salicylate concentration is always greater than might be expected on the basis of non-ionic diffusion alone, presumably because the rates of tubular secretion of salicylate and reabsorption of water are much faster than the rate of diffusion of non-ionized salicylic acid out of the tubules into the peritubular fluid. For this reason the direction of net non-ionic diffusion is always likely to be out of the tubule, even when the urine is more alkaline than plasma. The effect of alkalinization is thus to prevent reabsorption of salicylate. It is of some importance to know whether this effect is of appreciable magnitude, since alkaliniza-tion is not without danger (potassium depletion ; hypokalaemia). If, for instance, the diuresis was by far the more important component of the well-established forced alkaline diuresis regimen, then it would not be justifiable to alkalinize as well.

The relationship of blood salicylate clearance to the difference between urinary and arterial pH ($\triangle p$H) and to the rate of

about one-third of the improvement in the rate of excretion could have been due to alkalinization. The absence of correla-tion of clearance with urinary volume (Fig. 3) should not be interpreted as meaning that diuresis was unimportant, since the urinary volumes were all very high (between 8 and 16% of the assumed glomerular filtration rate of 120 ml./min.). Weiner and Mudge (1964) and Macpherson et al. (1955) have shown that although a marked dependence of salicylate clear-ance on urine volume exists at lower flows the relationship is less clear at flows of this order. Thus the major effect of diuresis has probably been achieved by bringing the urine flow from normal values up into this range.

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