MANAGEMENT

OF

ACUTE SALICYLATE POISONING

Studies concerning the diagnosis, assessment of severity and choice of treatment in acute salicylate poisoning in older children and adults.

SUBMITTED

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CONTENTS

SUMMARY

Acute salicylate poisoning has become increasingly more common in recent years. It is, at present, the third most frequent cause of acute intoxication and depending on age, the mortality rate varies from 1.0 to 7.0 per cent. Aspirin overdosage, therefore, constitutes a serious problem of management for all practising doctors.

The diagnosis and assessment of patients with this condition are discussed in the light of the clinical features and biochemical results found in 84 patients (39 males and 45 females) with moderate and severe acute salicylate poisoning admitted to the Poisoning Treatment Centre, Edinburgh Royal Infirmary. Measurement of the plasma level of salicylate is considered to be the best single investigation, both to confirm the diagnosis and to provide an index of the severity of the poisoning. The important clinical features and assessment of acid-base status are also discussed.

In addition to supportive measures to maintain vital functions it is generally agreed that rapid removal of salicylate from the body is the most important objective of treatment. This may be achieved by gastric aspiration and lavage to minimise the amount of drug absorbed from the gastro-intestinal tract. As all the patients in this series had ingested the overdosage, gastric aspiration and lavage was performed in every case. The value of this procedure in this poisoning is discussed.

After absorption has occurred, increased removal of salicylate from the body may be achieved in adults by many methods, including forced oral fluids, forced water diuresis, forced alkaline diuresis, peritoneal dialysis and haemodialysis. The use of the artificial kidney is the most efficient method, but the great demands on this form of treatment for other conditions, has prompted a search for alternative forms of treatment. The most suitable method for general use is forced diuresis using intravenous infusions, but there is much controversy regarding the most appropriate regime. Forced alkaline diuresis therapy, described by Dukes and his colleagues in 1963, is the most effective of these regimes. Several authorities, however, on theoretical grounds, stress that the administration of large amounts of alkali may cause severe metabolic alkalosis and potentially fatal tetany. The need for potassium supplements with this treatment, also remains undecided. The purpose of this investigation was to develop the safest regime of forced diuresis in adults, consistent with effective removal of salicylate.

Of the 84 patients with moderate or severe poisoning, 9 were treated with forced oral fluids, 11 with forced saline-laevulose, 51 with forced alkaline and 13 with forced "cocktail" diuresis, which is a modification of the Dukes' method. One patient died giving a mortality of 1.19 per cent. The effectiveness of these forms of treatment in increasing removal of salicylate are assessed. Detailed studies of changes in

acid-base status, and in plasma and urinary levels of potassium, sodium, magnesium and calcium were done, both during and after the main diuresis period. Despite significant and at times, alarming falls in these plasma cations and associated rises in arterial pH, tetany was rarely found. The significance of these changes are discussed.

The need for substantial potassium supplements is demonstrated and forced "cocktail" diuresis with standardised potassium administration is shown to be highly effective; it is also a safer and technically simpler regime of treatment than forced alkaline diuresis.

INTRODUCTION

In keeping with the steady increase in hospital admissions due to acute poisoning (H.M.S.O. report 1966; Matthew & Lawson, 1966), the incidence of acute salicylate overdosage has also risen and now accounts for approximately 16 per cent of all acute poisonings admitted to hospital (Graham, 1967). In the case of infants and toddlers, salicylates are almost as common causes of accidental overdosage as iron preparations. Young children are also peculiarly sensitive to the effects of aspirin and even relatively small doses of the drug, which would otherwise be regarded as therapeutic levels, may result in poisoning, (Craig, Ferguson and Syme, 1966).

Salicylate overdosage usually arises from an overdosage of aspirin itself or one of the bewildering variety of pharmaceutical preparations containing both mixtures of different salts of salicylic acid and also featuring aspirin as a constituent of compound analgesic tablets. When compound tablets containing aspirin, phenacetin and codeine are taken in overdosage, the most important toxic features are those of salicylism (Matthew and Lawson, 1967). Methyl salicylate, "Oil of Wintergreen", is occasionally taken by the inquisitive child as an accidental poisoning. This is very toxic since it is readily absorbed and has a high salicylate content; one teaspoonful is equivalent to twelve standard 300 mg. tablets of acetylsalicylate.

In Edinburgh, since the late 19th century, a ward has been developed to provide special facilities for the management, toxicological investigation and psychiatric assessment of patients

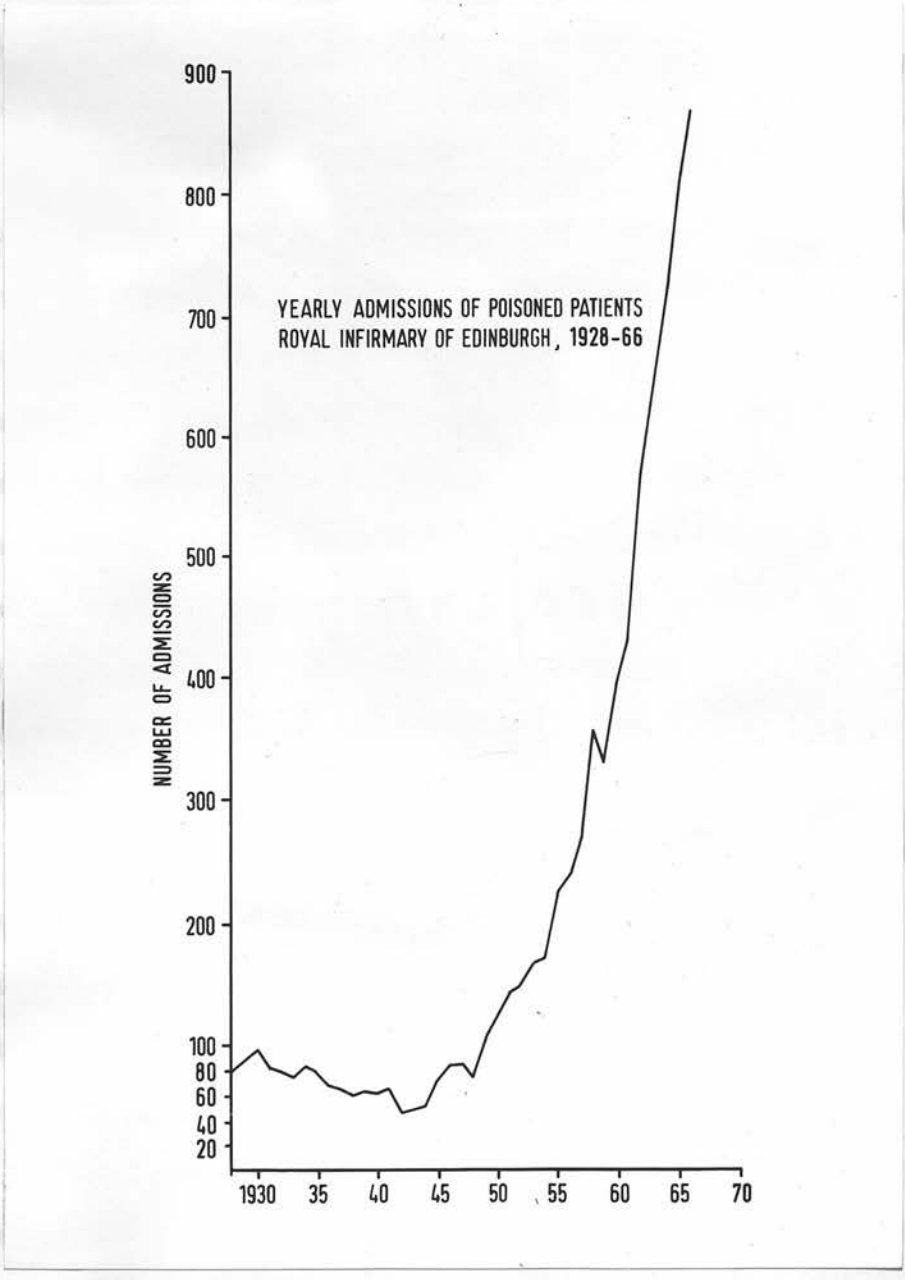

Figure 1.

Total annual admission rate to the Poisoning Treatment Centre, Edinburgh Royal Infirmary.

however, this is not a major cause of the general rise in this condition, as at the present time it still only accounts for about 10 per cent of the patients admitted. Similarly suicidal poisoning where the patient is truly intent on self-destruction is present in only a further 10 per cent. There is no doubt that the main cause of the increase of patients admitted with acute poisoning is a remarkable rise in the incidence of self-poisoning. This is a term instituted by Kessel (1965) to describe a conscious, often impulsive manipulative act by which patients seek to achieve a change in their environment. Such patients do not genuinely wish to die. Their motives for taking an overdosage of poison may be very varied. Confusion arises, however, as self-poisoning is in practice what many others refer to as attempted suicide. The latter term is preferably restricted to those patients who appear to have a very determined desire to end their life. Self-poisoning is responsible for up to 80 per cent of all admissions to the Poisoning Treatment Centre. So common is it nowadays that it appears to have replaced the Victorian vapours as a means of registering distress.

An important factor in the increase of self-poisoning is the ready availability of drugs. It is significant that the sharp rise in incidence of acute poisoning occurred apparently (Fig. 1) simultaneous to the start of the National Health Service. The natural inclination is to blame the ready availability of drugs on the abandon with which drugs are prescribed on the health service. There is no doubt that this is a major factor

as there must be few households in this country today who do not possess potentially lethal quantities of various drugs including barbiturates and salicylates. On the other hand the incidence of acute salicylate poisoning has also increased in keeping with the other poisonings (Fig. 2) and over half of the vast quantities of salicylates, 4,000,000,000 tablets, which are consumed in Britain every year are bought over the counter or from slot machines and not on prescription.

With this enormous annual consumption of salicylate containing tablets it is no surprise that acute salicylate poisoning is a common cause of admission. In the Poisoning Treatment Centre in Edinburgh over a two-year period (Fig. 3) acute salicylate overdosage was the second most common individual poisoning.

Acute poisoning is therefore nowadays a very real medical and social problem in developed countries. It is not isolated to any ethnic or social group and so it must concern every practising doctor.

Comparison between hospital and national death rates have indicated (Fig. 4) that infants have been sent to hospital in the great majority of cases but in the olderage groups, where intentional self-administration is the major cause of poisoning, this has in the past been far from the case. It may be that doctors have mistakenly given their patients the 'benefit of the doubt' in order to avoid the stigma of suicide. In recent years, with a greater awareness of the problems of acute poisoning, general practitioners are becoming quite rightly much more inclined

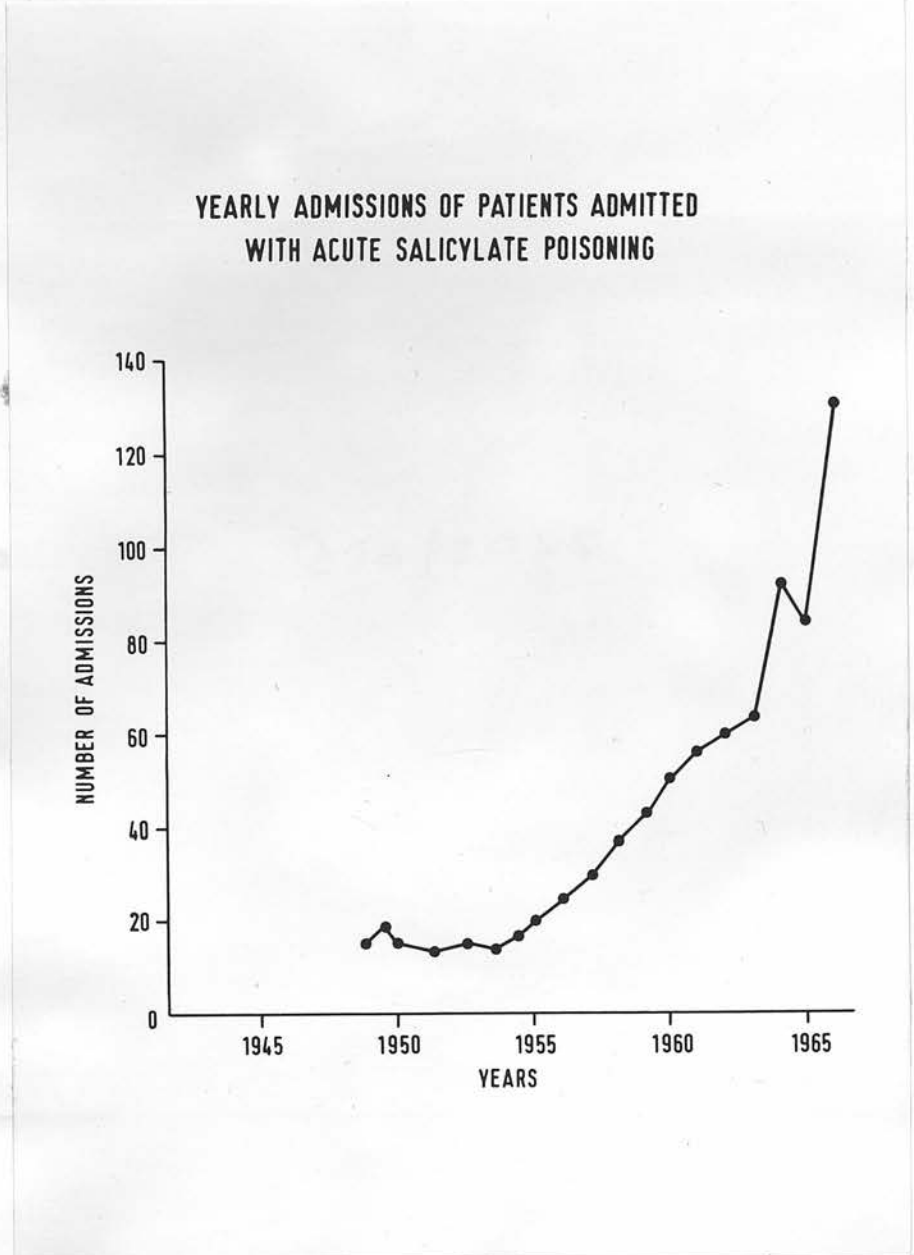

Figure 2.

Annual admission rate of patients with acute salicylate poisoning to the Poisoning Treatment Centre, Edinburgh Royal Infirmary.

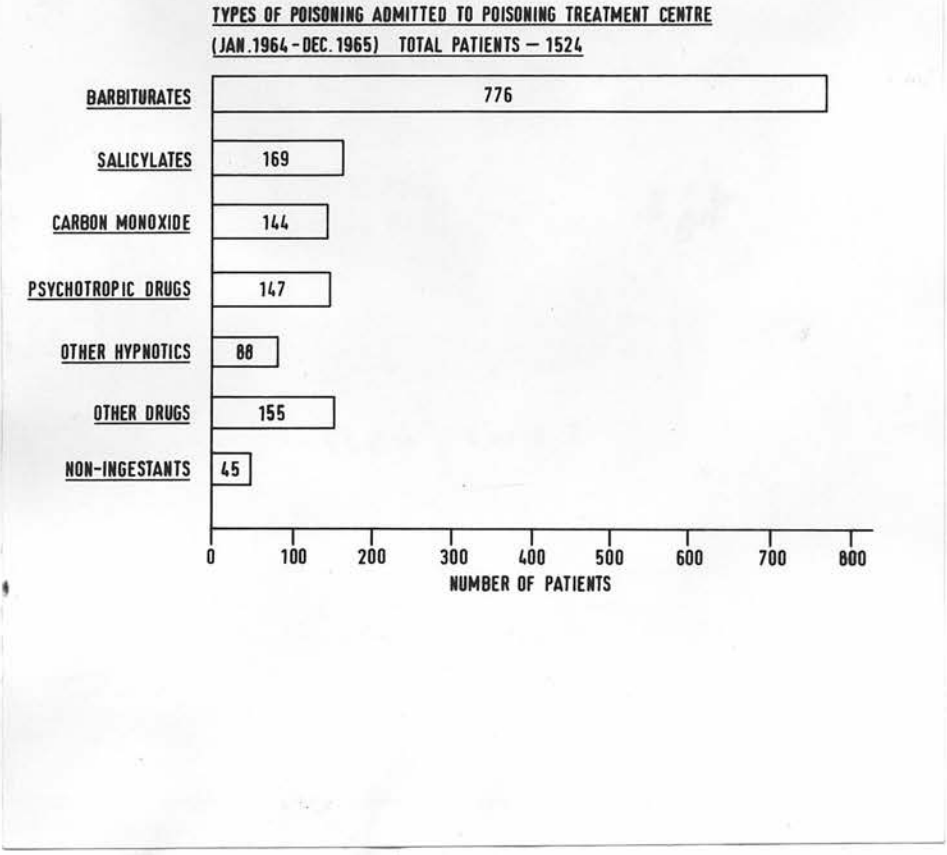

Figure 3.

Relative frequency of different types of poisoning admitted to the Poisoning Treatment Centre, Edinburgh Royal Infirmary in a two year period.

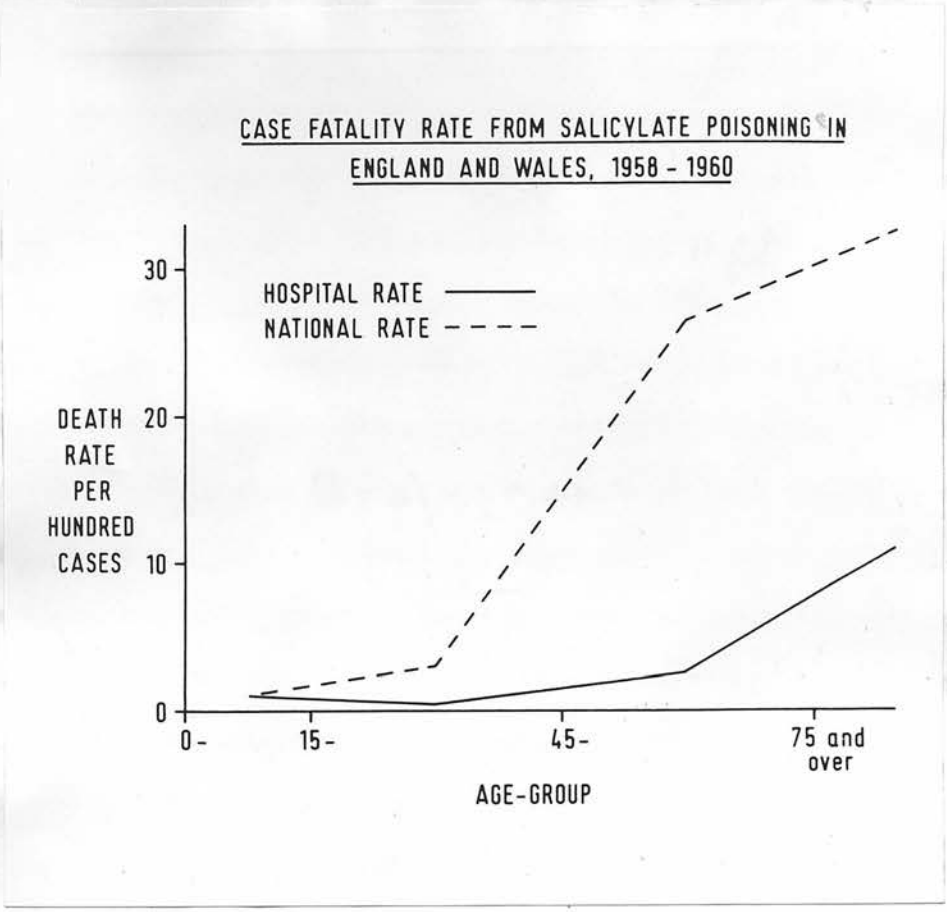

Figure 4.

Comparison between the case fatality rate in hospital and the total number of deaths due to salicylate poisoning in England and Wales (1958 - 1960).

to refer these patients to hospital. It is inevitable, therefore that many hospitals, including peripheral hospitals, will have to accept an increased load of patients with acute poisoning and many will be seriously ill. In the absence of effective treatment a number of these patients will die and many more will be 'near misses'.

Good medicine, therefore, demands a constant search for standardised, improved and safer methods of treatment in order that this considerable group of patients may be saved. Simplicity of method is of great importance, as it is essential that all doctors, even those working in hospitals where technical facilities and biochemical support are limited, may be able to use the regimes with safety. The purpose of this thesis is to review the general management and assessment of patients with acute salicylate poisoning and to describe detailed metabolic and acid-base studies carried out during four different regimes of forced diuresis. By suitable monitoring of the metabolic changes occurring during these different types of forced diuresis, a regime has been developed which is highly effective, technically simple and sufficiently safe to require only a minimum of biochemical control.

STATISTICS

In the last twenty years there has been an explosive increase in the incidence of acute poisoning in this country, and indeed in all the developed countries of the world, (Berman, Jeghers, Schreiner and Pallotta, 1956; Clemmeson and Nilsson, 1961; Ministry of Health Report, 1962; Montani and Perret, 1963; Matthew and Lawson, 1966). This is now a problem of the first magnitude not only from the point of view of management but also in the field of preventive medicine, and is an exacting challenge both to the general practitioner and also to the hospital doctor.

Each year from the 10 per cent sample survey of hospital in-patients the number of patients admitted to the hospital is increasing (Table I), and approximately 10 per cent of all acute admissions to general medical hospitals in Britain are suffering from this condition (Curry, 1965). More recent figures indicate that, in certain general medical hospitals, this proportion of acute emergency admissions due to poisoning has risen to as much as 25 per cent.

World Health Organisation statistics indicate that Scotland is in the disturbing position of having the highest incidence (Fig. 5) in fatal domestic accidents, the main cause of which is poisoning. Also the crude death rates due to poisoning (Table I) for England and Wales and (Table II) for Scotland, England and Wales are very high compared with other developed countries. Only Denmark with a death rate of 12.7 per 100,000 population has a similarly high rate. In Japan,

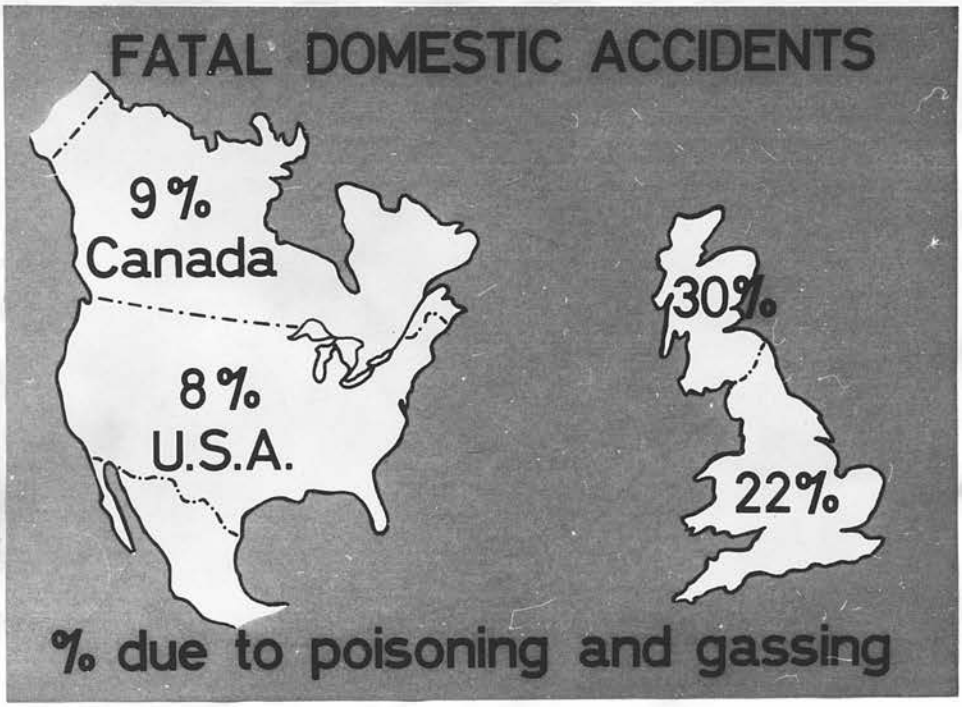

Figure 5.

Comparison between the percentage of fatal domestic accidents due to poisoning in Canada, U.S.A., England and Wales and Scotland.

TABLE I

Poisoning figures (Registrar General)

1957-1964, England and Wales

	All poisoning			
	Admissions to hospital (estimated total)	Deaths in hospital (estimated total)	Deaths per 1,000 admissions	Crude death rate per 100,000 persons
1957	15,900	523	32.9	10.9
1958	17,500	563	32.4	11.2
1959	20,200	477	23.6	11.3
1960	23,300	445	19.1	11.3
1961	27,900	540	19.4	11.5
1962	33,400	645	19.3	13.0
1963	45,942	887	19.3	14.1
1964	50,408	852	14.9	13.0

TABLE II

DEATHS FROM POISONING

Effects of poisons

Rates per 100,000 population

1963

Country	Persons	Males	Females
Canada	5.2	6.3	4.1
Japan	7.4	8.9	6.1
Belgium	5.9	5.9	5.8
Bulgaria	2.6	3.4	1.9
Denmark	12.9	15.1	10.8
France	5.2	5.5	4.9
Italy	2.1	2.4	1.9
Norway	3.7	4.9	2.4
Portugal	1.7	2.2	1.3
England and Wales	14.1	14.6	13.7
Northern Ireland	7.3	8.2	6.5
Scotland	12.7	15.5	10.0

Source: World Health Statistics Annual, 1963, Vol. I, p. 441.

Northern Ireland, Belgium, Canada and France rates lie between 5.2 and 7.4 per 100,000 persons and in Norway, Bulgaria, Italy and Portugal between 1.1 and 3.7. It is difficult to understand why the incidence of death due to accidental poisoning, in which carelessness is the most important factor, should be so different in countries which are otherwise relatively comparable. Variations in the method of registration and coding of causes of death may be a significant factor. Whatever the reason, these figures serve to emphasise the gravity of the situation in this country today in regard to the problem of acute poisoning.

Scottish deaths from poisoning reached a peak in 1962 and have declined since (Table III). A similar fall has occurred in England and Wales since 1963 (Table IV). Analysis of the place of death in 1963 and 1965 (Table IV) shows that the majority of patients die from acute poisoning at home.

Examination of age specific death rates for England and Wales for all forms of poisoning (Table V) shows that increases have occurred in children under 5 years of age. In patients between 5 and 25 years of age there has been little change in rates and at the present time, in the age group 25-34 years acute poisoning is the cause of 1 in 10 of all deaths. The greatest reductions in rates have been in the older patients in both sexes. The probable explanation for the reduction in death rate is that more patients are being referred to hospital and at an earlier stage. This is reflected in the increase in hospital admissions and the slight fall in the proportion of deaths occurring 'at home' (Table IV). A further important factor in the falling

TABLE III

Deaths from poisoning, Scotland, 1955-1965

Year	Accidental poisoning by solids, liquids, gases and vapours		Suicide and Self-Inflicted Injury, Poisoning by solids, liquids and gases	
	Males	Females	Males	Females
		Numbers		
1955	112	134	133	118
1956	102	122	139	113
1957	130	129	160	114
1958	132	166	162	113
1959	136	143	170	121
1960	126	147	140	113
1961	170	164	162	120
1962	215	185	203	145
1963	184	139	185	121
1964	145	155	137	138
1965	161	132	151	138
		Rates per million living		
1955	46	50	54	44
1956	42	46	57	42
1957	53	48	65	43
1958	54	62	66	42
1959	55	53	69	45
1960	51	55	56	42
1961	68	61	65	44
1962	86	68	81	54
1963	74	51	74	45
1964	58	57	55	51
1965	64	49	60	51

TABLE IV

Deaths from poisoning in England and Wales by place of death

Proportions per cent of deaths at particular sites

	All causes of poisoning			
	1963		1965	
	Males	Females	Males	Females
Total deaths	3,341	3,313	2,868	2,842
In hospitals	17.7	21.5	18.6	23.6
In institutions	0.5	0.5	0.5	0.5
At own home	65.2	67.8	61.0	64.8
At other place*	17.0	10.4	20.2	11.1

* "At other place" includes in private houses other than own home and any other place including death on the way to hospital.

TABLE V

Deaths from poisoning

Age specific death rates per 100,000 persons

1963-1965, England and Wales

Age	MALES			FEMALES		
	1963	1964	1965	1963	1964	1965
All Poisons						
0-	26	30	30	12	29	29
1-	36	36	41	21	32	23
5-	4	6	5	4	4	5
15-	71	57	62	36	36	31
25-	115	112	96	86	68	69
35-	150	140	144	121	111	112
45-	184	190	170	168	157	153
55-	285	239	217	221	228	199
65-	333	297	256	295	281	246
75-	564	448	440	496	402	327
85 and over	795	728	542	614	535	460

death rates is probably an improvement in methods and skills of treatment of those admitted.

There are two main sources of information concerning the national trends of acute salicylate intoxication. The first is the time honoured method of death certification which is, however, a relatively insensitive method and takes no account of non-fatal cases. The second is the ten per cent sample of all hospital in-patient records, which has been an effective statistical analysis since 1958.

In England and Wales, in the period 1951-1960 the mortality due to acute salicylate overdosage increased (Fig. 6). In the quinquennium 1951-55 it was 3.9 per million whereas in the next five years it was 4.7 per million, an increase of 20 per cent. From 1955 to 1960 the total mortality remained over two hundred per annum. The mortality rate for hospital admissions of acute salicylate poisoning is about one per cent, whereas for all cases it is in the region of seven per cent. The mortality due to acute salicylate poisoning also has increased in Scotland (Table VI). The relation of the hospital fatality rate for the three years 1958-1960 to a calculated national fatality rate is shown in Figure 4. It was not possible to obtain any figures for non-fatal cases not admitted to hospital and so the national fatality rate was calculated on the basis of registered deaths plus hospital discharges as giving the total number of cases to be considered. The ratio of registered deaths to this total of cases provided an estimate of the national fatality rate. There was a striking difference between the hospital and national

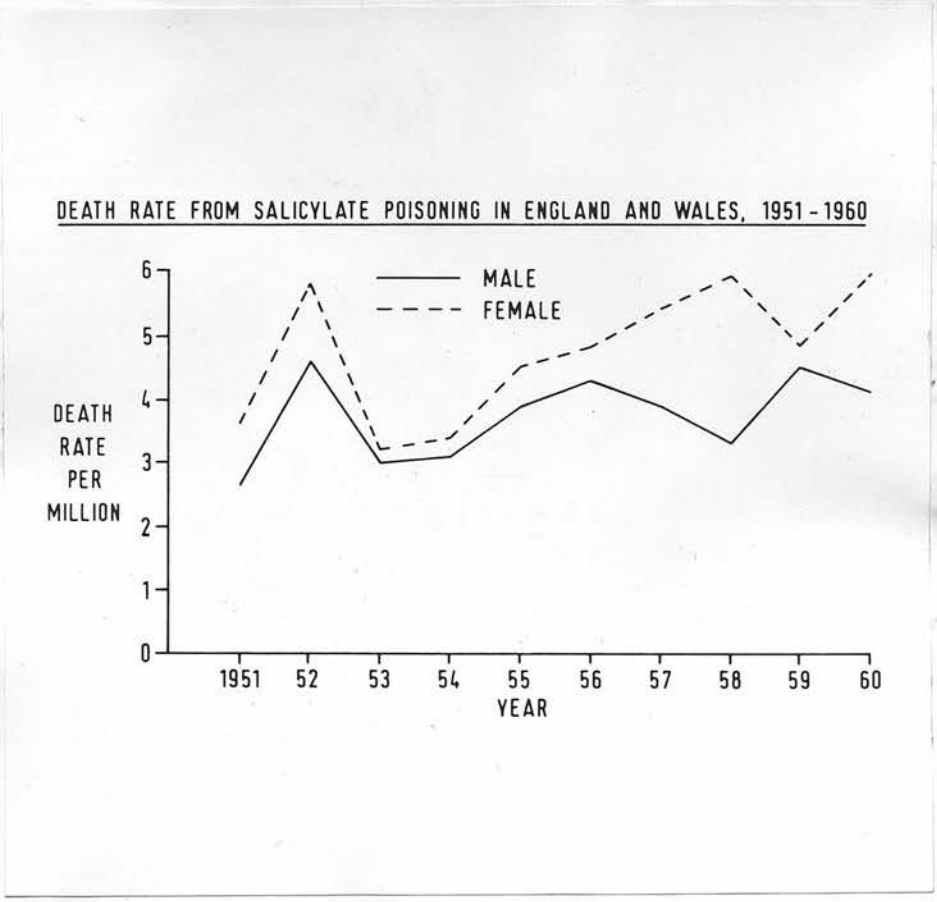

Figure 6.

Trends in mortality due to acute salicylate poisoning in England and Wales (1951 - 1960).

TABLE VI

Deaths from acute poisoning due to aspirin and salicylate in Scotland (1962-66)

	1962		1963		1964		1965		1966	
	Sex									
	M	F	M	F	M	F	M	F	M	F
Accidental	3	1	5	1	3	2	7	3	6	3
Intentional	2	4	2	3	3	7	2	3	1	6
Total	5	5	7	4	6	9	9	6	7	9
	10		11		15		15		16	

figures. This suggested that in 1960 there was a very large number of people, particularly in patients over the age of fifteen, who died due to aspirin poisoning and did not have the benefit of hospital care. The remarkable contrast in the above figures would almost certainly be accentuated if information was also available for the total number of non-fatal incidents.

Deaths from salicylate poisoning are accidental, the result of self-poisoning episodes or genuinely suicidal. Twenty per cent of all such deaths are due to accidents and the remainder result from the other two causes. The differences for sex and age in patients dying from acute salicylate overdosage are shown in (Fig. 7). The figures for self-poisoning and true suicide have been added together and are referred to as 'suicide'. Infants and toddlers are at risk from accidental poisoning and these deaths are all the more tragic as they are all preventable. Death due to this cause is uncommon during school age, but after adolescence the mortality in both sexes rises steadily up to the age of sixty-five years. In these older groups intentional self-administration is by far the main cause of poisoning.

Morbidity statistics give much more detailed information regarding the true incidence of poisoning from salicylates. Different forms of poisoning predominate in each age group. Salicylate is the choice of the teenager, which is in contrast to coal gassing which is commonest in older patients (Matthew and Lawson, 1967). This is reflected in the Figure for the mean annual Hospital In-Patient Rate per million population in England and Wales for 1958-1960 (Fig. 8). These figures show some

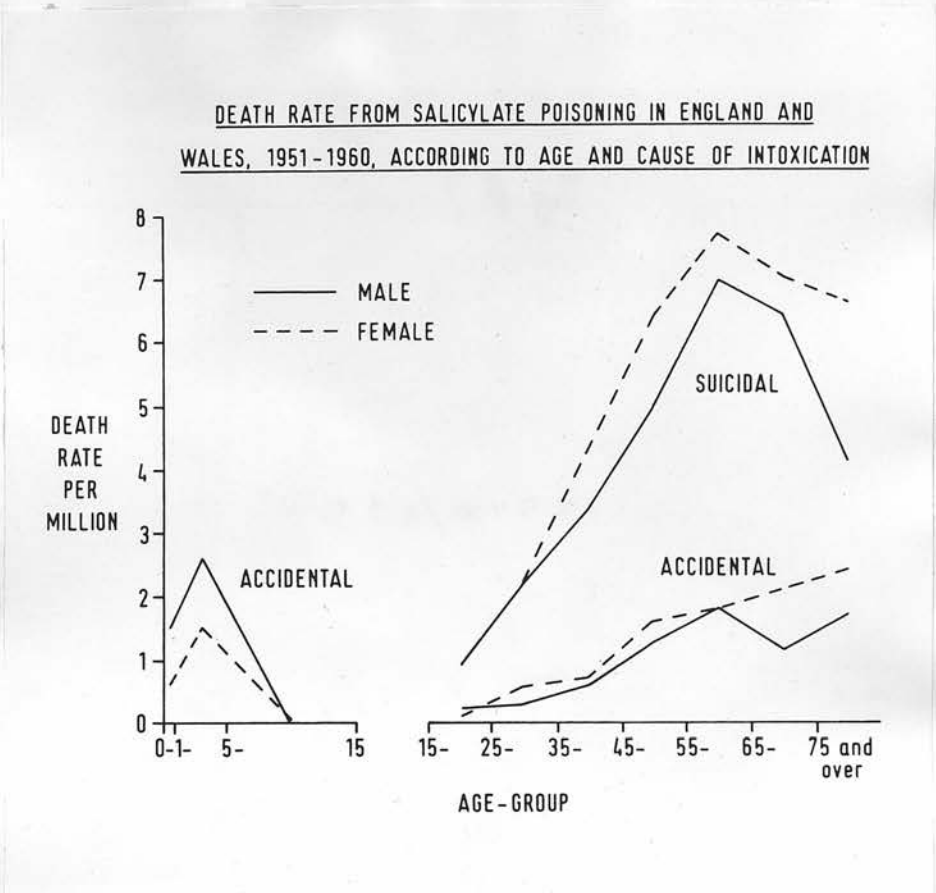

Figure 7.

Differences for sex, age and cause of poisoning in patients dying from salicylate poisoning in England and Wales (1951 - 1960).

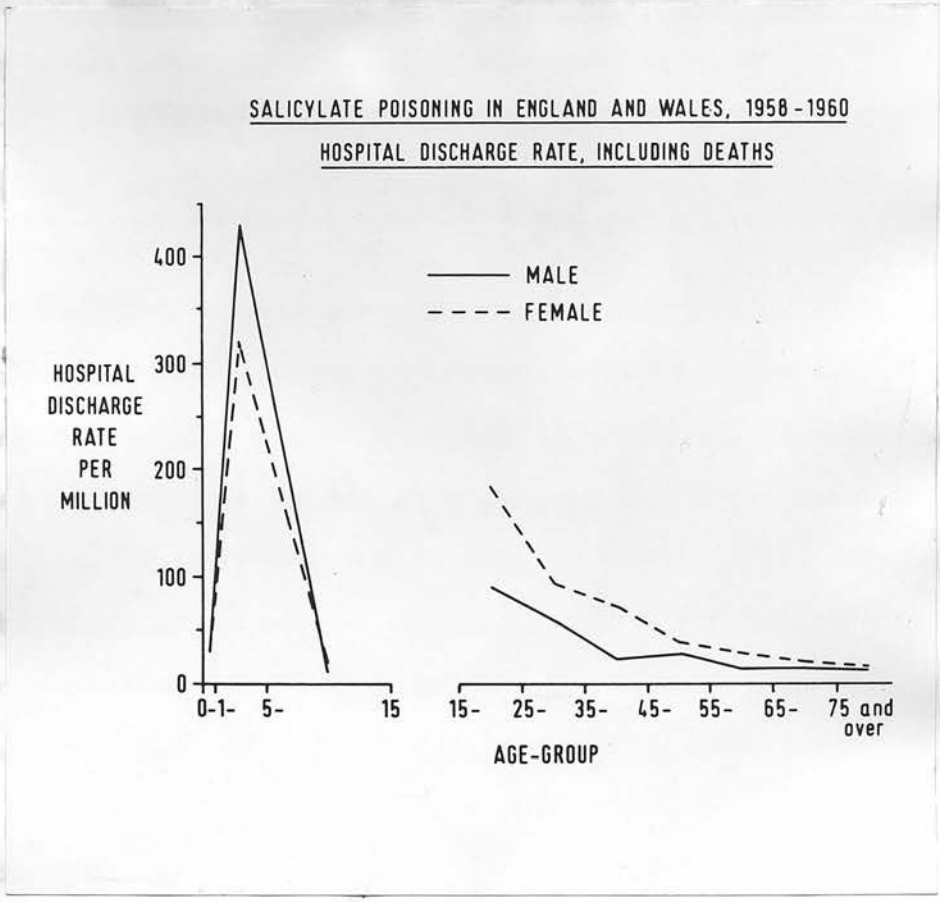

Figure 8.

Mean hospital in-patient rate per million population in England and Wales (1958 - 1960).

interesting differences from those shown in (Fig. 7) for death rates according to age and cause of intoxication. The peak for infants and toddlers is much more prominent and boys remain more frequent than girls. The second peak in terms of hospital admissions occurs in the adolescent and early adult period for both sexes although females seem much more at risk. In the older age groups there is a steady decline in incidence which is in contrast to the corresponding death rate.

Acute salicylate poisoning is likely to present as a medical emergency wherever aspirin is readily available. The high incidence of this type of overdosage is therefore not surprising, when one considers the vast quantities of aspirin consumed in this country every year and the fact that over half of these tablets are bought without prescription in a wide variety of shops and even from slot machines. An interesting experiment regarding this ready availability of aspirins was carried out by the Edinburgh University Department of Psychological Medicine. This young girl volunteer (Fig. 9) was sent out into the city maintaining the expression and general manner shown. She was to visit any chemist shop she encountered and to ask for one hundred aspirin tablets. In half an hour she visited five shops and in (Fig, 10) is shown the number of tablets she bought. In only one was any comment made about her obvious state of distress. In none of the shops was any objection or even hesitancy shown to the giving of the tablets. In one chemist's she was offered a cup of tea and if one was being facetious it might be suggested that this was given simply to wash down her tablets!

Figure 9.

Appearance of volunteer maintained during the experiment.

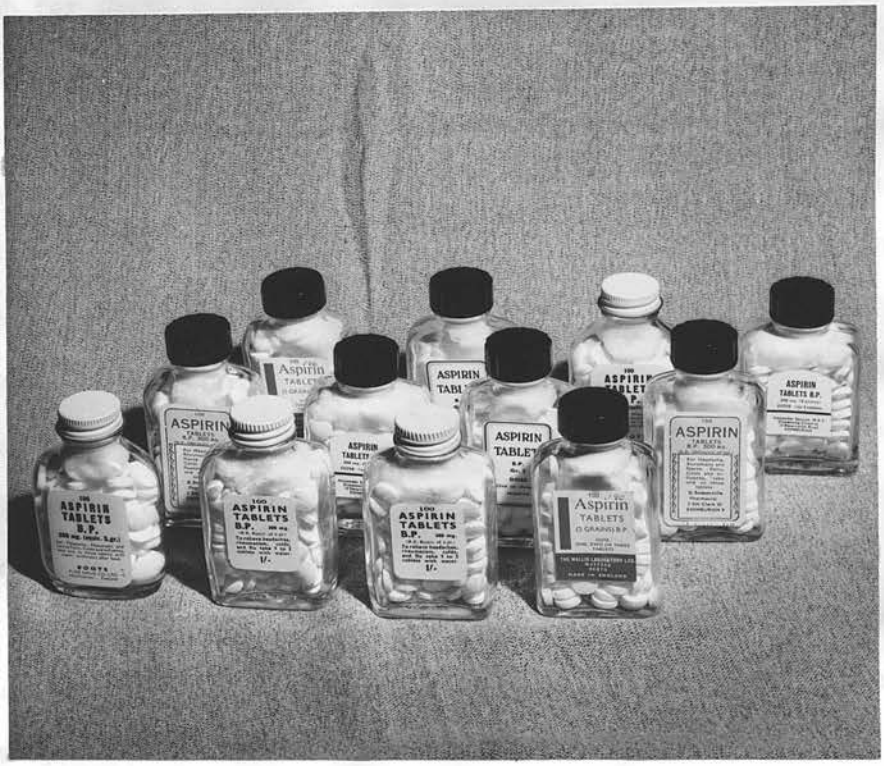

Figure 10.

Number of tablets acquired in 30 minutes.

This type of poisoning remains dangerous with a significantly high mortality. In addition to those who die there are many who are seriously ill. Serious complications may arise with little or no warning, even when patients are being carefully monitored both for their clinical and biochemical progress. The main reason for this is that, despite numerous studies of the subject, the metabolic and acid-base upsets associated with acute salicylate poisoning remain incompletely understood. Also there have been many different types of treatment advocated for these patients, including extracorporeal haemodialysis, peritoneal dialysis, exchange transfusion, anion exchange resins and various types of forced diuresis. All have advantages and disadvantages and the indications for the correct use of these treatments remains largely a matter for conjecture.

The development and standardisation of an effective yet simple form of treatment, which was sufficiently safe to make its use appropriate in all medical units would be an important contribution to a reduction not only in the mortality but, perhaps more important, in the morbidity resulting from acute salicylate poisoning.

DIAGNOSIS OF ACUTE SALICYLATE POISONING

Acute salicylate intoxication may result from a number of different preparations of salicylic acid and by a number of different routes. Acetyl salicylic acid was first introduced to medicine in 1899 by Dreser and marketed by Bayer under the trade name of aspirin as a palatable and non-irritant form of salicylic acid. Aspirin is now sold by the ton and, quite apart from its wide therapeutic use by the medical profession, the lay public take it with great frequency and all too often with gay abandon for every conceivable complaint. It is no surprise, therefore, that this preparation of salicylate is by far the most commonly taken in overdosage. Sodium salicylate, although an older fashioned preparation, is still prescribed and occasionally may be taken in excessive amounts. Methyl salicylate (Oil of Wintergreen, Gaultheria Oil, Betula Oil, Sweet Birch Oil), which is the main ingredient of many counter-irritant liniments, also maybe the cause of acute salicylate poisoning. Preparations containing methyl salicylate are usually taken accidentally by the inquisitive toddler but are occasionally intentionally self-administered by adults. This is a particularly dangerous form of poisoning as methyl salicylate is the most toxic of the salicylates weight for weight. For example, one teaspoonful (5 ml.) of methyl salicylate mixture is equivalent to twelve 300 mg. tablets of acetyl salicylate.

Acute salicylate poisoning occurs not only by ingestion of the drug. It may follow the over-enthusiastic skin application

of ointments containing salicylic acid, such as salicylic acid ointment, B.P. and benzoic and salicylic acid ointment, N.F. This is especially the case when extensive areas are being treated and when the skin surface is broken. (von Weiss and Lever, 1964).

Doctors must be aware of all these possible routes of entry if the diagnosis of acute salicylate poisoning is not to be overlooked.

It is a common misconception amongst doctors generally that patients with acute salicylate overdosage are unconscious. Impairment of level of consciousness can certainly occur in young children. In older children and adults with poisoning due to salicylate alone, this only happens in the most severe types of intoxication and is a rare occurrence in clinical practice (Matthew and Lawson, 1967). On the contrary, such patients are characteristically very alert and hyperkinetic. So unusual is impairment of level of consciousness that, if it occurs, the presence of concomitant poisoning with some other toxic substance, particularly sedative or tranquillising drugs, should be carefully considered.

In practice, as the great majority of patients are fully conscious, there is seldom much difficulty in diagnosis. Patients, especially those with self-poisoning, frequently either exaggerate or understate the dose which they have taken; but only a few deny having taken the tablets. In these, provided the diagnosis is considered, the clinical features are usually sufficiently characteristic to permitcorrect diagnosis.

Clinical Features

Central Nervous

The effects on the nervous system function are numerous. Headache, dizziness, tinnitus, deafness, dimness of vision, apprehension and mental confusion may all be present in moderately severe or even mild acute salicylate poisoning (Robin, Davis and Rees, 1959; Done 1965; Goodman and Gilman, 1965). In young children, drowsiness, convulsions and frank coma are not uncommon even when relatively small quantities of salicylate have been ingested. In older children and adults in severe overdosage effects on the central nervous system may become more pronounced and include delirium, mania, hallucinations, generalised convulsions and loss of consciousness. This fully developed syndrome has been called the "salicylate jag" (Goodman and Gilman, 1965). The toxic effects of salicylate on the central nervous system may result in a clinical presentation very similar to hysteria. Unless the possibility of acute salicylate overdosage is considered serious errors in diagnosis may be made.

Cardiovascular

The circulation is generally hyperactive with tachycardia and a full bounding pulse. Sustained 'shock' may occur but is an unusual complication. On the other hand sudden cardiovascular collapse is a well recognised mode of death, (Done, 1965).

Respiratory

Hyperpnoea is a very common feature of salicylism. This

effect is probably mediated by the anterior hypothalamus, since lesions in this area may reduce or totally abolish the stimulatory effect of salicylate on ventilation (Robin and Hume, 1965). Acute pulmonary oedema may occasionally occur (Granville-Grossman and Sergeant, 1960) and is considered to be due to sodium retention. Acute respiratory arrest may occur and is the usual terminal event resulting in death, (Done, 1965).

Gastro-intestinal

Toxic effects on gastro-intestinal function are usually prominent. Epigastric tenderness and actual pain, nausea, vomiting and anorexia are all common. According to Goodman and Gilman (1965), more than half of the individuals with even moderate salicylate poisoning have nausea. It is fortunate, indeed, that so many patients do in fact vomit shortly after having taken the tablets, as, by doing so, they may lose a considerable number of the aspirins taken and not infrequently save themselves from very severe salicylate poisoning. Haematemesis due either to the local irritant effect on the gastric mucosa or else to the bleeding tendency which some patients develop as a toxic effect of the absorbed salicylate may occur but is less frequent than many authors suggest.

Renal

Oliguria is commonly found as the great majority of patients are dehydrated to a greater or lesser degree. The effects on renal function of acute overdosage of salicylates varies, depending on whether or not the patient has been taking regular therapeutic

doses of the drug in the period immediately before the acute poisoning. If the patient has not recently been exposed to the drug, albuminuria, urinary casts and a sharp increase in the urine cell count will be found. The cells are predominantly renal tubular cells (Scott, Denman and Dorling, 1963; Prescott, 1965), but red cells and leucocytes are also present in considerable numbers. The presence of albuminuria and celluria does not necessarily indicate serious renal damage (Smith and Smith, 1966). According to Scott et al., (1963), the rise in urine cell count is a transient finding and there is a refractory period of about a month during which further salicylate insult to the kidneys produces only a diminished response.

Gross and Greenberg (1948) concluded that salicylates in acute overdosage could cause nephritis and acute tubular necrosis has been described by Bracey (1951), Locket (1957), Campbell and Maclaurin (1958) and Granville-Grossman and Sergeant (1960). Further evidence of tubular damage due to large doses of salicylate was presented by Ben-Ishay (1964) who reported aminoaciduria in adult males. From these findings there is little doubt that acute overdosage of salicylates can result in renal damage but Ghose and Joekes (1964) and Smith and Smith (1966) regard the incidence of acute renal failure in this condition to be rare.

Haematological

These changes are seldom marked and only occasionally cause problems in management. The most frequently reported blood disorder which occurs is a bleeding tendency due to hypoprothrombinaemia.

Quick and Clesceri (1960) demonstrated that this was due to decrease of Factor VII. They also found that the dose of salicylate required to cause even a slight prolongation of the prothrombin time was relatively large (6.0 g. per 70 kg.). This would require the ingestion of approximately 20 standard tablets of aspirin. Bleeding tendency during acute salicylate poisoning may also result from increased capillary fragility (Frick, 1956; Smith and Mackinnon, 1951), thrombocytopenia (Rappaport, Nixon and Barker, 1945) or impaired platelet stickiness (Beaumont, Willie and Lenegre, 1955).

Intravascular haemolysis occasionally may occur to a significant degree.

Metabolic

Hyperthermia is a common feature of acute salicylate poisoning. In older children and adults this is usually mild and seldom gives rise to a serious problem of management (Smith and Smith, 1966). In young children, however, there is frequently severe pyrexia and fatalities may occur (Segar and Holliday, 1958).

The mechanism of the hyperthermia is increased heat production at tissue level due to the uncoupling action of salicylate on oxidative phosphorylation. This allows the energy produced to be dissipated as heat rather than stored, as is normally the case. As a result of hyperthermia, sweating is a common finding. This may be profuse and contributes to the development of dehydration, which may be severe.

Acute salicylate poisoning is almost invariably associated with an abnormality of acid-base equilibrium and the severity and complexity of the upset is closely related to the severity of the overdosage. The mechanism of this abnormality has interested many but is still not completely understood. Until quite recently it was generally accepted (Singer, 1954; Segar and Holliday, 1958; and Winters, White, Hughes and Ordway, 1959; Eichenholz, Mulhausen and Redleaf, 1963) that the general sequence of events was an initial respiratory alkalosis which progressed to metabolic acidosis. However more recently (Winters, 1963; McLaughlin, 1965; and Smith, 1966) have supported a somewhat more rational approach in so far as they suggest that there is always a mixed disturbance with multiple simultaneous independent actions each of which may result in imbalance of acid-base equilibrium in one direction or another. The net result in any one patient will depend on the individual response to the poisoning and also to other factors such as age. It is well known for example that infants and toddlers are peculiarly sensitive to acid-base shifts in acute salicylate poisoning. They characteristically develop a severe metabolic acidosis whereas in older children and in adults, the usual finding is predominantly that of respiratory alkalosis. The exact mechanism of these abnormalities remains highly controversial and reports in the literature may at times be remarkably contradictory. On the other hand, it is very important to recognise that whatever the mechanism the net result is a complex disturbance.

Smith (1966) has summarised the situation as far as is known at the present time. He points out that the acid-base disturbance of the acute salicylate poisoning may be described under three main headings,

Respiratory Alkalosis

Respiratory Acidosis

Metabolic Acidosis.

Respiratory Alkalosis

The respiratory alkalosis results from the stimulation of the medullary respiratory centre by salicylate itself. It is generally agreed that at least a partial explanation of this stimulation is that salicylate increases the sensitivity of the respiratory centre to relative changes in the partial pressure of CO_2 and the pH of arterial blood (Alexander, Spalter and West, 1955; Tenney and Miller, 1955). Williams, Winters, Clapp, Hollander and Welt (1958) suggested that this effect of salicylate may be mediated by its effect in stimulating metabolic oxidative reactions. This, however, has not been established. The ability of salicylate to produce hyperventilation appears to be mediated by the anterior hypothalamus since damage in this area may reduce or totally abolish the stimulatory effect of salicylate on ventilation, (Robin, et al., 1959).

As a result of the increased alveolar ventilation, which may be sustained for long periods of time during the poisoning, there is a consequent fall in the partial pressure of carbon dioxide (pCO_2) in the alveolar air and also in the arterial blood.

Initially, this disturbance results in a rise in the arterial blood pH, which is limited by compensatory buffer mechanisms including haemoglobin/oxyhaemoglobin and the secretion of an alkaline urine containing bicarbonate together with an exchange of intracellular hydrogen ions for extracellular cations. An actual alkalaemia only occurs if the compensatory mechanisms do not operate sufficiently adequately to prevent a significant change in blood pH. The degree to which alterations in blood pH occur by this mechanism, therefore depends on the integrity of these buffer mechanisms. It therefore, depends on the severity and duration of the poisoning and amongst other functions on the integrity of kidney function.

Some authors have reported their experience in the use of various measures to reduce the increased respiratory exchange in salicylate intoxication. Harvie and Singer (1955) attempted to do this by administering a gas mixture with a high carbon dioxide content. Eichenholz, Mulhausen and Redleaf (1963) claimed that they were able to prevent the onset of the subsequent metabolic acidosis by administering a mixture of 4 per cent carbon dioxide in air, thereby preventing any reduction in blood pCO_2 level. There are, however, objections to this form of treatment. The respiratory centre is already more sensitive to the effect of changes in pCO_2 and administered carbon dioxide would ultimately produce depression of the respiratory centre. Freier, Neal, Nisbet, Rees, and Wilson (1957) concluded that the inhalation of carbon dioxide in acute salicylate poisoning was

effective only at the expense of accentuated respiratory dysfunction and that its use required very skilled administrations together with close control and monitoring of respiratory function involving highly developed techniques.

Respiratory depressant drugs such as barbiturates and other sedatives have also been used by Rapaport and Guest (1945) to eliminate the hyperpnoea of the poisoning. It was found, however that salicylates seemed in some curious way to increase the sensitivity of the subjects to these drugs. Even average doses of barbiturates resulted in prolonged coma and in some experimental animals in death. On the whole, no specific treatment for the respiratory alkalosis need or should be given (Ghose and Joekes, 1964).

Respiratory Acidosis

A now well known metabolic effect of salicylates is their uncoupling action on oxidative phosphorylation reactions. The degree to which this occurs is proportional to the severity of the overdosage. As a result of this uncoupling action there is an increased metabolic production of carbon dioxide at tissue level due to increased substrate oxidation. Direct experimental evidence in favour of this mechanism has been provided in the dog by Tenney and Millar (1955) and in the rat by Smith (1959). This effect must also occur in humans as it has been demonstrated that salicylate will increase the basal oxygen consumption, (Hetzel, Charnock and Lander, 1959). Respiratory acidosis will therefore result in a rise in pCO_2.

There are therefore two apparently opposing effects on the pCO_2 levels and the net result will depend upon the relative intensity of the two mechanisms. In practice increase in alveolar ventilation as a result of the intense hyperpnoea of acute salicylate overdosage is so marked that the pCO_2 falls, resulting in a net respiratory alkalosis.

Metabolic Acidosis

The metabolic acidosis of acute salicylate intoxication is as yet incompletely understood. However, Winters et al. (1959) demonstrated that the plasma of these patients contained a significant fraction of undefined anions. They considered that these anions of organic acids were the main reason for the fall in buffer bicarbonate. Other factors including the salicylate itself, have been suggested as being contributory towards the metabolic acidosis. Winters and his associates (1959), however, have demonstrated that the contribution of the salicylate is relatively small. For example, a plasma salicylate concentration of 70 mg. per 100 ml. is equivalent to only 5 mM. Hyperchloraemia has also been suggested as a contributory factor in the acidosis. Winters and his colleagues rejected this concept and considered that any rise in plasma chloride was only the result of secondary compensatory changes and not the primary cause of the acidosis.

Eichenholz et al. (1963) reported that there was an increase in the concentrations in the blood of pyruvate and lactate in dogs poisoned with salicylate, but Done (1963) found that the plasma lactate level was normal in patients with this type of overdosage.

On the other hand, he agreed that pyruvate levels were elevated in the plasma of children with salicylate poisoning, but he did not feel that they were sufficiently high to account for the overall acidosis which was present. Increases in the levels of the acidic ketone bodies, aceto-acetic acid and β-hydroxy-butyric acid both in plasma and in urine have been recognised for some considerable time, (Barnett, Powers, Benward and Hartmann, 1942 and Erganian, Forbes and Case, 1947).

In a detailed study of organic acids in salicylate intoxication Schwartz and Landy (1965) concluded from their data that the major factor in the development of metabolic acidosis in salicylate poisoning was the excessive production of organic acids. In addition to acidic ketones there was also a considerable increase in organic acid production from the Kreb's cycle. Since all these acids have pK's below those of the major physiological buffers, the latter are displaced isohydrically by the organic acids until these are metabolised or excreted in the urine. An accumulation of organic anions in the plasma may result from two separate actions. Firstly, the increase in substrate oxidation as a result of the uncoupling action of salicylates leads to an increased formation of pyruvate. Secondly, salicylate has been shown to inhibit several Kreb's cycle enzymes including α-Keto-butyric dehydrogenase and succinic dehydrogenase (Kaplan, Kennedy and Davis, 1954). Results of such an inhibition would result in interference with the Tricarboxylic acid cycle. Smith (1966) has suggested that salicylate also affects glutamate metabolism via inhibition of glutamic-pyruvic transamination. As a result

of these enzyme inhibitions there will be a reduction in the conversion of pyruvate to either lactate or alanine. So pyruvate ion will accumulate and its conversion to acetyl coenzyme A will be increased. The acetyl coenzyme A formed will not completely enter the tricarboxylic acid cycle because of the above enzyme inhibitions and there will result an accumulation of organic acids such as malate, fumarate and citrate. Also much of the acetyl coenzyme A which fails to enter the tricarboxylic acid cycle, will be converted to aceto-acetyl coenzyme A and this would lead to an increased production of aceto-acetic acid and B-hydroxy-butyric acid with resultant ketosis. Yoshida, Metcoff and Kaiser (1961) have confirmed the defects in the above enzymes in in-vitro studies on tissues and in addition they have demonstrated numerous other enzymes defects but the significance of these remains rather uncertain and will require further research.

The effects of the metabolic acidosis in patients with acute salicylate intoxication varies very markedly with age. Infants and toddlers have been shown to be remarkably sensitive to the development of metabolic acidosis, and Done (1963) reported that there was a direct age relationship to the increase in plasma anions noted, but this was not found to be the case when the relationship was examined for pCO_2 in the blood. In regard to the respiratory components of the acid-base upset there appears to be little or no age relationship and all patients would appear to be equally prone to these abnormalities.

The metabolic effects of salicylate in interfering with tissue enzyme actions is not confined to the carbohydrate metabolism

and Bodie in 1956 demonstrated that there was also an impairment of fatty acid metabolism which would also tend to promote keto-acidosis.

Summary

The total sequence of events which might lead to the acid-base disequilibrium, which occurs in acute salicylate overdosage may be summarised (Fig. 11). The phase of respiratory centre stimulation results in a decrease in carbon dioxide tension, a rise in blood pH and the excretion of bicarbonate buffer in the urine. According to the isohydric principle all other buffers are affected so that a redistribution between haemoglobin and bicarbonate occurs in the blood. At this stage an increase in pyruvate and lactate production together with the excretion of bicarbonate results also in some depletion of buffer although respiratory alkalosis is present. As the other effects of salicylate become manifest in diverse tissues, such as muscle, liver, kidney and brain, related production of organic acids increases and exceeds the rate of metabolism and/or excretion of these via the urine. Under such circumstances a metabolic acidosis rapidly supervenes because these endogenous acids are inadequately buffered. The excretion of these metabolic acids does not restore displaced buffer completely since they are relatively stronger acids. When the urinary pH exceeds 5, more than 50% of the organic acids must be excreted in the ionised form, rather than an unassociated acid. To the extent that the ionised form is excreted, a loss of buffer ensues. The only

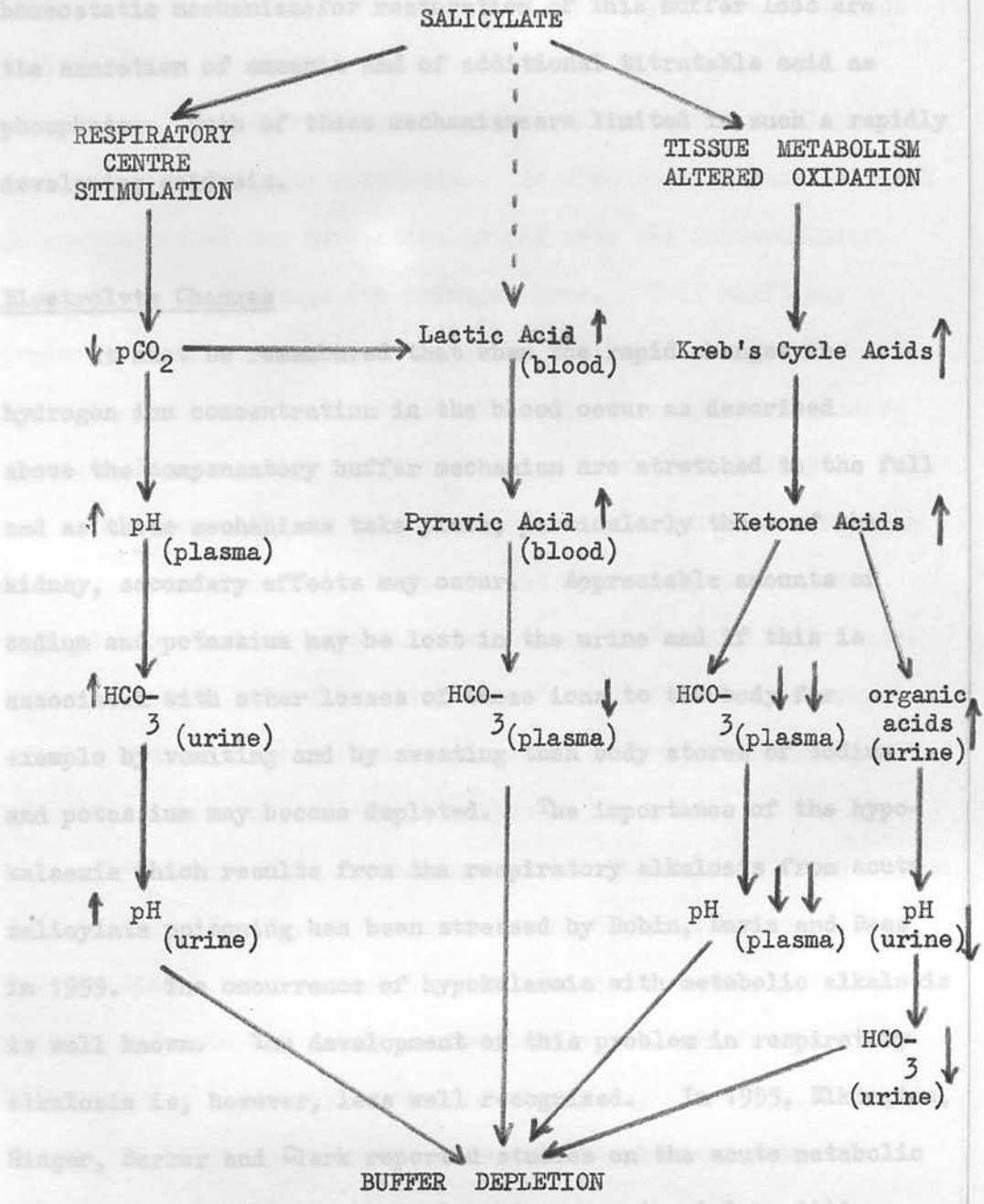

Fig. 11

Sequence of events leading to acid-base imbalance in acute salicylate poisoning.

homeostatic mechanisms for restoration of this buffer loss are the excretion of ammonia and of additional titratable acid as phosphate. Both of these mechanisms are limited in such a rapidly developing acidosis.

Electrolyte Changes

It must be remembered that when the rapid changes in hydrogen ion concentration in the blood occur as described above the compensatory buffer mechanism are stretched to the full and as these mechanisms take place, particularly those of the kidney, secondary effects may occur. Appreciable amounts of sodium and potassium may be lost in the urine and if this is associated with other losses of these ions to the body for example by vomiting and by sweating then body stores of sodium and potassium may become depleted. The importance of the hypokalaemia which results from the respiratory alkalosis from acute salicylate poisoning has been stressed by Robin, Davis and Rees in 1959. The occurrence of hypokalaemia with metabolic alkalosis is well known. The development of this problem in respiratory alkalosis is, however, less well recognised. In 1955, Elkington, Singer, Barker and Clark reported studies on the acute metabolic effects of respiratory alkalosis under experimental conditions. They failed to demonstrate any marked cellular or renal potassium shifts during voluntary hyperventilation. The studies however were carried out over a very short period of time and the stimulus to hyperventilation was a mild one. In salicylate intoxication on the other hand there is a very high respiratory minute volume which may be maintained for many hours (Robin et al.,

1959). As a result of this the alkalosis may be severe and prolonged.

There are several factors responsible for the development of hypokalaemia during alkalosis. An alkaline pH tends to shift potassium out of the extracellular and into the intracellular compartment in exchange for hydrogen ions. This shift may produce hypokalaemia without total body potassium depletion and hypokalaemia itself may produce electrocardiographic and neuromuscular changes independent of changes in the total body potassium stores (Robin et al., 1959). A second factor is that alkalosis may produce hypokalaemia and ultimately potassium depletion because of excessive renal loss. Thirdly salicylates themselves have been shown to have a direct effect on the renal tubular mechanisms involved in potassium excretion resulting in a further increased loss of potassium in the urine.

The primary renal mechanism for the development of potassium depletion in alkalosis is related to the ion exchange mechanism for the distal tubular reabsorption of sodium whereby potassium is secreted into the urine and is closely involved in the mechanism for the acidification of the urine, (Berliner, Kennedy and Orloff, 1951). There is a competition between potassium and hydrogen ions during the distal tubular reabsorption of sodium. In alkalosis the deficit of hydrogen ions favours the exchange of potassium for sodium leading to significant depletion of potassium ion from both the intracellular and extracellular spaces.

A further significant factor undoubtedly operative in

patients with salicylate intoxication is the mutual aggravation of alkalosis and potassium depletion. With a stimulus for the renal secretion of potassium, the entrance of hydrogen ion into the intracellular compartment will aggravate the extracellular alkalosis providing further stimulus for potassium depletion.

The secretion of an alkaline urine is not an invariable finding in respiratory alkalosis and it is well known that in other forms of alkalosis a 'paradoxical' aciduria may occur (Gamble and Ross, 1925 and Robin et al., 1959). The exact cause of this is not entirely clear. It has been suggested that it is due to the potassium depletion primarily and to the consequent decrease in relative availability of potassium ion in competition for hydrogen ion in the distal reabsorption of sodium, (Berliner and Kennedy, 1948). Another explanation, which has been offered, is that it may be due to the relative cellular acidosis following the exchange between the extracellular and the intracellular spaces of hydrogen ion for potassium ion during the development of potassium depletion and alkalosis (Cooke, Segar, Cheek, Corille and Darrow, 1952). Whatever the cause the result in either case is the production of an acid urine despite a severe systemic alkalosis.

Alterations in plasma sodium are quite frequently found but the significance of this in itself is rather difficult to assess. Granville-Grossman and Sergeant, (1960) suggested that acute pulmonary oedema may occur as a result of sodium retention. The evidence for this however is rather incomplete. Plasma electrolyte patterns encountered in patients with acute salicylate poisoning particularly in infants and children are often those of dehydration

and there is no doubt that plasma electrolyte patterns in themselves may be difficult to interpret. It is therefore important to consider every facet of an individual case in order that appropriate treatment may be given.

On the whole the diagnosis of acute salicylate poisoning on clinical grounds is not difficult as the features of salicylism are familiar to all practising doctors. There is no doubt, however that in a minority of patients especially those who deny having taken the poisoning, the features may not be characteristic. Further difficulties arise as the clinical features may sometimes be present at very low levels of plasma salicylate or they may be absent even when the patient is severely poisoned. In addition, particularly in patients who indulge in self-poisoning, the classical features of salicylate intoxication may be obscured by the patient having taken some other preparation, in particular sedative and hypnotic drugs.

In terms of clinical presentation acute salicylate overdosage may mimic a number of other well-recognised clinical presentations. These include frank hysteria and organic delirium. The patient may be thought to be suffering also from diabetic ketosis as glycosuria and ketonuria may be found in acute salicylate poisoning. Also as papilloedema may be a feature of this particular poisoning, a diagnosis of intracranial space occupying lesion may be mistakenly made, and the patient exposed to all manner of unpleasant and even dangerous procedures.

For all these reasons it is clear that clinical diagnosis alone may be very uncertain. A more certain proof of salicylate

overdosage is required and is provided by measurement of the plasma salicylate level. There are a number of commonly used means of analysis of salicylate in biological fluids. These include the colorimetric methods of Brodie, Udenfriend and Coburn, (1944), and more recently described by Routh and Dryer, (1961.) Other methods include those of Smith and Talbot (1950) and of Trinder (1954) as described by Macdonald (1965). The first of these is perhaps the most sensitive and specific but the second is subject to interference from a number of other drugs notably phenacetin and phenolphthalein. Trinder's method is the least sensitive of those mentioned and it also has the disadvantage that the absorption spectrum of the ferric salicylate complex may be rather ill defined and is subject to changes in external factors such as temperature, pH and ionic strength. If phosphates are also present in the mixture they interfere by preferentially kelating with the reagent. These limitations are particularly troublesome in measuring salicylate in urine, but in the case of plasma the results can be obtained with adequate reproducibility and accuracy in the range from 25 to 75 mg. per 100 ml., which for clinical purposes is the most important. A great advantage of Trinder's method is that it is technically very simple and can be carried out in approximately 10 minutes. For these reasons Trinder's method is the most suitable for clinical purposes and may even, with relative ease, be set up as a side room procedure. The technique has been described in some detail by MacDonald (1965). The reaction is carried out on specimens of heparinised venous blood and the equipment required consists simply of disposable

tubes (10 ml. plain bottles, Stayne Laboratories Ltd.). The absorbance is measured in standard cuvettes (Eel spectra).

REGIME

Principle

Trinder's reagent reacts with salicylate to produce a purple colour.

Reagents

1. Trinder's reagent.
2. Standard salicylate solution 40 mg./100 ml. which is kept in a refrigerator.

Procedure

1. Centrifuge 5 ml. heparinised blood and separate the plasma.
2. Set the Eel spectrophotometer to a wavelength (520 mμ).
3. Set up three tubes as follows:

	Blank	Test	Standard
Water	0.5 ml.		
Plasma		0.5 ml.	
Standard			0.5 ml.
Trinder's reagent	4.5 ml.	4.5 ml.	4.5 ml.

4. Mix well and allow to stand for five minutes.
5. Centrifuge and remove the clear supernatant carefully with a pasteur pipette and transfer to a clean dry tube for measurement.

6. When the machine is sufficiently heated for stable recording the three solutions Blank, Test and Standard are transferred in rotation to the flow cell and the measurements made. The scale reading gives mg. of salicylate per 100 ml. plasma directly.

7. After use wash out flow cell with 1 N HCl and allow to drain then rinse with water and allow to drain.

8. If more than one 'unknown' is being read rinse the flow cell with reagent blank.

In practice, this very simple and rapid technique will provide a definitive confirmation or exclusion of the diagnosis of acute salicylate poisoning. The plasma salicylate level should always be done whenever this poisoning is suspected. In particular it is wise to perform this simple test in any patient with otherwise unexplained pyrexia, hyperpnoea, nausea or vomiting. Also a diagnosis of hysteria or delirium should be made only after due consideration of the possibility that the patient is suffering from an overdosage of salicylates.

ASSESSMENT OF THE SEVERITY OF ACUTE SALICYLATE POISONING

The intensity of treatment given to any individual patient depends upon the severity of poisoning. The assessment of the severity of the intoxication in acute salicylate overdosage is unfortunately not a simple matter. There are three basic approaches to the problem. These are,

Clinical Assessment of the Patient

Measurement of Plasma Salicylate Level

Estimation of the Acid-Base Upset.

In the two periods 1st October, 1963 to 1st October, 1964 and from 1st October, 1965 to 1st June, 1967 there were 307 patients (127 males and 180 females) admitted with acute salicylate poisoning to the Poisoning Treatment Centre, Royal Infirmary, Edinburgh. Of these 84 patients (39 males and 45 females) were considered to have moderate or severe poisoning (Fig. 12). From this histogram it will be seen that, although these 84 patients were selected in terms of severity of poisoning, their age and sex distribution was very similar to that of the total group of patients. The remaining patients were mildly poisoned and presented no problem of treatment. For these reasons, the assessment of patients with acute salicylate overdosage will be discussed under the above three headings with specific reference to the 84 patients with moderate or severe poisoning.

Clinical Assessment of the Patient

There is general agreement that clinical assessment of the

Histogram of the Age and Sex distribution for 307 patients with Acute Salicylate Poisoning. Inset - Corresponding histogram for 84 of these patients with Severe Poisoning.

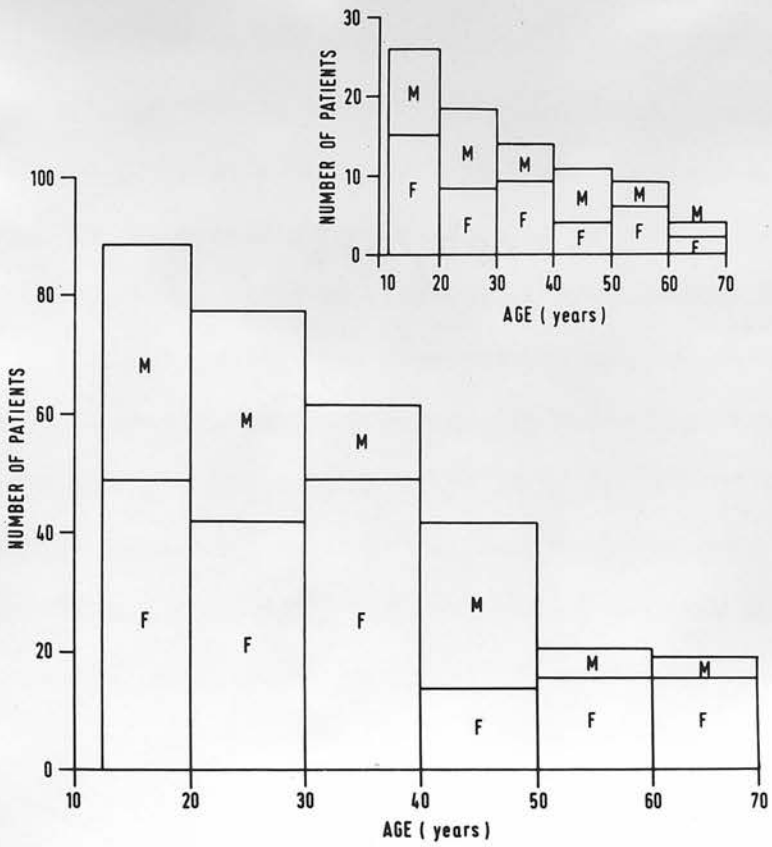

Figure 12.

Comparison between the age and sex distribution of the patients with moderate or severe poisoning compared with the total number of admissions due to acute salicylate poisoning.

patient alone not only is not very satisfactory in this condition, but may befrankly misleading (Done, 1960; Rea and Robertson, 1963; Beveridge, Forshall, Munro, Owen and Weston, 1964; Brown, Cameron and Matthew, 1967 and Smith, 1967). The clinical assessment is complicated by variable sensitivity of individuals to the drug, (Smith 1966) and also by the time which has elapsed since moment of ingestion of the salicylate. Clinical features of acute salicylate intoxication are well known (Goodman and Gilman, 1965) and have been described in some detail in the previous chapter. The clinical features of acute salicylism are sufficiently characteristic, when they are present, to be of assistance in diagnosing that the patient is suffering from salicylate overdosage, but will give little indication of the severity of the poisoning. It is true that some features, particularly severe and sustained hyperpnoea, impaired level of consciousness, and cardiovascular depression are indications of severe poisoning. On the other hand several authors (Done, 1960 and 1965; Rea and Robertson, 1963; Brown et al, 1967 and Smith, 1967) have reported patients, who present with few or no clinical signs or symptoms and who have nevertheless ingested a large amount of salicylate. In short most authorities would agree with Cumming, Dukes and Widdowson (1964), who stated that in general the clinical features of acute salicylate poisoning in older children and adults provide little information, which may be regarded of prognostic value.

Complex acid-base disturbances may occur and are influenced by the dose of salicylate taken, the duration of poisoning, antecedent illness, and most importantly, the age of the patient.

The net result of these disturbances may be either alkalosis, particularly in adults, or acidosis, especially in young children. It might be expected that such gross disturbances would lead to fairly typical patterns of clinical presentation. Robin et al. (1959) were, however, at pains to stress that the clinical features of both alkalosis and acidosis in acute aspirin poisoning are to all intents and purposes identical. Hyperventilation is regarded by many as being a feature of acidosis as a result of the increased hydrogen ion concentration stimulating the respiratory centre. Hyperpnoea, however, may also be present and is frequently of the Kussmaul type in salicylate poisoning even in the presence of severe alkalosis. This results from the primary effects of the salicylate in stimulating the respiratory centre.

Also patients may be flushed due to marked vasodilatation, and will have a high cardiac output with bounding pulse, tachycardia and marked apical impulse both in the presence of respiratory alkalosis or metabolic acidosis. These facts are not widely appreciated and as a result many have been misled into a wrongful interpretation of the clinical features in terms of acid-base status (McLaughlin, 1965). The clinical features found in the 84 patients with severe acute salicylate intoxication admitted to the Poisoning Treatment Centre, Edinburgh Royal Infirmary are shown in Table VII.

Tinnitus and Deafness

These are frequently regarded as cardinal symptoms of acute salicylate poisoning. It is therefore of interest to note that

TABLE VII

Clinical Features	Number of Patients	Incidence (%)
Tinnitus	56	66.6
Deafness	36	42.8
Sweating	46	54.8
Pyrexia	23	27.3
Hyper-reflexia	15	17.9
Agitation and Restlessness	30	35.6
Impaired Level of Consciousness	0	0
Hyperpnoea	54	64.3
Pulmonary Oedema	0	0
Tachycardia	60	71.4
Hypotension	3	3.5
Nausea	30	35.6
Vomiting	21	25.0
Renal Impairment	1	1.2
No Symptoms	8	9.8

The clinical features found in 84 patients with severe acute salicylate poisoning.

in this series these features were present in only a proportion of the patients studied. Also no close relationship between the plasma level of salicylate and these features was noted. Indeed many of the patients with the highest plasma levels did not suffer from any auditory disturbance. Myers, Bernstein and Fostiropolous in 1965 reported a clinical study on salicylate ototoxicity and found that in overdoses of this drug the presence of ototoxicity was directly dose related and was not commonly found in patients who had blood salicylate levels below 30 mg. per 100 ml. It is a reasonable assumption, therefore, that if tinnitus and deafness are present in a patient, who has recently taken an overdosage of aspirins, that patient is likely to have a plasma level of salicylate of 30 mg. per 100 ml. or above. These features will, however, give no more precise indication of the severity of the poisoning in an individual case.

Sweating and Pyrexia

Sweating was a fairly common feature in this group of patients and was a contributory factor in the development of dehydration. It is interesting, however, to note that twice as many patients had severe sweating as those who were found to have significant pyrexia. Significant pyrexia was regarded as any patient having a recorded rectal temperature consistently in excess of 37.4°C. None of the patients had marked fever and it presented no serious problems of therapy. The highest temperature recorded in any patient was 38.4°C and it rapidly returned to within normal limits during the course of treatment.

Hyper-reflexia

Exaggeration of the limb reflexes was present in approximately one in five of the patients studied and when present it was a rather striking feature. It usually occurred in patients in whom generalised agitation and restlessness was a marked feature. None of the patients on admission showed any features of tetany and all the patients had normal plantar responses.

Agitation and restlessness

Hyperkinesis and general agitation was a prominent feature in about a third of the patients. In itself it did not cause any serious problems of management and it settled down fairly rapidly after specific treatment for the poisoning was given. Its main importance was that it could resemble a hysterical syndrome very closely and in these patients, unless salicylate overdosage is considered, there is a danger that the correct diagnosis may be overlooked. None of the patients in this series showed any evidence on admission of impaired level of consciousness.

Hyperpnoea

Hyperventilation was a very prominent and common sign. It may be readily overlooked particularly in patients who have features of agitation and so the significance of this valuable feature may not be appreciated. It tended to occur particularly in patients who were very severely poisoned and this would confirm the suggestion of Ghose (1967) who suggested that hyperpnoea could be used as a useful index of the severity of the poisoning. This index of severity of poisoning must be used with some caution,

however, especially in patients who have indulged in self poisoning, as these patients may be very anxious and excited and these states in themselves may result in overbreathing. Another interesting feature of the hyperpnoea observed subsequently in these patients was that it tended to persist for many hours, even when the plasma salicylate had fallen to what would be otherwise regarded as a non-toxic level.

Tachycardia

As with hyperpnoea, tachycardia was a prominent and common feature in these patients. Also, on the whole, the degree of tachycardia was related to the severity of the overdosage. It is, on the other hand, a very non-specific clinical sign and the reservations and precautions stressed regarding the use of hyperpnoea in the assessment of the severity of the poisoning, are even more pertinent in the case of tachycardia.

Hypotension

This was present in three of the patients studied. Hypotension was regarded as being present when the systolic blood pressure fell below 90 mm. of mercury in a patient over the age of 50 and below 80 mm. of mercury in younger patients. This was not a very serious complication in the three patients, as in each case the fall in blood pressure was not marked and was relatively transient. In all cases the hypotension responded to simple elevation of the foot of the bed and required no more active therapy. So mild was it that all of the patients subsequently had a successful form of forced diuresis treatment.

Nausea and Vomiting

These are commonly considered to be frequent and marked features of acute salicylate poisoning. In this series nausea was a prominent feature in only about one third of the patients and actual vomiting occurred in only one patient in four. None of the patients developed haematemesis, but four patients, during gastric aspiration and lavage were noted to have slight bleeding in the recovered fluid. This was regarded as probably traumatic in origin rather than the result of a primary effect of the drug overdosage.

Renal Impairment

Mild impairment of renal function was demonstrated in only one patient. This developed subsequent to forced diuresis therapy and simply took the form of a mild rise in the plasma urea level to 60 mg./100 ml. This subsequently returned to within normal limits quite spontaneously and no further action was required. Renal impairment is generally reported to be a very uncommon finding in acute salicylate poisoning, (Robin et al., 1959; Beveridge et al., 1964 and Done, 1965). It is however very important to remain always vigilant for the development of impairment of renal function in this overdosage, as forced diuresis therapy, which is dependant on good kidney function, is frequently used.

No Symptoms

Eight of the patients had no symptoms or signs of acute salicylate poisoning, despite the fact that they had all ingested

large amounts of aspirin and all had high levels of plasma salicylate. Even the rather non-specific but commonly found signs of hyperpnoea and tachycardia were absent. This serves to emphasise the possible difficulties of assessing patients with acute salicylate toxicity on a clinical basis and confirms similar findings in several other reports (Schreiner, Berman, Griffin and Feys, 1955; Rea and Robertson, 1961; and Beveridge et al., 1964). The absence of symptoms and signs of salicylism in no way excludes the possibility that an overdosage of aspirin has been taken. None of the patients in the total group showed any significant features of haemorrhagic disorder.

Hypoprothrombinaemia

In almost every textbook in which the treatment of acute salicylate poisoning is discussed doctors are advised that vitamin K_1 should be given to counteract the development of hypoprothrombinaemia in acute salicylate overdosage. In Table VIII results are shown for prothrombin ratios which were carried out on 25 consecutive patients suffering from severe salicylate poisoning. Significant impairment of the prothrombin time was considered to be present when the prothrombin ratio was higher than 1.25. On this basis only five of the 25 patients studied had any real impairment of prothrombin time. The highest prothrombin ratio measured was 1.5. This occurred in a patient with the relatively low peak salicylate level of 44 mg. per 100 ml. Three other patients had prothrombin ratios of 1.4 and the corresponding peak plasma salicylate levels were 56, 60 and 50 mg. per 100 ml. respectively. In the fifth patient who had

TABLE VIII

		PLASMA SALICYLATE (mg. per 100 ml.)					
		30-39	40-49	50-59	60-69	70-79	80+
Prothrombin Ratio	1.0-1.25	2	4	5	4	1	4
	1.26-1.50	-	1	2	2	-	-

Relationship between peak plasma salicylate level and prothrombin ratio (prothrombin time $\frac{\text{patient}}{\text{normal control}}$) in 25 patients with acute salicylate poisoning.

a prothrombin ratio of 1.3 the peak plasma salicylate level was 63 mg. per 100 ml. From these figures, therefore, hypoprothrombinaemia is seldom likely to be a serious hazard in acute salicylate poisoning. Also there was little relationship between the degree of prolongation of the prothrombin time and the peak level of plasma salicylate. None of the patients showed any bleeding tendency. Quick and Clesceri (1960) discovered that the increased prothrombin time caused by salicylates in man was due to a decrease in the stable factor, Factor VII. They also found that in normal subjects a dosage of acetylsalicylic acid of 6 g. per 70 kg. of body weight was required to demonstrate even a slight prolongation of the prothrombin time.

In acute salicylate poisoning there are several other factors which may promote a bleeding tendency. These include capillary fragility (Frick, 1956); thrombocytopenia (Rappaport, Nixon and Barker, 1945) and decreased adhesiveness of blood platelets (Beaumont, Willie and Lenegre, 1955). There is considerable doubt, therefore, (Smith, 1966) that hypoprothrombinaemia is the main causative factor in haemorrhage in acute salicylate poisoning and its importance as a serious toxic effect of this drug has almost certainly been overstated. The results of the prothrombin ratios, admittedly on only 25 patients, supported Smith's reservations. For these reasons and as haemorrhage is in fact an uncommon complication of acute salicylate overdosage, it was decided that vitamin K_1 supplements would not be given in a routine manner to any of the patients subsequently studied in this investigation.

In conclusion, from the point of view of clinical assessment, in any patient suspected of suffering from acute salicylate poisoning, the presence of prominent signs and symptoms particularly tinnitus, deafness, hyperpnoea, tachycardia and sweating, indicates that the patient is probably suffering from a significant overdosage of the drug. These features however, will give no indication beyond this of the actual severity of the poisoning. It must always be remembered that the familiar clinical symptoms or signs of salicylism may be absent even when the patient is very severely poisoned.

Plasma Salicylate Levels

Measurement of the plasma salicylate level is an essential part in the investigation of any patient suspected of having this poisoning. In addition to confirming the diagnosis admission levels of blood salicylate have been advocated as a very valuable means of assessing the severity of the intoxication (Beveridge et al., 1964; Brown et al., 1967). The use of isolated observations of blood salicylate levels as a means of assessing the poisoning, has been criticised by several authorities including Done (1960), Rea and Robertson (1963), Cumming et al., (1964) and Smith (1966). They point out that a random sample of the plasma salicylate level provides only a measure of the resultant effect of elementary absorption, renal excretion and biotransformation of the ingested salicylate. There is therefore always the possibility that subsequent measurements of the plasma salicylate may show very considerable rises compared with the

initial admission level and so may not provide accurate information of the actual severity of poisoning. This fact has been accepted by Brown et al. (1967) who pointed out that serial estimations may be required in order that a full and adequate assessment of the situation may be made.

As with many other poisonings there is also the problem of individual variation of response to salicylate, which in certain instances may be quite striking. Riley and Worley (1956) reported five deaths occurring in children who had maximum salicylate levels of from only 20-40 mg. per 100 ml, despite the fact that some authorities have quoted 35-40 mg. per 100 ml. as a relatively safe range (Spector, 1958).

Done (1960) in particular, has produced evidence that isolated and random levels of the plasma salicylate may be extremely misleading. In 38 patients he found that there was little correlation between the salicylate levels measured and the severity of poisoning as assessed on a clinical basis. In an effort to correct this discrepancy, therefore, he reported a method which allows the serum salicylate level to be considered as a function of time. It is known that once absorption from acute ingestion is complete, the rise in serum salicylate concentration both in experimental animals and in humans assumes the characteristics of a first-order reaction. He demonstrated that after six hours, absorption of an ingested dose was usually fairly complete and thereafter the serum salicylate level fell at a relatively constant rate, which did not change appreciably over the following 24 hours. In the 38 patients with acute

salicylate overdosage, whom he investigated, Done then extrapolated back and determined salicylate values to time 0 for the highest salicylate level attained. He called these theoretical values S_o. He then claimed that these theoretical values correlated well with severity of toxic symptoms. He also calculated the "half-life" of plasma salicylate and this averaged 20 hours under normal conditions of metabolism, biotransformation and excretion. The correlation which he obtained between the magnitude of S_o and severity of symptoms was considerably better than that obtained with the measured salicylate value itself. S_o was calculated from the following formula,

$$\log S_o = \log S + 0.015t$$

where

S_o = 0 time serum salicylate level,

S = the serum salicylate level in the random blood sample,

0.015 = the mean slope of regression curve for the serum salicylate level and

t = the time in hours between the ingestion of salicylate and the collection of the random blood specimen.

This calculation of S_o is subject to a number of theoretical and practical objections. It ignores several variables governing salicylate metabolism including protein binding, intracellular dispersion and urinary pH. It is also based on the assumption that a single dose of salicylate has been ingested and that the rate of removal of circulating salicylate does not appreciably differ from the mean "half-life" of 20 hours. The calculation

itself also depends upon accurate information regarding the time since ingestion of the poisoning. Many of the patients have indulged in self poisoning and frequently exaggerate or minimise the size of dose taken and also the time interval which may have elapsed. For this reason the information regarding the time interval may be extremely unreliable. Nevertheless there is a considerable weight of evidence that calculation of S_o has provided a useful means of clarifying apparent discrepancies between an observed serum salicylate level and the patient's clinical condition.

In considering the different reports regarding the value of serum salicylate levels in the assessment of patients, it is important to recognise that both in the series reported by Beveridge et al. (1964) and by Brown et al. (1967) the majority of the patients were admitted within a short period of time after the actual ingestion of the asprin. In other reports, including Done (1960) and Rea and Robertson (1963), the time interval since ingestion was on the whole considerably longer and so time factors were of much greater importance. Therefore if the patient is admitted within six hours of ingestion calculation of S_o is probably unnecessary and as absorption is unlikely to be complete the Done formula is not theoretically applicable. Under these circumstances it is more appropriate to follow the advice of Brown et al. (1967) who suggested that not only the actual measured level of the serum salicylate be considered, but also the rate of change of plasma salicylate in the period immediately following admission. They also pointed

out that subsequent to gastric lavage being carried out there may well be an increase in plasma salicylate level of between 5 and 10 mg. per 100 ml. in the immediate post lavage period. All these considerations are important in the accurate assessment of the poisoning by means of measurement of plasma salicylate levels.

An alternative calculation of S_o has been suggested by Cumming et al. (1964). This involves retrospective measurement of the total absorption of salicylate which is calculated from the total quantity recovered in the urine plus assessment of the quantity remaining in the body after clinical recovery. This total absorption of salicylate is then divided by a calculated salicylate space, which is defined as the body fluid compartment in which salicylate is uniformly distributed after intravenous injection and for which the mean value has been found to be 0.22 l. per kg. body weight. From the point of view of assessment of the poisoning with a view to therapy, however, this method of Cumming et al. (1964) is unsuitable as it is of a retrospective nature.

Most currently available methods for measuring plasma salicylate measure total plasma salicylate, which includes both free and protein bound salicylate. The toxic effects of this drug are related to the amount of free salicylate present in the circulation, Ghose (1967). It may be that even greater accuracy may be achieved by measuring the free rather than the total fraction of salicylate. This has the very considerable disadvantage, however, that it requires more advanced biochemical

technique such as equilibrium dialysis or ultra-filtration methods (Goldstein, 1949 and Smith, Gleason, Stoll and Ogorzalek, 1946).

The relationship between the measured plasma salicylate levels and the clinical features of salicylate toxicity present in the patients with severe salicylate overdosage is shown in Figure 13. As a result of the admission arrangements to the Poisoning Treatment Centre at the Royal Infirmary in Edinburgh the great majority of patients were admitted within a short time of having ingested the poison. In this group of 84 patients the mean time following ingestion of the poison was 5.5 hours with a standard error of the mean (S.E.M.) 0.69. As therefore the great majority of patients were admitted within six hours of having taken the salicylate, the actual measured value of the plasma salicylate was used as an index of the severity of poisoning and S_o was not calculated. With few exceptions, patients with plasma salicylate levels in excess of 40 mg. per 100 ml. were suffering from definite features of acute salicylism. There were six patients, however, who had plasma salicylates which were above what is generally regarded as toxic levels, yet had no clinical features which could be detected. This serves to emphasise what has been stated previously that in a small but important percentage of the patients significant and sometimes serious salicylate poisoning may be present in the absence of any characteristic clinical features of this condition. Nevertheless, in general, it may be said that in this series there was found to be relatively good correlation between the measured plasma

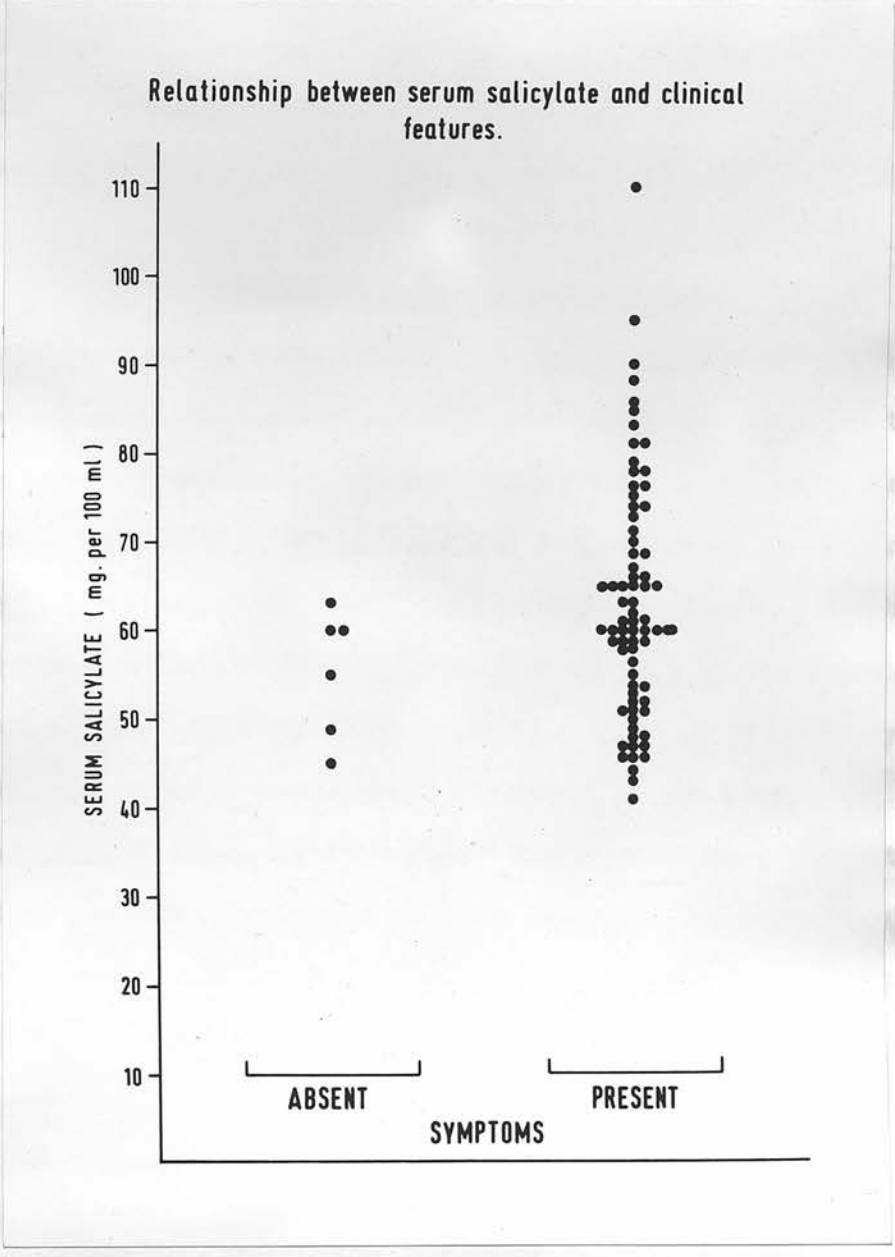

Figure 13.

Relationship between plasma salicylate and clinical features in 84 patients with moderate and severe poisoning.

salicylate and the presence of toxic features of acute salicylate poisoning. It can also be claimed that the measured level of plasma salicylate provided useful additional evidence of actual severity of the poisoning.

Measurement of Acid-Base Status

The complex nature of the metabolic upset resulting from acute salicylate overdosage has been already described and the importance of assessing the acid-base status in all patients with severe salicylate poisoning has been stressed by Singer (1954), Winters et al. (1963) and McLaughlin (1965). Metabolic acidosis is usually the predominant upset seen in children. Adults are more likely to be found in a state of respiratory alkalosis or to have a mixed disturbance; a few others may also present with metabolic acidosis. The time-honoured concept of salicylate pathophysiology in which initial respiratory alkalosis progresses to metabolic acidosis does not appear as rational as the mixed disturbance which was described by Winters et al. (1963). In this view a tripartite action of salicylate simultaneously produces ketosis, stimulation of respiration and increase in metabolic rate. Complex interaction of these metabolic effects may result in respiratory alkalosis, metabolic acidosis or mixed acid-base disturbance.

The only satisfactory way to investigate this upset is the measurement of arterial blood gases. The importance of arterial blood studies is now well established (Winters et al., 1963; Forland and Pullman, 1963; Ghose and Joekes, 1964;

McLaughlin, 1965; and Ghose, 1967).

The results of acid-base studies in 36 consecutive patients with severe salicylate overdosage are shown in Figure 14. The great majority of patients had values of arterial pH with the range 7.40 to 7.48 and so were either normal or only mildly alkalotic. However there were a number, who had more severe acid-base upsets. Some were distinctly alkalotic in terms of pH and a few were considerably acidotic. The fact that the pH lay within normal limits did not mean that therewas no acid-base upset present. It merely represented a compensated phase and was still compatable with a severe degree of poisoning. Therefore, from the point of view of assessment of patients, when the pH is outwith the normal range, it must be assumed that the normal compensatory mechanisms in the kidney and in the body buffer systems have been overcome. In these cases the acid-base upset is marked which indicates that the toxic effects of the drug are severe, irrespective of the plasma salicylate level. Apart from its very considerable value in the general assessment of the patient measurement of the acid-base upset may be of important prognostic significance.

The relationship of the peak plasma salicylate level and the associated arterial pH in the same 36 patients is shown in Figure 15. There was no correlation demonstrated as the correlation co-efficient r was 0.0086. This lack of correlation is not surprising when one considers that the pH is merely the net result of what is in this case a very mixed metabolic upset affecting acid-base status. The relationship between the lowest measured

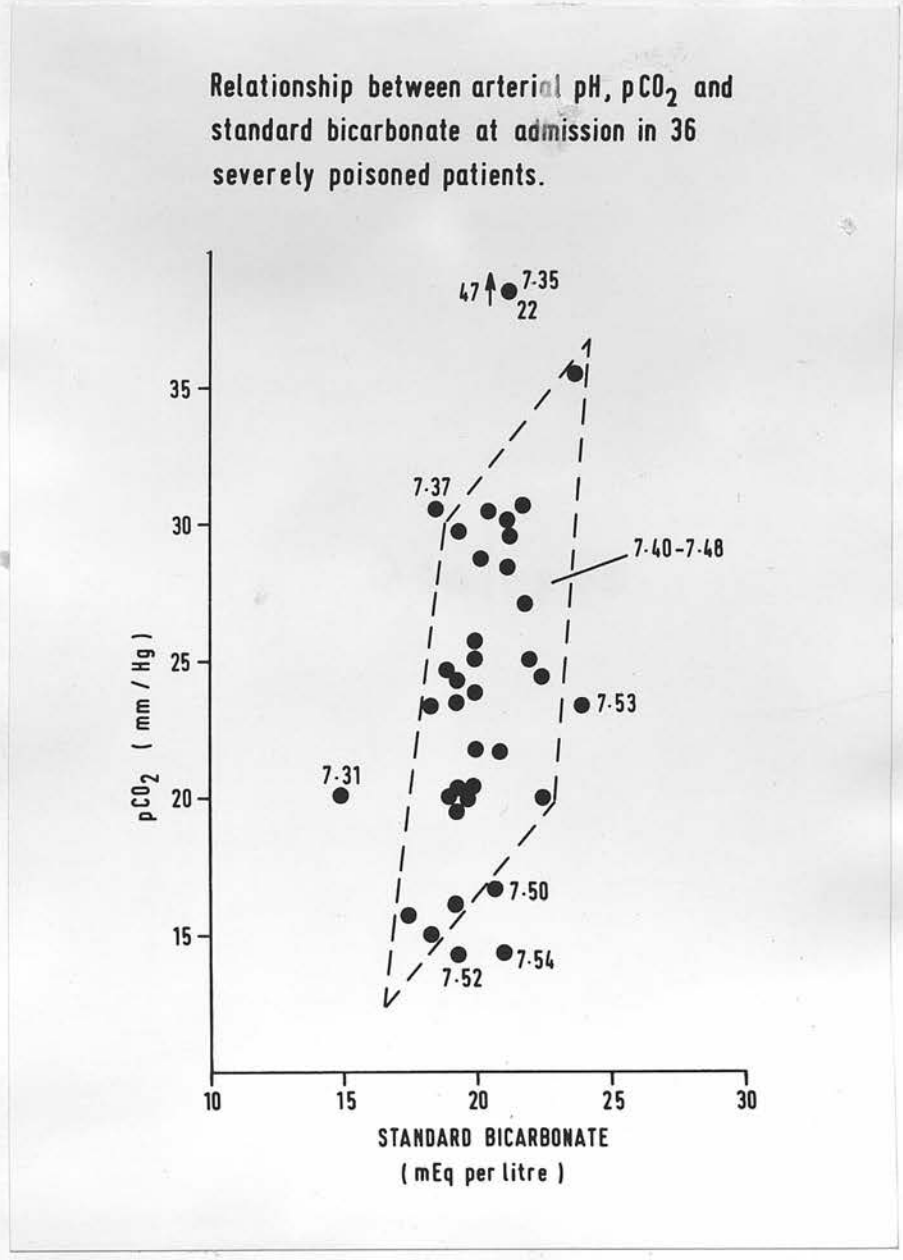

Figure 14.

Relationship between arterial pH, pCO_2 and standard bicarbonate in 36 severely poisoned patients.

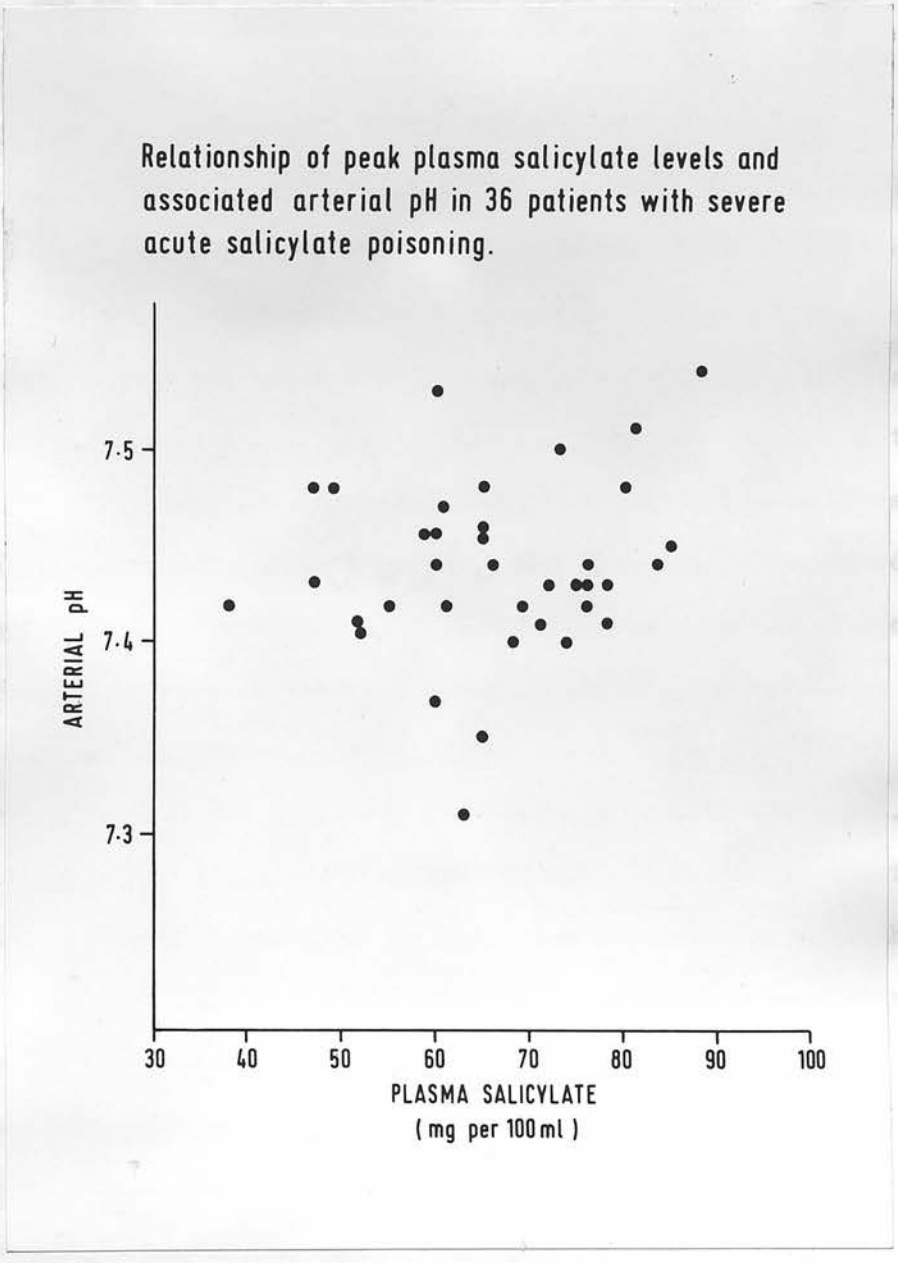

Figure 15.

Relationship of peak plasma salicylate levels and the corresponding arterial pH in 36 patients with severe salicylate poisoning.

pCO_2 and the peak plasma salicylate level in the same group of patients is shown in Figure 16. Again the correlation was not very good ($r = -0.35$) and this did not attain a level of significance the probability $p = 0.10$. It was noted, however, that low levels of the pCO_2 were closely associated with the clinical presence of hyperpnoea. Also when the pCO_2 was initially low this tended to remain at a low level for many hours, even in the presence of a falling plasma salicylate. This has been observed by Winters et al. (1963) and may represent continuance of a degree of metabolic acidosis with persisting hyperpnoea and low arterial standard bicarbonate. The relationship between the peak plasma salicylate level and associated arterial standard bicarbonate levels is shown in the next Figure 17. Again there was no significant correlation between these two measurements ($r = 0.287$, $p = 0.10$). This again may reflect the effects of a mixed metabolic upset with varying influences on the acid-base status. As with the arterial pCO_2 the levels of arterial standard bicarbonate were low and remained so for up to 24 hours even when the plasma salicylate had fallen to within "non-toxic levels". This may have resulted in two ways as both respiratory alkalosis and metabolic acidosis may result in reduction in the standard bicarbonate levels. In respiratory alkalosis bicarbonate is excreted in the urine as a compensatory mechanism and in the presence of metabolic acidosis bicarbonate is utilised as a buffer to neutralise the excessive amounts of hydrogen ion present.

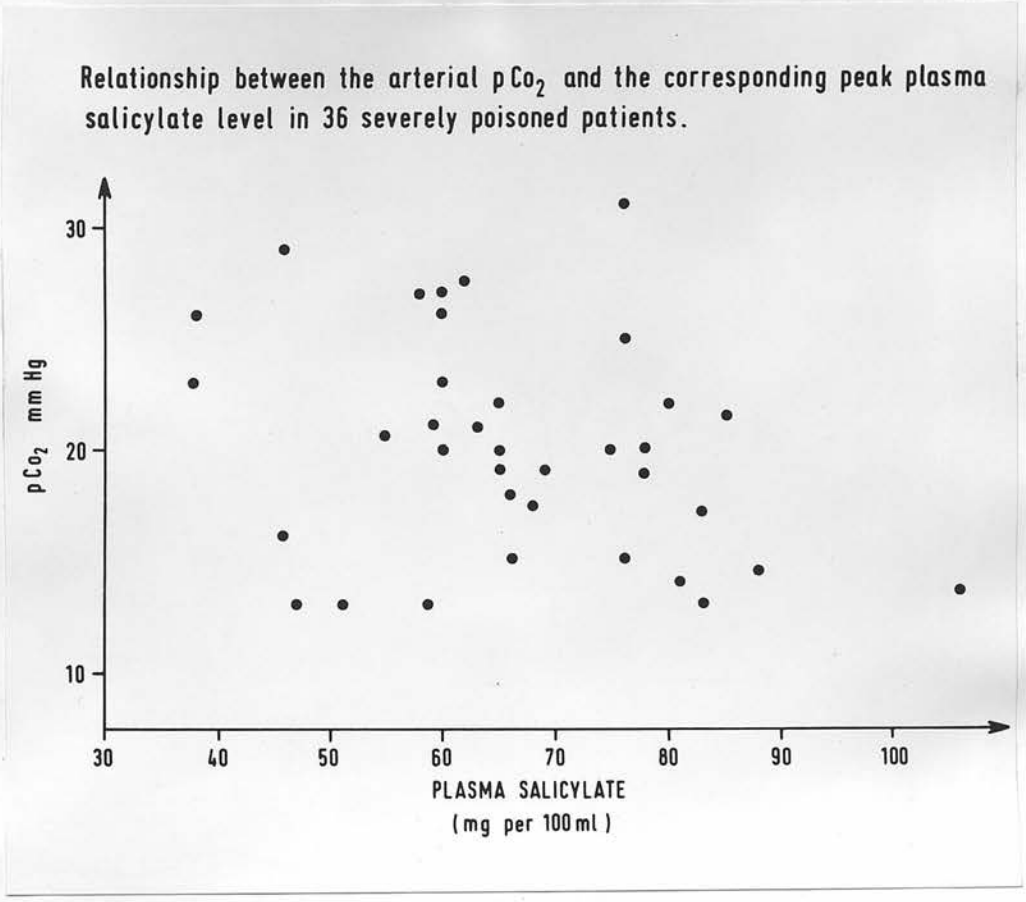

Figure 16.

Relationship of the peak plasma salicylate levels and the corresponding arterial pCO_2 in 36 patients with severe salicylate poisoning.

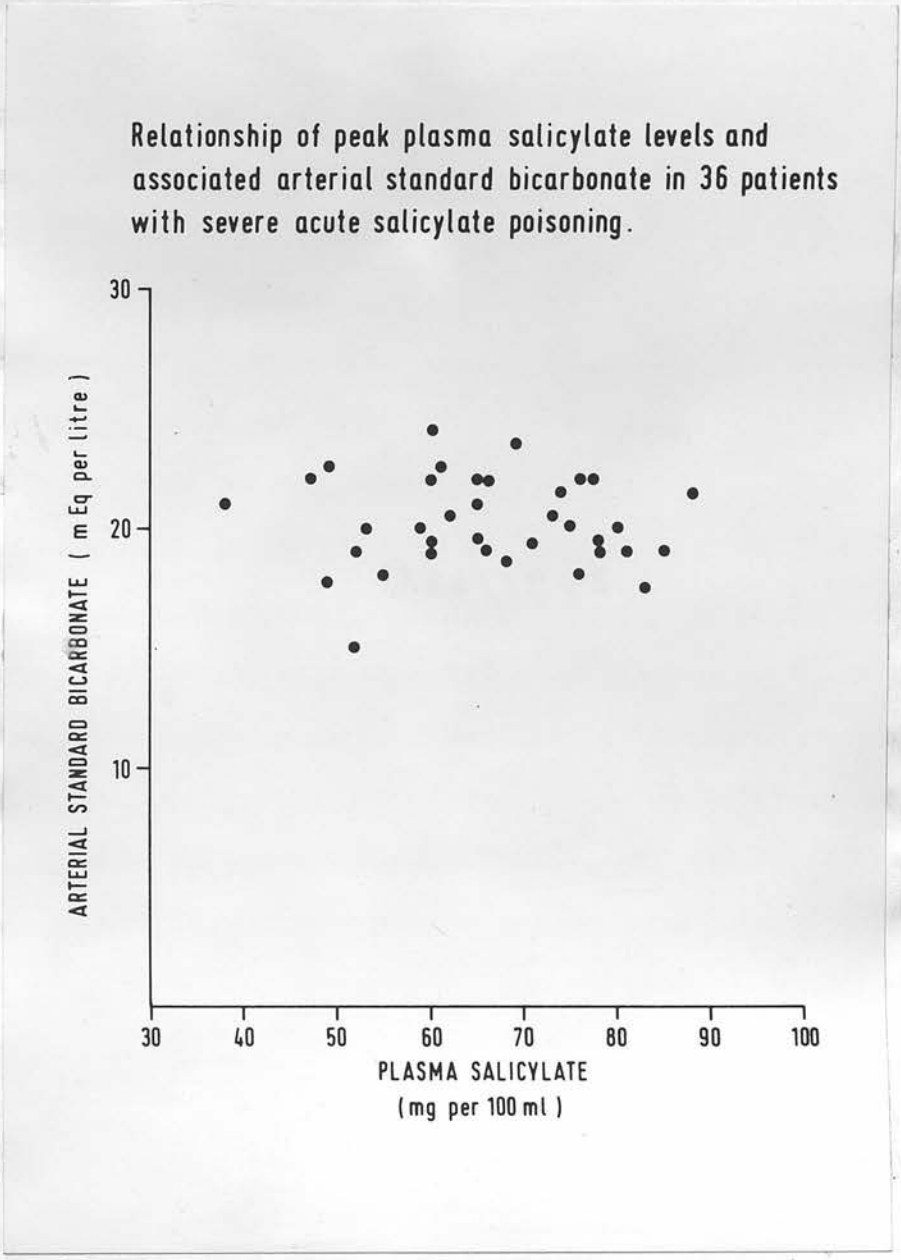

Figure 17.

Relationship of the peak plasma salicylate levels and the corresponding arterial standard bicarbonate in 36 patients with severe salicylate poisoning.

Urinary pH

Urinary pH is often used in error to differentiate respiratory alkalosis from metabolic acidosis (Robin et al., 1959; Ghose, 1967). This is an unreliable guide to the pH of extracellular fluid during respiratory alkalosis. Spector and McKhann (1948) reported the finding of acid reactions in most of the urine specimens of their cases of acute salicylate intoxication although the blood pH found was always over 7.45. The presence of an acid urine pH in the face of severe extracellular alkalosis may be related to potassium depletion. It is well known that in other forms of alkalosis a "paradoxical" aciduria may occur. It may be due to coincident potassium depletion primarily with consequent decrease in relative availability of potassium ion to compete for hydrogen ion in the distal tubular reabsorption of the sodium in the kidney (Berliner and Kennedy, 1948), or it may result from the relative cellular acidosis consequent to the exchange between the extracellular and intracellular spaces of hydrogen ion for potassium ion during the development of potassium depletion and alkalosis (Cooke, Segar, Cheek, Corille and Darrow, 1952). The exact mechanism remains obscure but the result in either case is the production of an acid urine despite severe systemic alkalosis. Patients with metabolic acidosis also produce urine with an acid pH. The urinary pH, therefore, is not a useful index of the acid-base status of the patient.

Summary

Full assessment of a patient suffering from acute salicylate poisoning entails due consideration of the clinical features

present, assessment of the plasma salicylate level and measurements of the arterial blood gases in order to assess the acid-base status. None of these three considerations will in themselves provide a complete assessment of any individual patient. Measurement of the plasma salicylate is the most valuable index but should where possible be supported by measurement of the arterial blood gases.

1. If a patient has marked clinical features compatable with the diagnosis of acute salicylate poisoning and there is a clear history of him having taken an overdosage of salicylate it may be assumed that he is suffering from moderate or severe salicylate intoxication.

2. When there is any doubt, measurement of the plasma salicylate must be done to confirm the diagnosis. If the patient is admitted within 6 hours of having ingested the poison the measured level of plasma salicylate itself and in appropriate cases the rate of change of the plasma salicylate measured over the immediate period after admission to hospital, will provide a satisfactory index of the severity of the overdosage. If the patient has been admitted however more than 6 hours after having taken the salicylate, calculation of S_o should be carried out. In general, levels of plasma salicylate above 40 mg. per 100 ml. are found in patients with moderately severe poisoning and levels above 60 mg. per 100 ml. are in keeping with severe salicylate poisoning. In a few cases levels above 100 mg. per 100 ml. of the plasma salicylate will be found. This must be regarded as very severe poisoning and demands the institution of vigorous

active therapy to remove the poison as a matter of great urgency.

3. Measurements of arterial blood gases are necessary to provide an adequate assessment of the acid-base status of the patient and if there is a significant deviation of the arterial pH either towards acidosis or alkalosis, the patient should be regarded as being severely poisoned, even if the plasma salicylate level is not very high. On the whole an acid pH is of more serious import than an alkaline pH (Eichenholz et al., 1963). Measurements of the pCO_2 and arterial standard bicarbonate will provide useful indications of respiratory alkalosis and metabolic acidosis in instances where the pH remains within the normal range.

TREATMENT OF ACUTE SALICYLATE POISONING

i. GENERAL CARE

The successful treatment of patients with acute salicylate poisoning depends largely on the application of the principles of good general medicine.

The general care of such patients is in effect the application of the basic concepts of Intensive Supportive Therapy, which is a modification of the Scandinavian method of treatment of poisoned patients, developed in Copenhagen by Clemmesen and Nilsson (1961). The regime of Intensive Supportive Therapy has been described in detail by Matthew and Lawson (1966). For clarity general care will be discussed under headings referring to major system upsets.

Cardiovascular

Cardiogenic shock is a very uncommon complication of acute salicylate poisoning. It is nevertheless important and may be serious when it does occur. It is a well recognised mode of death in this type of intoxication. Therapy simply takes the form of general principles of treatment of shock resulting from any other cause of myocardial failure. In addition, however, hypokalaemia is a common complication of acute salicylate overdosage (Robin et al., 1959) and should any arrhythmia or hypotension occur, an electrocardiograph should always be done with specific search for the features of hypokalaemia. This, of course, should be supported in every case by measurement of the plasma potassium. When hypokalaemia is present appropriate potassium supplements may be all that is necessary to correct the cardiovascular upset.

As has already been mentioned, tachycardia is a very common feature of this type of poisoning and usually is a compensatory mechanism associated with the increased metabolic rate, which is one of the main toxic effects of this poisoning. Specific treatment for the tachycardia is therefore seldom required but occasionally signs of cardiac failure may result if the tachycardia is severe and prolonged. This complication is more common in older patients. In this case appropriate digitalization should be carried out again after suitable precautions have been taken that the patient does not have significant hypokalaemia.

Respiratory

Hyperventilation is often a marked feature of acute salicylate overdosage. As with tachycardia, hyperpnoea is frequently a compensatory mechanism for the stimulation of metabolic activity, which occurs as a direct effect of salicylates. Treatment to reduce hyperventilation is, therefore, unnecessary and may even be harmful. The use of respiratory depressant drugs such as barbiturates to decrease the hyperpnoea of poisoning has been advocated (Eichenholz et al., 1963). Rapoport and Guest (1945), however, demonstrated that there was an enhanced toxicity of salicylates, when patients were treated with such respiratory centre depressants. Such therapy, therefore, may be dangerous, (Robin et al., 1959) and the combination of salicylate intoxication and respiratory centre depressants may lead to irreversible cellular changes and death.

Many of the patients suffer from respiratory alkalosis.

A theoretical consequence of this metabolic upset may be interference with tissue oxygen transport, as alkalosis shifts the oxyhaemoglobin dissociation curve to the left. For a given oxygen saturation there is less oxygen available for diffusion into tissues. This factor would be of greater importance in salicylate poisoning than in other causes of alkalosis. One of the main actions of salicylate is to stimulate cellular metabolism. In the face of an increased oxygen demand and possible diminished oxygen supply, cellular hypoxia may develop in this disorder. Robin and his colleagues in 1959 considered this factor to be of sufficient importance that they routinely administered oxygen to all their patients with this overdosage in the hope that the amount of oxygen in physical solution in the blood would thereby be increased with a greater availability of oxygen to the tissues. This treatment is not generally accepted and its place in the routine management of patients with this disorder must remain undecided.

Occasionally patients with very severe poisoning have such severe hyperpnoea and respiratory alkalosis may become so profound that physical exhaustion is produced. This may result in respiratory depression, which may culminate in acute respiratory failure. It is generally agreed that respiratory stimulants are contra-indicated in this situation (Done, 1965) for two reasons. Respiratory stimulation is already maximal and stimulatory drugs may potentiate the convulsant effects of the salicylate. The management of choice in this situation is artificial respiration possibly with curarisation of the patient.

An uncommon complication of salicylate intoxication is pulmonary oedema (Granville-Grossman and Sergeant, 1960). Perhaps the most plausible explanation for this type of abnormality has been suggested by the experiments of Hetzel, Charnock and Lander (1959). These experiments showed that when salicylates were given to healthy subjects, sodium and water were retained. They therefore suggested that the development of oedema in patients with this poisoning was related to sodium retention. Whatever the exact aetiology may be the treatment is appropriate diuretic therapy with, in severe cases, salt restriction.

Gastro-intestinal

Nausea and actual vomiting are of course common features of salicylate poisoning. Only when these symptoms are severe and prolonged is any specific treatment required. Treatment with an anti-emetic such as 50 mg. of cyclizine intramuscularly will usually be sufficient.

Haematological

The main blood disorder arising from acute salicylate poisoning is the development of a bleeding tendency. Frank bleeding most commonly occurs from the gastric mucosa and presents either as haematemesis or as bleeding into gastric aspiration fluid. As has been described it may result from a number of possible factors including hypoprothrombinaemia, capillary fragility and thrombocytopenia. The time-honoured practice of treating patients with acute salicylate poisoning routinely with vitamin K_1

supplements is probably not justified. Vitamin K supplements should only be given when the patient has been shown to have hypoprothrombinaemia. Blood transfusion is only occasionally required.

Central Nervous System

The commonly observed agitation and restlessness seldom require any specific therapy but occasionally these features progress to grand mal convulsions. These may be of sufficient severity to require treatment with barbiturates. These drugs, however, should be used with caution as their effects tend to be potentiated by the salicylate group of drugs (Eichenholz et al., 1963). The convulsions may be associated with cerebral oedema and at times papilloedema both of which features probably result from sodium retention as in the case of pulmonary oedema (Greer, Ward and Corbin, 1965). If these features are marked, hypertonic solutions of mannitol (10 or 20 per cent) should be given. These should be administered rapidly by intravenous infusion, 500 ml. in the first 15 minutes followed by 500 ml. of 5 per cent dextrose over the subsequent four hours.

Metabolic

From the point of view of treatment, one of the commonest complications is pyrexia. It is usually mild and simple tepid sponging is all that is required. On the other hand, there are numerous reports in the literature of high pyrexias occurring particularly in young children. In these cases more active therapy

to reduce the body temperature, such as the use of damp sheets and fans, may be necessary.

Both hypo- and hyperglycaemia may occur as side-effects of salicylate when it has been taken in toxic doses. Treatment is simply that of hypo- or hyperglycaemia due to other causes. The carbohydrate upset is usually very transient and seldom constitutes a serious problem.

Hypernatraemia is reported by numerous workers, and this may result from relative dehydration, but also in some instances there is little doubt that true sodium retention will occur. Marked peripheral oedema may result. When this is severe a regime of sodium restriction and appropriate diuretic therapy should be given. The danger of hypokalaemia, which is a common complication of this poisoning, has been described in detail by Robin et al. (1959) and by others including Beveridge et al. (1964). Its treatment is simply by appropriate potassium supplements.

As a result of vomiting, sweating, hyperpnoea and pyrexia, dehydration is a common feature of this type of overdosage. Correction of fluid and electrolyte balance must be regarded as an integral part of any form of treatment of acute salicylate poisoning. In mild types oral fluids may be all that is needed but in more severe overdosages and especially where nausea and vomiting are prominent features, parenteral treatment must be given.

Renal

Renal failure is a most unusual complication of acute

salicylate poisoning (Ghose and Joekes, 1964). The main reason for this is probably that most of the patients, who take overdoses of salicylates are in the younger age groups and have healthy kidneys. It is well known that salicylate will cause renal irritation with resultant increase in celluria due to desquamation of the tubular cells. However it tends to be a rather transient feature and is seldom associated with any significant functional impairment (Scott, Denholm and Dorling, 1963 and Prescott, 1965). Acute renal failure however can occur and of course when it does it is of the utmost importance and must be treated with the usual supportive therapy including fluid restrictions and dietary measures including low protein intake. In very severe cases haemodialysis may be necessary.

TREATMENT OF ACUTE SALICYLATE POISONING

ii. SPECIAL CARE

Specific therapy for any internal poisoning consists of efforts to detoxify the poison substance, to degrade it, or to remove it from the body. Neither of the first two approaches is applicable to the management of acute salicylate poisoning, for no method has been devised which will reduce the toxicity of the salicyl radicle, and while approximately 20 per cent of salicylate is normally degraded in humans, no means of augmenting this process is available. Hence specific therapy has been directed entirely towards effecting rapid removal of the salicylates from the body. Recovery of the poison from the patient may be achieved in two different ways.

1. Prevention of further absorption of the poison by aspiration and lavage of gastric content.

2. By increasing removal of the poison from the circulating blood and extra-cellular fluid, after the toxic substance has already been absorbed from the gastro-intestinal tract.

As it is the next step in treatment after emergency measures have been applied to support the vital functions where necessary, it is appropriate to consider gastric aspiration and lavage, in the first instance. Spontaneous vomiting is a relatively common feature of acute salicylate intoxication and there is little doubt that many patients are saved from having very severe poisoning as a result of this. There is evidence however, (Arnold, Hodges, Barta, Spector, Sunshine and Wedgewood, 1959) that spontaneous

vomiting is an inefficient method of emptying the stomach of aspirin. Arnold and his colleagues reported the results of studies on dogs but there is little doubt that the same occurs in humans (Matthew, Mackintosh, Tompsett and Cameron, 1966). Rushton (1963) reported that at post mortem examination large quantities of aspirin are occasionally found in the stomach. This is probably related to the fact that large doses of salicylate will promote gastric stasis in humans (Cumming, 1961). Similar findings have also been demonstrated in experimental animals (Smith and Irving, 1955). It is not surprising therefore, that removal of considerable quantities of salicylate from the gastic contents may be achieved many hours after ingestion (Thomson and Alstead, 1960). It is good practice, even when patients have had spontaneous vomiting either before or immediately after admission to hospital, to perform gastric aspiration and lavage in order to achieve the most complete gastric emptying which is possible. The conclusion of Ghose and Joekes (1964) that gastric emptying is unlikely to be of great importance in the treatment by the time the patient has been admitted to hospital with acute salicylate poisoning is unjustifiable.

Various methods of promoting gastric emptying have been suggested and the use of syrup of ipecacuanha has been enthusiastically advocated, particularly in the North American continent (Done, 1965). There are a number of serious objections to the use of this preparation, as the emetic effect is generally too slow and too uncertain and in addition when vomiting does not occur the emetine content of the drug may be absorbed and itself

produce toxicity. Another danger which is common to all methods of inducing gastric emptying is that if there is any impairment of conscious level, the patient may inhale vomitus during the emptying process. In Scandinavia also, copper preparations have been employed with increasing frequency, particularly in children, but these are on the whole no more efficacious than ipecacuanha and have little advantage over other methods.

Outside hospital there is little doubt that the best method still of inducing vomiting is the traditional one of irritation of the pharynx by the finger or a blunt spoon handle, the patient having been laid on his side with the head dependent. In children they should be placed in the spanking position (Matthew and Lawson, 1967). In hospital, providing the patient has an adequate cough and gag reflex or else is sufficiently unconscious to allow introduction of a cuffed endotracheal tube, the lungs thereby being protected, gastric aspiration and lavage is the most efficient method of recovering the salicylate.

A number of objections have been raised to the use of this method of treatment, the main criticism being the risk of aspiration pneumonia. In acute salicylate poisoning, however, the great majority of patients when they present in hospital, at least in older children and adults, are fully conscious and have efficient cough and gag reflexes. Therefore in this regard there is little contra-indication to employing the treatment. A further and perhaps more important objection is that the introduction of lavage fluid into the stomach may promote the entry of more

salicylate into the small intestine; thus causing a sharp increase in the absorption of the poison and thereby defeating the object of the exercise. It is true that frequently there is a rise in plasma salicylate in the immediate post-lavage period and Brown and his colleagues in 1967 estimated that there may be a rise of between 5 and 10 mg. per 100 ml. following gastric lavage. This effect, therefore, must be accepted but the rise is a modest one and perhaps is of less significance than has been suggested by some. Finally it has been claimed that gastric lavage is not an efficient method of removing solid materials from the stomach. On the other hand, large amounts of salicylate have been removed from the stomach by this means both by Beveridge et al. (1964) and Matthew et al. (1966). Therefore, provided that the techniques of gastric aspiration and lavage are performed correctly an efficient recovery of the poison can be achieved. In general the advantages of gastric aspiration and lavage far out-weight any possible disadvantages and there is general agreement that gastric lavage should be undertaken in all cases (Beveridge et al., 1964; Today's Drugs, British Medical Journal, 1964; Matthew et al., 1966; Smith, 1966 and Matthew and Lawson, 1967).

Gastric aspiration and lavage is a simple technique and a safe one provided that appropriate precautions are taken. In the first instance all patients must have an adequate cough and gag reflex or else be sufficiently unconscious to permit endotracheal intubation to protect the air-way. To lessen the risk of aspiration pneumonia all patients must be laid on their

side with the head dependent. The correct equipment is absolutely essential if the procedure is to be effective. It is quite remarkable how often a narrow naso-gastric tube is used as the lavage tube. This will inevitably fail to recover any significant gastric content which is of a solid nature. In older children and adults an adequate size of tube may be regarded as a 30 English gauge Jacques tube, which, of course, is passed through the mouth. This is large enough to permit removal of semi-solid food material and drugs from the stomach and an added advantage is that it is also of sufficient size to make it extremely unlikely that it will enter the trachea. This is a much more significant hazard when using narrower naso-gastric tubes. Once the tube is securely in position, gastric aspiration is carried out using a Dakin's syringe and subsequently lavage is carried out using 300 ml. portions of warm water at 38°C. The lavage is then continued until the recovered fluid runs clear. In children, of course, it is necessary to select appropriate sizes of tubes and quantities of lavage fluid for the size and age of patient.

Different authors have suggested different types of lavage fluid for the procedure. These include isotonic saline (Rentsch and Marsh, 1959) and dilute sodium bicarbonate solution (Cumming, 1961). The use of sodium bicarbonate solution has been criticised both by Harvie and Singer in 1955 and Rentsch and Marsh (1959), who state that this solution should not be used as it may promote absorption of salicylate from the gastric mucosa. This criticism of the use of bicarbonate solutions was made also by Lipman,

Krasnoff and Schless (1949). Simple water alone has been shown to be a perfectly satisfactory lavage fluid, Beveridge et al. (1964) and Matthew et al. (1966).

In 1959 Polson suggested that a litre of 5 per cent sodium bicarbonate should be left in the stomach subsequent to lavage. This is unnecessary and indeed contra-indicated as patients with salicylate intoxication are frequently nauseated and are liable to further vomiting. There is a hazard of aspiration pneumonia in these cases. This danger is even greater than with gastric lavage as the vomiting may occur without warning and when the patient is not in the ideal position in which he should be during the procedure of aspiration and lavage.

Such is the weight of evidence in favour of using these valuable techniques of gastric aspiration and lavage that it was the policy in the Poisoning Treatment Centre, Edinburgh Royal Infirmary to wash out every patient with salicylate poisoning. All the patients in the present series had this procedure carried out, quite independently of the time since ingestion. The view that it is never too late to aspirate in acute salicylate was taken at all times.

Methods to increase removal of salicylate

Many methods have been used to increase the removal rate of poisons from the body. Before considering any of these methods, however, it is essential to consider whether the toxic substance can be removed in an active form by excretion through the patient's own kidneys or else by one or other method of artificial dialysis. In the absence of vomiting, 90 per cent

of ingested salicylate is excreted by the kidney (Oliver and Dyer, 1960) and insignificant amounts are excreted either in the sweat or in the stool (Smith, 1966). It is eliminated in three forms; free salicylate, combined with glycine as salicyluric acid and with glucuronic acid as salicyl acyl and phenolic glucuronides (T'Sai Fan Yu and Gutman, 1959). The remaining 10 per cent of ingested salicylate can not be recovered in the urine as salicyl compounds because of metabolic conversion to gentisic acid and other degradation products. When the urine is acid, only about 20 per cent of the salicylate is excreted as free salicylate. This is of considerable importance as it is the concentration of free salicylate in the unbound fraction of plasma salicylate which probably determines clinical toxicity (Ghose, 1967). A considerable proportion of the circulating plasma salicylate (between 50 and 80 per cent) is bound to plasma albumen. The percentage binding falls when the plasma salicylate concentration rises, suggesting saturation of binding sites. The unbound blood salicylate may exist in the free form or as a conjugate. Two hours after salicylate ingestion the ratio of free to conjugated salicylate in the blood is 70:1 but 24 hours later the ratio is 15:1 (Milne, 1963). Free salicylate is excreted mainly in the urine by processes which depend on glomerular filtration, proximal tubular secretion, urine volume and urinary pH. Salicylate conjugates are excreted also by glomerular filtration and tubular secretion but are not apparently influenced by urine volume or pH.

The influence of urine volume on excretion of free salicylate

was reported in 1955 by MacPherson, Milne, and Evans. Since 1931 it has been known that when the urine is alkaline the rate of renal excretion of salicylates is accelerated (Morris and Graham, 1931). As the urine pH rises above 7.0 both the relative percentage and the total amount of free salicylate increase progressively (Smith, Gleason, Stall and Ogorzalek, 1946; Hoffman and Nobe, 1950; Davis and Smith, 1951; MacPherson, Milne and Evans, 1955 and Gutman, Yü and Sirota, 1955). In this way it has been shown that at a urinary pH 8.0, free salicylate accounts for from 75 to 80 per cent of the total salicylate excreted. This amounts to a total salicylate excretion of as much as four times that occurring at pH 5.0. It follows that alkalinisation of the urine must be very valuable in the treatment of acute salicylate overdosage.

Different authorities advocate different measures to increase removal of absorbed salicylate. These include forced oral fluids, forced water diuresis, forced alkaline diuresis, peritoneal dialysis, haemodialysis, exchange transfusion in children and the use of anion exchange resins. The optimal management of patients with acute salicylate overdosage remains a matter of dispute.

Forced Oral Fluids

Use of forced oral fluids in patients with acute salicylate poisoning has not met with any great success (Done, 1965). This is perhaps not surprising as the amounts of fluid which can be tolerated by a patient, who has recently taken an overdosage of

aspirins is very often limited by nausea or actual vomiting. The oral administration of sodium bicarbonate in addition to simple fluids has been advocated by a few with the idea that the alkali will be absorbed and assist in the elimination of salicylates through the urine. Done (1965), however, has pointed out that this practice is contraindicated as it may enhance the absorption of more salicylate and in this way do more harm than good. Oral fluids therefore are of no value in the treatment of patients with severe poisoning, but on the other hand, it is generally agreed that in the very mild cases maintenance of a good oral intake of fluids is all that is necessary.

Forced Water Diuresis

Forced water diuresis using parenteral fluids has been tried by Doolan, Walsh, Kyle and Wishinsky (1951) and also by MacPherson, Milne and Evans (1955). They failed to demonstrate any significant increase in the salicylate clearance by using these techniques and so they suggested that they were of limited value. The regimes of fluid therapy, which they used, however, were somewhat conservative by modern standards and it may be that their failure to demonstrate any very significant increase in the recovery of salicylate by their forced diuresis was related to the limited urinary flow which was achieved. Ghose and Joekes, (1964) reported good recoveries of salicylate using forced water diuresis supplemented by hypertonic mannitol solutions. They commented that it was not clear why osmotic diuresis should greatly increase salicylate excretion, when a water diuresis is

relatively ineffective. The probable reason was that the urine flow which they produced by using this method, was greater than that achieved by those using a simple water diuresis alone. The recoveries of salicylate, which they found, were therefore related to this rather than to any specific effect of the hypertonic mannitol.

Forced Alkaline Diuresis

Of all the regimes of forced diuresis the one which achieves greatest recovery of free salicylate is that which produces an alkaline polyuria. Such a method has been widely used in children poisoned with salicylates. In general, the serum salicylate level has been halved in between 2-5 hours following the commencement of the diuresis therapy and the treatment has not been associated with any untoward side-effects, (Oliver and Dyer, 1960; Whitten, Kesaree and Goodwin, 1961 and Summit and Etteldorf, 1964). In children, however, the usual net metabolic upset of acute salicylate poisoning is metabolic acidosis and there is, therefore, no real objection to administering alkali to them. Winters in 1959, however, pointed out that alkalinisation of the urine even in children requires much larger quantities of sodium bicarbonate than are required to correct the acidosis. He therefore, expressed reservations about alkalinisation of the urine because of the hazards from the metabolic alkalosis provoked by the administration of the sodium bicarbonate. The dangers, which concerned him, were largely theoretical and included the development of acute hypokalaemia

and severe tetany. In addition to the dangers of promoting alkalosis as a result of this therapy, Feuerstein, Finberg and Fleishman, (1960) have also stressed the danger of promoting hypernatraemia. This, however, can be avoided by appropriate adjustments of the infusion regime. On the other hand, Eichenholz, Mulhausen, Anderson and Macdonald (1962) have pointed out that metabolic acidosis on the whole is less well tolerated than other types of acid-base upsets, particularly in children. It would seem, therefore, that despite the possible objections to this form of therapy the benefits from rapid removal of salicylate from the patient, outweigh any disadvantages.

Forced alkaline diuresis has not been so widely accepted for the treatment of older children and adults. The predominant acid-base upset in these patients is usually respiratory alkalosis. Several authorities have regarded this respiratory alkalosis as a contraindication to forced alkaline diuresis (Robin et al., 1959; Ghose and Joekes, 1964; Done, 1965 and McLaughlin, 1965). They point out that a dangerous state of severe alkalosis may develop and state that the possibility of precipitating severe and even fatal alkalotic tetany is real. They also stress the possibility of the development of acute and severe hypokalaemia in the state of severe alkalosis. Contrary to this opinion others, including Dukes, Blainey, Cumming and Widdowson (1963) and Cumming, Dukes and Widdowson (1964) consider that again, as in the case of children, the advantages of accelerating the removal of salicylate from the patient are greater than any

potential dangers inherent in the therapy. Cumming et al. (1964) reported the use of a regime of forced alkaline diuresis in five patients and did not find any serious clinical complications from the therapy. On the other hand, high levels of plasma pH were found and the plasma potassium was found also to fall considerably during the course of this treatment.

There are two other methods, which will produce alkalinisation of the urine. The first is the use of acetazolamide ("Diamox") which is an inhibitor of carbonic anhydrase activity. MacPherson et al. (1955) have demonstrated a marked salicyluria following the administration of this drug to adult volunteers. There are however serious objections to its clinical use. Winters (1959) has pointed out that if itis used in patients who are already acidotic, or who have a mixed acid-base disturbance, it may fail to produce an alkaline urine and it may even produce a systemic metabolic acidosis, which would accentuate the pre-existing acidosis. This is particularly likely in small children (Oliver and Dyer, 1960). Kaplan and del Carmen (1958) demonstrated a much higher mortality in rats who received acetazolamide than in animals who were given bicarbonate after the administration of toxic doses of salicylate. Further, in a clinical study, Schwartz, Fellers, Knapp and Yaffe (1959) reported detailed investigations in three children with acute salicylate poisoning, who were treated with acetazolamide. From the point of view of salicylate recovery, the therapy was successful but there were very severe changes in the pattern of urinary electrolytes and the administration of large quantities

of intravenous bicarbonate was necessary to control the systemic acidosis, which developed in these three patients. As evidence of the severity of these changes, they described the occurrence of convulsions in two of the children and papilloedema was found on ophthalmoscopy. Feurstein et al. (1960) reported more favourably on the use of this drug as a form of treatment in this poisoning but on the whole they have failed to convince others and this method has therefore fallen into general disrepute.

The other method of alkalinising the urine, is the administration of the organic buffer tris (2-amino-2-hydroxy-methylpropane-1,3-diol) which is now commonly referred to as THAM. The early reports of Nahas and Ligou, (1959) indicated that THAM increased urinary output and also achieved alkalinisation of the urine. These effects have led to the use of this substance in the treatment of acute salicylate poisoning. Israels and Davies (1961) have reported favourably on the use of this form of treatment both in rabbits and dogs and also in five children suffering from this poisoning and similar results were also found in rats in experiments carried out by Strauss and Nahas (1960). Further clinical studies have been done by Strauss, Nahas and Clark, (1961), by Duval and Leveau, (1962) and by Rangno, Gourley and Israels (1962). Gaultier, Fournier, Gervais, and Bignon, (1963) discussed the use of THAM to produce an alkaline diuresis and it may be that this agent will prove a valuable addition to present regimes of therapy. There is as yet, however, insufficient evidence of a clinical nature to

substantiate that THAM has any real advantages over other forms of alkalinisation.

Gaultier and his colleagues also point out a number of hazards in using THAM. They state that the agent may in some instances both modify or even potentiate the action of certain toxic substances. This statement is based largely on experimental animal work and whether it is the case with salicylates remains to be seen. There are, however, more definite dangers of the treatment. Careful and close monitoring of the arterial pH is essential, as rapid and severe changes in acid-base state may occur during the course of this treatment and dangerous and even lethal levels of alkalosis may be reached. THAM may also produce hypokalaemia by a mechanism similar to that of bicarbonate infusions. It has also an important depressant effect on respiration and diminution of arterial oxygen saturation may be of such severity that the patient may require assisted respiration. Severe hypoglycaemia has also been recorded and this treatment may cause quite severe hypotension, which may be of sudden onset. Lastly THAM itself is a very alkaline substance and therefore must be given in a large vein by means of a polythene catheter. Exudation outside the vein will cause severe pain locally and possibly necrosis of tissues. How significant all these complications are, remains to be fully evaluated, but it would seem likely that the use of THAM is at least as hazardous, if not more so, than treatment with bicarbonate infusions.

Peritoneal dialysis

Etteldorf, Montcalvo, Kaplan and Sheffield (1960) described the results of the use of intermittent peritoneal lavage as a means of treating salicylate intoxication in dogs. They found that it was necessary to add 5 per cent human albumen in order to obtain satisfactory recovery of salicylate. In 1959 Doolan, Murphy, Wiggins, Carter, Cooper, Watten and Alpen found that considerable amounts of salicylate could be removed by intermittent peritoneal dialysis. Elliot and Crichton (1960) found this in three patients with severe salicylate intoxication. These results were confirmed in a further three patients, on this occasion in infants, by Segar, Gibson and Rhemy (1961). Peritoneal dialysis has also been reported to be a successful form of treatment in children (Etteldorf, Dobbins, Summit, Rainwater and Fischer, 1961) and more recently by Summit and Etteldorf (1964).

The disadvantages of the technique are that it is more complex than forced alkaline diuresis and that it requires more skilled nursing care. There is also a very considerable danger of infection in the peritoneal cavity: as the great majority of patients, particularly older children and adults, are conscious, they frequently complain of considerable discomfort and some find great difficulty in tolerating it. This can only partially be overcome by the addition of local anaesthetics to the dialysis fluid.

In terms of recovery it is only about 25-50 per cent as effective as extracorporeal dialysis using an artificial kidney.

Its main value is perhaps in situations, where the patient is not suitable for forced diuresis therapy and yet an artificial kidney is not readily available. In these instances, peritoneal dialysis provides a useful alternative form of treatment.

Exchange transfusion

Since Heymann, Javett and Rudolph (1954) first reported the successful treatment by exchange transfusion of an infant, who had ingested an overdose of acetylsalicylic acid, numerous other reports of the use of this technique in infants have been published including those of Done and Otterness, (1956); Radebaugh and Emery (1957); Bruton, (1958) and Leikin and Emmanouilides (1960). This has been used almost exclusively in the treatment of small children; partly because it is technically simpler than other methods, such as haemodialysis, in these patients. Cumming (1961), however suggested that it may be of some value in adults also. It is not as effective in recovering salicylate from the circulation as forced alkaline diuresis, however, and would therefore not seem appropriate for the treatment of older children or adults.

Anion Exchange Resin

The removal of salicylate ion from the blood by passage through a column of anion exchange resin has been reported by Clark, Finley, Davis and Finley (1961). It is suggested that up to 90 per cent of the salicylate is removed in a single

passage of a sample of blood through the column containing the resin. These studies were done on dogs and suggested that the serum salicylate concentration could be halved between 2 and 4 hours after starting treatment. There are no reports as yet, however, of a clinical application of this method and so its place in the treatment of patients must await further study.

Haemodialysis

There is no doubt that this form of therapy is the most effective means of removing salicylate from the blood (Schreiner, Berman, Griffin and Feys, 1955; James, Kimbell and Read, 1962; Parson, 1963 and Jorgensen and Wieth, 1963). There have been various studies comparing the effectiveness of haemodialysis with other means of increasing removal of salicylate. Doolan, Walsh, Kyle and Wishinsky (1951) reported that the recovery of salicylate with haemodialysis was 5-7 times greater than that achieved with normal renal excretion. In studies on dogs, James, Kimbell and Barham (1961) compared the effects of exchanged transfusion, peritoneal dialysis, haemodialysis and various forms of forced alkaline diuresis. Their results indicated that haemodialysis was the most effective method and forced alkaline diuresis using sodium bicarbonate as the alkalinising agent was second in effectiveness. Exchange transfusion and peritoneal dialysis with added albumen in the lavage fluid were approximately half as effective as haemodialysis. In clinical studies in humans, James et al. (1962) showed that

haemodialysis using an artificial kidney was about four times as rapid in recovering salicylate as peritoneal dialysis and, according to Jorgensen and Wieth (1963), was between two and five times as efficient as osmotic diuresis. Cumming, Dukes and Widdowson (1964) found that haemodialysis was approximately twice as effective as either exchange transfusion or forced alkaline diuresis.

Haemodialysis is nowadays a safe technique in older children and adults. In young children, its use is more debatable. A number of authors including Breakey, Woodruff and Reus (1961); Moorehead, Edwards and Goldsmith (1965); Hickman and Scribner (1962) and Anderson, Lee and Stroud (1965) have reported successful treatments of small children by this method. They all, however, note that there are dangers involved in the procedure particularly regarding the maintenance of the circulation, body weight and appropriate levels of hydration. Moorehead et al. (1965), for example, have reported deaths following acute haemodialysis in infants due to cerebral oedema and brain stem compression. This tends to become more likely the more intensely the dialysis is applied and it is thought that the cerebral oedema may be the result of osmotic gradients between vascular and extravascular compartments. Kennedy, Linton, Luke, Renfrew and Dinwoodie (1964) suggested that this complication may be avoided if extra glucose is added to the dialysing fluid. Mackay (1961) and Seegar (1961) have emphasised the importance of parenteral fluid therapy and the hazards of other procedures particularly in children.

Many methods of treatment therefore have been usedfor patients with acute salicylate poisoning and there seems little argument that salicylate intoxication is a potentially fatal condition which demands active management. The therapeutic aim should be to accelerate the removal of salicylate from the patient, as rapidly as possible. Despite numerous reports in the literature of different techniques of achieving the removal of the salicylate in this poisoning there is no accepted or standardised form of treatment. The reports provide a bewildering variety of opinions and approaches to treatment, which are at times paradoxical.

In view of the efficiency of haemodialysis in recovering salicylates, a number of authors have suggested that this method is without any doubt the treatment of choice in patients with very severe salicylate poisoning (Beveridge et al., 1964 and Smith, 1966). In theory this suggestion cannot be challenged. However in practice there are a number of serious criticisms, which may be made. Dukes et al. (1963), for example, pointed out quite rightly that there was a delay in making haemodialysis available. The artificial kidney machine must first of all be 'primed' with compatable blood. If one takes into account this delay the effect of forced alkaline diuresis ab initio will achieve almost comparable recoveries in a given interval of time. This criticism is perhaps less valid today as the artificial kidney machine can be prepared with much greater speed but a certain delay is inevitable still. A far greater and more important criticism is one purely of

availability of apparatus and skilled medical and nursing staff. Throughout this country artificial kidney units are working to absolute capacity. All doctors working in these units find themselves in the distressing situation of having to refuse treatment to patients with severe renal failure, due to renal disease itself, purely on the grounds of limitation of facilities, equipment and staff. It is therefore unjustifiable to add to this burden, a request for artificial kidney time for the treatment of patients, who might be treated effectively and safely by other methods.

As patients with acute salicylate poisoning are in the main in the younger age groups, it is a relatively rare occurrence to find a patient who has severe cardiovascular or respiratory disorder, or impairment of renal function, which would prevent the safe and successful use of one or other method of forced diuresis. This opinion has been presented by Ghose and Joekes (1964) and experience in treating patients with acute salicylate poisoning in the Poisoning Treatment Centre at Edinburgh Royal Infirmary would lend support to this viewpoint.

It was therefore decided to study the effects of different forced diuresis regimes on blood salicylate and urinary salicylate excretion. The effects on the serum and urinary potassium, sodium, magnesium and calcium were also monitored together with changes in acid-base status.

As a result of these studies there has been devised a safe, simple yet highly effective method of treatment which is suitable for use in even small hospitals with limited biochemical support. This type of treatment has also been shown to be effective in

the great majority of patients with acute salicylate overdosage. Therefore, except in a very few patients who suffer from complications which make forced diuresis unsuitable, referral of these patients to an artificial kidney unit for haemodialysis is unnecessary. The study was carried out on 84 patients admitted with acute salicylate poisoning to the Poisoning Treatment Centre at Edinburgh Royal Infirmary and who were judged to be suffering from moderate or severe salicylate overdosage.

POTASSIUM SUPPLEMENTS IN FORCED ALKALINE DIURESIS

The basic regime of therapy, which was selected for use in the Poisoning Treatment Centre at Edinburgh Royal Infirmary for patients with moderate or severe acute salicylate poisoning, was adapted from that of Dukes, Blainey, Cumming and Widdowson (1963). In a later paper, Cumming et al. (1964) reported on the biochemical changes induced by forced alkaline diuresis. Although they found falls in the levels of plasma potassium, they did not consider it necessary to administer potassium supplements with the bicarbonate to prevent intracellular potassium loss, since the urinary excretion of potassium over the trial period was not large and of the order of 80 mEq. They did, however, conclude by stating that further work might indicate the place of potassium supplements in therapy.

From the work of Robin et al. (1959) changes in the extracellular potassium during forced alkaline diuresis, cannot be regarded as without significance, as electrocardiographic changes and abnormalities of nerve conduction may occur in the presence of hypokalaemia, even when the total body potassium remains unchanged. Also Winters et al. (1963), Ghose and Joekes, (1964) and McLaughlin, (1965) have all stressed the possibility of precipitating severe and even fatal alkalotic tetany by rapid infusions of alkali. In theory, therefore, the development of dangerous hypokalaemia was considered to be a significant hazard with this regime. In the absence of any clear guidance as to which patients would require potassium

supplements and how much should be given, potassium replacements were initially administered in a somewhat arbitrary manner depending upon the levels of plasma potassium in each patient. Much depended upon intelligent guess work. As an initial part of the study, therefore, it was decided to assess whether in fact potassium supplements were necessary.

Patients and Methods

The investigation took the form of two studies, the first was a retrospective study of 15 patients, 7 males and 8 females (Group A), who had been treated with the full infusion regime of forced alkaline diuresis and who had also been given potassium supplements during the main period of diuresis. These supplements varied from 2.0 g. of potassium chloride (26.0 mEq.K.) intravenously every hour in some patients to 0.5 g. of potassium chloride (6.5 mEq.K.) intravenously every hour in others. For comparison, a prospective study was carried out in 25 patients, 9 male and 16 females (Group B), who were treated with the full infusion regime of forced alkaline diuresis but no potassium supplements were given in the first six hours of the diuresis treatment. The regime of forced alkaline diuresis used was:

0.9%	sodium chloride	- 500 ml.
5%	dextrose	- 500 ml.
1.26%	sodium bicarbonate	- 500 ml.

These solutions were infused in rotation at a rate of 2.0 litres per hour for the first three hours, thereafter the

rate was reduced to 1.0 litre per hour. This regime was continued subject to the patient maintaining a normal jugular venous pressure and to the absence of signs of pulmonary congestion. The pulse, respiration and blood pressure were charted every half hour and careful note was taken of the fluid intake and output.

Specimens of blood were withdrawn for measurement of plasma salicylate in all patients immediately before starting treatment and at two-hourly intervals thereafter until six hours after starting diuresis therapy. Five patients in Group A had plasma salicylate levels measured also eight hours following starting treatment and in Group B the plasma salicylate was measured in eight patients, 12-hours after starting treatment.

Measurements of the plasma potassium were carried out in all the patients in Group A immediately before starting treatment and six hours later. In all the patients in Group B, plasma potassium levels were measured immediately before starting treatment and at two-hourly intervals up to the end of the six hour period. Also in the latter group measurements of the urinary salicylate and the urinary potassium were made in three consecutive four-hour collections of urine, the collections commencing at the beginning of the forced diuresis therapy.

Salicylate levels in plasma and urine were measured photometrically by the method of Trinder (1954). Plasma and urinary potassium levels were measured by manual methods with a standard technique using an Eel flame photometer.

Results

Although there were more patients in Group B, than in Group A, the two groups could be regarded as comparable in terms of age, numbers of tablets taken, time since ingestion and peak plasma salicylate levels (Tables IX and X). The range of age in Group A was from 14-59 years and in Group B from 14-56 years. The means respectively were 30 and 29 years. The peak plasma salicylate levels, which were used as an index of the severity of the poisoning, ranged in Group A from 35 to 110 mg. per 100 ml. In Group B the range was 41 to 95 mg. per 100 ml. The respective means were 62 and 59 mg. per 100 ml. There was no great discrepency also in the time between ingestion of the tablets and the measurement of the peak plasma salicylate level. The mean time in Group A was five hours and in Group B, seven hours. The numbers of tablets taken also were relatively comparable although this was of less importance than the other parameters mentioned as the information regarding numbers of tablets tends to be unreliable and there was little relationship between the number of tablets said to have been taken and the resulting peak plasma salicylate level. For example in patient 11, 100 tablets were supposedly ingested and the peak plasma salicylate level reached only 35 mg. per 100 ml. In patients 1 and 2, however, in whom there was said to be the same number of tablets taken, the peak plasma salicylate level was almost double at 65 and 62 mg. per 100 ml., despite the fact that patient 1 had vomited prior to measurement of the blood level.

TABLE IX

PATIENTS		Age (Years)	Number of tablets ingested.	Time since ingestion (Hours)	Peak Plasma Salicylate level (mg. per 100 ml.)
M	1	18	100	10	65
	2	28	100	4	62
A	3	18	50	1	37
L	4	45	150	4	47
	5	21	80	8	58
E	*6	42	80	4	79
S	7	55	200	6	110
	*8	17	20	8	39
F	9	54	60	4	81
E	*10	59	130	5	63
M	11	38	100	2	35
A	12	17	60	5	83
L	13	15	40	1	35
E	14	41	150	6	58
S	15	14	70	4	67

* Vomited after ingestion and before admission.

Characteristics of 15 patients admitted with acute salicylate poisoning who were subsequently treated with forced alkaline diuresis with potassium supplements.

TABLE X

PATIENTS		Age (Years)	Number of tablets ingested	Time since ingestion (Hours)	Peak Plasma Salicylate level (mg. per 100 ml.)
	16	56	150	1	95
M	*17	24	200	2	90
	18	18	100	1	43
A	19	36	67	7	57
	20	22	60	2	50
L	21	42	150	5	82
	22	21	65	4	51
E	23	21	120	24	79
	*24	18	80	9	70
S					
	25	25	75	2	45
	26	36	60	6	60
	27	56	50	12	44
F	*28	22	120	4	60
	29	27	40	6	60
E	30	33	50	10	57
	31	43	75	5	63
M	32	17	75	3	61
	33	31	60	5	52
A	34	21	60	6	63
	35	51	200	12	74
L	36	23	60	6	61
	37	14	20	24	54
E	38	18	50	7	53
	39	30	100	2	41
S	40	45	90	3	46

* Vomited after ingestion and before admission.

Characteristics of 25 patients admitted with acute salicylate poisoning who were treated with forced alkaline diuresis without potassium supplements.

Clinical Progress

All of the patients were successfully given the full diuresis regime and none showed any features of excessive overloading of the circulation. All the patients in both groups made a full recovery from the poisoning. In Group A, the clinical progress was entirely satisfactory. In Group B, however, patient 29 developed frank tetany during the regime, and patient 17 was found to have electrocardiographic changes of hypokalaemia (Fig. 18). Both these patients responded satisfactorily to potassium supplements. The other patients in Group B showed no untoward clinical features.

Changes in Plasma Salicylate Level

The results are shown in Tables XI and XII and also Fig. 19. All the patients showed a satisfactory reduction in plasma salicylate on forced alkaline diuresis. The reduction in plasma salicylate levels was similar in the two groups. In the six hours of observation the plasma levels fell progressively and the mean half excretion time of salicylate for the 40 patients was 6 hours. One patient, 31, showed a rise in plasma salicylate level in the first two hours after starting treatment but thereafter the fall in plasma salicylate was similar to the other patients. This rise was presumably associated with further absorption of the drug from the gastro-intestinal tract.

Urinary Recovery of Salicylate

The amounts of salicylate recovered in the urine in 9

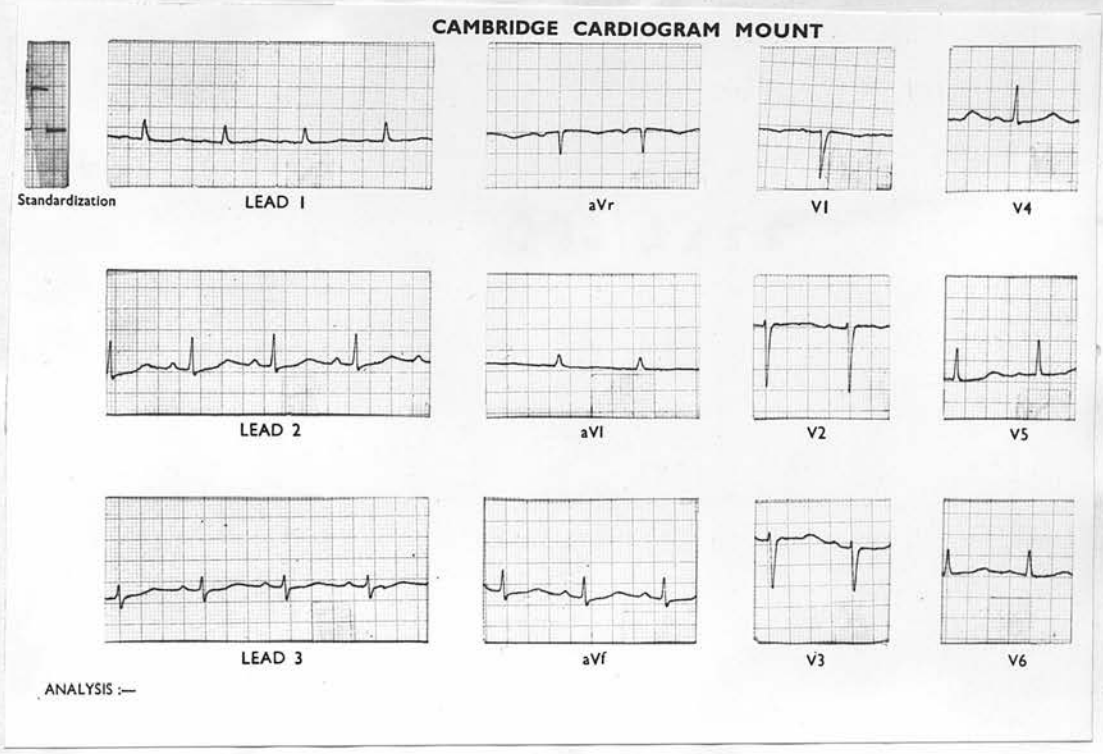

Figure 18.

Electrocardiograph carried out in Patient 17 six hours after starting forced diuresis.

TABLE XI

PATIENTS		PLASMA SALICYLATE LEVELS (mg. per 100 ml.)				
		Time (Hours)				
		Pretreatment				
		0	2	4	6	8
MALES	1	65	45		34	20
	2	62		50	40	
	3	37	36		24	15
	4	47	43.5	35	30	
	5	51	40	33	24	
	6	79	59	38	32	16.5
	7	110	76	55	40	
FEMALES	8	37	36	22	19	
	9	81	53	33	25	
	10	61	42	36		28
	11	53	44	37	31	
	12	83	65	35	28	
	13	35	33	25	16	
	14	58	38	32		
	15	67	59	50	37	24

Changes in plasma salicylate during forced alkaline diuresis with potassium supplements in the 15 patients in Group A.

TABLE XII

PATIENTS		PLASMA SALICYLATE LEVELS (mg. per 100 ml.)				
		Time (Hours)				
		Pretreatment				
		0	2	4	6	12
	16	95	49		36	24
	17	90		74		53.5
M	18	40	43	36	33	12
A	19	51	57	57	49	
L	20	42	38	36	30	26
E	21	82	59	47	33	
S	22	51	47	43	39	
	23	59			38	26
	24	70	51	45	44	25
	25	45		38	35	
	26	60	55	38		
	27	44			14	
	28	60			29	
	29	63	47	26		
F	30	57	50	48	34	
E	31	52	63	48	37	
M	32	61	36	30	15	9
A	33	52	39	27	20	
L	34	49	43	39		
E	35	74	67	45	36	
S	36	61	43		36	
	37	54	43		34	26
	38	53	45	24		
	39	43	41	32	28	
	40	46		42	27	

Changes in plasma salicylate in the patients in Group B treated with forced alkaline diuresis without potassium supplements.

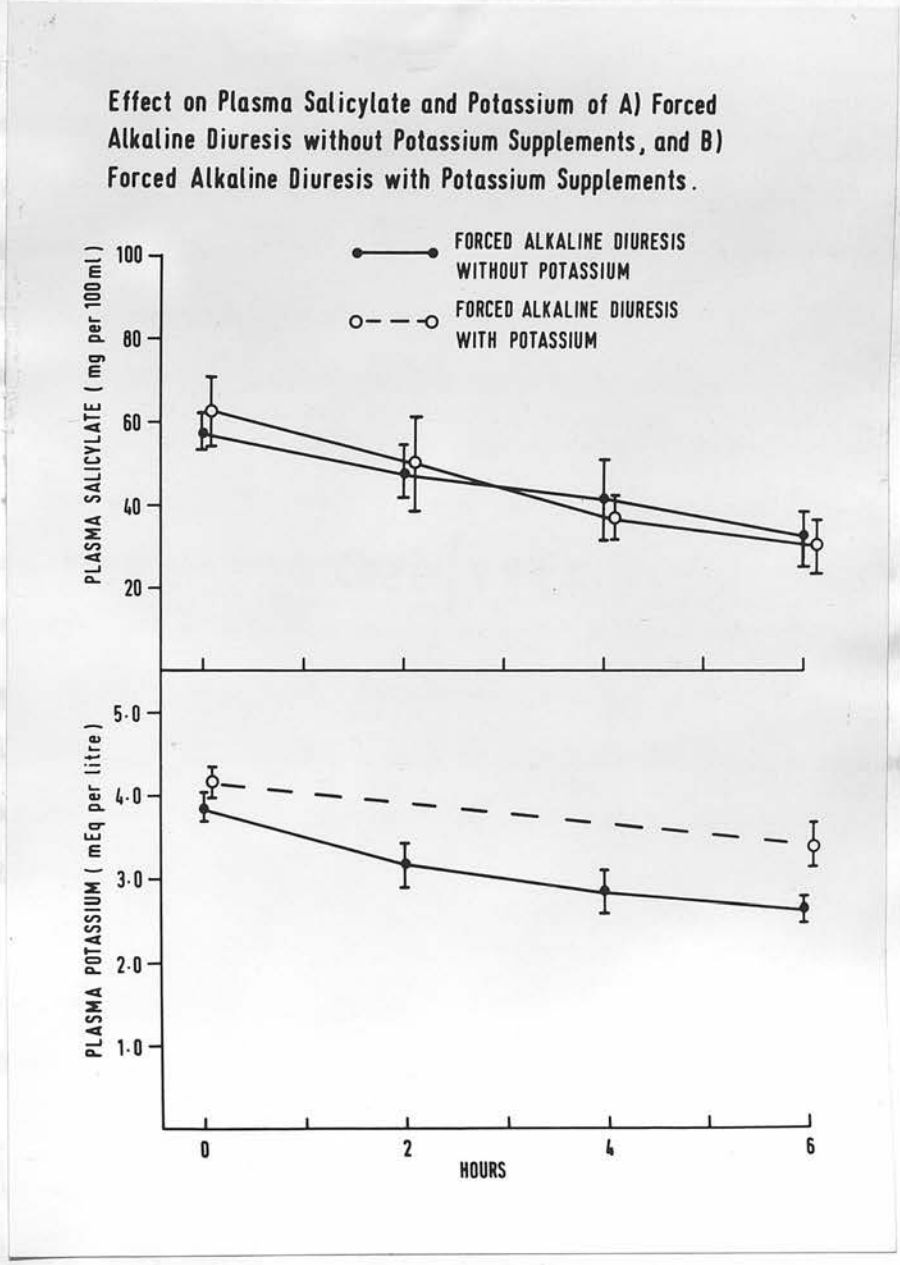

Figure 19.

Changes in the mean plasma salicylate (± standard error of the mean S.E.M.) and in the mean plasma potassium (± S.E.M.) in the patients in Group A and Group B treated with forced alkaline diuresis.

patients in Group B are shown in Table XIII and Figure 20. During the main period of the diuresis the amount of salicylate recovered in the urine was relatively high. Thereafter the amounts excreted decreased as the diuretic regime was relaxed. In a period of 12 hours after starting infusion therapy the mean recovery of urinary salicylate was approximately 7.0 g. There was a considerable variation in the recoveries of salicylate. This in large measure depended upon the initial peak salicylate level. For example, patient 17, who had a high initial level of plasma salicylate and who showed a very satisfactory response to treatment, had a recovery of salicylate in the urine of 13.5 g. On the other hand, patient 18, who had a much lower initial level and who showed a much slower fall during the course of treatment was found to have a total recovery of only 3.6 g. of salicylate.

Changes in Plasma Potassium Level

The changes, which were observed in plasma potassium during the course of the diuresis regime are shown in Tables XIV and XV and also in Figure 19. The normal level of plasma potassium by this method is 3.5-5.0 mEq. per litre. Taking these levels as the normal range, before treatment three patients, 1, 3 and 11, in Group A were relatively hypokalaemic before starting treatment and in Group B, there were four such patients 16, 32, 35 and 37. None of these patients were severely hypokalaemic, with the exception of patients 35 and 37, who had plasma potassium levels of 2.4 and 3.1 mEq. per litre respectively.

TABLE XIII

PATIENTS	URINARY SALICYLATE (g.)			
	Hours			
	0 - 4	5 - 8	9 - 12	Total
17	6.7	3.1	3.7	13.5
18	2.0	1.0	0.6	3.6
22	6.2	2.2	1.6	10.0
24	3.5	0.7	1.5	5.7
26	6.2	3.5	2.7	12.4
28	4.1	0.5	1.8	6.4
34	4.1	1.7	0.5	6.3
36	0.3	0.7	0.6	1.6
39	3.1	1.7	1.0	5.8

Urinary excretion of salicylate in 9 patients (Group B) during twelve hours after starting forced alkaline diuresis without potassium supplements.

TABLE XIV

PATIENTS		PLASMA POTASSIUM LEVELS (M.Eq. per litre)	
		Time (Hours)	
		Pretreatment	0	6
MALES	1	3.2	3.4
	2	3.6	3.2
	3	3.4	3.0
	4	3.6	3.2
	5	4.3	3.8
	6	5.0	4.2
	7	5.5	3.0
FEMALES	8	4.5	3.6
	9	4.4	3.2
	10	4.6	3.6
	11	3.2	3.1
	12	5.5	3.0
	13	4.3	3.6
	14	4.5	3.1
	15	3.9	3.0

Changes in plasma potassium in the patients in Group A before and after forced alkaline diuresis with potassium supplements.

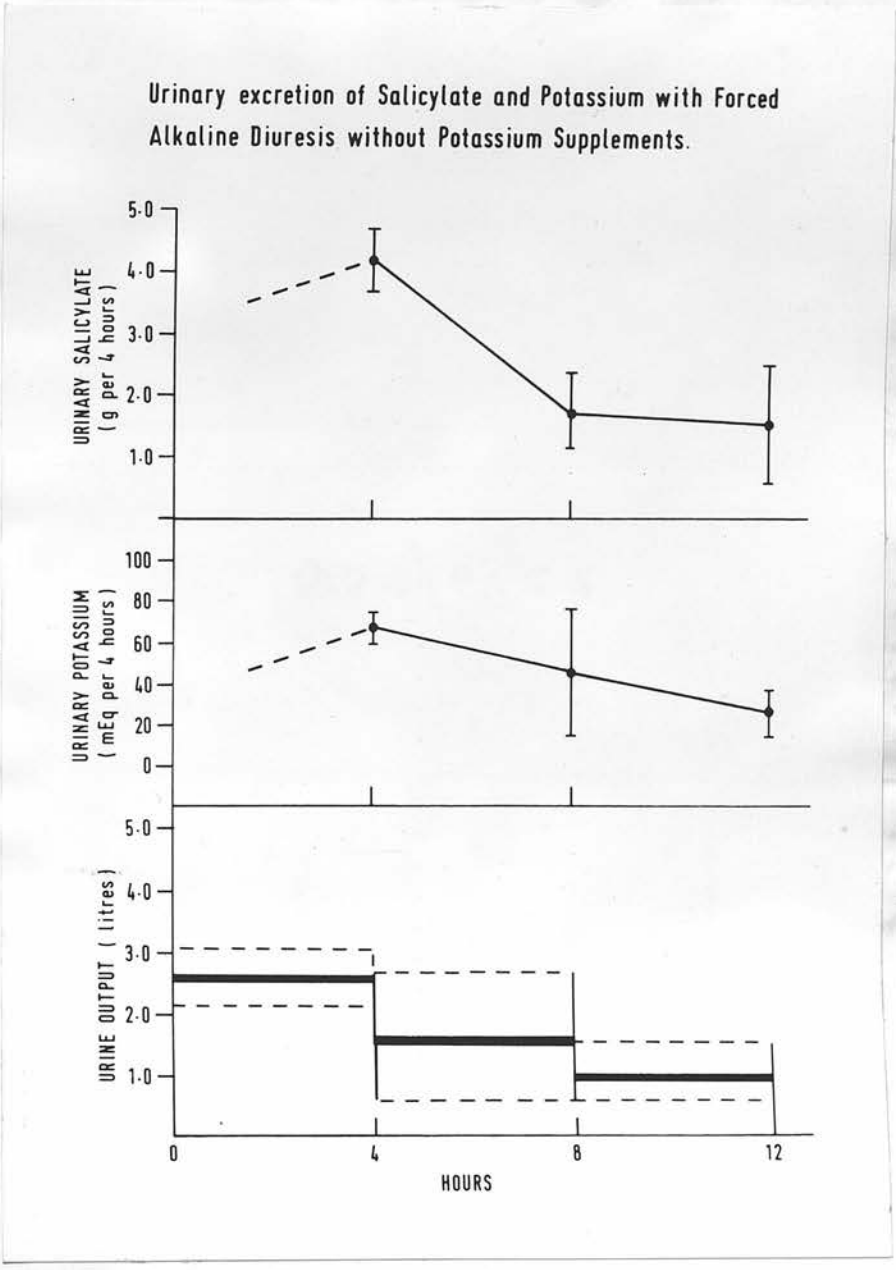

Figure 20.

Relationship between the reduction in mean urine volumes (± S.E.M.) and the mean urinary excretion of salicylate (± S.E.M.) and of potassium (± S.E.M.) in 9 patients treated with forced alkaline diuresis without potassium supplements.

TABLE XV

	PATIENTS	Plasma potassium (m.Eq. per litre) Time (Hours) Pretreatment 0	2	4	6
MALES	16	3.4	2.1		2.2
	17	5.0		4.1	2.3
	18	4.9	3.8	2.6	2.8
	19	4.4	3.6		3.1
	20	3.6	3.4	3.0	2.8
	21	4.8	4.0	3.5	2.8
	22	3.5	3.2	2.5	2.6
	23	3.7		3.2	3.0
	24	4.7	2.9	2.5	2.4
FEMALES	25	4.6	4.2		3.0
	26	4.0	3.6	4.0	3.2
	27	3.6		2.8	2.5
	28	4.6		3.0	3.1
	29	4.2	2.7	1.2	2.7
	30	3.8	3.5	3.0	2.4
	31	4.0	3.6	2.9	2.5
	32	3.3	3.1	2.9	2.5
	33	4.0	3.2	2.5	2.6
	34	3.7	2.5		2.6
	35	2.4		1.8	2.0
	36	3.9	2.7	2.3	2.4
	37	3.1	2.8	2.6	2.7
	38	3.7		3.0	2.8
	39	3.5	3.6	3.1	3.0
	40	4.0		3.8	2.9

Changes in plasma potassium in the patients in Group B treated with forced alkaline diuresis without potassium supplements.

Both these patients were admitted to the unit some considerable time after having ingested the poisoning. They were also severely poisoned. It is therefore more likely that the acid-base disturbance was of a more severe nature in these two patients than in the others. If this was the case, it would almost certainly be the reason for them being more hypokalaemic than the other patients. In neither of these two patients was there any other obvious cause of a low plasma potassium, such as renal impairment or gastro-intestinal upset. During the six hours of observation, 14 of the patients, who had potassium supplements (Table XIV) showed significant falls in plasma potassium compared with the pre-treatment level. In only one patient, patient 1, was there any increase in plasma potassium. In Group B all of the patients without exception showed hypokalaemia and in 18 of them this could be regarded as severe (Table XV). In two patients, 29 and 35, the hypokalaemia was alarming.

Another feature was that in some patients the hypokalaemia developed very rapidly and six patients were seriously hypokalaemic two hours after starting treatment. Comparison between Groups A and B is shown in Figure 19. The mean fall in plasma potassium in Group A was relatively small and severe hypokalaemia was not demonstrated. In Group B however, the reduction in plasma potassium was much more marked. It is therefore surprising that in only two patients were there any obvious features suggestive of severe hypokalaemia. Patient 17 in whom there was found to be a fall in plasma potassium from an initial level of 5.0 to 2.3 mEq. per litre at the 6-hour period was found to have electrocardiographic

changes of severe hypokalaemia. These responded satisfactorily to appropriate subsequent potassium administrations. Patient 29 developed clinical tetany four hours after starting treatment and this was apparently related to a reduction in the plasma potassium from 4.2 to 1.2 mEq. per litre during the period of treatment. The tetany continued until after the diuresis regime had been stopped and until appropriate potassium supplements had been given. It is likely that tetany resulted from acute metabolic alkalosis, which promoted the rapid fall in plasma potassium.

Urinary potassium

The results are shown in Table XVI and also in Figure 20. As with the urinary salicylate, the urinary excretion pattern of potassium was maximal during the initial four hours of the diuresis. Thereafter as the urinary volume fell so the urinary potassium excretion also fell (Fig. 20). The total losses over the 12-hour period were considerable and ranged from 80.1 mEq. to 177.0 mEq. with a mean value of 126 mEq. There is little doubt that the amount of potassium excreted in the urine, to a considerable degree, was related to the urine flow, but this was not always the case. The results for the urine volumes for nine patients in Group B (Table XVII) revealed that there is a considerable discrepancy between the volumes of urine produced in individual patients and the amount of potassium excreted. The urinary volumes produced in patient 17 and patient 36 were low relative to the whole group. On the other hand, the excretion of potassium during the same period of time in these two patients was high being 177 and 145 mEq. respectively. In contrast patient 22 had

TABLE XVI

PATIENTS	URINARY POTASSIUM (m.Eq.)			
	0 - 4	5 - 8	9 - 12	Total
17	93.0	36.0	48.0	177.0
18	56.0	17.7	6.4	80.1
22	7.4	147.3	18.0	172.7
24	69.0	9.7	29.4	108.1
26	87.0	31.0	31.0	149.0
28	57.0	19.7	11.5	88.2
34	82.8	7.2	11.4	101.4
36	59.0	51.0	35.0	145.0
39	30.2	60.0	23.5	113.7

Urinary excretion of potassium in 9 patients in Group B during twelve hours after starting forced alkaline diuresis without potassium supplements.

TABLE XVII

PATIENTS	URINE VOLUME (litres) HOURS 0 - 4	5 - 8	9 - 12	Total
17	1.6	0.7	1.3	3.6
18	3.5	1.4	0.5	5.4
22	2.6	5.3	0.7	8.6
24	2.3	0.5	0.7	3.5
26	2.6	1.7	1.7	6.0
28	3.8	2.1	0.5	6.4
34	2.3	0.5	1.4	4.2
36	0.4	1.2	1.2	2.8
39	4.2	1.1	0.5	5.8

URINE VOLUMES in 9 patients in Group B during twelve hours after starting forced alkaline diuresis without potassium supplements.

a urinary volume of more than twice that of either patient 17 or 36 and yet his potassium excretion was 172.7 mEq. which, although high, was not as much as patient 17.

Discussion

Whitten et al. (1961) and Cumming et al. (1964) both agreed that the most satisfactory measurement to use as an index of efficiency of treatment is the rate at which the plasma salicylate concentration falls. On this basis, comparison between these two groups of patients showed that there was no difference in the relative effectiveness of the two regimes in the treatment of acute salicylate poisoning. The mean half excretion time of salicylate in both groups was approximately 6 hours, which was similar to the results which have been previously reported by Oliver and Dyer (1960) and also by Cumming et al. (1964), who used similar regimes of forced diuresis. The diuresis treatment in this study, therefore, was a satisfactory one from the point of view of the removal of salicylate.

When the changes in the plasma potassium occurring during the treatment were considered, however, there was less reason for complacency. Even in the group of patients, who were given potassium supplements, there was a significant number, who developed hypokalaemia. The reduction in plasma potassium in the patients who did not receive potassium supplements was striking and in many cases alarming. A number of patients were relatively hypokalaemic before the start of the diuresis regime. These results confirm the reports of Robin et al. (1959) of the importance of hypokalaemia in acute salicylate poisoning. Admittedly the

reduction in plasma potassium found in the present series of patients was less marked than that reported by Robin and his colleagues. The incidence of clinical complications due to hypokalaemia was also less. A possible reason for this was that most of Robin's patients had been admitted to hospital considerably longer after the time of ingestion than is usually the case in patients admitted to the Poisoning Treatment Centre in Edinburgh. It is probable that in addition to the severity of overdosage the degree and frequency of hypokalaemia in patients with this condition are related to the duration of the poisoning. In support of this in the present series the two patients who had the most severe hypokalaemia before treatment was started were admitted 12 and 24 hours after taking the tablets. This was a considerably longer time before admission to hospital than in the remaining patients.

The reasons for the fall in plasma potassium noted in the patients during the course of forced alkaline diuresis were almost certainly the result of a complex series of changes. Urinary excretion of potassium was considerably increased during the period of diuresis and there is no doubt that this played some part in the development of the hypokalaemia. On the other hand, the changes in plasma potassium occurred very rapidly and it would seem likely that shifts of potassium ion from the extracellular to the intracellular compartment were also occurring. During the first six hours of the diuresis almost 3,000 mEq. of sodium are administered and approximately 950 mEq. of bicarbonate are also given. For practical purposes the excretion of potassium

depends almost exclusively on the tubular secretion of potassium in exchange for sodium. Filtered potassium plays very little part. As most of the body potassium is intracellular the external control of potassium relates to tubular cell content of the ion. Also since potassium excretion depends upon an exchange with sodium, it is regulated by the amount of sodium delivered to the exchange site in the distal tubule, to the avidity with which sodium is reabsorbed and to the availability of the intracellular potassium for exchange. Thus the delivery of more sodium to the distal tubule, during sodium diuresis, increases the excretion of potassium. It is likely, therefore, that the excessive load of sodium during this diuresis regime will be a contributory factor in the production of excessive potassium loss. In addition to this, the large amount of bicarbonate administered will both promote the movement of potassium from the extracellular compartment to the intracellular compartment and in addition aggravate further potassium loss in the urine. It was surprising that no more marked clinical features of hypokalaemia were demonstrated in the patients particularly in Group B.

The possibility of precipitating severe and even fatal alkalotic tetany using this type of regime of therapy has been stressed by Winters et al. (1963), by Ghose and Joekes, (1964) and again more recently by McLaughlin in 1965. These possibilities have largely been on a theoretical basis and the reports of patients with acute salicylate poisoning who develop actual tetany are extremely few. The only well documented example was reported by Freier et al., (1957). Of the two patients in Group B, who were

found to have definite clinical features of severe alkalosis and potassium depletion, one had demonstrable changes on ECG of severe hypokalaemia and this resolved with appropriate replacement of potassium; the other patient developed clinical tetany. This was probably due to the induction of metabolic alkalosis resulting from the infusions of bicarbonate. In addition this patient was shown to develop severe and rapidly developing hypokalaemia. Unfortunately there were no measurements of acid-base status done in any of these patients. However after stopping bicarbonate therapy and the administration of potassium the tetany subsided.

From the results of this study, there seems little justification for the conclusion of Cumming et al. (1964), in which they considered it unnecessary to administer potassium with bicarbonate during the course of forced alkaline diuresis. Indeed the changes in plasma potassium observed in the patients in Group A who were given intravenous potassium supplements, suggested that vigorous potassium replacement therapy is required if serious and rapid changes in the plasma potassium are to be avoided.

The results of this initial study demonstrated that forced alkaline diuresis, as suggested by Cumming et al. (1964), is an extremely efficient method in reducing the plasma salicylate in patients suffering from acute salicylate overdosage. It is a therapy, however, which has a number of inherent dangers, which are associated not only with the brisk diuresis produced, but more particularly, with the large quantities of sodium and bicarbonate, which are administered in the course of the regime. The main complication was the high incidence of hypokalaemia.

Few clinical features of potassium deficit were observed but the rapidity and degree of changes of plasma potassium, which occurred, were alarming and could only be regarded as potentially hazardous. Tetany, which was probably related to the rapid development of alkalosis, occurred in another patient and, although an uncommon finding, did suggest that this regime of treatment may provoke harmful changes in acid-base status.

A number of workers including Cumming et al. (1964) have acknowledged these complications of the therapy but as they were unable to demonstrate any serious clinical features resulting from the changes in acid-base status and in plasma potassium, they considered that the advantages of rapid reduction in plasma salicylate more than compensated for any possible hazards, which might exist. Considerable controversy still exists, regarding the advantages and disadvantages of forced diuresis in acute salicylate overdosage and about the exact regimes, which should be used. It was decided, therefore, to conduct a detailed clinical and biochemical study of the effects of different regimes of forced diuresis with the intention of developing a safe and standardised form of treatment.

FORCED ORAL FLUIDS

Forced oral fluids were reported to be ineffective in the treatment of patients with severe salicylate poisoning (Doolan, et al., 1951). On the other hand, correction of dehydration and maintenance of fluid balance by this means is widely used in the treatment of the less severe forms of this poisoning. It was decided, therefore, in the first instance to gather a group of patients who were judged to be only moderately poisoned, who had not vomited and in whom nausea was not a marked feature. The protocol used for this study was similar to the one employed for patients who had more severe forms of the overdosage and in whom more elaborate forms of diuresis were used.

Biochemical Methods

The same methods of biochemical measurements were used throughout the whole study.

The arterial pH, partial pressure of carbon dioxide (pCO_2) and Standard bicarbonate, were determined at 38°C by the micro Astrup method (radiometer PHM 27) of Siggaard-Andersen (1962). The urine pH was measured at room temperature using a glass electrode (radiometer PHM 25); the pH meters were calibrated with precision phosphate buffers. The packed cell volume (PCV) was measured using a micro-haematocrit centrifuge (Hawksley). Plasma and urinary salicylate was assayed photometrically (EEL Spectra) by the Method of Trinder (1954). Plasma and urinary sodium and potassium were measured manually by conventional methods (EEL flame photometer). Plasma calcium was measured by automated

colourimetry (Auto Analyzer) according to the method of Gitelman (1967). Plasma and urinary magnesium and urinary calcium was estimated by atomic absorption spectrophotometry (Perkin-Elmer 303) by the technique described by Thin and Thomson (1967). These electrolyte determinations were made using primary standards (B.D.H., analar), which were themselves checked against control sera (Hyland or Versatol).

Patients and Methods

Nine patients, 4 males and 5 females were studied whilst under treatment with forced oral fluids. Characteristics of these nine patients are shown in Table XVIII. They had all been admitted to hospital a relatively short time after ingestion (mean time 4.3 hours). The peak plasma salicylate level found in these patients ranged from 38 to 62 mg. per 100 ml. On this basis a number of the patients were fairly severely poisoned but none of the patients had very severe symptoms and were not unduly distressed. As they were to be carefully monitored it was, therefore, considered justifiable to treat them with this form of therapy alone.

All the patients in this group were encouraged to drink as much fluid as possible, particularly during the six hours of treatment. It was found that the fluid intake was considerably limited by nausea, which was precipitated relatively easily, even in patients who had not previously spontaneously complained of this. The fluids used were in the main simply iced water although in some patients dilute solutions of fruit juice were

TABLE XVIII

PATIENTS		Age	Number of tablets ingested	Time since ingestion (hours)	Peak Plasma Salicylate Level (mg. per 100 ml.)	Arterial blood gases at peak plasma salicylate level		
						pH	pCO_2	Standard Bicarbonate (mEq./litre)
M	41	17	50	5	60	7.46	27.0	22.0
A	42	46	70	2	53	7.41	24.0	20.0
L	43	24	150	$3\frac{1}{2}$	51	-	-	-
E	44	41	50	4	53	-	-	-
S								
F								
E	45	14	100	$1\frac{1}{2}$	62	7.40	27.5	20.5
M	46	18	40	3	55	7.42	23.0	18.0
A	47	20	80	6	47	7.48	29.0	22.0
L	48	35	40	9	38	7.42	30.5	21.0
E	49	19	60	5	51	7.47	17.0	18.0
S								

Characteristics of 9 patients treated only with forced oral fluids.

given, as they were better tolerated. Fluid intake achieved ranged from 170 to 210 ml. per hr. with a mean of 190 ml. per hr. With all the regimes of forced diuresis studied the period chosen for close observation was the six hours after the start of treatment. This period represented the phase of maximum diuresis in the case of the intravenous regimes. Also during these first six hours the patients were given only the treatment regimes stated; in particular, there were no complicating factors such as the need for potassium supplements other than those contained in the type of treatment under study. Also no food was given to the patients during the six hour period.

The arterial blood gases were measured in seven of the nine patients at the time of the peak plasma salicylate level. Subsequently these measurements were monitored for six hours after the commencement of treatment. The blood gas measurements were made on blood taken from the brachial artery by routine arterial puncture. The usual precautions of collection and preservation of the samples of arterial blood were made. The blood gas measurements were all carried out within 30 minutes of the time of arterial puncture. The plasma salicylate was measured in all patients at the time of admission to hospital and hourly for six hours after the beginning of treatment. In a number of patients, the further measurements of the plasma salicylate were made at eight hours and in a few up to 24 hours. The plasma salicylate was carefully monitored incase it would rise significantly above 60 mg. per 100ml. as this would have required a more active form of therapy. The urinary salicylate was

measured in consecutive hourly specimens of urine and the urine volumes were also carefully noted. The plasma potassium was also measured in all patients and monitored at hourly intervals for six hours, in a number of patients for eight hours and in a few up to 24 hours. Urinary excretion of potassium was measured at hourly intervals for six hours after commencement of treatment. Plasma magnesium levels were estimated in six patients at hourly intervals from the beginning of treatment up to the end of the six hour period, and the plasma calcium was determined in four of the patients in a similar manner. In each patient the plasma sodium was measured every two hours for the first six hours and the urinary excretion of sodium was also measured during the same period.

Results

Clinical Response

All of the nine patients ultimately made a complete and uneventful recovery, from the poisoning. In each patient, who had any features of salicylism, however, it was noticeable that symptoms persisted for up to 24 hours after starting treatment. None of the patients had to be treated subsequently with any more active form of therapy to remove salicylate.

Changes in Plasma Salicylate and Acid-Base Status

The results are shown in Table XIX. In five patients (42, 43, 44, 45 and 47) the plasma salicylate was found to rise somewhat during the first four hours of treatment. In all these

TABLE XIX

PATIENTS		PLASMA SALICYLATE (mg. per 100 ml.)							
		Time (Hours)							
		Pretreatment 0	2	4	6	8	12	18	24
MALES	41	48	44	43	38	33			
	42	48	49	53	34				16
	43	42	51	49	35	20			
	44	44	49	53	34				
FEMALES	45	45	51	62	50	46		39	
	46	52	52	49	49	47			
	47	46	48	40	36	32	28		
	48	38	38	34	30	30	15		
	49	51	49	46	46	50	48	43	

Changes in plasma salicylate in 9 patients with acute salicylate poisoning treated only with forced oral fluids.

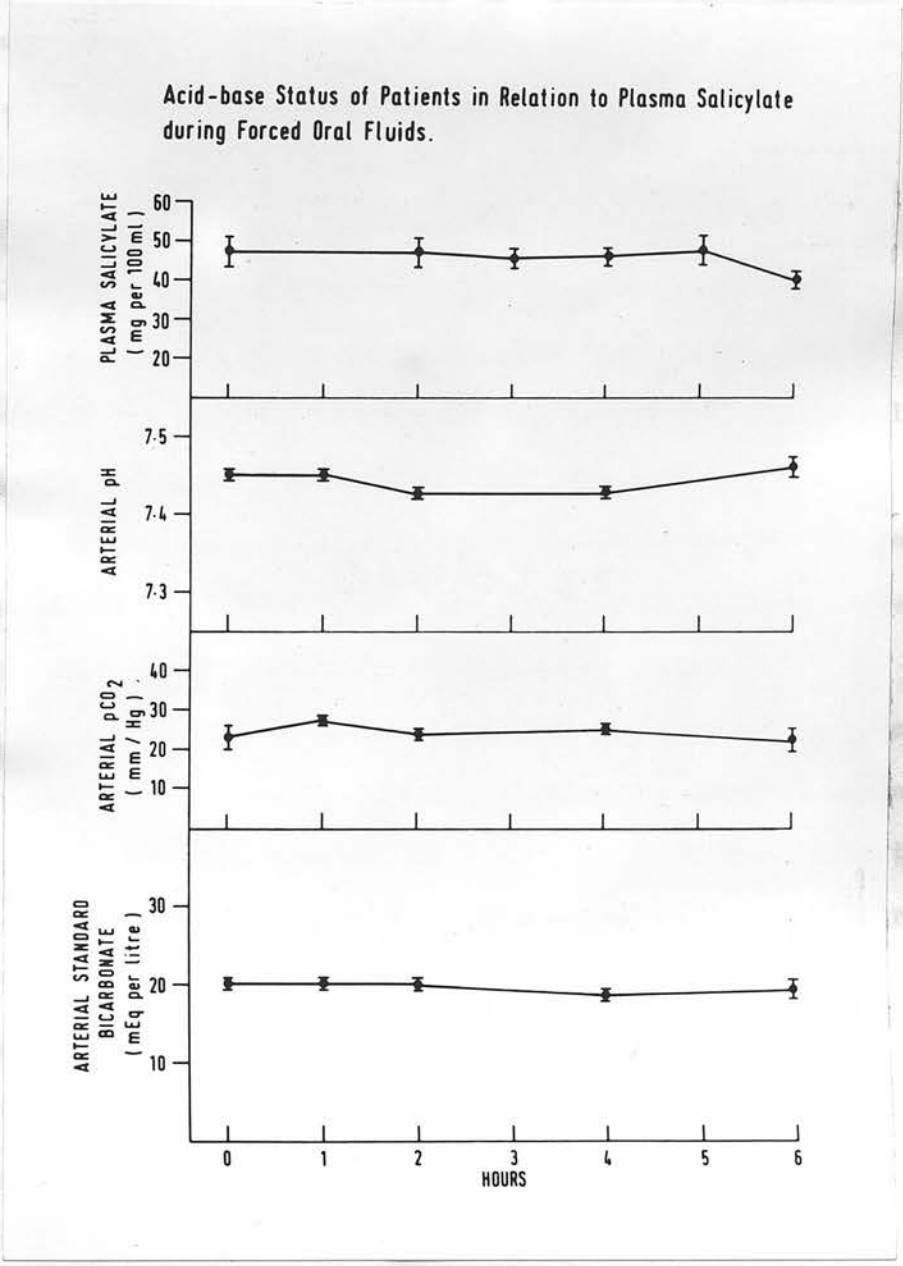

Figure 21.

The mean values of arterial pH, pCO_2 and standard bicarbonate ($\pm$ SEM) in relation to changes in the mean levels of plasma salicylate ($\pm$ SEM) in 9 patients treated with forced oral fluids.

patients, however, the blood level subsequently fell. The mean results for the group of nine patients are shown in Figure 21. During the first six hours of treatment there was a fall of rather less than 10 mg. per 100 ml. on the average. On extrapolation of this data, the mean half excretion time for salicylate for this group of patients was between 20 and 24 hours.

In Table XVIII is shown the acid-base status observed in seven of the patients in relationship to the peak plasma salicylate levels. Four of these patients had normal pH levels. In three patients (41, 47 and 49) a moderate alkalosis was present and the associated low levels of pCO_2 and standard bicarbonate suggested that this was predominantly a respiratory alkalosis.

Mean changes in arterial pH, pCO_2 and standard bicarbonate are shown in Figure 21. The normal range for arterial whole blood pH in this laboratory is 7.39-7.43. On the whole, the mean arterial pH remained slightly elevated or in the high range of normal and overall there was little change in the level throughout the period of observation. The normal range of pCO_2 for this method is 37-42 mm.Hg. and the results show that the mean values of pCO_2 at different times during the six hour period remained consistently low. As with the arterial pH there was little fluctuation in the actual levels measured during the six hour period. In the case of standard bicarbonate, the normal level ranged from 25-28 mEq./l. and here again the levels remained steady but generally low.

Relationship Between Changes in Plasma Salicylate and Urinary Salicylate

The changes in plasma salicylate and the urinary excretion

of salicylates over the first six-hour period are shown in Tables XIX and XX. Comparison between the mean values and the appropriate standard errors for plasma salicylate, urinary salicylate, urinary pH and urinary volume are shown in Figure 22. As has already been seen, there was only a modest fall in the plasma salicylate during the six-hour period. The graph of the urinary salicylate would indicate that at first there was a high excretion of salicylate. This quickly fell and after two hours and for the rest of the six hours remained fairly constant at a relatively low level. These changes in salicylate excretion corresponded to changes in urinary volume during the same period of time. The apparently high initial levels of salicylate excretion were probably false as the measurements of urinary salicylate and the urinary volume at 0 hours did not represent an accurate one hour collection of urine and was simply the urine collected when the patient emptied his bladder immediately at the commencement of treatment. It therefore, in most cases, reflected several hours urinary excretion and was not comparable with the remaining part of the graph.

The total urinary outputs of salicylate (Table XX) were relatively constant, with one exception, patient 44, who showed an excretion of about two times that of any of the other members of the group. The urinary volume found in this patient was not excessive and averaged 300 ml. per hour. Possibly a more significant factor was that the urinary pH in this patient ranged between 6.5 and 7.0 which was significantly higher than the levels found in the other patients studied. Mean values of urinary pH for the whole group of patients remained relatively low in the region of 6.25. The average p^H before treatment however was

TABLE XX

PATIENTS		URINARY EXCRETION OF SALICYLATES (mg. per hour)							
		Time (Hours)							
		Pretreatment							
		0	1	2	3	4	5	6	Total (mg.)
MALES	41	948	387	387	149	140	154	136	2301
	43	340	236	240	440	85	185	100	1626
	44	360	720	520	520	520	750	750	4140
FEMALES	45	261	230	236	185	160	85	100	1257
	46	817	217	225	210	140	132	149	1890
	48	909	85	95	76	80	94	84	1423
	49	117	320	340	230	222	9	9	1247

Urinary excretion of salicylate in 7 patients during diuresis on forced oral fluids.

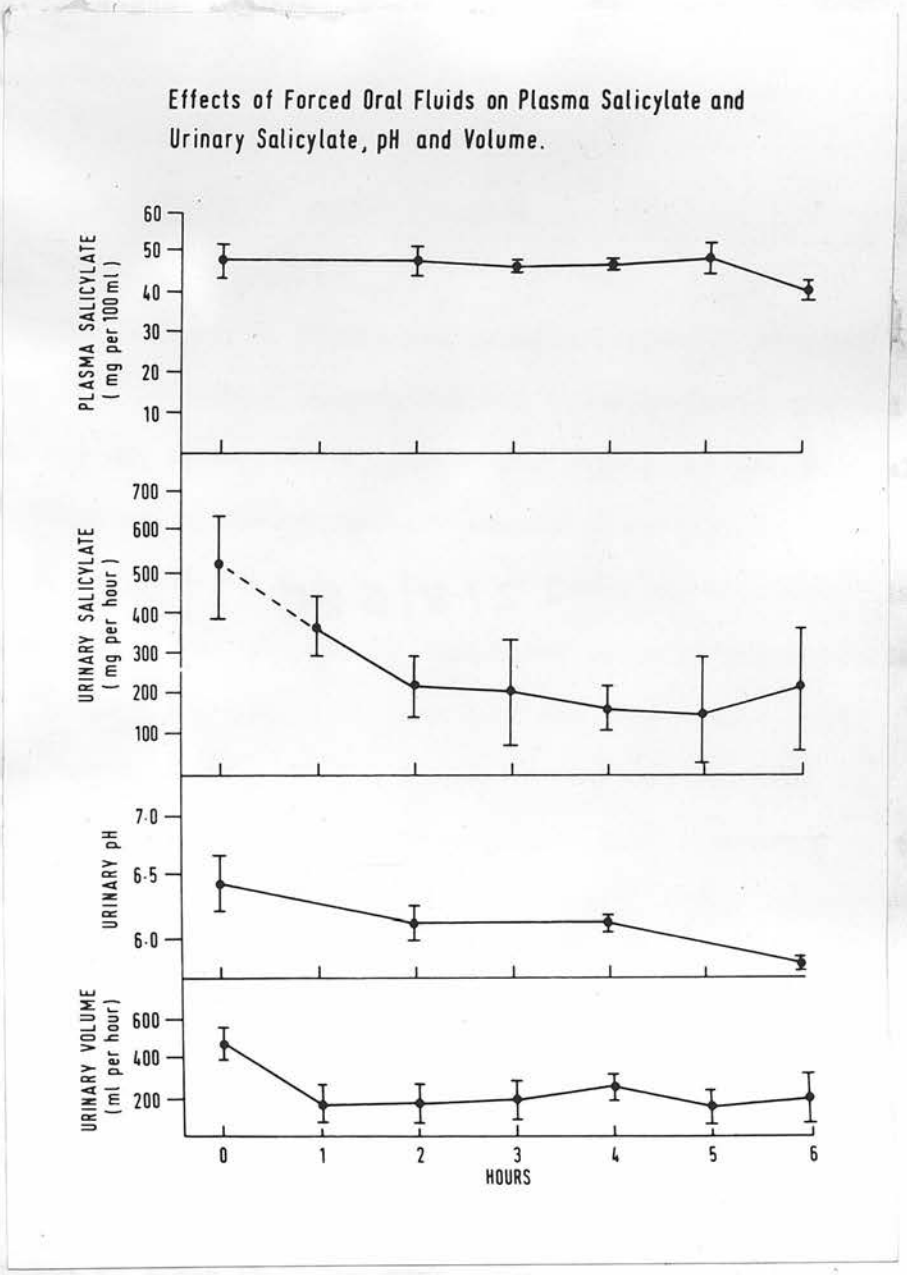

Figure 22.

Comparison between the mean changes (± S.E.M.) of plasma salicylate, urinary salicylate, urinary pH and urinary volume in nine patients treated with forced oral fluids.

rather higher than subsequent measurements and the urinary pH tended to fall as the period of observation progressed.

Changes in Plasma Potassium and Urinary Potassium in Relationship to Arterial pH and Urinary pH

The changes in plasma and urinary excretion of potassium during the period of observation are shown in Tables XXI and XXII and the relationship between the changes in the mean values of plasma potassium and urinary potassium are plotted in relationship to the mean values of arterial and urinary pH in Figure 23. One patient, 48, was found to be mildly hypokalaemic before the commencement of treatment and he remained mildly hypokalaemic throughout the period of observation. In two patients, 43 and 44, there was no significant alteration in the plasma potassium during the period of study. The remaining six patients all developed a modest degree of hypokalaemia. In the few measurements taken beyond the eight hour period it seemed that the nadir of the curve for hypokalaemia occurred between six and eight hours following the start of treatment.

The urinary excretion of potassium in seven of these patients is shown in Table XXII. The losses of potassium during the six hour period were relatively small, with one exception, patient 44, who as with urinary salicylate losses, excreted considerably more potassium than any of the other patients studied. Despite this there was no demonstrable change in his plasma potassium. The mean losses of the urinary potassium (Fig. 23) tended to fall as the study progressed. From the graph this appeared to be related to the fall in urinary pH, which was

TABLE XXI

PATIENTS		PLASMA POTASSIUM (m.Eq./litre)							
		Time (Hours)							
		Pretreatment							
		0	2	4	6	8	12	18	24
M									
A	41	4.3	3.3	3.0	3.1	3.3			
L	42	3.7		4.0	3.2				
E	43	4.2		4.3					
S	44	4.1	4.0		4.2				
F									
E	45	4.2			3.4	3.3		3.6	3.5
M	46	3.8	3.6	3.6	3.0	2.8			
A	47	3.5	3.6	3.5	3.4	3.4			
L	48	3.4	3.8	3.4	3.4	3.1			
E	49	3.6		3.5	3.1		3.8		3.5
S									

Changes in plasma potassium in 9 patients with acute salicylate poisoning treated only with forced oral fluids.

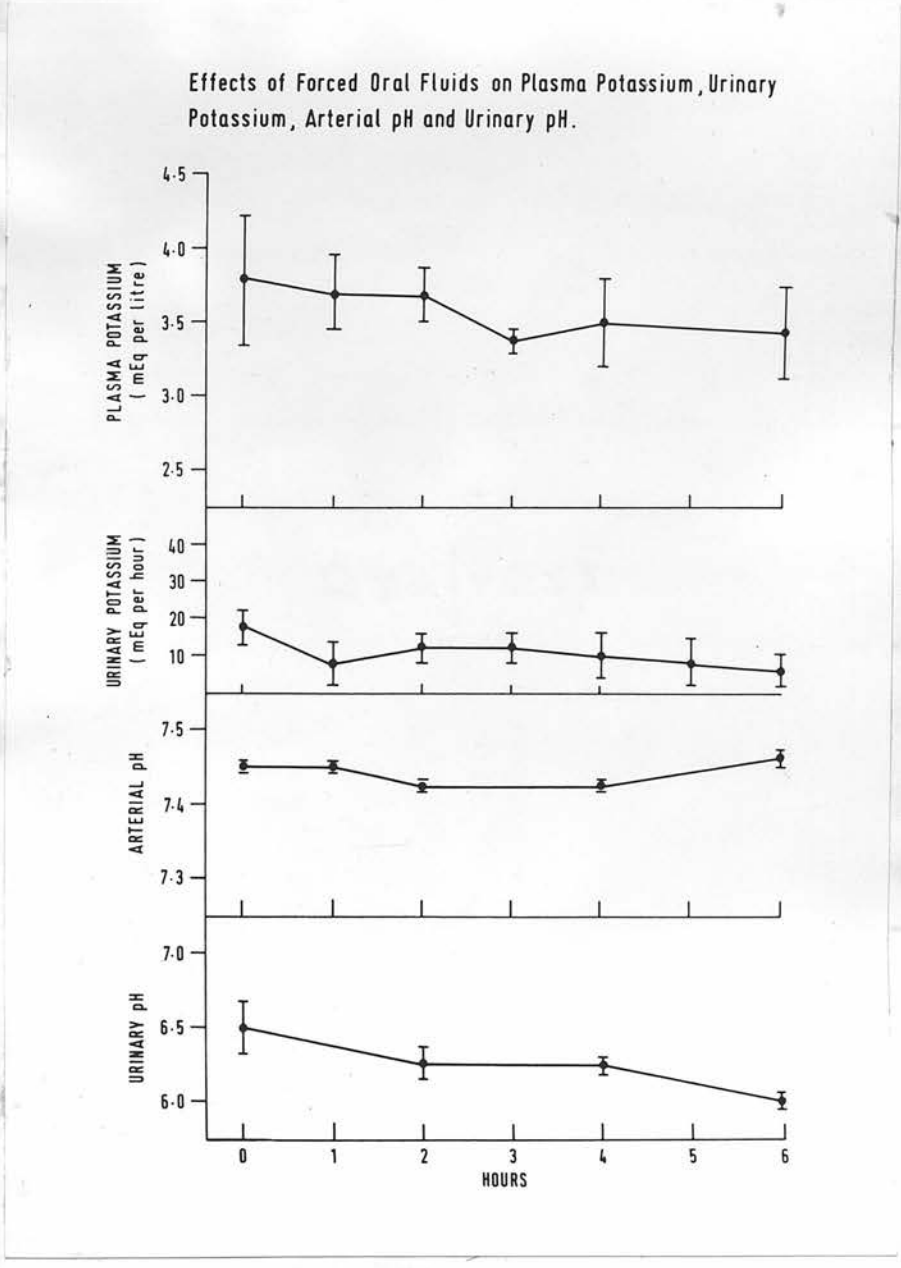

Figure 23.

Changes in the mean values (± S.E.M.) of plasma potassium, urinary potassium, arterial pH and urinary pH in nine patients treated with forced oral fluids.

TABLE XXII

PATIENTS		URINARY EXCRETION OF POTASSIUM (m.Eq./hour)							
		Pretreatment	Time (Hours)						
		0	1	2	3	4	5	6	Total
MALES	41	35.0	15.0	15.0	8.25	8.25	8.25	8.25	63.0
	43	11.0	7.5	7.5	2.7	4.0	4.0	4.3	41.0
	44	23.0	26.0	26.0	26.0	26.0	17.0	17.0	161.0
FEMALES	45	3.3	2.0	2.3	2.3	2.3	2.3	5.6	20.1
	46	21.2	8.1	8.1	8.3	3.8	3.8	3.8	57.1
	48	20.0	1.6	1.6	1.6	1.4	1.8	1.3	29.3
	49	5.0	10.0	9.6	8.5	8.5	0.5	0.5	42.6

Urinary excretion of potassium in 7 patients during diuresis on forced oral fluids.

also demonstrated. Another important factor was that the urinary output also fell at the same time. It would seem, therefore, that the tendency for the plasma potassium to fall was not due to any excessive loss in urine. The mean values of the plasma potassium reflect the very modest degree of hypokalaemia which was found in these patients.

Changes in Plasma Potassium, Magnesium and Calcium in Relation to Arterial pH and P.C.V.

The changes in plasma magnesium in six patients and in plasma calcium in four patients are shown in Tables XXIII and XXIV. The relative changes in the mean values within each group over the six hour period for plasma potassium, magnesium, calcium and arterial pH and P.C.V. are shown in Figure 24. The normal range of plasma magnesium for the method used was 1.7 to 2.4 mg. per 100 ml. All of the patients (Table XXIII) had normal levels of plasma magnesium throughout the period of study. Similarly for plasma calcium, none of the patients showed a reduction of plasma calcium below the lower limit of normal for this technique of measurement which was 8.5 mg. per 100 ml. (Table XXIV). In Figure 24 there is shown the slight fall in the packed cell volume from the third to the sixth hour. This reduction was small and of doubtful significance, but it may indicate a slight degree of haemodilution. This may have been a factor in the slight reductions in plasma potassium and plasma calcium, which were noted also during the latter three hours of observation.

TABLE XXIII

PATIENTS		PLASMA MAGNESIUM (mg. per 100 ml.)			
		Time (Hours)			
		Pretreatment 0	2	4	6
MALE	41	2.24	1.91	1.83	2.16
FEMALES	45	2.3	2.45		2.25
	46	2.08	2.04	2.00	2.08
	47	2.28	2.08	2.24	2.24
	48	2.08	1.83	1.95	2.04
	49	2.30	2.25	2.20	2.25

Changes in plasma magnesium in 6 patients treated only with forced oral fluids.

TABLE XXIV

PATIENTS	PLASMA CALCIUM (mg. per 100 ml.)			
	Time (Hours)			
	Pretreatment 0	2	4	6
FEMALES				
45	9.1	8.8		8.5
47	10.2	9.4	8.9	9.3
48	11.2	10.6	9.5	9.4
49	10.6	9.9	8.8	9.4

Changes in plasma calcium in 4 patients treated only with forced oral fluids.

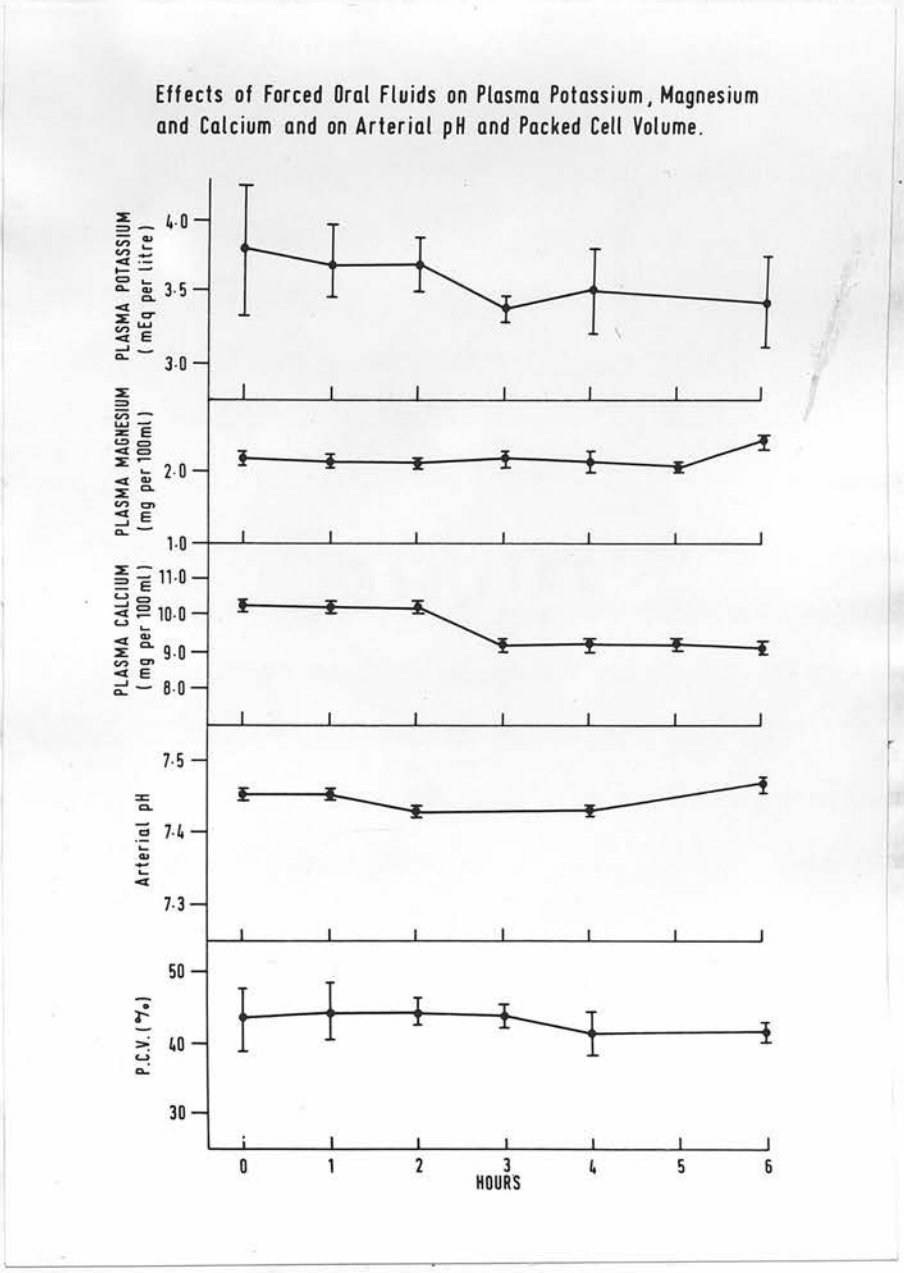

Figure 24.

Changes in the mean values (± S.E.M.) of plasma potassium, magnesium, calcium, arterial pH and P.C.V. in patients treated with forced oral fluids.

Changes in Plasma and Urinary Sodium

Changes in the levels of plasma sodium are shown in Table XXV. The normal range for plasma sodium was 135-143 m.Eq. per litre. The plasma levels remained relatively constant during the six hours and none of the patients developed significant hyponatraemia. The urinary excretions of sodium in the six hours varied from 37.0-108 m.Eq. (mean 83 m.Eq.).

Discussion

The fluid intake achieved in this group of patients was relatively small and only a limited diuresis was achieved. Assessing the method in terms of reduction in plasma salicylate there was no difference between the calculated mean half excretion time for salicylate compared with that which has been reported in untreated cases (Cumming et al., 1964). This form of therapy, therefore, was of no value except possibly in the case of the very mildly poisoned patients in whom simple rehydration is all that is required. This group of patients however provided a valuable control group for comparison with the more intensive forms of diuresis therapy.

In terms of acid-base disturbance, this small group of patients demonstrated the mixed type of acid-base disturbance, which occurs in acute salicylate poisoning. In the seven patients in whom measurements of acid-base status were made four had arterial pH's within the normal range and three were alkalotic. All of these patients without exception had consistently low arterial pCO_2 and standard bicarbonate levels. This suggested

TABLE XXV

PATIENTS		PLASMA SODIUM (m.Eq. per litre)			
		Time (Hours)			
		Pretreatment 0	2	4	6
MALES	41	145	142	145	140
	42	144	138	138	134
	43	140	140	141	141
	44	140	144	140	143
FEMALES	45	137	138	138	137
	46	137	138	145	138
	47	140	136	134	134
	48	135	137	136	138
	49	144	140	140	142
Mean Values		140	139	140	138

Changes in plasma sodium in 9 patients treated only with forced oral fluids.

that there was an element of respiratory alkalosis, which was not of sufficient severity to prevent the normal buffer mechanisms of the body from containing the blood pH within the normal level in four of the patients but was of greater significance in the remaining three. In two of the patients with alkalosis the standard bicarbonate levels were relatively high indicating a degree of compensation for the respiratory alkalosis. In the last patient however there was no sign of this in that both the arterial pCO_2 and standard bicarbonate remained low. The fact that the arterial pCO_2 levels remained persistently low in all the patients was not surprising. The plasma salicylate levels remained high and so there would be a continued stimulatory effect on the respiratory centre. This is an effect, which has been noted by a number of authors including Tenney and Miller, (1955); Winters, Lowder and Ordway (1958); Oliver and Dyer, (1960) and Whitten, Kesaree and Goodwin, (1961).

The urinary recoveries of salicylate were rather low with the one exception mentioned in the results. This patient also was the one patient, who showed significant losses of potassium in the urine. It was noted that the pH of this patient's urine was higher than that of the other patients in the group. As the urinary flow achieved was limited this was not a major factor. It is more likely that the increases in excretion of salicylate and potassium were related to the differences in pH present. The more alkaline the urinary p^H the more salicylate and potassium will be lost by this route (Robin et al., 1959; Cumming et al., 1964). The urinary pH found in the whole group was in the

acid range throughout the six hour period of observation. This was reflected in the falling excretion rates of salicylate.

Hypokalaemia, although present in several patients was only mild in degree and so not considered to be of very great significance from the therapeutic point of view. The changes in hypokalaemia may be explained primarily as a result of the salicylate intoxication itself (Robin et al., 1959) rather than any effects of the therapy, which was given. All patients made a satisfactory recovery without the need for potassium supplements and no significant changes in the other three cations investigated, magnesium, calcium and sodium were demonstrated.

In conclusion, therefore, the changes in plasma salicylate and particularly the calculated mean half excretion time of salicylate in patients treated with oral fluids alone were little different from those found in patients who are given no specific therapy. This therapy was ineffective in patients with moderate or severe intoxication and in all but the mildest types of poisoning, it fails to relieve the symptoms of salicylism which may persist for many hours after starting therapy.

FORCED SALINE - LAEVULOSE DIURESIS

In previous reports, Doolan et al. (1951) concluded that, what they called forced water diuresis, was ineffective in increasing the removal of salicylate from patients with acute overdoses of this drug. The rate of infusion given was, however. considerably less than that used in the forced alkaline diuresis regime suggested by Cumming et al. (1964). The latter regime involves a very considerable administration of sodium ion and also of bicarbonate both of which have been incriminated in causing other severe biochemical and acid-base upsets. It was, therefore, decided to investigate a group of patients with moderate and severe acute salicylate poisoning to determine the effectiveness of forced saline-laevulose diuresis using the same rate of infusion as that used in forced alkaline diuresis in reducing the plasma salicylate. Studies were also made of the biochemical and acid-base changes which occurred during the course of this treatment.

Patients and Methods

Eleven patients, 8 males and 3 females, were treated by this method. The regime of infusion used was,

0.9 per cent sodium chloride - 500 ml.
5.0 per cent laevulose - 500 ml.
5.0 per cent laevulose - 500 ml.

These solutions were given in rotation at a rate of 2.0 litres per hour for 3 hours and 1.0 litre per hour thereafter. In 4 patients (all of whom were male) (Table XXVI), no potassium

TABLE XXVI

PATIENTS		Age (Years)	Number of Tablets Ingested	Time Since Ingested (Hours)	Peak Plasma Salicylate Level (mg. per 100 ml.)	Arterial Blood Gases Relative to Peak Salicylate		
						pH	pCO_2 (mm.Hg.)	Standard Bicarbonate (m.Eq./litre)
M	50	18	150	$6\frac{1}{2}$	60	7.44	21.5	19.5
A	51	40	250	3	60	7.53	23.0	24.0
L	52	19	100	5	65	7.48	25.0	22.0
E	53	20	40	6	46	7.40	31.5	21.0
S								

Characteristics of 4 patients treated with forced saline-laevulose diuresis without potassium supplements.

supplements were added to the regime, but in the remaining 7 patients, 4 males and 3 females (Table XXVII) a standard administration of 2.0 g. KCl (26 m.Eq.K^+) was given intravenously in every 500 ml. bottle after the fifth bottle in the regime.

The patients were all moderately or severely poisoned, the plasma salicylate varying from 46-83 mg. per 100 ml. (mean 64 mg. per 100 ml.). All had been admitted to hospital relatively soon after having taken the tablets (range 2-9 hours; mean 4.8 hours). As in the group of patients treated with oral fluids alone, the main period of investigation using forced saline-laevulose diuresis was the first six hours following the start of treatment.

In each patient the plasma salicylate was measured immediately before starting treatment and at hourly intervals for four hours thereafter and then two hourly up to eight hours. In two patients further measurements were made up to 24 hours. Measurements of the arterial pH, pCO_2 and standard bicarbonate were made on blood taken from the brachial artery by routine arterial puncture, immediately before starting treatment and twice at three hourly intervals after the infusion began. The usual precautions of collection and preservation of the samples of arterial blood were made. The blood gas estimations were all carried out within 30 minutes of the time of arterial puncture. Measurements of the plasma potassium, calcium and magnesium and the packed cell volume (P.C.V.) were made on venous blood taken at the time of the arterial punctures. Levels of plasma sodium were measured in all the patients given potassium supplements,

TABLE XXVII.

PATIENTS		Age (Years)	Number of Tablets Ingested	Time Since Ingested (hours)	Peak Plasma Salicylate Level (mg. per 100 ml.)	pH	Arterial Blood Gases Relative to Peak Salicylate	
							pCO_2 (mm.Hg.)	Standard Bicarbonate (m.Eq./litre)
MALES	54	38	150	5½	78	7.41	19.0	19.5
	55	32	90	5	65	7.46	21.0	19.5
	56	39	250	3	60	7.52	24.0	23.0
	57	20	150	2	60	7.42	22.0	19.0
FEMALES	58	58	100	9	83	7.44	16.5	17.5
	59	67	80	5½	66	7.44	15.0	19.0
	60	23	80	3	61	7.47	24.0	22.5

Characteristics of 7 patients treated with forced saline-laevulose diuresis with standard potassium supplements.

before treatment and at two hourly intervals for six hours.

The patients emptied their bladders at the start of treatment and the volumes of this urine and hourly collections of urine for six hours after starting treatment, were carefully measured. Aliquots of the pretreatment collection of urine and also of those made at the third, fifth and sixth hours were carefully taken into a well fitting syringe, when the urine was fresh, and capped as with the arterial specimens for blood gases. The urine pH was estimated on each of these specimens. The urinary salicylate and potassium levels were measured on each of the hourly collections of urine and the total six hour urinary magnesium, calcium and sodium excretions were measured in 8 patients. The plasma osmolality was monitored in 4 patients using semi-micro osmometer tubes (Advanced Instruments).

Results

A. Forced Saline-Laevulose Diuresis Without Potassium Supplements

Clinical Progress

The acid-base status of the 4 patients is shown in Table XXVI. Two patients had a normal arterial pH and the other two, 51 and 52, were alkalotic. The corresponding levels of pCO_2 and standard bicarbonate suggested that this was a partially compensated respiratory alkalosis. The levels of pCO_2 and standard bicarbonate were moderately reduced in all patients.

All of the four patients made a full recovery from the poisoning. None of them showed any features of tetany or of hypokalaemia in the form of electrocardiographic changes or muscle weakness. As with the patients treated with oral fluids,

the clinical signs and symptoms of salicylism, particularly tinnitus, deafness, hyperpnoea and sweating, were not relieved rapidly by this method of treatment. These features when present tended to persist for up to 12 hours after starting infusion.

Changes in Plasma Salicylate in Relation to Urinary Salicylate, Urinary pH and Urinary volumes

Results are shown in Table XXVIII and Figure 25. In all patients there was a steady fall in plasma salicylate during the period of observation. From these figures the calculated mean half excretion time for salicylate in these 4 patients was between $9\frac{1}{2}$ and 10 hours.

The pattern of urinary excretion of salicylate showed a steady fall from the second hour of the diuresis until the end of the period of study. This occurred despite the fact that a good diuresis was achieved. Two hours after starting the infusion a urine flow of 500 ml. per hour or more was achieved and this was maintained for the remainder of the diuresis. The urine pH remained acid throughout and there was a tendency for the acidity to increase as the diuresis proceeded. The total six-hour recovery of salicylate in the urine for the four patients is shown in Table XXIX. There was a considerable increase compared with the pretreatment values but the actual recoveries were of only modest amounts ranging from 2.6-4.5 g. salicylate.

Relationship Between Changes in Plasma Salicylate and Acid-Base Status

Results are shown in Fig. 26.

TABLE XXVIII

	PATIENTS	PLASMA SALICYLATE (mg. per 100 ml.)				
		Time (Hours)				
		Pretreatment 0	2	4	6	8
MALES	50	60	54	49	49	49
	51	60	53	43	43	33
	52	65	60	52	50	47
	53	65	51	50	47	36

Changes in plasma salicylate in 4 patients treated with forced saline-laevulose diuresis without potassium supplements.

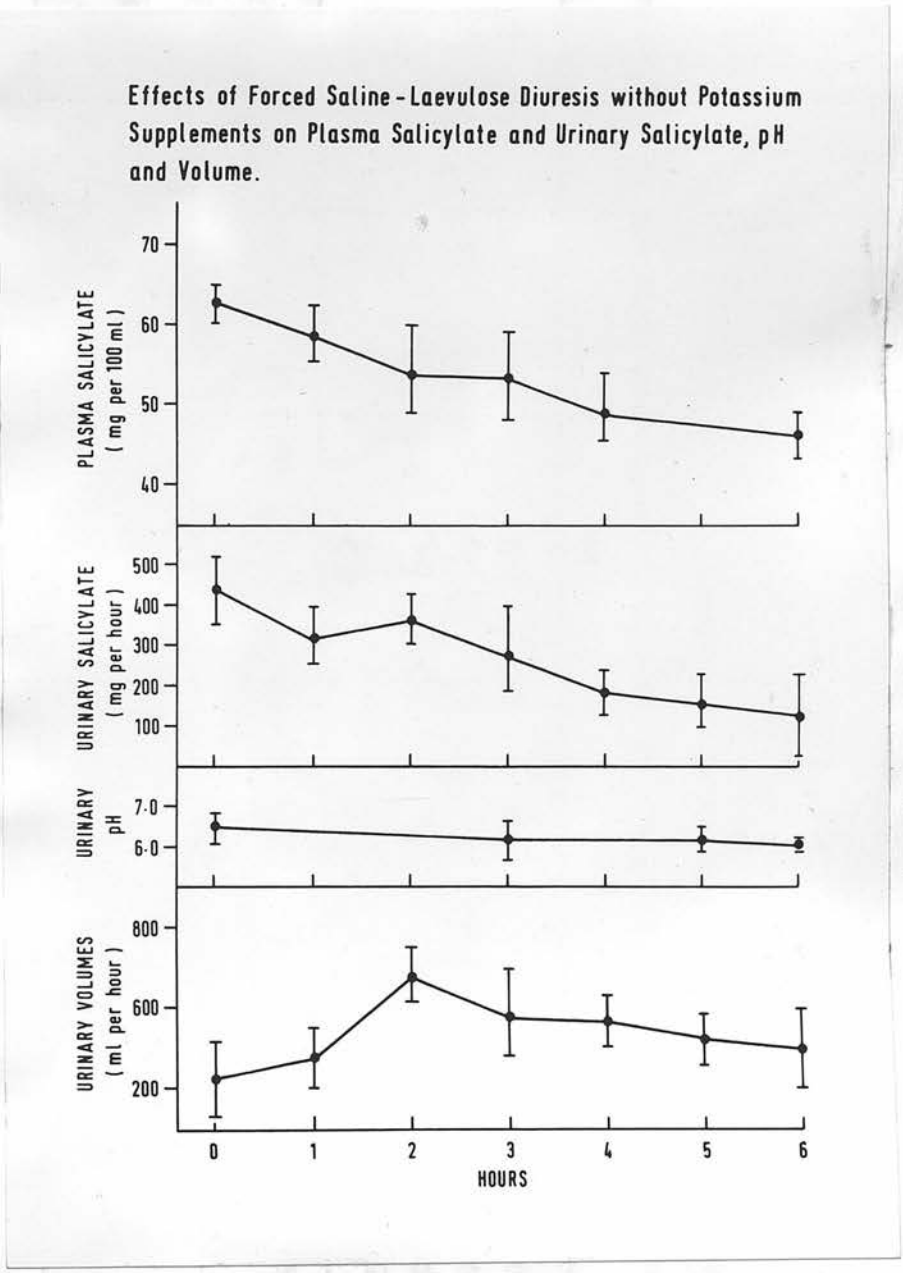

Figure 25.

Changes in the mean values (± S.E.M.) of plasma and urinary salicylate, urinary pH and urine volumes in four patients treated with forced saline-laevulose diureses without potassium supplements.

TABLE XXIX

PATIENTS		URINARY EXCRETION												FLUID DEFICIT (LITRES)
		PRETREATMENT						DIURESIS						
		Volume (Litres)	K (m.Eq.)	Ca (mg.)	Mg. (mg.)	Salicylate (g.)	pH	Volume (Litres)	K (m.Eq.)	Ca (mg.)	Mg. (mg.)	Salicylate (g.)	Peak pH	
MALES	50	0.2	6.5	-	-	0.7	6.4	10.9	75.0	-	-	4.5	6.8	3.5
	51	0.3	31.0	13.0	5.0	0.3	-	3.3	30.0	170	56	4.1	6.6	1.5
	52	0.4	20.0	-	-	0.4	6.3	5.6	44.0	54	33	2.6	6.3	6.7
	53	0.13	9.0	-	-	0.5	6.4	4.0	48.0	-	-	3.5	6.7	2.0

Fluid balance and urinary excretion patterns of potassium, calcium, magnesium and salicylate before and after forced diuresis with saline-laevulose without potassium supplements.

Acid-Base Status of Patients in Relation to Plasma Salicylate during Forced Saline-Laevulose Diuresis without Potassium Supplements.

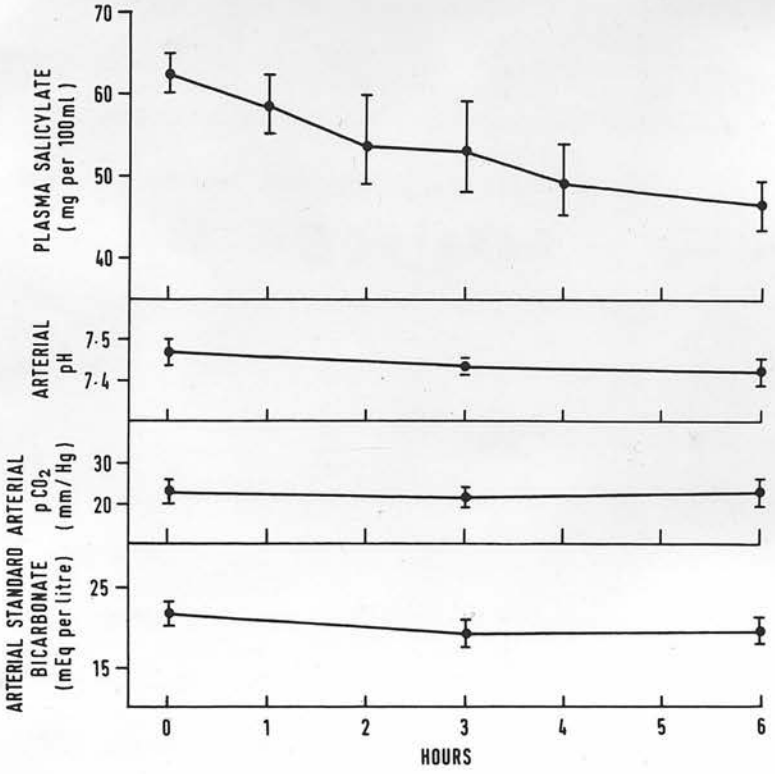

Figure 26.

Changes in the mean values (± S.E.M.) of plasma salicylate in relation to the mean values (± S.E.M.) of arterial pH, pCO_2 and standard bicarbonate in four patients treated with forced saline-laevulose diuresis without potassium supplements.

Despite a fall in mean plasma salicylate from 62.5 to 47 mg. per 100 ml. in 6 hours no significant changes were noted in the mean levels of arterial pH, pCO_2 or standard bicarbonate. The mean level of arterial pH remained within normal limits whereas the arterial pCO_2 and standard bicarbonate were consistently low.

Changes in Plasma and Urinary Potassium in Relation to Alteration in Arterial and Urinary pH

The changes in plasma potassium are shown in Table XXX and the mean values for the four parameters are plotted in Fig. 27. The general trend of mean values showed that there was a reduction in plasma potassium over the six hour period. The reduction, however, was relatively small and only one patient, 53, who was mildly hypokalaemic before treatment, developed any significant hypokalaemia. He did not, however, have any clinical features of potassium deficit.

The curve for urinary potassium showed an initial elevation, which was probably related to the fact that the pretreatment collection of urine was not an accurately measured hour collection and reflected the urinary excretion of potassium for a longer period of time than the other collections shown. From one hour to the end of the diuresis period the average hourly excretion of potassium remained remarkably constant. The total excretion of potassium for the individual patients is shown in Table XXIX. Only modest losses of potassium occurred during the six hour period ranging from 30.0 to 75.0 m.Eq.K^+ (mean 49.25 m.Eq.).

TABLE XXX

PATIENTS		PLASMA POTASSIUM (m.Eq. per litre)		
		Time (Hours)		
		Pretreatment 0	3	6
MALES	50	3.8	3.6	3.5
	51	4.2	3.8	3.6
	52	4.2	3.8	3.6
	53	3.2	3.0	2.9

Changes in plasma potassium in 4 patients treated with forced saline-laevulose diuresis without potassium supplements.

Effects of Forced Saline-Laevulose Diuresis without Potassium Supplements on Plasma Potassium, Urinary Potassium, Arterial pH and Urinary pH.

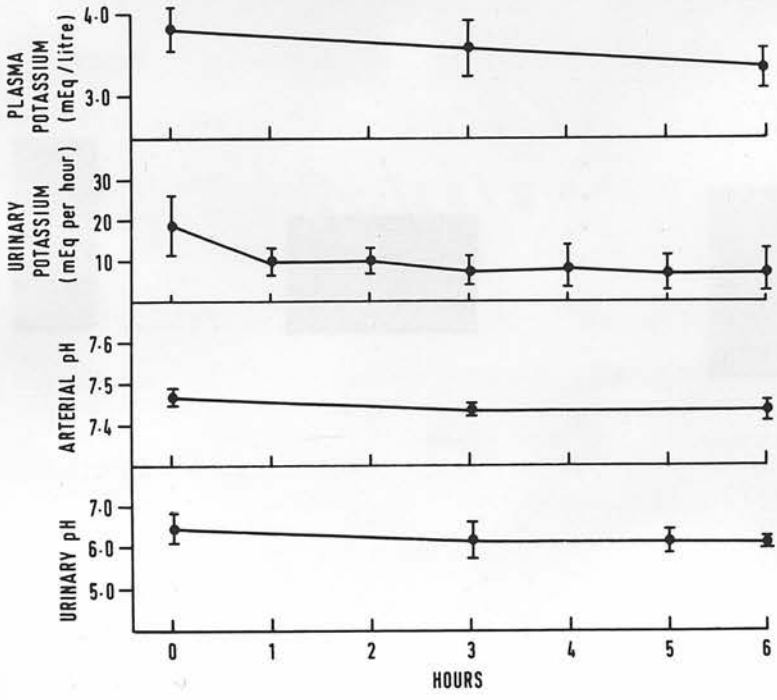

Figure 27.

Changes in the mean values (± S.E.M.) of plasma and urinary potassium and the arterial and urinary pH in four patients treated with forced saline-laevulose diuresis without potassium supplements.

There was no significant change noted either in the arterial or urinary pH and so changes in acid-base probably had little influence on changes in plasma potassium in these patients.

Changes in Plasma Potassium, Magnesium and Calcium in Relation to Changes in Arterial pH and P.C.V.

Mean results are plotted in Fig. 28.

The changes in plasma magnesium and calcium in three of the patients are shown in Tables XXXI and XXXII. Two of the three patients, 51 and 52, were found to have significant hypomagnesaemia and hypocalcaemia towards the end of the six hour diuresis period. The urinary loss of both magnesium and calcium over the 6 hour period in these two patients are shown in Table XXIX. In neither patient was the magnesium loss excessive and also the calcium loss in patient 52 was not remarkable. In patient 51, however, the calcium loss in the urine was considerable and associated with the greater urinary loss, also showed the most dramatic fall in plasma calcium.

Simultaneous with the reductions in plasma potassium, magnesium and calcium there was also a 16 per cent reduction in P.C.V. over the 6 hours. The average fall in plasma potassium was 13 per cent and in plasma magnesium was 27 per cent. The mean fall in plasma calcium was 18 per cent.

Fluid Balance

The fluid balance was calculated in all patients from the time of starting treatment until the end of infusion therapy. This was determined both by a reduction in plasma salicylate to below 35 mg. per 100 ml. and provided that the patient was able to tolerate an adequate oral intake of fluids. This time varied considerably

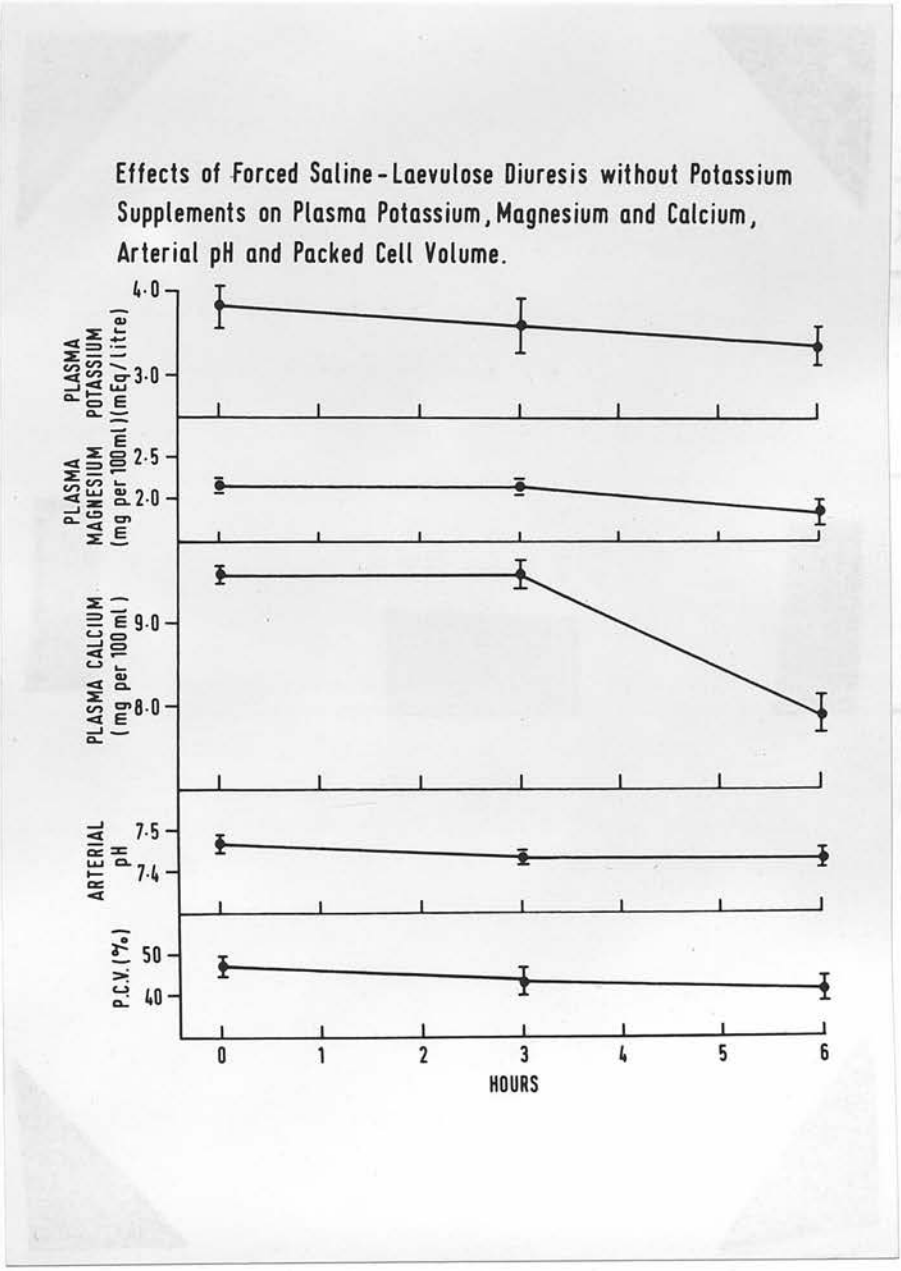

Figure 28.

Changes in the mean values (± S.E.M.) of plasma potassium, magnesium and calcium, arterial pH and P.C.V. in patients treated with forced saline-laevulose diuresis without potassium supplements.

TABLE XXXI

	PATIENTS	PLASMA MAGNESIUM (mg. per 100 ml.)		
		Time (Hours)		
		Pretreatment		
		0	3	6
M				
A	50	2.10	2.20	2.05
L	51	2.25	2.45	1.70
E	52	2.40	2.10	1.75
S				

Changes in plasma magnesium in 3 patients treated with forced saline-laevulose diuresis without potassium supplements.

TABLE XXXII

PATIENTS	PLASMA CALCIUM (mg. per 100 ml.)		
	Time (Hours)		
	Pretreatment		
	0	3	6
MALES 50	9.7	9.8	8.5
51	9.9	9.4	7.3
52	9.2	9.8	8.0

Changes in plasma calcium in 3 patients treated with forced saline-laevulose diuresis without potassium supplements.

from patient to patient as might be expected. In these four patients the duration of infusion therapy ranged from 8-14 hours. It is of interest to note (Table XXIX) that all the patients were found to have a fluid deficit ranging from 1.5-6.7 litres. This was in spite of copious fluids intravenously and the fact that all the patients had a brisk urine flow during the period of diuresis. None of the patients showed any clinical features of dehydration.

B. Forced Diuresis with Saline-Laevulose with Potassium Supplements

Clinical Progress

All of the patients treated with this regime made a full recovery from the poisoning. None of them showed any clinical evidence of tetany or hypokalaemia. However, as in the previous group of patients, clinical features of salicylism tended to persist for 12 or more hours after the infusion regime was started. The main features which persisted were nausea, sweating, hyperpnoea and tachycardia.

Acid-Base Status of the Patients

Results are shown in Table XXVII. Four patients had arterial pH levels within the normal range. The remaining three patients (55, 56 and 60) were alkalotic. The levels of arterial pCO_2 and standard bicarbonate were low in all patients.

Changes in Plasma Salicylate in Relation to Urinary Salicylate, Urinary pH and Urinary volumes

Results are shown in Table XXXIII and Fig. 29. In all

TABLE XXXIII

PATIENTS		PLASMA SALICYLATE (mg. per 100 ml.)							
		Time (Hours)							
		Pretreatment							
		0	2	4	6	8	12	16	24
MALES	54	78	67	62	60	55		42	36
	55	65	60	52	50	48			
	56	60	53	43	43	33			
	57	60	54	49	51	51	49		
FEMALES	58	83	60	52	49	49	46		
	59	66	50	49	50	47	45	43	41
	60	61	59	53	42	38	33		

Changes in plasma salicylate in 7 patients treated with forced saline-laevulose diuresis with potassium.

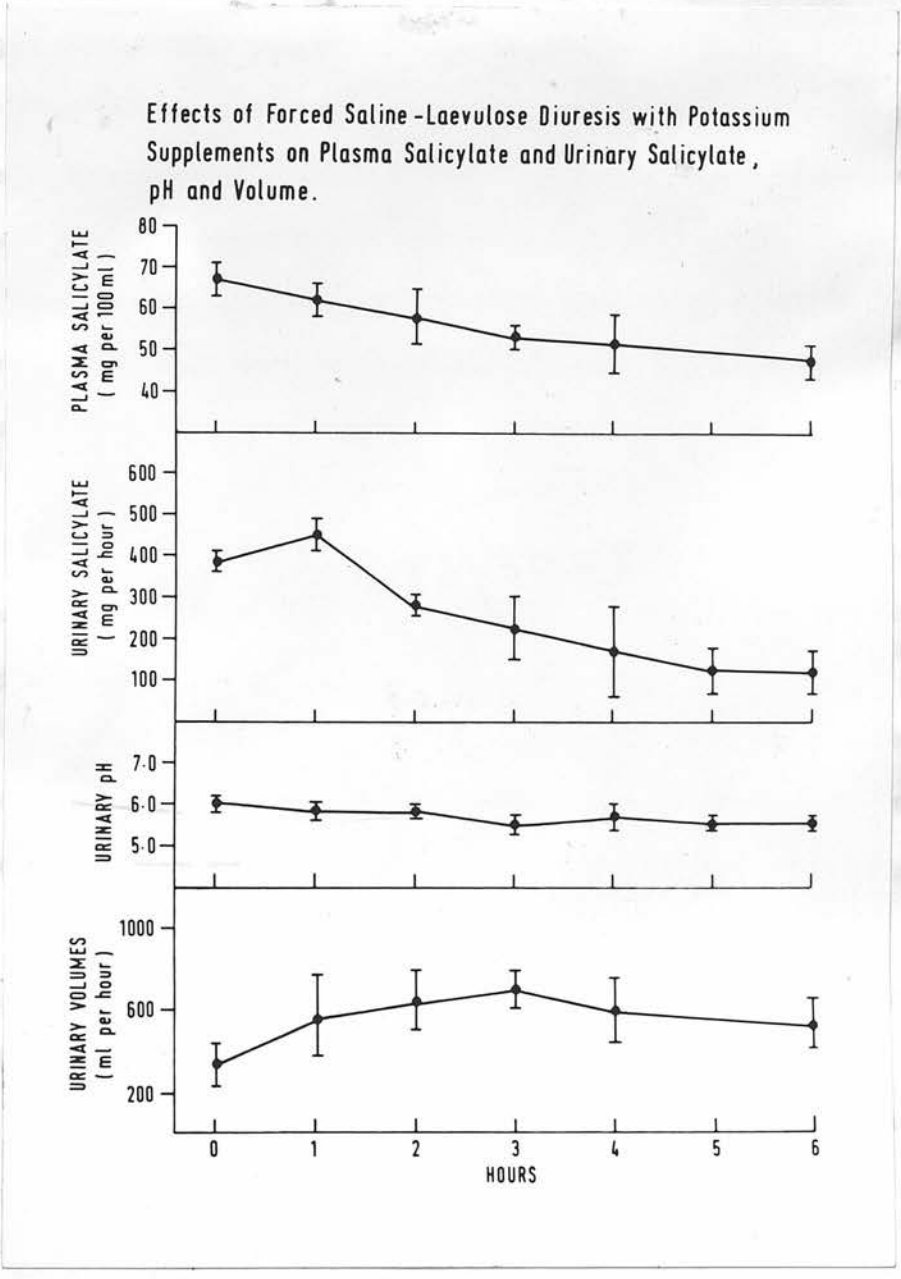

Figure 29.

Changes in the mean values (± S.E.M.) of plasma salicylate, urinary salicylate, urinary pH and urine volumes in 7 patients treated with forced saline-laevulose diuresis with potassium supplements.

patients there was a steady reduction in plasma salicylate. The calculated mean half excretion time for plasma salicylate, in this group of patients, was 11.8 hours. In some patients, 54, 57 and 59, in whom plasma salicylate levels were measured for longer periods the half excretion time was longer than that calculated.

Despite again a satisfactory urine flow which averaged 600 ml. per hour throughout the period of observation, the pattern of urinary excretion of salicylate, after an initial rise in the first hour, steadily fell as the diuresis proceeded. The total amounts of salicylate recovered in each patient over the six hour period are shown in Table XXXIV. The recoveries ranged from 1.2 to 4.8 g. salicylate (mean 3.0 g.).

The urine pH remained acid throughout and over the six hour period there was a tendency for the mean urine pH to become even more acid.

Relationship Between Changes in Plasma Salicylate and Acid-Base Status

The changes in arterial pH, pCO_2 and standard bicarbonate are shown in Table XXXV. The mean changes in these relative to mean changes in plasma salicylate are plotted in Fig. 30. In all the patients there was a fall in arterial pH. The three female patients, all became mildly acidotic. There was a tendency for the pCO_2 to rise in the second 3 hours of the observation period, but only one patient, 56, had a pCO_2 within the normal range. There was little change in the levels of standard bicarbonate in the four males, but the three female patients all had increased levels at the end of the main period of diuresis. The mean levels of standard

TABLE XXXIV

PATIENTS		URINARY EXCRETION												FLUID
		PRETREATMENT						DIURESIS						
		Volume (Litres)	K (m.Eq.)	Ca (mg.)	Mg. (mg.)	Salicylate (g.)	pH	Volume (Litres)	K (m.Eq.)	Ca (mg.)	Mg. (mg.)	Salicylate (g.)	Peak pH	DEFICIT (LITRES)
MALES	54	0.3	14.0	-	-	0.23	6.6	3.7	66	100	44	2.7	6.5	8.7
	55	0.2	31.0	5.4	8.4	0.4	5.6	6.3	34	10	21	1.2	5.2	5.5
	56	0.3	31.0	13.0	5.0	0.3	5.9	3.3	30	170	54	4.0	6.5	1.8
	57	0.2	6.8	-	-	0.5	6.4	3.5	45	-	-	4.3	6.7	3.5
FEMALES	58	0.2	6.5	-	-	0.5	6.4	7.7	72	105	40	4.8	6.3	5.8
	59	0.2	14.0	17.0	7.8	0.2	5.9	5.3	65	74	45	2.8	5.9	2.6
	60	0.4	4.0	21.0	4.2	0.2	6.3	6.9	119	110	33	1.3	6.0	2.3

Fluid balance, and urinary excretion patterns of potassium, calcium, magnesium and salicylate before and after forced saline-laevulose diuresis with potassium supplements.

TABLE XXXV

PATIENTS		ARTERIAL BLOOD GASES					
		pH		pCO_2 (mm./Hg.)		Standard Bicarbonate (m.Eq./litre)	
		Peak Level	Lowest level	Peak Level	Lowest level	Peak Level	Lowest level
MALES	54	7.43	7.41	20.0	19.0	19.5	18.0
	55	7.50	7.46	22.0	21.0	20.0	19.0
	56	7.52	7.46	29.0	23.0	24.0	22.0
	57	7.48	7.41	22.5	20.0	21.0	19.0
FEMALES	58	7.44	7.37	16.5	13.0	19.5	12.0
	59	7.46	7.37	22.0	15.0	20.0	16.0
	60	7.47	7.39	24.0	21.0	22.5	13.0

Acid-Base changes during the period of observation in 7 patients treated with forced saline-laevulose diuresis with potassium supplements.

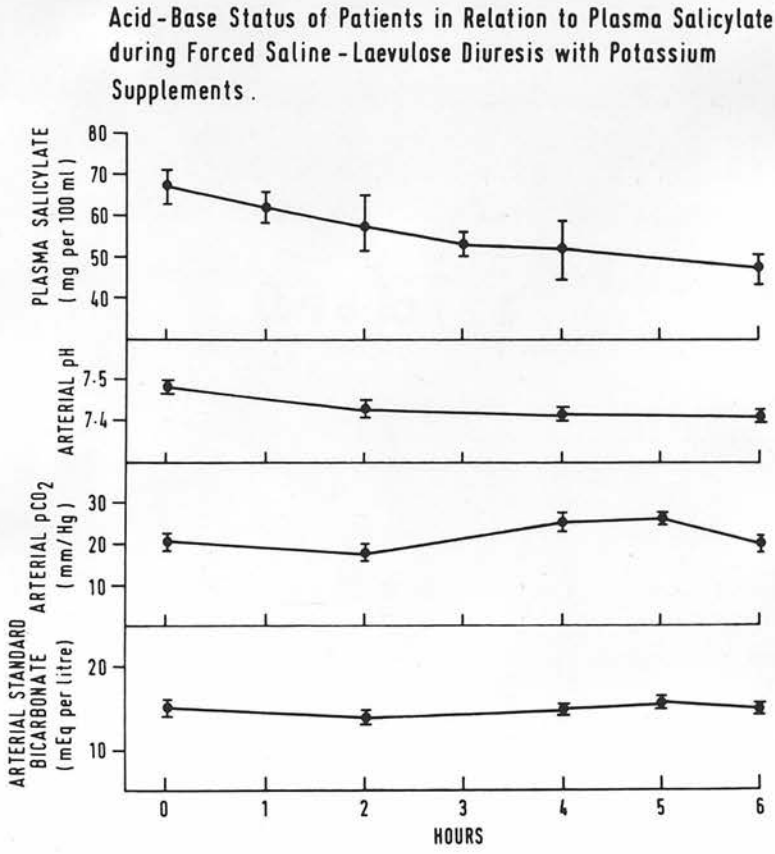

Figure 30.

Changes in the mean values (± S.E.M.) of plasma salicylate in relation to changes in the mean values (± S.E.M.) in arterial pH, pCO_2 and standard bicarbonate in 7 patients treated with forced saline-laevulose diuresis with potassium supplements.

bicarbonate did not change during the six hours after starting treatment.

In general the changes in blood gases and pH were associated with the fall in plasma salicylate.

Changes in Plasma and Urinary Potassium in Relation to the Arterial and Urinary pH

Results are shown in Tables XXXIV and XXXVI and the mean values are plotted in Fig. 31. There was little change in the average levels of plasma potassium in this group of patients. Only at the fifth hour was mild hypokalaemia found. Two patients, 55 and 60, were significantly hypokalaemic before the start of treatment, but with the regime of potassium supplements the plasma levels rose in both patients and within four hours had reached normal levels. Another two patients, 54 and 58, became hypokalaemic at 12 hours, but in both the plasma levels had returned to normal within 24 hours.

The hourly urinary potassium remained steady throughout the first six hours of observation, with the exception of the pretreatment excretion which was higher than subsequent measurements. The pretreatment collection was not a measured hour's collection and probably reflected excretion which had occurred over a longer period of time. The arterial pH fell slightly, but the urinary pH did not change significantly during the six hour period. The total recoveries of potassium in the urine were not large with the exception of patient 60, who excreted 119 m.Eq.K^+. The range of urinary potassium was 30 to 119 m.Eq.K^+ (mean 62 m.Eq.).

TABLE XXXVI

PATIENTS		PLASMA POTASSIUM (m.Eq./litre)						
		Time (Hours)						
		Pretreatment 0	2	4	6	8	12	24
MALES	54	4.2	4.4	4.0	5.0		3.1	3.8
	55	3.0	3.2	3.5	3.4	3.6		
	56	4.2	3.8	3.7	3.6	4.8		
	57	3.8	3.5	3.6	3.6	3.8	3.7	
FEMALES	58	3.8	4.3	4.2	3.4	3.3	2.8	3.4
	59	4.4	4.6	4.0	4.6	4.5		4.4
	60	3.0	3.2	3.5	3.4	3.6		

Changes in plasma potassium in 7 patients treated with forced saline-laevulose diuresis with potassium supplements.

Effects of Forced Saline-Laevulose Diuresis on Plasma Potassium, Urinary Potassium, Arterial pH and Urinary pH.

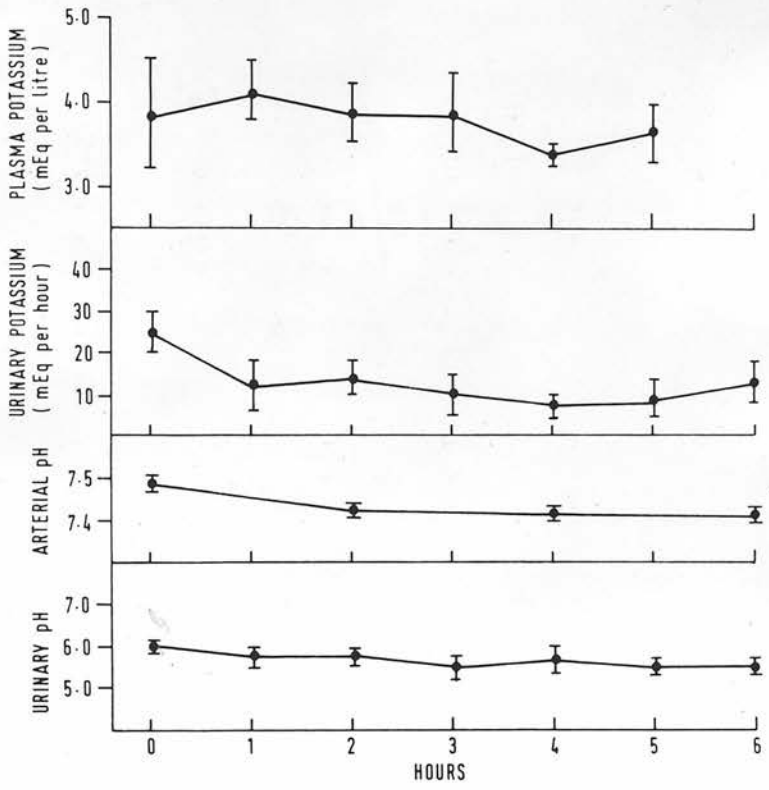

Figure 31.

Changes in the mean values (± S.E.M.) in plasma and urinary potassium, arterial pH and urinary pH in 7 patients treated with forced saline-laevulose diuresis with potassium supplements.

Changes in Plasma Potassium, Magnesium and Calcium in Relation to Changes in Arterial pH and P.C.V.

The relative changes in mean values are shown in Fig. 32. The changes in plasma magnesium and calcium and packed cell volume are recorded in Tables XXXVII and XXXVIII and XXXIX. Of the six patients in whom plasma magnesium was monitored, three patients, 56, 58 and 59 developed hypomagnesaemia. The nadir of the curve occurred between four and six hours of the diuresis regime. In all cases the plasma magnesium was found to return spontaneously to normal levels.

All of the six patients with the exception of patient 57 developed hypocalcaemia. This change occurred within two hours after starting treatment in patients 58 and 59 and was of a severe nature in patients 54, 58, 59 and 60. As with magnesium the lowest levels were found about the fourth hour of treatment and spontaneous recovery of the plasma levels to normal occurred in the patients in whom the plasma calcium was subsequently monitored. None of the patients were given supplements of either calcium or magnesium and no patient demonstrated any clinical abnormality such as tetany which could have been related to these mineral changes.

The urinary losses of potassium in the six hour period (Table XXXIV) have been described and were not excessive. Similarly the urinary losses of magnesium in the same time were not great and ranged from 21 to 54 mg. (mean 39.5 mg.). Four patients, 54, 56, 58 and 60 were found to have considerable losses of calcium (Table XXXIV) and all of them developed hypocalcaemia.

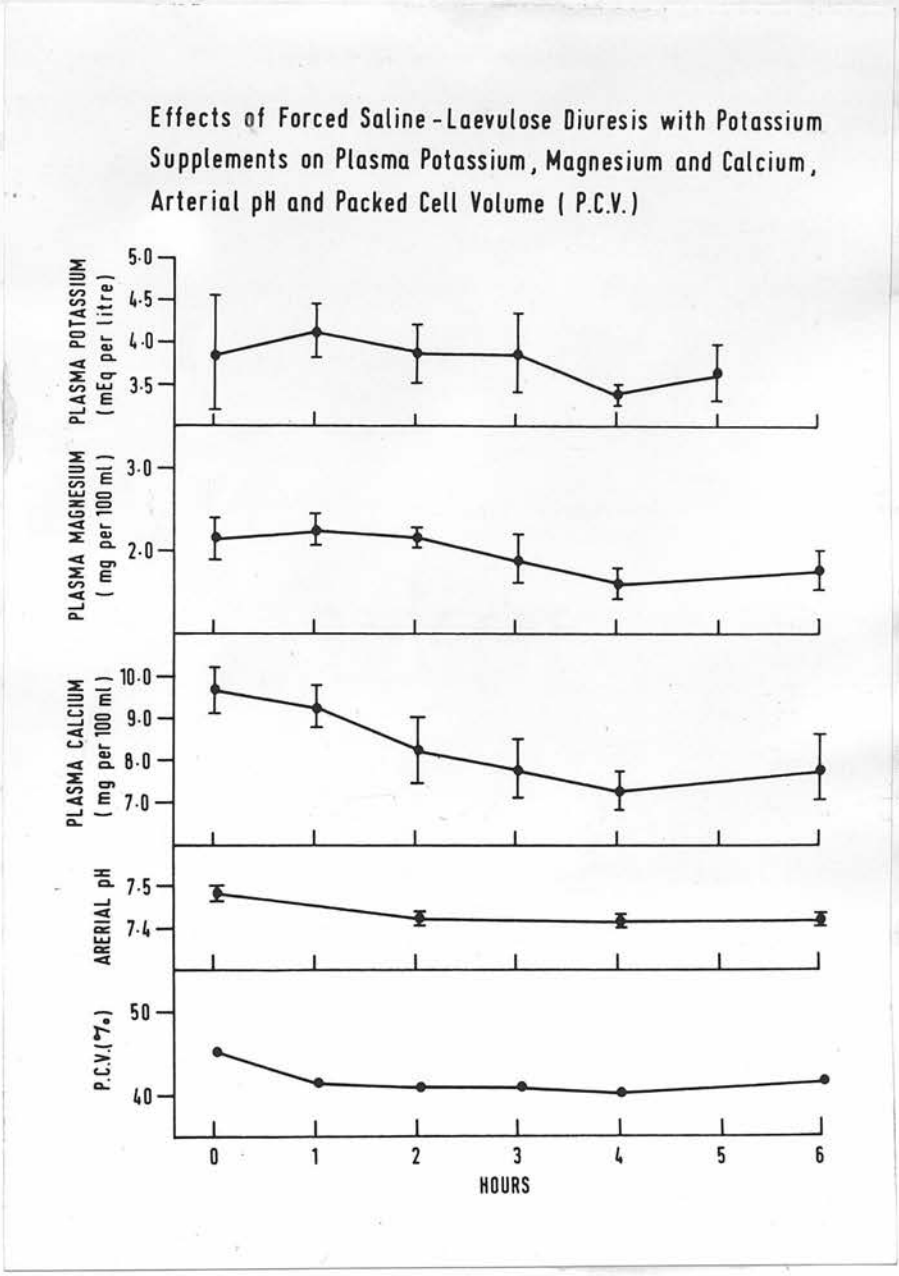

Figure 32.

Changes in the mean values (± S.E.M.) in plasma potassium, magnesium and calcium, arterial pH and P.C.V. in patients treated with forced saline-laevulose diuresis with potassium supplements.

TABLE XXXVII

PLASMA MAGNESIUM (mg. per 100 ml.)

PATIENTS		Time (Hours)							
		Pretreatment							
		0	2	4	6	8	12	16	24
MALES	54	2.75	2.35	2.1	2.05	2.3	2.55	2.2	
	56	2.25		2.45	1.7	1.85			
	57	1.9	1.9	2.1	2.2	2.0			
FEMALES	58	2.3	2.15	1.25	1.4	1.5	1.45	1.55	2.3
	59	2.5	2.0	1.65	1.6	1.7	1.75	2.05	2.25
	60	2.5	2.25	1.85	2.05	2.5			

Changes in plasma magnesium in 6 patients treated with forced saline-laevulose diuresis with potassium supplements.

TABLE XXXVIII

PATIENTS		PLASMA CALCIUM (mg. per 100 ml.)							
		Time (Hours)							
		Pretreatment							
		0	2	4	6	8	12	16	24
MALES	54	10.2	8.7	7.4	7.5	8.1	8.6	8.9	
	56	9.2	9.8		8.0	8.0			
	57	9.1	9.2	9.7	9.8	8.6			
FEMALES	58	9.9	7.3	6.2	6.6	7.0	6.9	7.2	8.0
	59	9.3	7.2	7.3	7.6	7.7	8.1	8.1	8.6
	60	10.3	8.8	7.3	5.8		9.1		

Changes in plasma calcium in 6 patients treated with forced saline-laevulose diuresis with potassium supplements.

TABLE XXXIX

PATIENTS	PACKED CELL VOLUME (P.C.V.) - per cent								
	Time (Hours)								
	Pretreatment								
	0	2	4	6	8	12	16	24	
MALES	54	48	48	45	43	45			
	55	45	44	43	40	38			
	56	49	51	50	45	46			
	57	47	47	46	46	45	45		
FEMALES									
	58	49	42	41	42	38	38	40	39
	59	39	39	33	31			32	32
	60	41	40	38	38				

Changes in P.C.V. in 7 patients treated with forced saline-laevulose diuresis with potassium supplements.

The nadirs of the curves for plasma potassium, magnesium and calcium all occurred at the fourth hour of treatment. The P.C.V. was also found to fall in association with the levels of these three cations, the lowest average levels being also at the same time. The average percentage reduction in P.C.V. was 11 per cent and that for plasma potassium was 13 per cent. The figure for plasma magnesium was 29 per cent and for plasma calcium was 25 per cent.

There was no clear relation between the changes in plasma potassium, magnesium and calcium and the alterations in arterial pH.

Changes in Plasma and Urinary Sodium

Results are shown in Table XL. In all seven patients the plasma level of sodium tended to fall during the first four hours of treatment, but by six hours in most patients the plasma levels were beginning to rise once again. Rather marked hyponatraemia was found in patients 55, 56, 57 and 58. On the average, the major reduction in level occurred at the same time as that for plasma potassium, magnesium, calcium and P.C.V.

The urinary losses of sodium in the six hour period varied considerably from patient to patient, the range being 59 to 350 m.Eq. Na^+. The urinary losses in the patients who developed severe hyponatraemia also varied considerably. Patient 55 lost only 59 m.Eq. Na^+ whereas patient 58 lost 272 m.Eq. On the other hand patient 60 excreted 350 m.Eq. Na^+ in six hours and yet did not develop a marked hyponatraemia. There was little relationship

TABLE XL

PATIENTS		PLASMA SODIUM (m.Eq. per litre)			
		Time (Hours)			
		Pretreatment 0	2	4	6
MALES	54	145	141	140	142
	55	134	125	130	130
	56	143	136	130	126
	57	146	128	125	128
FEMALES	58	135	131	125	122
	59	148	137	130	139
	60	140	136	134	134
Mean Values		141	134	130	132

Changes in plasma sodium in 7 patients treated with forced saline-laevulose diuresis with potassium supplements.

therefore between the urinary losses of sodium and the changes in the blood levels of this cation.

Facilities for measuring plasma osmolality were not available during the most of these studies. However, it was possible to estimate this in four of the patients, 52, 54, 58 and 60, treated with forced saline-laevulose diuresis. The levels found are recorded in Table XLI together with levels of plasma calcium and magnesium measured at the same time. The normal range for the method of measuring plasma osmolality was 285 to 295 m.osmol. per litre. In patients 52 and 58 the plasma calcium and magnesium levels fell at six hours in unison with the plasma osmolality but by 24 hours the osmolality was normal although the plasma calcium remained low. Similar trends occurred in patients 54 but to a lesser degree. In patient 60 the plasma osmolality actually rose considerably at times when the levels of calcium and magnesium had fallen significantly. These results support the findings of the P.C.V. that although haemodilution was a factor in producing the lowered plasma cations it could not explain all the changes which occurred, and in many patients, it was of comparatively little importance.

Fluid Deficit

All the patients in this group were found to have a calculated fluid deficit over the total infusion period. The deficits ranged from 1.8 to 8.7 litres (Table XXXIV). As in the patients treated with forced saline-laevulose diuresis without potassium supplements, the degree of fluid deficit was related to

TABLE XLI

	Time (Hours)											
	0			3			6			24		
	Plasma Osmolality m.osmol/litre	Plasma Ca (mg%)	Plasma Mg (mg%)	Plasma Osmolality m.osmol/litre	Plasma Ca (mg%)	Plasma Mg (mg%)	Plasma Osmolality m.osmol/litre	Plasma Ca (mg%)	Plasma Mg (mg%)	Plasma Osmolality m.osmol/litre	Plasma Ca (mg%)	Plasma Mg (mg%)
52	289	10.3	2.45	284	9.8	2.35	278	8.3	1.90	288	8.3	2.20
54	292	10.2	2.75	282	8.7	2.35	278	8.2	2.2	286	8.6	2.55
58	310	9.9	2.30	305	8.6	2.00	295	6.3	1.45	288	7.2	1.55
60	289	10.3	2.50	288	8.8	2.25	302	7.0	2.15	302	9.1	2.50

Relationship between changes in plasma osmolality and plasma magnesium and calcium found in 4 patients.

the severity of the poisoning as judged by the peak plasma salicylate levels.

Discussion

The effectiveness of forced saline-laevulose diuresis was rather limited in that the plasma salicylate level fell rather slowly, the mean half excretion time for salicylate being intermediate between that quoted for untreated patients (Oliver and Dyer, 1960 and Cumming et al., 1964), and patients treated with forced alkaline diuresis. This was despite the fact that a good urine flow was achieved, which was similar to that found with the full forced alkaline diuresis therapy of Dukes et al. (1963). In both groups of patients treated with forced saline-laevulose diuresis, the urine remained acid throughout the period of study despite the fact that it has been claimed that the best way to alkalinize the urine of patients with acute salicylate poisoning is to give adequate supplements of potassium (Robin et al., 1959). In this study very adequate infusions of potassium were given to seven patients during the period of diuresis but no rise in urinary pH was demonstrated.

A further important consideration is that the relative proportion of free salicylate, which is excreted in the presence of an acid urine, is limited (Ghose, 1967). It is generally agreed that it is the amount of circulating free salicylate which determines the toxicity in any individual case. In keeping with a limited elimination of active drug, the clinical features of salicylism were not quickly relieved in either group of patients treated with a forced saline-laevulose regime.

Persistence of clinical features whilst using this treatment has been noted previously by Whitten et al (1961) but the authors were unable to offer an explanation for this. The reasons are certainly not clear, but it is well-known that the effects of salicylate for example on the respiratory centre may persist for many hours even when the plasma level is falling. The level of C.S.F. salicylate may be more important in these cases than the plasma level. Also, although biotransformation occurs at a relatively slow rate, tissue levels of salicylate may become persistently and significantly elevated with prolonged effects on such processes as enzyme systems and metabolic oxidation. Biotransformation becomes a more significant factor the longer the blood salicylate levels remain elevated.

There were no marked changes in acid-base status in the eleven patients studied. The main abnormalities found were in keeping with mild and moderate respiratory alkalosis which was compensated in some and not so in others. Some patients in the group given potassium supplements became mildly acidotic. This was a little surprising but may have been due to the development in these patients of a degree of metabolic acidosis. Such a change has been described by Eichenholz et al. (1963). These authors stressed that the change may occur with great rapidity and without there being any obvious change in the clinical state of the patients.

Hypokalaemia was not an important complication of this therapy, even when the patients were not given potassium supplements. Serious hypokalaemia was not found except in one male patient, in whom there were no clinical features of hypokal-

aemia and who made a full recovery without any added potassium being administered. An interesting observation in the patients given potassium supplements was that, although they were given 338 m.Eq. of potassium in the course of the six hour period of observation, the urine losses of potassium were similar to those found in the patients, who were not given potassium supplements. Despite this the patients on potassium supplements did not become hyperkalaemic. Haemodilution was not a major factor and so the most likely explanation was that the excess potassium had passed from the extracellular to the intracellular compartment. Whatever the explanation, no untoward effects were noted.

In most textbooks of medical treatment the highest suggested rates of intravenous potassium infusions are 25 m.Eq. per hour and 200 m.Eq. per day. The amounts of potassium given during this therapy were far greater than these recommendations. The results obtained justified the rate of administration used and supported the views of Seftel and Kew (1966), Abramson and Arky (1966) and Pullen, Doig and Lambie, (1967) all of whom have reported that the treatment of patients with potassium depletion may demand intravenous potassium administration at rates considerably in excess of those currently recommended.

The changes in plasma magnesium and calcium are of considerable interest, especially as none of the patients showed any features of tetany. The urinary losses of magnesium were not large and it is unlikely that they could have explained the changes in blood levels found. From the associated changes in P.C.V. and plasma osmolality haemodilution did not appear to be the

main factor. Therefore, the fact that the blood levels of this cation were shown to recover spontaneously and fairly quickly to normal levels, is in favour of shifts having occurred from the extracellular to the intracellular compartment. The distribution of exchangeable magnesium within the body has been estimated by radioactive magnesium studies. The results are rather inconclusive but there seems to be three pools of exchangeable magnesium; a fast rate, an intermediate rate and a slow rate turnover pool. The fast is believed to be mainly extracellular magnesium; the intermediate in the vital organs and the slow in the muscle. Bone magnesium on the whole, does not appear to be readily exchangeable. In order that the changes in plasma magnesium should occur at the speed found in this study it would seem likely that the main exchanges occurred between the extracellular magnesium and that of the vital organs.

In the case of calcium, urinary losses during the six hour period were of much greater significance and the greatest urinary losses of calcium occurred in the patients, who developed the most marked degrees of hypocalcaemia. These urinary losses, however, were not sufficient to account for the reductions in plasma calcium.

Comparison of the mean values of plasma potassium, calcium and magnesium revealed an approximate correlation between the changes in these cations. It is therefore surprising that none of the patients developed tetany. Magnesium deficiency causes changes in nerve conduction, transmission at themyoneural junction and muscular contraction. With a lowered concentration of

magnesium or calcium, the stimulation threshold of the motor nerve is lowered. In muscle, because of actions on a number of enzyme systems, which are interrelated, the effects of magnesium are opposite to those of calcium. Low concentrations of magnesium enhance contractions; low concentrations of calcium inhibit contractions. Conditions at the myoneural junction are most complex, for magnesium concentration affects the quantity of acetylcholine liberated, the activity of acetylcholinesterase and the excitability of the pre-synaptic nerve and the muscle membrane. An increase in transmission at the motor end-plate is the overall result of a decrease in concentration of magnesium or of calcium. Tetany should, therefore, have been a marked feature in these patients.

On the basis of the present data it is only possible to speculate on the reasons why this did not occur. The amount of ionised calcium in the blood must have remained above the critical level for the development of tetany. The graphs of the mean levels of plasma potassium, sodium, magnesium and calcium and P.C.V. all showed the lowest levels at four hours after starting treatment. This suggested that haemodilution may have been an important factor in the reductions found in the plasma levels of these cations. Haemodilution could not have explained all the changes, which occurred, particularly in magnesium and calcium levels. Another possible explanation is that salicylate is to a considerable degree bound to the same plasma proteins as magnesium and calcium. It is possible that there is, in the early stages of the poisoning, a competition for the protein

binding sites between the salicylate and these two cations. If this is the case, the ratio of ionised calcium and magnesium to unionised cation may have been relatively increased. Therefore, even if there is considerable loss of mineral during the period of diuresis, the level of ionised magnesium and calcium may not fall below the critical level to provoke tetany. Whatever the actual mechanism was, there was no serious change noted in the clinical states of the patients treated and all made a full recovery from the poisoning. Every patient with significant changes in the levels of plasma cations returned to biochemical normality without any specific mineral replacement other than potassium.

The changes in plasma sodium were more closely related to haemodilution effects than was the case with the other cations measured. No relationship was demonstrated between the amounts of sodium excreted in the urine and corresponding plasma levels in individual patients.

The fluid deficits on the fluid balance charts were of considerable interest. The balances were calculated with an allowance of 500 ml. as insensible fluid loss. In patients with acute salicylate poisoning who have hyperpnoea and marked sweating this is clearly an underestimate. Indeed the fluid deficits recorded are almost certainly due to these factors as the patients all achieved a satisfactory diuresis, which would not have occurred in the presence of hypovolaemia. Cumming et al. (1964) stressed the importance of extrarenal fluid losses in the assessment of patients with acute salicylate poisoning. For this reason also patients in this study who were given any

forced diuresis regime were allowed to go up to two hours after starting the infusion without passing urine, before it was considered necessary to reassess the patient's renal function.

Conclusion

Forced saline-laevulose diuresis will effect only a moderate removal of salicylate from the body even when the plasma salicylate is quite high . In association with this the clinical features of salicylate toxicity tend to persist for an unsatisfactorily long time after starting treatment. Hypokalaemia was not a serious problem with this therapy but significant changes in plasma magnesium and calcium were found. The clinical significance of these changes is obscure but none of the patients showed any features of tetany.

FORCED ALKALINE DIURESIS WITH STANDARD POTASSIUM SUPPLEMENTS

From the results obtained in the patients treated with saline-laevulose diuresis it was apparent that 'water' diuresis in itself failed to achieve a rapid removal rate of salicylate. The main defect in the regime was that the urine remained strongly acid. This could be corrected by the addition of alkali to the regime (Cumming et al., 1964). Whitten et al. (1961) also reported that an alkali infusion quickly relieved their patients' symptoms. For these reasons it was decided to treat a group of patients with forced alkaline diuresis according to the regime of Dukes et al., (1963). In view of the severe hypokalaemia found in patients treated with a similar regime early in these investigations, standardised potassium supplements were also given to every patient.

Patients and Methods

Eleven patients were treated, 4 males and 7 females (Table XLII). The ages of the patients varied from 16-63 years (mean age 33). All of the patients had moderate or severe aspirin poisoning, the peak plasma salicylate levels varying from 49 to 88 mg. per 100 ml. (mean 71 mg. per 100 ml.). The average time since ingestion of the tablets was 6.4 hours. One patient, 65, was alkalotic and 2 patients, 69 and 70, were significantly acidotic. The levels of pCO_2 and standard bicarbonate were reduced in all patients. None of the patients had any known renal impairment and none had any disorder of respiratory or cardio-vascular function.

TABLE XLII

PATIENTS		Age (Years)	Number of tablets ingested	Time Since ingestion (hours)	Peak Plasma Salicylate level (mg. per 100 ml.)	Arterial blood gases at peak plasma salicylate level		
						pH	pCO_2 (mm./Hg.)	Standard Bicarbonate (m.Eq./litre)
M	*61	60	80	3	85	7.45	24.0	19.0
A	62	36	120	4	75	7.43	26.0	20.0
L	*63	43	180	1	71	7.41	23.5	19.5
E	64	17	70	6	69	7.42	35.5	23.5
S								
F	*65	63	150	12	88	7.54	14.0	21.5
E	*66	35	170	5	76	7.44	27.0	22.0
M	*67	20	120	3	76	7.43	15.0	18.0
A	*68	39	80	9	68	7.40	24.0	18.5
L	69	17	50	13	63	7.31	20.0	15.0
E	70	16	60	4	60	7.37	31.0	19.0
S	71	18	100	11	49	7.43	13.2	17.9

* Vomited after ingestion and before admission.

Characteristics of 11 patients treated with forced alkaline diuresis with standard potassium supplements.

The forced diuresis regime given was,

0.9 per cent sodium chloride	500 ml.
5 per cent laevulose	500 ml.
1.26 per cent sodium bicarbonate	500 ml.

These solutions were given in rotation at an infusion rate of 2 litres per hour for the first 3 hours and 1 litre thereafter until the plasma salicylate had fallen to less than 35 mg. per 100 ml. After the fifth bottle of the regime 26 m.Eq.K. were given in the form of 2.0 g. KCl in every 500 ml. bottle of solution. The reason for the delay in giving potassium was to allow for rehydration of the patient and to allow time for a urine flow to be established. In this way the dangers from a rapid administration of intravenous potassium were minimised.

Measurements of plasma salicylate and potassium were made in all the patients immediately before starting treatment and at hourly intervals for the next six hours. In a number of patients further measurements were made up to 24 hours after starting treatment. The plasma magnesium was measured at the same time intervals in 10 patients and the plasma calcium was estimated at similar times in eight patients. Plasma sodium levels were measured before treatment and at two hourly intervals for the next six hours. The P.C.V. was measured at two hourly intervals in six patients. Similar serial measurements of the arterial pH, pCO_2 and standard bicarbonate were made in all patients. As this required frequent samples of arterial blood an intra-arterial cannula was introduced into the brachial artery in all the patients, using the Seldinger technique (Seldinger, 1953).

Clotting within the catheter was avoided by filling the catheter after each sampling with 0.9 per cent saline containing heparin in a concentration of 10 units per ml.

Careful collections of urine were made at hourly intervals throughout the period of observation. The volumes were noted and the hourly excretion of salicylate and potassium was measured. The total excretion of magnesium, calcium and sodium over the six hour period was also measured. The urinary pH was also measured at hourly intervals for six hours after starting treatment.

Results

Clinical Response

Ten of the eleven patients made a complete and uneventful recovery from the poisoning. In particular there were no features of tetany or hypokalaemia in these patients. Patient 70 died after an apparent satisfactory response to the diuresis therapy and the case report will be discussed in some detail. The infusion therapy was given successfully in all patients and there were no signs of overloading of the circulation.

Changes in Plasma Salicylate Relative to the Urinary Salicylate, pH and Urinary Volumes

Results are shown in Table XLIII and Fig. 33. The plasma salicylate levels fell steadily in all patients throughout the period of study. The calculated mean half excretion time for

TABLE XLIII

PATIENTS		PLASMA SALICYLATE (mg. per 100 ml.)						
		Pretreatment						
		0	2	4	6	8	12	16
MALES	61	85	73	51	40	39	32	
	62	75		52	39		16	
	63	71	65	65	52	39	34	25
	64	69	60	60	39	38		
FEMALES	65	88	56	35	26	22	16	13
	66	76	46	39	34	25	17	12
	67	76	55	40	29			
	68	68	53	40	36	32		
	69	63	59	49	38			
	70	60	45	39	34	17	10	
	71	49	44	42	42	40	27	

Changes in plasma salicylate in 11 patients treated with forced alkaline diuresis with standard potassium supplements.

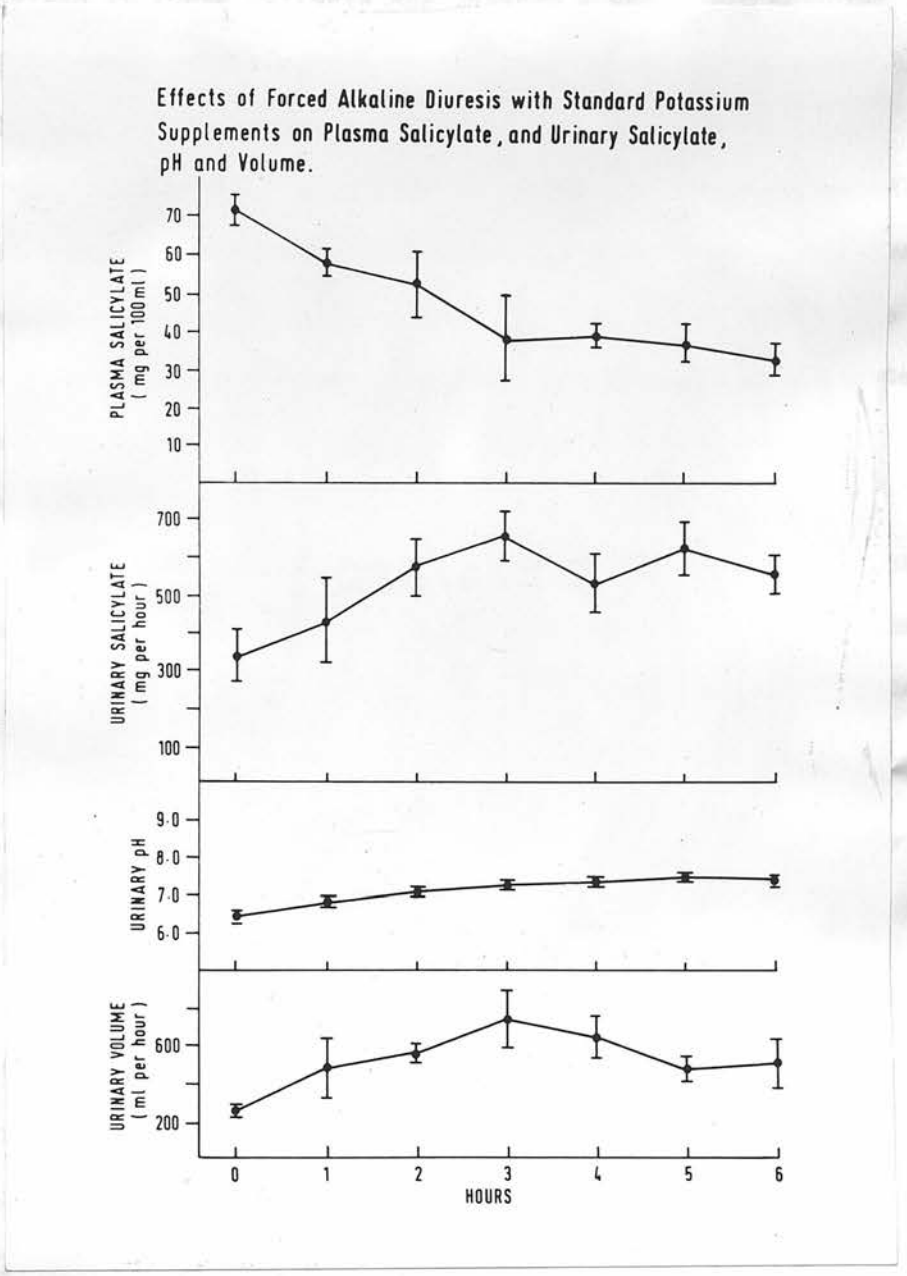

Figure 33.

Changes in the mean values (± S.E.M.) in plasma salicylate urinary salicylate, urinary pH and urine volumes in 11 patients treated with forced alkaline diuresis with standard potassium supplements.

salicylate in these patients was between 4 and 5 hours. The total recovery of salicylate ranged from 3.4 to 9.8 g. (mean 5.5 g.) (Table XLIV).

The mean urinary excretion of salicylate increased rapidly in the first two hours of treatment and then averaged approximately 600 mg. per hour. Associated with the increase in salicylate excretion the urine volumes increased on average to approximately 600 ml./hr. and also the mean urinary pH rose and was maintained above 7.0. In none of the patients did the urinary pH exceed 8.0. In Fig. 34 there is shown to be a significant relationship between the changes in plasma salicylate and urinary salicylate ($r = -0.62$; $p = 0.001$). There was also a significant relationship (Fig. 35) between the urinary excretion of salicylate and urinary pH. ($r = 0.63$; $p = 0.01$).

Changes in Acid-Base Status Relative to the Plasma Salicylate

Results are shown in Table XLV and Fig. 36. During the first six hours of the diuresis therapy the arterial pH tended to rise. In all of the patients except 63, 69 and 71 a very considerable degree of metabolic alkalosis was induced and in two patients, 65 and 70, the arterial pH rose to 7.63. On the average, Fig. 36, there was little change demonstrated in arterial pCO_2 but considerable individual variations occurred. Patients 64 and 70 showed reductions in pCO_2 from 35.5 to 19.0 and 31.0 to 17.0 respectively. On the other hand in patients 65 and 71, rises were noted from 14.0 to 23.0 and 13.2 to 31.8.

As might have been expected with a brisk infusion of sodium

TABLE XLIV

PATIENTS		URINARY EXCRETION												FLUID DEFICIT (LITRES)
		PRETREATMENT						DIURESIS						
		Volume (litres)	K (mEq)	Ca (mg)	Mg (mg)	Salicylate (g.)	pH	Volume (litres)	K (mEq)	Ca (mg)	Mg (mg)	Salicylate (g.)	Peak pH	
MALES	61	0.2	9.0	18.0	7.9	0.3	5.8	5.7	40.0	46.0	17.0	6.2	7.5	3.0
	62	0.1	10.0	-	-	0.2	5.2	3.1	40.9	-	-	3.5	7.4	7.6
	63	0.6	8.0	14.0	11.0	0.2	5.2	5.0	121.0	40.0	17.0	5.8	7.6	1.9
	64	0.17	12.2	-	-	0.5	6.3	6.9	66.0	-	-	4.9	7.8	4.5
FEMALES	65	0.4	23.0	3.0	1.6	0.8	6.4	2.6	19.0	5.2	12.0	4.9	6.7	9.0
	66	0.1	12.0	3.6	0.2	0.5	6.7	4.5	65.0	18.0	0.5	5.1	7.7	4.3
	67	0.4	10.4	-	-	0.3	6.3	8.0	72.0	64.0	1.6	9.8	7.8	3.6
	68	0.2	31.0	-	-	0.4	6.3	6.2	98.0	-	-	4.7	7.0	6.4
	69	0.3	49.0	-	-	0.9	6.0	5.4	56.0	-	-	9.0	7.1	3.5
	70	0.6	9.4	-	-	0.6	5.4	3.0	70.0	48.0	27.0	3.5	7.7	6.0
	71	0.3	43.0	-	-	1.0	5.8	9.1	57.0	-	-	3.4	7.4	5.0

Fluid Balance and urinary excretion patterns of potassium, calcium, magnesium and salicylate before and after forced alkaline diuresis with standard potassium supplements.

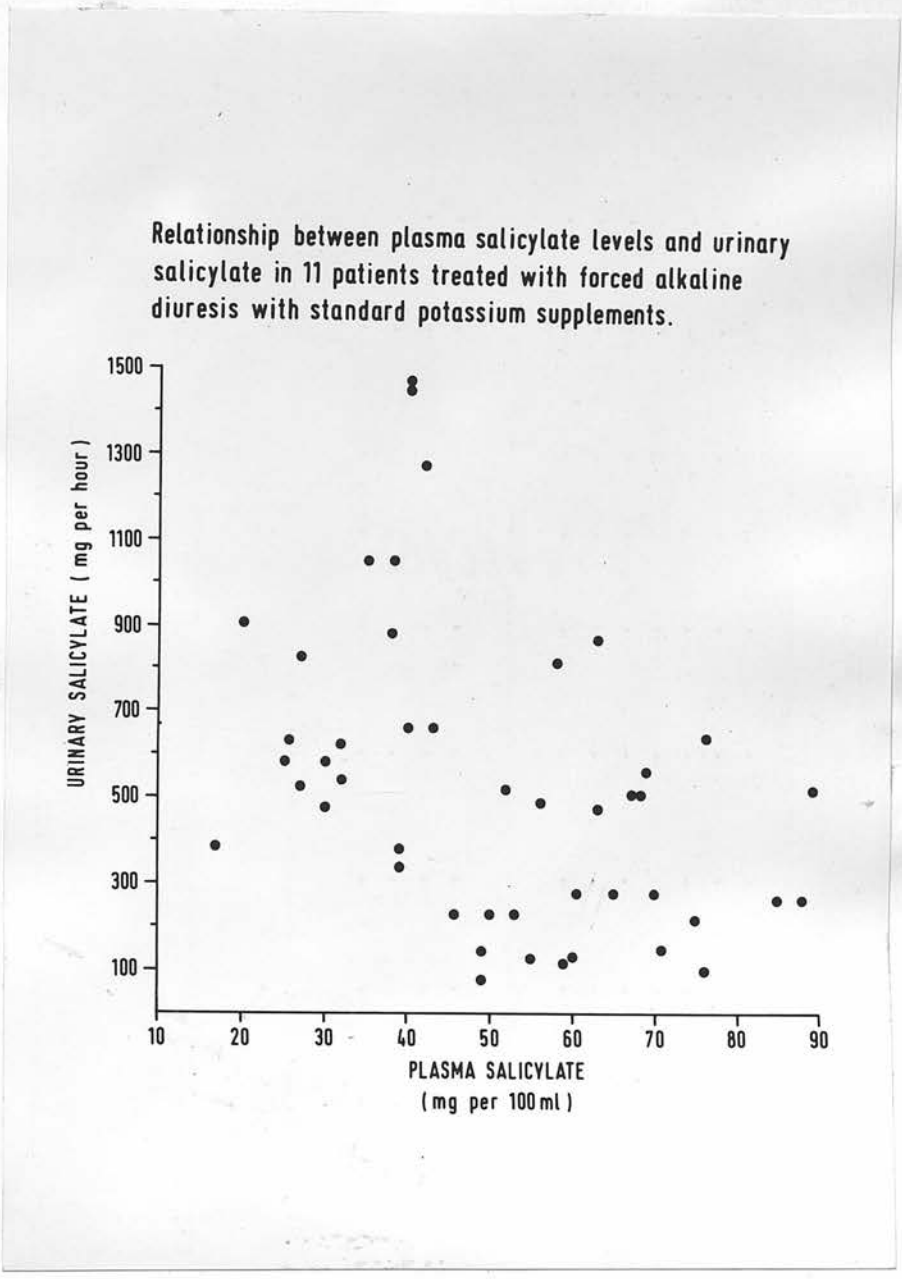

Figure 34.

Relationship between the levels of plasma salicylate and urinary salicylate in 11 patients treated with forced alkaline diuresis with standard potassium supplements.

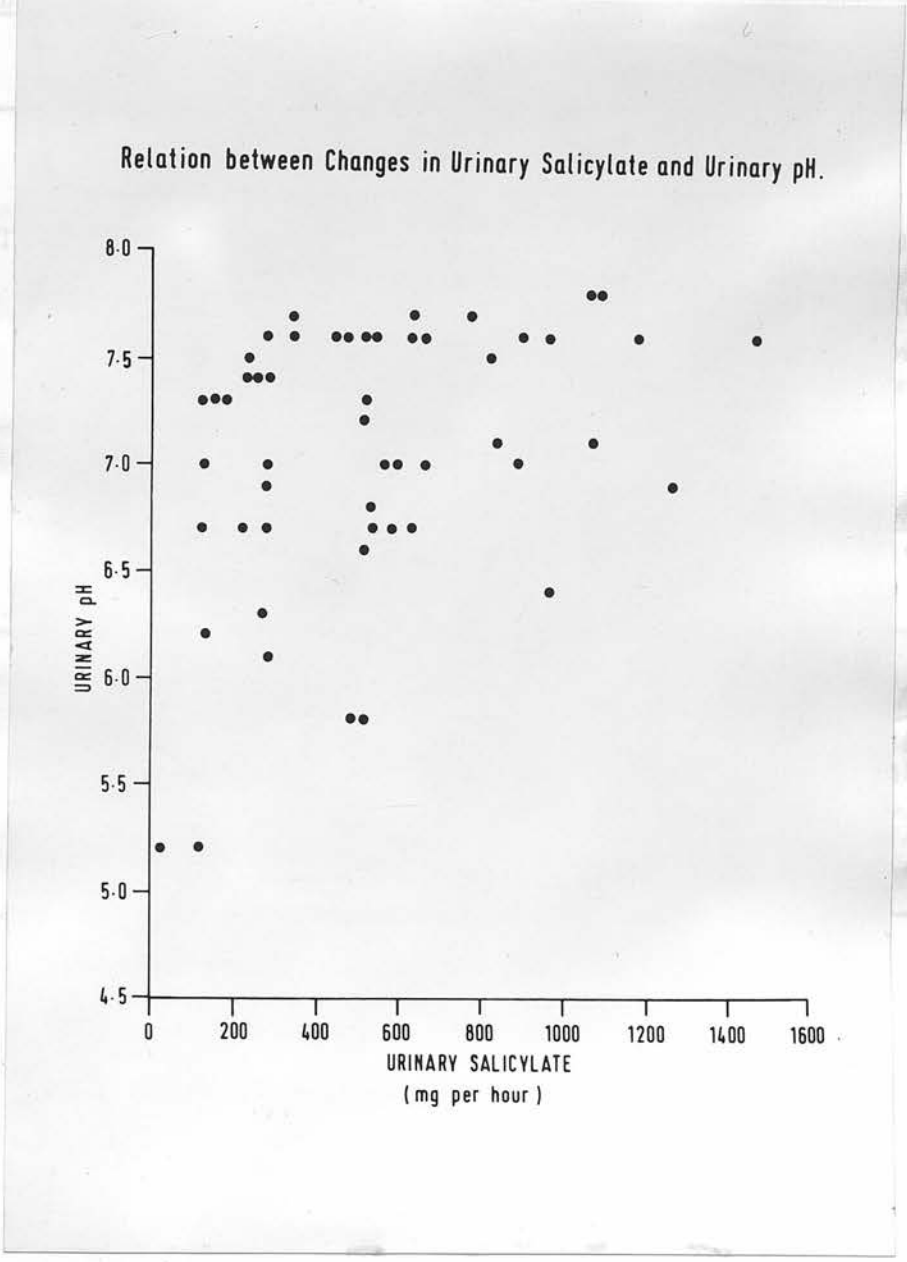

Figure 35.

Relationship between the levels of urinary salicylate and urinary pH in 11 patients treated with forced alkaline diuresis with standard potassium supplements.

TABLE XLV

PATIENTS		ARTERIAL BLOOD GASES					
		pH		pCO_2 (mm/Hg)		Standard Bicarbonate (mEq per litre)	
		Peak Level	Lowest Level	Peak Level	Lowest Level	Peak Level	Lowest Level
MALES	61	7.58	7.45	28.5	21.5	26.0	19.0
	62	7.56	7.43	30.0	20.0	30.0	20.0
	63	7.46	7.41	25.5	18.0	20.5	19.5
	64	7.56	7.42	35.5	19.0	24.8	20.5
FEMALES	65	7.63	7.54	23.0	14.0	27.0	13.7
	66	7.56	7.44	30.0	25.0	25.0	22.0
	67	7.50	7.43	29.5	15.0	24.0	18.0
	68	7.58	7.40	24.0	17.5	24.0	18.5
	69	7.47	7.31	20.0	13.0	20.0	15.0
	70	7.63	7.37	31.0	17.0	28.0	14.0
	71	7.44	7.43	31.8	13.2	17.9	16.1

Acid-Base changes during the period of observation in 11 patients treated with forced alkaline diuresis with standard potassium supplements.

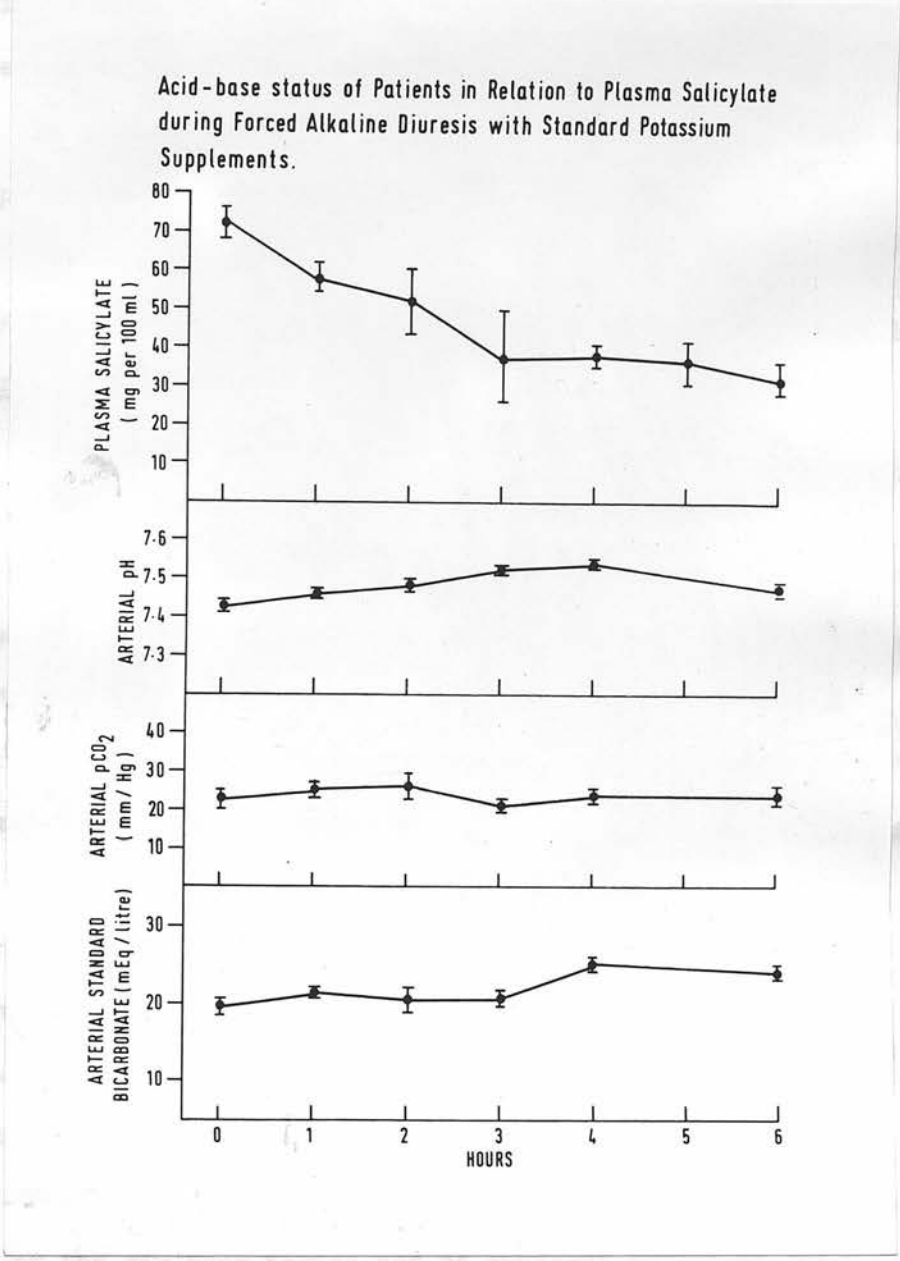

Figure 36.

Changes in the mean values (± S.E.M.) in plasma salicylate and the mean changes (± S.E.M.) in arterial pH, pCO_2 and standard bicarbonate in 11 patients treated with forced alkaline diuresis with standard potassium supplements.

bicarbonate the levels of standard bicarbonate in general rose and in patients 62, 65 and 70, the standard bicarbonate was increased to normal levels.

In general therefore as the metabolic alkalosis increased the plasma salicylate fell (Fig. 36).

Changes in Plasma Potassium in Relation to Urinary Potassium and Arterial and Urinary pH

Results are shown in Table XLVI and Fig. 37. Three patients, 65, 70 and 71, were hypokalaemic before treatment.

Despite the infusion of 338 mEq of potassium, nine of the 11 patients became hypokalaemic during the first six hours of treatment. In contrast one patient, 65, who was initially severely hypokalaemic, attained normal plasma potassium levels during the course of treatment.

The urinary excretion of potassium remained constant at about 10 mEq per hour despite the potassium supplements given. The total excretions of potassium are given in Table XLIV. The range of potassium losses was 19.0 to 121 mEq with a mean loss of 64 mEq.

The rises in arterial and urinary pH levels over the second half of the six hour period had no apparent effect on the urinary excretion of potassium. In Fig. 37 there appeared to be a correlation between the rise in arterial pH and the fall in plasma potassium. This, however, did not attain a level of significance ($r = 0.16$; $p = 0.30$) (Fig. 38).

TABLE XLVI

PATIENTS		PLASMA POTASSIUM (mEq per litre)							
		Time (Hours)							
		Pretreatment							
		0	2	4	6	8	12	16	24
MALES	61	3.7	3.8	3.2	2.9	3.0	3.1		3.0
	62	4.9	3.4	2.9	3.5	3.3			3.6
	63	4.3	5.5	5.0	5.2	4.2	3.2	2.8	
	64	4.3	4.0	2.6	3.0	2.9			
FEMALES	65	2.6	2.8	3.4	4.7	3.7	4.2		
	66	4.0	3.2	2.9	2.4	3.0	3.5		4.0
	67	3.6	3.0	2.9	3.0	2.8	3.4		
	68	3.5	3.7	3.1	2.6	2.3	2.6	3.2	
	69	3.7	3.8	4.0	3.0	2.8			
	70	3.3	3.0	2.9	3.0	2.8	3.4		
	71	3.4	3.6	3.1	3.2				

Changes in plasma potassium in 11 patients treated with forced alkaline diuresis with standard potassium supplements.

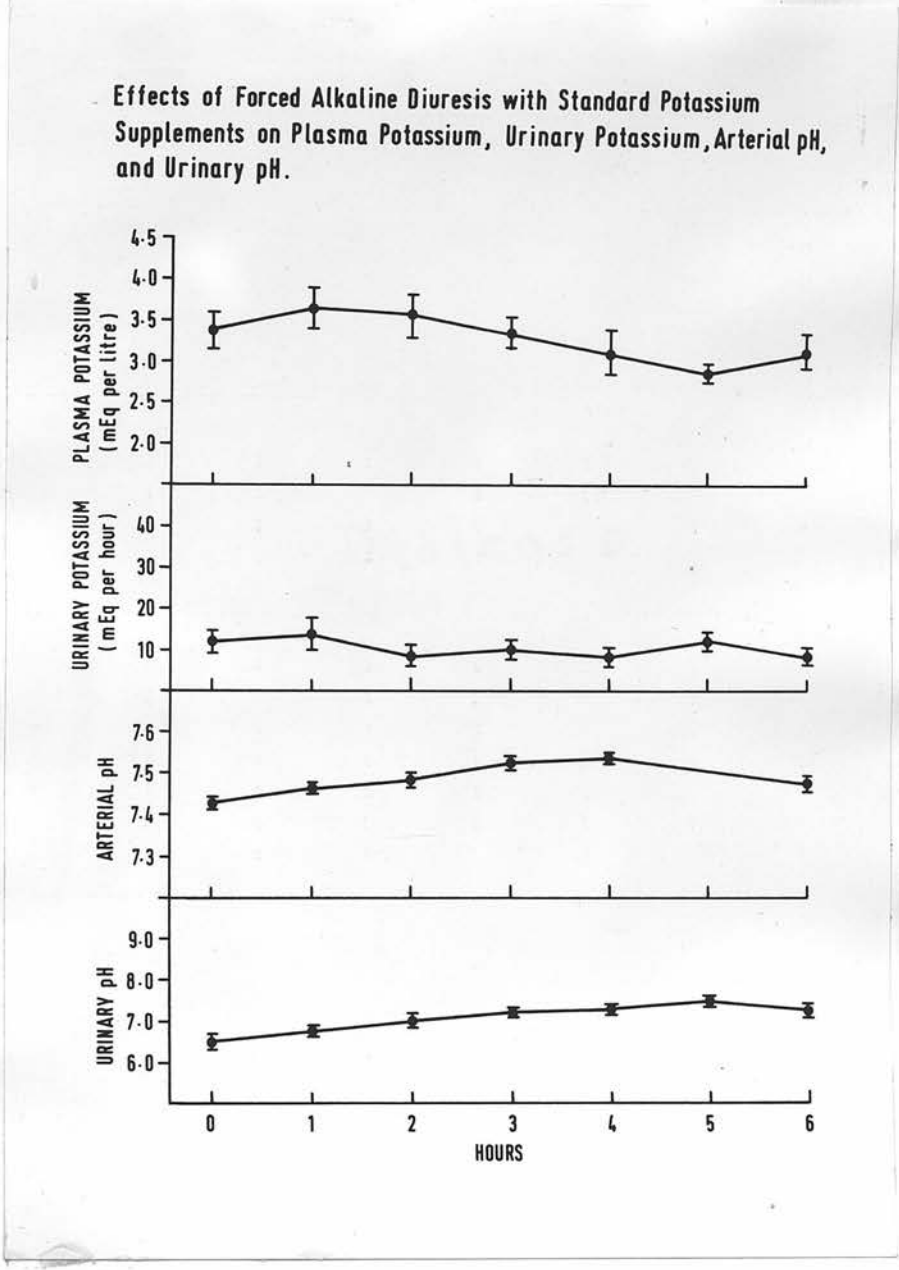

Figure 37.

Changes in the mean values (± S.E.M.) in plasma and urinary potassium, arterial pH and urinary pH in 11 patients treated with forced alkaline diuresis with standard potassium supplements.

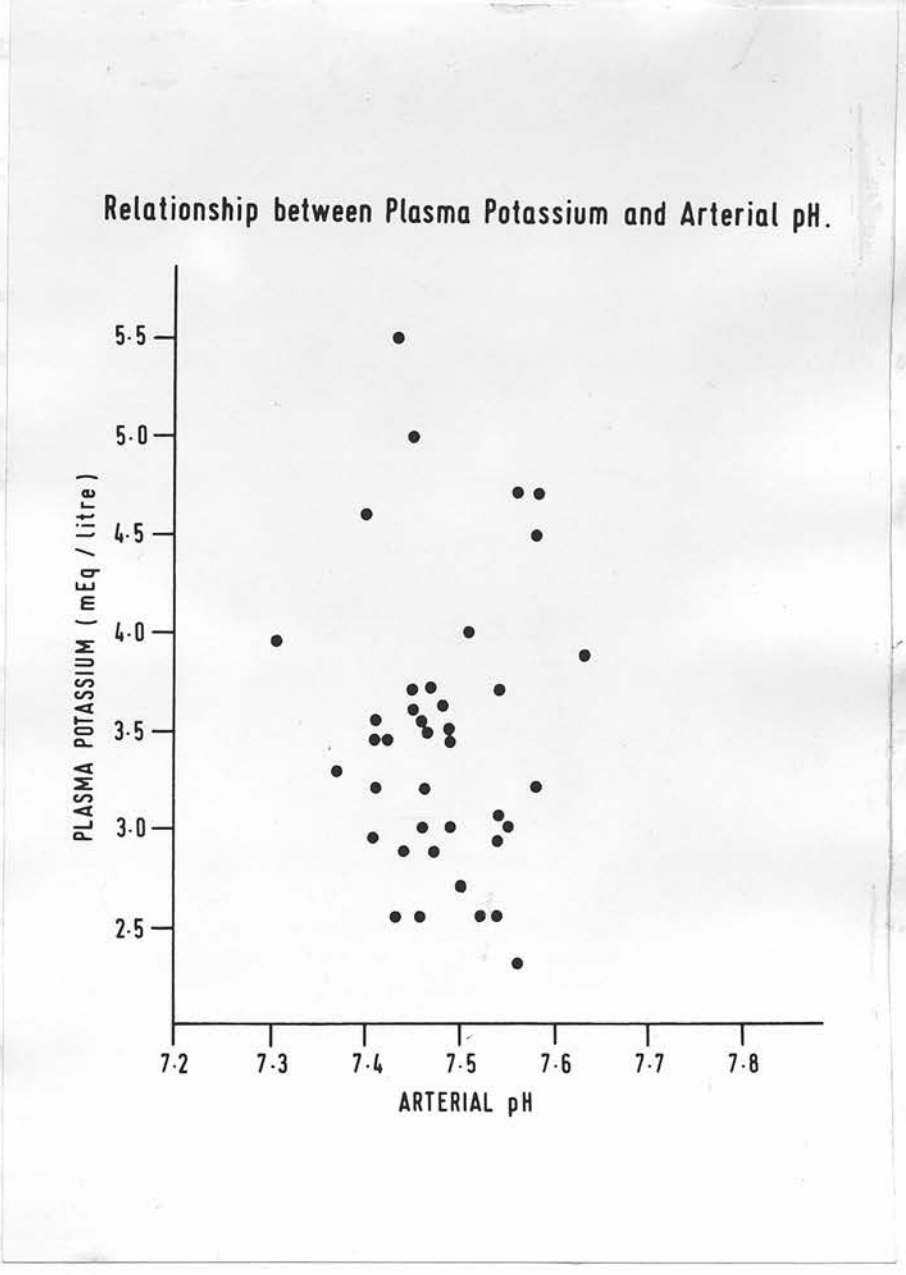

Figure 38.

Relationship between arterial pH and plasma potassium in 11 patients treated with forced alkaline diuresis with standard potassium supplements.

Relationship Between Plasma Potassium, Magnesium and Calcium and Changes in Arterial pH and P.C.V.

Results are shown in Fig. 39 and Tables XLVI, XLVII, XLVIII and XLIX.

All the patients had plasma magnesium levels within the normal range before starting treatment. After the infusion regime was started, there was a general tendency for the levels to fall during the first three hours then to remain low till the end of the six hour period. Subsequent levels which were done in a few patients showed a spontaneous return towards normal. The nadir of the curve occurred between the fourth and sixth hour of treatment. The urinary losses of magnesium in six patients (Table XLIV) ranged from 0.5 to 27.07 mg. (mean 12.5 mg.) during the six hour period.

Plasma calcium levels were measured in eight patients. Before treatment the plasma calcium was normal in all patients. As with magnesium the levels subsequently fell in every case with again a tendency to spontaneous recovery after 24 hours. Despite the alarming low levels of magnesium and calcium recorded, none of the patients showed any clinical features of tetany. The excretion of calcium in the six hour period in six of these patients (Table XLIV) was 5.2 to 64 mg. (mean 37 mg.).

The P.C.V. was monitored in six patients (Table XLIX). There was an initial fall in the average levels during the first three hours but in the second half of the six hour period the levels rose to the pre-treatment values. As the mean values of potassium, magnesium and calcium fell, the arterial pH rose and the

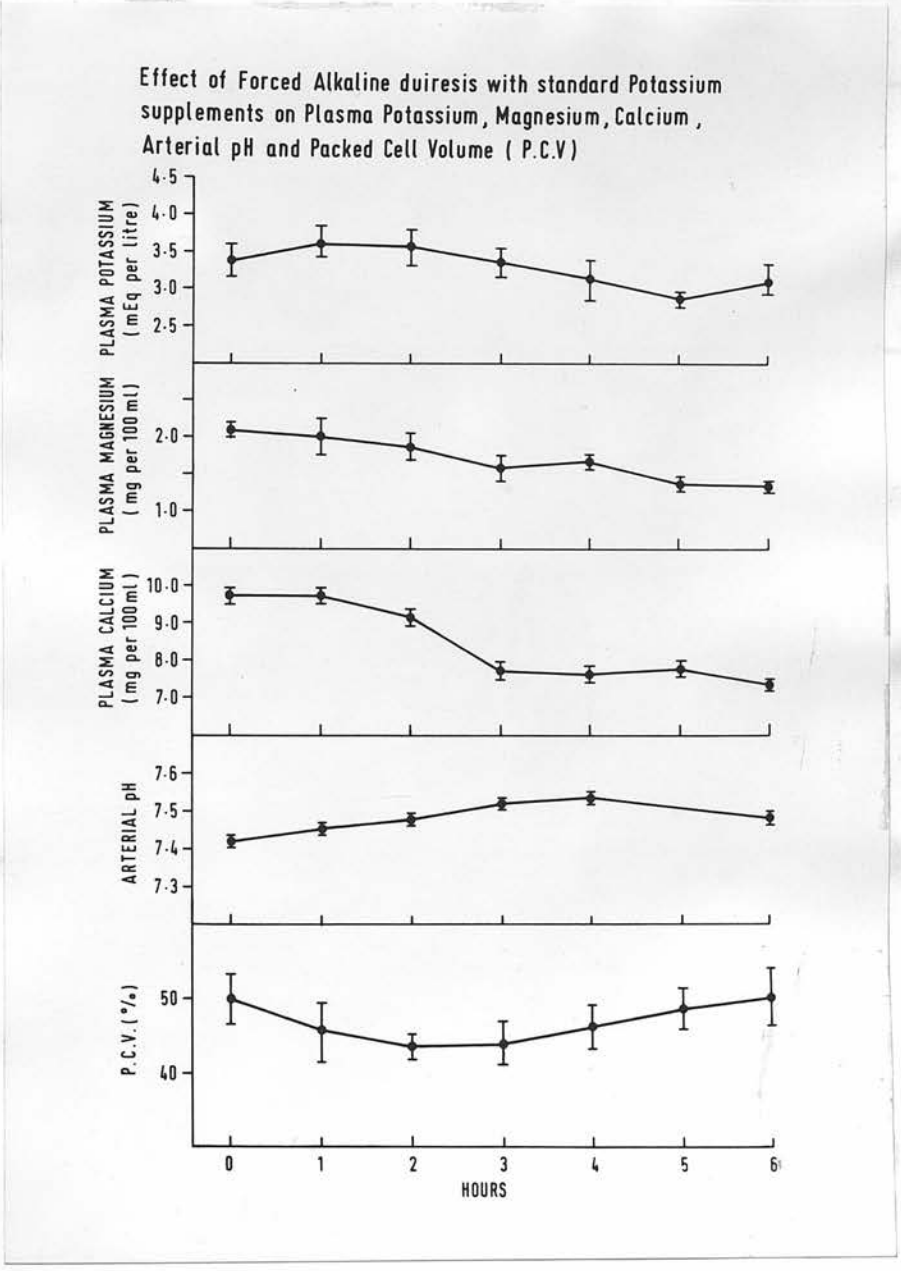

Figure 39.

Changes in the mean values (± S.E.M.) in plasma potassium, magnesium and calcium, arterial pH and P.C.V. in patients treated with forced alkaline diuresis with standard potassium supplements.

TABLE XLVII

PATIENTS		PLASMA MAGNESIUM (mg per 100 ml)							
		Time (Hours)							
		Pretreatment 0	2	4	6	8	12	16	24
M									
A	62	2.37	1.86	1.75	1.70				
L	63	1.95	2.12	2.25	1.66				
E	64	1.75	1.46	1.21	1.16				
S									
F	65	1.74	1.37	0.91	1.21				
E	66	2.4	2.45	1.95	1.5	1.45	1.7	1.5	2.2
M	67	2.55	2.30	2.0	1.9	2.05	2.06		
A	68	1.7	1.7	1.29	1.33	1.58	1.54	1.79	1.95
L	69	1.79	1.83	1.62	1.37				
E	70	2.05	2.05	2.07	2.05	1.2	1.4	1.45	
S	71	2.25	2.25	1.7	2.0				

Changes in plasma magnesium in 10 patients treated with forced alkaline diuresis with standard potassium supplements.

TABLE XLVIII

		PLASMA CALCIUM (mg per 100 ml)							
PATIENTS		Time (Hours)							
		Pretreatment 0	2	4	6	8	12	16	24
MALES	62	9.8	7.9	7.4	7.4	7.3			7.9
	63	10.1	10.4	10.5	8.1				
FEMALES	66	10.0	10.3	9.5	7.2	7.3	7.6	7.0	9.6
	67	10.5	9.6	8.4	8.1	8.4	8.6		
	68	9.4	8.3	7.2	7.5	7.2	7.0	7.9	9.3
	69	9.1	9.1	7.8	7.2				
	70	9.6	8.7	8.3	8.4	7.6	8.1	7.5	
	71	9.2	9.2	7.8	8.0				

Changes in plasma calcium in 8 patients treated with forced alkaline diuresis with standard potassium supplements.

TABLE XLIX

PATIENTS	PACKED CELL VOLUME (per cent)					
	Pretreatment	Time (Hours)				
	0	2	4	6	8	16
MALES						
	61	39	33	30	42	32
	64	55	41	42	43	
FEMALES						
	67	43	47	43	42	
	69	57	56	57	54	51
	70	39	37	38	43	44
	71	55	56	50	52	

Changes in P.C.V. in 6 patients treated with forced alkaline diuresis with standard potassium supplements.

metabolic alkalosis, which occurred, persisted up to the 6 hour period. As the levels of plasma potassium, magnesium and calcium remained low during the second half of the six hour period of the observation whilst the P.C.V. returned to normal made it unlikely that haemodilution was a significant factor in the causation of low levels of the cations.

Changes in Plasma and Urinary Sodium

Results are shown in Table L.

One patient, 71, was considerably hyponatraemic before starting treatment, but the other patients all had initially normal plasma sodium levels. In general, there was a tendency for the plasma sodium levels to fall as the diuresis proceeded but only one patient, 62, developed marked hyponatraemia and this was transient. During diuresis the hyponatraemia improved in patient 71. Throughout the six hour period of observation there was little change in the mean values of plasma sodium. The total urinary excretion of sodium during the six hour period ranged from 74 to 304 mEq (mean 177 mEq). As in the group of patients treated with forced saline-laevulose diuresis there was no relation between the amounts of sodium excreted in the urine and changes in plasma levels. It is true that patient 71, who had marked hyponatraemia, excreted rather large amounts of sodium, 247 mEq in the six hours but patient 67, who had the greatest losses of sodium of 304 mEq actually increased her plasma level during the time of study.

TABLE L

PATIENTS		PLASMA SODIUM (mEq. per litre) Time (Hours 0	2	4	6
MALES	*61	149	140	137	140
	62	136	135	128	131
	*63	140	137	135	141
	64	133	131	132	135
FEMALES	*65	141	136	136	135
	*66	135	135	137	135
	*67	136	137	136	140
	*68	137	135	133	132
	69	139	142	140	140
	70	146	143	142	139
	71	125	124	130	130

* Vomited after ingestion and before admission.

Changes in plasma sodium in 11 patients treated with forced alkaline diuresis with standard potassium supplements.

Fluid Deficits

In keeping with the results obtained in other groups of patients with severe acute salicylate overdosage, all of the patients treated with forced alkaline diuresis were found to have calculated fluid deficits (Table XLIV) ranging from 1.9 to 9.0 litres (mean 5.0 litres).

Patient 70 was the one patient who died, in the whole series of 307 patients. She was a young girl aged 16 and had been in excellent health prior to taking the overdosage of aspirins apart from a tendency to be depressed from time to time. On the night of her admission to hospital the patient had told her boy friend that their relationship was finished and then, whilst he was still there, took 60 aspirin tablets. She did not vomit and was admitted to the ward just over three hours after having taken the overdosage.

On examination she was fully conscious, warm and sweaty, but her temperature was only 37.4°C. Tachypnoea was present and she had a tachycardia of 116 per minute in sinus rhythm. She was moderately deaf with tinnitus and, although she complained of nausea, vomiting was not initially a marked feature. Routine medical examination was otherwise entirely normal. Her initial plasma salicylate of 60 mg. per 100 ml. confirmed that she had severe acute salicylate poisoning. A metabolic acidosis was present before treatment, the arterial pH being 7.37, pCO_2 31 mm./Hg. and standard bicarbonate 19 mEq. per litre. The prothrombin ratio was normal as were the haematological indices and platelet count. On the basis of this assessment she was treated with

forced alkaline diuresis with standard potassium supplements, as has been described. The levels of plasma magnesium, sodium and calcium before treatment were normal and the plasma potassium was only slightly low. The response to treatment is shown in Figs. 40 and 41. A brisk diuresis was achieved and at the end of six hours the plasma salicylate had fallen to a satisfactory level of 27 mg. per 100 ml. This then continued to fall until by 20 hours it was only just detectable in the plasma. During the main diuresis period she became mildly hypokalaemic but by 12 hours this had risen to an acceptable level and at no time was the plasma potassium dangerously low. Also for the first six hours after starting treatment there was no evidence of serious hypocalcaemia, hypomagnesaemia or hyponatraemia.

In keeping with these satisfactory biochemical findings there was considerable clinical improvement in the patient's condition. Her symptoms of salicylism disappeared with the exception of continuing nausea and periodic vomiting, the vomitus being small in amount and consisting only of slightly bile-stained fluid. Her progress was regarded as satisfactory but because of the vomiting the intravenous fluids were continued at an infusion rate of 500 ml. per hour for eight hours and thereafter reduced as shown in Fig. 40.

About 10 hours after starting treatment she had a minor epileptiform convulsion, which lasted for only about 30 seconds before subsiding spontaneously. There was no other evidence of tetany and Chvostek's and Trousseau's signs were negative. Ocular fundal examination was normal and there were no abnormalities

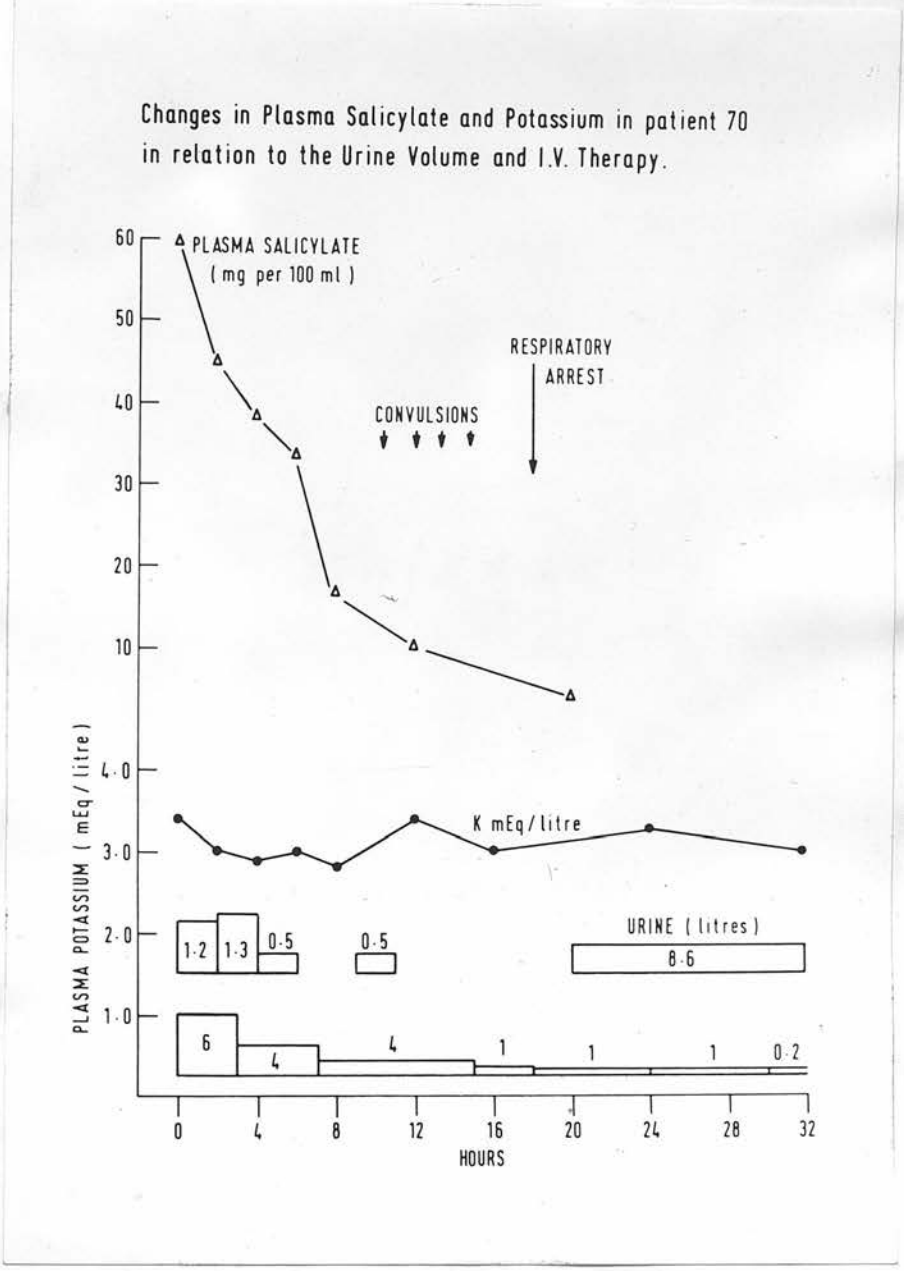

Figure 40

Response of patient 70 to forced alkaline diuresis with standard potassium supplements.

Changes in Plasma Sodium, Calcium and Magnesium and in Arterial pH found in patient 70.

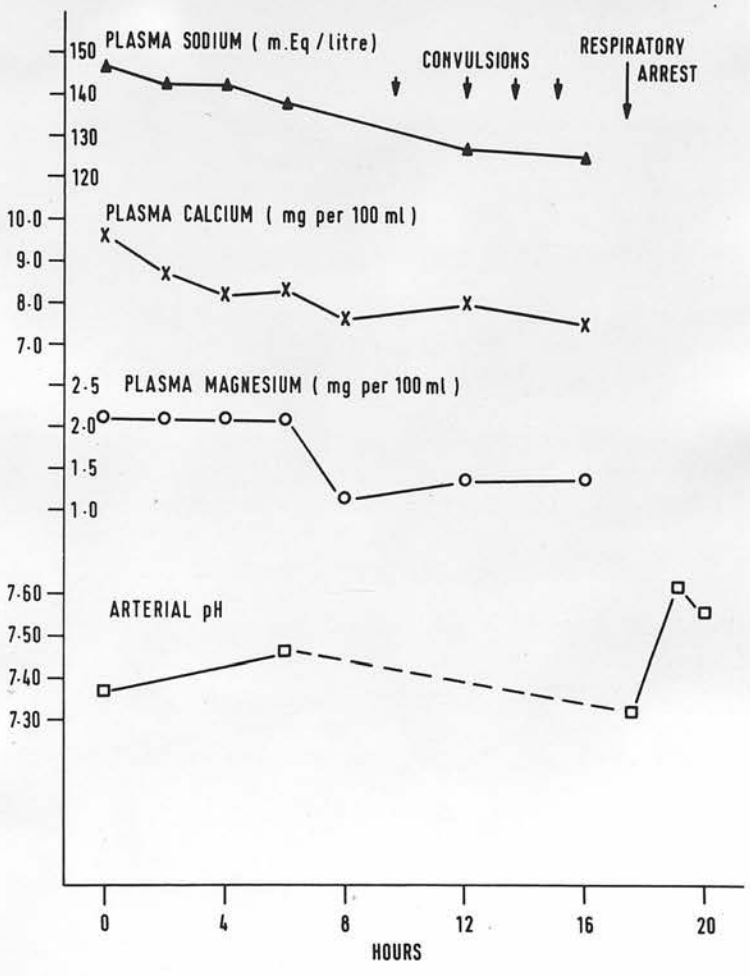

Figure 41.

Changes in plasma sodium, calcium and magnesium and in arterial pH found in patient 70 in response to forced alkaline diuresis with standard potassium supplements.

elicited on neurological examination. In the course of the next four hours she had three further episodes, all of which were of a similar, transient nature. Eighteen hours after her admission to hospital she was talking to a nurse, when she suddenly collapsed became apnoeic and unconscious. Mouth-to-mouth respiration was started immediately, despite which she remained cyanosed, but when intubated and ventilated with 100 per cent oxygen she became pink at once. At no time was there any cardiac arrhythmia or arrest and an electrocardiograph, done during the period of intensive resuscitation was entirely normal. The pupils, however, became partially dilated and showed little, if any, reaction to light and there was no return of spontaneous respiration. She remained deeply unconscious but there was no evidence of localised neurological abnormality. The plantar responses were flexor and there was a slight withdrawal reflex. Otherwise there was no response to stimulation. Blood gas analysis just after the arrest showed pH 7.32, pCO_2 20.3, standard bicarbonate 14.4 mEq per litre, pO_2 410 mm./Hg. and the plasma potassium was 3.0 mEq. per litre.

In Fig. 41 marked degrees of hyponatraemia, hypomagnesaemia and hypocalcaemia were present from the eight hour period until just before the respiratory arrest. Unfortunately these measurements were not available until after the arrest had occurred and so no specific therapy was given to correct them.

As there was no sign of recovery of spontaneous respiration, she was mechanically ventilated using a Bennet respirator. She was easily ventilated and the minute volume had to be reduced

below 4 litres per minute to allow the arterial pCO_2 to approach normal.

In the course of the 12 hours after the arrest occurred she developed polyuria and passed 8.6 litres of urine in this time whereas the fluid administration during the same period was approximately 2.0 litres. The polyuria continued for the next 24 hours, the urine output being 11,155 ml. and to compensate for this loss, 10,300 ml. of fluid in the form of 0.9 per cent saline and 5.0 per cent dextrose were given intravenously. The urine was dilute, the specific gravity remaining consistently low, varying between 1.004 and 1.006. It appeared that she had developed diabetes insipidus and she was given aqueous vasopressin 0.5 ml. intramuscularly. This reduced the urine flow to 80 ml. per hour. The patient, became temporarily oedematous but this subsided after adjustment of the fluid balance.

She remained very deeply unconscious with no response to painful stimulation apart from a slight withdrawal response on plantar stimulation. A lumbar puncture was performed, which was normal in manometrics and appearance. There was no abnormality on biochemical and bacteriological study of the cerebrospinal fluid; in particular the C.S.F. protein was normal at 45 mg. per 100 ml. An electroencephalograph was done, which showed virtually no activity from the brain in any lead.

Five days after her admission to hospital, she became hypotensive with a systolic blood pressure of 80 mm./Hg. This responded initially to 2.5 mg. metaraminol ('Aramine') intramuscularly but she then developed pulmonary oedema and died a few hours later.

Post Mortem Findings

Post mortem examination was performed 10 hours after death occurred.

The macroscopic appearances of the pleural, pericardial and peritoneal sacs were normal. The organs of the alimentary system were also normal and no abnormality was found in the genito-urinary and cardiovascular system with the exception of two diffuse subendocardial haemorrhages in the left ventricle. In the respiratory system both lungs were intensely congested and oedematous with bilateral bronchopneumonia. The thyroid and suprarenal glands were normal. There was no skull fracture and there was no extra or subdural haemorrhage. The leptomeninges and superficial vessels including the Circle of Willis were normal. The brain showed marked generalised swelling and was extremely soft. There was marked swelling, congestion and softening of both cerebral hemispheres, the brain stem and cerebellum. The changes were those of autolysis rather than infarction, and in the white matter liquefaction was occurring. In the right occipital lobe the ribbon of cortical grey matter was becoming separated from the underlying white matter. In the right mammillary body there was a focus of congestion 4 mm. in diameter.

Microscopic examination was made of representative sections from both cerebral hemispheres, including the basal ganglia, brain stem and cerebellum. In all sections severe changes were seen in the grey and white matter. These were of an autolytic nature and indistinguishable from those found as the result of advanced post mortem autolysis.

The grey matter showed patchy pallor of staining of ground substance and severe pericellular vacuolation; the neurones were in the main shrunken and had lost their Nissl substance. Some had small pyknotic nuclei, but in many the nuclei failed to stain. In some areas the neurones had either disappeared or merged imperceptibly into the pale eosinophilic ground substance. The most striking feature was the virtual total absence of any glial, mesodermal or vascular response. The neuroglia showed similar autolytic changes.

The white matter was less affected than the grey; vacuolation was slight but practically all the neuroglial nuclei were markedly pyknotic. The vessels throughout the pia arachnoid were much better preserved.

Similar changes were seen in the brain stem and cerebellum. In the brain stem the damage was particularly severe in the tegmentum.

In the pituitary gland there was practically total necrosis of the anterior and posterior lobes unaccompanied by any reactive change.

Discussion

Forced alkaline diuresis achieved rapid and satisfactory recoveries of salicylate and in this respect this regime was clearly superior to a similar infusion rate of saline-laevulose. As the diuresis produced by these two forms of treatment was similar, the difference in removal of salicylate was presumably related to the alkalinisation of the urine. The benifits of

raising the urinary pH in promoting salicylate excretion by the kidney has been established by numerous authors including Robin et al. (1959), Whitten et al (1961), Oliver and Dyer (1960) and Cumming et al. (1964). A further important consideration in this regard is that the amount of "free" salicylate removed is greatly increased in the presence of an alkaline pH. It may be assumed therefore that not only was the total recovery of salicylate increased by this regime but that a considerable amount was "free" salicylate. In support of this was the fact that all patients, who had marked clinical features of the poisoning, obtained rapid relief on this treatment.

The major criticism which has been made against the use of alkalis in the treatment of patients with acute salicylate poisoning has been the possibility of causing dangerous alkalosis and possibly fatal tetany (Winters et al., 1963; McLaughlin, 1965; Done, 1965 and Ghose and Joekes, 1966). In this group of patients significant hypokalaemia was found in several despite the considerable potassium supplements. Alkalosis, which in some patients was severe, was produced and marked hypomagnesaemia and hypocalcaemia occurred. When the blood levels of these minerals and the associated acid-base status is considered, it was indeed surprising that tetany was not a marked feature. The urinary losses of potassium, magnesium and calcium in this group of patients were insufficient to explain the reductions in plasma levels and haemodilution was not a significant factor. It is likely, therefore, that there were considerable shifts of these cations from extracellular to intracellular sites. Cellular uptake of

potassium in response to alkalosis is well known (Briggs and Findley, 1967; Whang and Reyes, 1967, and many others), but the participation of magnesium and calcium in the maintenance of acid-base equilibrium is perhaps less generally recognised. The mineral portion of the skeleton is thought to exist in the form of a vast number of tiny, flat, hexagonal crystallites which present an enormous total surface area. Cations such as Na^+, K^+, Ca^{++} and Mg^{++} appear to be loosely combined at the surface of the crystallites, so that they can exchange with cations in the surrounding extracellular fluid. This bone material is very sensitive to changes in plasma pH. With an increase in H^+ concentration there is a shift of the above cations out of bone and in a state of alkalosis the opposite occurs (Robinson, 1961). Bergstrom (1956) has described these events in some detail and stressed that these changes may occur with great rapidity. It is, therefore, probable that in this group of patients the reductions in plasma sodium, potassium, magnesium and calcium were primarily due to ion shifts in response to the alkalosis produced by the therapy. The changes in plasma sodium and potassium were reduced by the amounts of these cations given in the regime. In support of ion shifts being the major factor operating was the fact that the plasma levels of these cations tended to return to normal spontaneously before the patients were established on diet and in the absence of specific replacements of these minerals being given other than sodium and potassium. The fact that tetany was not produced, suggests that in some way the ionised calcium in the circulation did not fall below critical levels. Competition

between salicylate and magnesium and calcium for protein-binding sites may have been the main factor but in the absence of specific data regarding the relative protein binding of the salicylate and these minerals this must remain speculative.

The absence of clinical features of hypokalaemia and of tetany despite the changes observed in acid-base state and in plasma potassium, magnesium and calcium levels, prompts a consideration of how important these changes are from the practical point of view. In many instances, the changes which occurred were rapid in onset and of a severe nature. Such a state of instability of H^+ concentration and of important cations must be regarded as potentially dangerous and must lend support to those, who criticise forced alkaline diuresis on the grounds of the dangerous side-effects associated with its use.

The results obtained in the girl, who died, provide a good example of this. Despite the fact that she responded very satisfactorily to the treatment in terms of reduction of plasma salicylate and although hypokalaemia was not a serious problem, she nevertheless died suddenly of acute respiratory arrest. It is true that she was pronounced dead some five days later having been kept alive by artificial means but the post mortem which was done only a few hours after death was declared, showed that the brain had undergone advanced autolysis. The findings were in fact an example of "deanimation" or dissociated death, in which the brain has "died" at least some few days before the body (Kramer, 1963). It is a rare but well recognised occurrence in individuals who, because of some pre-existent brain damage, fail

to breathe spontaneously and have to be kept alive on a mechanical respirator. The polyuria which developed before death was amply explained by the damage to the pituitary gland seen at autopsy.

The crux of the problem, however, remains. Why did the respiratory arrest occur? For a few hours before the arrest occurred she had a number of minor convulsive episodes, which, as was discovered later, occurred at the same time as significant falls in the levels of plasma magnesium and calcium. Severe hypomagnesaemia and hypocalcaemia occurred, both of which may cause convulsions (Hanna, Harrison, MacIntyre and Fraser, 1960 and Vallee, Wacker and Ulmer, 1960). There is no proof that these changes were the cause of her convulsions and ultimate respiratory arrest but the circumstantial evidence in favour of this was strong. The most common mode of death in acute salicylate poisoning is respiratory or cardiac arrest, which often occurs without warning. Such deaths are usually regarded in despair as "electrolyte" deaths. Further study of the effects of changes in plasma magnesium and calcium in this poisoning may well throw some light on this important problem.

Another criticism which has been made of the use of forced alkaline diuresis is that it may cause severe hypernatraemia (Feuerstein et al., 1960). In this group of patients this was not found. On the contrary, the plasma levels of sodium tended to fall during the course of treatment. It would seem, therefore, that hypernatraemia need not be considered to be a serious complication of this regime.

All the patients were found to have a calculated fluid deficit as in previous groups of patients studied and again there appeared to be a correlation between the magnitude of the fluid deficit and the severity of the poisoning in terms of plasma salicylate level.

Conclusion

Forced alkaline diuresis according to the Dukes' regime was demonstrated to be an extremely effective means of reducing the plasma salicylate in patients with acute overdosage of this drug. On the other hand, severe and rapid changes occurred in acid-base balance, plasma potassium, magnesium and calcium. One patient died despite the fact that the plasma salicylate had been successfully reduced to low levels. There was some evidence that this death may have resulted from changes in the plasma magnesium and calcium. Winters and others were fully justified when they expressed reservations about the use of this regime of forced alkaline diuresis. It is likely that the metabolic changes induced by the treatment are of considerable significance and constitute a hazard to the patient, which may occasionally be fatal. At the very least, this method of treatment demands the closest biochemical monitoring.

FORCED 'COCKTAIL' DIURESIS

Although the regime of forced alkaline diuresis was very efficient in reducing the plasma salicylate, it was not an ideal regime in that marked changes in H^+ concentration and in important plasma cations occurred during the course of treatment. The main abnormalities seemed to be related to the metabolic alkalosis produced and so, rather than increase the amounts of potassium administered, which may have been dangerous in itself, it was decided to reduce the total amount of bicarbonate given. Also it was thought more appropriate to give a continuous infusion of fluid and alkali rather than the intermittent regime given in Dukes method of forced alkaline diuresis. For this purpose a composite infusion solution was devised, which, for simplicity, was referred to as the 'cocktail'.

The mixture consisted of,

0.9 per cent saline	500 ml.
5.0 per cent laevulose	1000 ml.
1.26 per cent sodium bicarbonate	500 ml.

These solutions were mixed in 2 litre bottles and prepared and sterilised by the hospital dispensary. In this way a supply was always kept available. To each bottle was added 3.0 g. potassium chloride, just before administration to the patient. The rate of infusion given using the 'cocktail' was the same as with the other regimes of forced intravenous fluids. Two litres were administered intravenously every hour for three hours and then 1 litre per hour until the plasma salicylate had fallen to less than 35 mg. per 100 ml. and the patient was able to tolerate an

adequate oral fluid intake. The fact that the mixture was set up in 2 litre bottles simplified the regime for the nursing staff and reduced the number of times the bottles had to be changed. In the course of a six hour period of main diuresis 682.5 m.Eq. of Na^+ and 175 m.Eq. of K^+ were administered using the forced 'cocktail' diuresis. By comparison, using forced alkaline diuresis, 912.6 m.Eq. of Na^+ and 169 m.Eq. of K^+ were given. Perhaps the major difference between the two regimes was that with forced alkaline diuresis in six hours 37.8 g. of sodium bicarbonate were given, whereas with the forced 'cocktail' only 28.4 g. sodium bicarbonate were infused in the same time.

Patients and Methods

Thirteen patients, 7 males and 6 females, were treated with forced 'cocktail' diuresis (Table LI). All the patients were suffering from moderate or severe acute salicylate overdosage The plasma salicylate ranged from 48 to 81 mg. per 100 ml. (mean 67 mg. per 100 ml.). All had been admitted relatively soon after ingestion of the tablets (1-8 hours; mean 4.5 hours). Five patients, 72, 76, 79, 82, 83 and 84, were alkalotic on admission and one patient, 75, was acidotic. The remaining patients all had arterial pH levels within the normal range. The pCO_2 and standard bicarbonate levels were reduced in all patients except patient 75 in whom the pCO_2 was slightly elevated. This was probably a reflection of the metabolic acidosis present. The patients were aged from 16 to 63 with a mean age of 30.

The plasma salicylate was measured in all patients before

TABLE LI.

PATIENTS		Age (Years)	Number of Tablets Ingested	Time Since Ingested (Hours)	Peak Plasma Salicylate level (mg. per 100 ml.)	Arterial Blood Gases Relative to Peak Salicylate		
						pH	pCO_2 (mm/Hg)	Standard Bicarbonate (mEq/litre)
	72	46	100	8	80	7.48	22.0	20.0
M	73	27	100	4	76	7.42	31.0	22.0
A	74	17	90	4	74	7.40	30.0	21.5
L	*75	16	50	1	65	7.35	47.0	22.0
E	76	15	60	4	59	7.46	25.0	20.0
S	77	18	80	6	52	7.41	20.0	19.0
	78	29	100	7	48	7.42	21.0	19.0
F	79	31	50	4	81	7.52	14.0	19.0
E	80	59	100	3	78	7.43	20.0	19.0
M	81	43	100	6	74	7.42	21.0	18.0
A	82	20	80	5	73	7.50	17.0	20.5
L	83	33	100	6	65	7.46	22.0	21.0
E	84	26	60	1	48	7.48	20.0	22.5
S								

* Vomited after ingestion and before admission.

Characteristics of the 13 patients treated with forced "cocktail" diuresis.

treatment and at hourly intervals up to six hours after starting the infusion. In a number of patients subsequent measurements were made up to 24 hours after starting treatment. Similar monitoring of the plasma potassium was done. Plasma magnesium levels were estimated in eight patients at three hourly intervals up to six hours, and at 12 hours after starting treatment. Similar measurements were made of the plasma calcium in 12 patients and plasma inorganic phosphorus in 7 patients. The P.C.V. was monitored in 10 patients and serial measurements of arterial pH, pCO_2 and standard bicarbonate were made on blood taken from the brachial artery in all patients before treatment and at two, four and six hours after starting forced diuresis. At similar time intervals, the plasma sodium levels were measured on venous blood.

Careful measurements of the urine volume, urinary excretion of salicylate and potassium and urinary pH were made at hourly intervals for the first six hours of the diuresis. The total six hour urinary excretion of sodium magnesium and calcium was also estimated.

The usual precautions of collection and preservation of the specimens for arterial blood acid-base measurements and urinary pH were observed. If the specimens for plasma potasssium sodium, magnesium, calcium and inorganic phosphorus were not measured immediately, the plasma was separated and stored in the deep freeze. The plasma inorganic phosphate was measured using the Technicon autoanalyser by a modification of the method of Fiske and Subbarow (1925).

Results

Clinical Response

All the patients made a very satisfactory recovery from the poisoning and there were no clinical complications observed. Every patient, who had significant complaints of salicylism, was rapidly relieved of symptoms.

Comparison Between the Changes in Plasma Salicylate, Urinary Salicylate, Urinary pH and Urine Volumes.

Results are shown in Tables LII and LIII and in Fig. 42. The plasma salicylate levels fell progressively during the first 6 hours of treatment and the fall was maintained up to 24 hours. The mean level had fallen from 68 to 44 mg. per 100 ml. in four hours and the calculated mean half excretion time for salicylate was 6.7 hours. After an initial peak of 900 mg. per hour the mean excretion rate of salicylate fell to approximately 550 mg. per hour, but this was then maintained for the remainder of the six hour period. The mean urinary pH rose to 7.0 after two hours treatment and remained steady at this level thereafter, the highest urinary pH reached being 7.8.

The urine flow per minute averaged 700 ml. per hour for most of the main diuresis period, but fell to 400 ml. per hour at the end of the six hour period.

The total urinary excretion of salicylate over the 6 hours was 2.4 to 8.0 g. (mean 5.4 g.), which was almost five times the excretion of salicylate before treatment (Table LIII).

TABLE LII

PATIENTS		PLASMA SALICYLATE (mg per 100 ml)							
		Time (Hours)							
		Pretreatment							
		0	2	4	6	8	12	16	24
MALES	72	80		45	42			14	
	73	76	73	64	52				
	74	74	62		34				
	75	65	58	50	42		22	20	7
	76	59	56	38	30		28		5
	77	52	48		33			28	
	78	48		37	23			20	
FEMALES	79	81	78	49	40			23	14
	80	78	77		46			32	
	81	74		58	40		31		23
	82	73	44	31	26		18		
	83	65		57	37				
	84	49		36	30			7	

Changes in plasma salicylate in 13 patients treated with forced "cocktail" diuresis.

TABLE LIII

PATIENTS		URINARY EXCRETION												
		PRETREATMENT						DIURESIS						FLUID DEFICIT (LITRES)
		Volume (litres)	K (mEq)	Ca (mg)	Mg (mg)	Salicylate (g.)	pH	Volume (litres)	K (mEq)	Ca (mg)	Mg (mg)	Salicylate (g.)	Peak pH	
MALES	72	0.7	64.0	18.0	5.4	1.9	6.7	6.3	72.0	33.0	4.0	6.7	7.5	4.9
	73	0.6	91.0	-	-	2.1	6.8	4.8	68.0	-	-	8.0	7.9	11.1
	74	0.4	27.0	11.0	6.1	0.6	6.4	4.0	119.0	39.0	18.0	6.0	7.4	6.2
	75	0,9	22.0	7.0	16.0	1.3	7.2	4.9	105.0	44.0	30.0	6.1	7.6	6.5
	76	0.4	16.0	16.0	8.8	0.5	6.6	4.3	104.0	41.0	13.0	3.8	7.6	6.7
	77	0.6	59.0	11.0	13.0	1.3	6.6	2.9	110.0	23.0	15.0	2.4	6.7	5.8
	78	0.2	63.9	-	-	1.2	5.8	5.8	69.0	-	-	4.2	7.4	7.4
FEMALES	79	0.5	28.0	-	-	0.9	6.5	7.1	161.0	-	-	6.0	7.3	3.9
	80	0.8	35.0	-	-	1.3	6.9	6.5	76.0	-	-	6.5	7.8	5.9
	81	0.7	47.0	-	-	1.4	6.4	8.0	65.0	-	-	7.9	7.3	4.8
	82	0.8	26.0	-	-	0.7	6.6	2.9	81.0	28.0	12.0	2.7	7.2	7.0
	83	0.7	22.0	-	-	1.2	6.2	5.8	115.0	-	-	5.8	7.7	3.5
	84	0.5	18.0	-	-	0.6	6.8	7.6	104.0	-	-	4.6	7.9	3.8

Fluid balance and urinary excretion of potassium, calcium, magnesium and salicylate before and after forced "cocktail" diuresis.

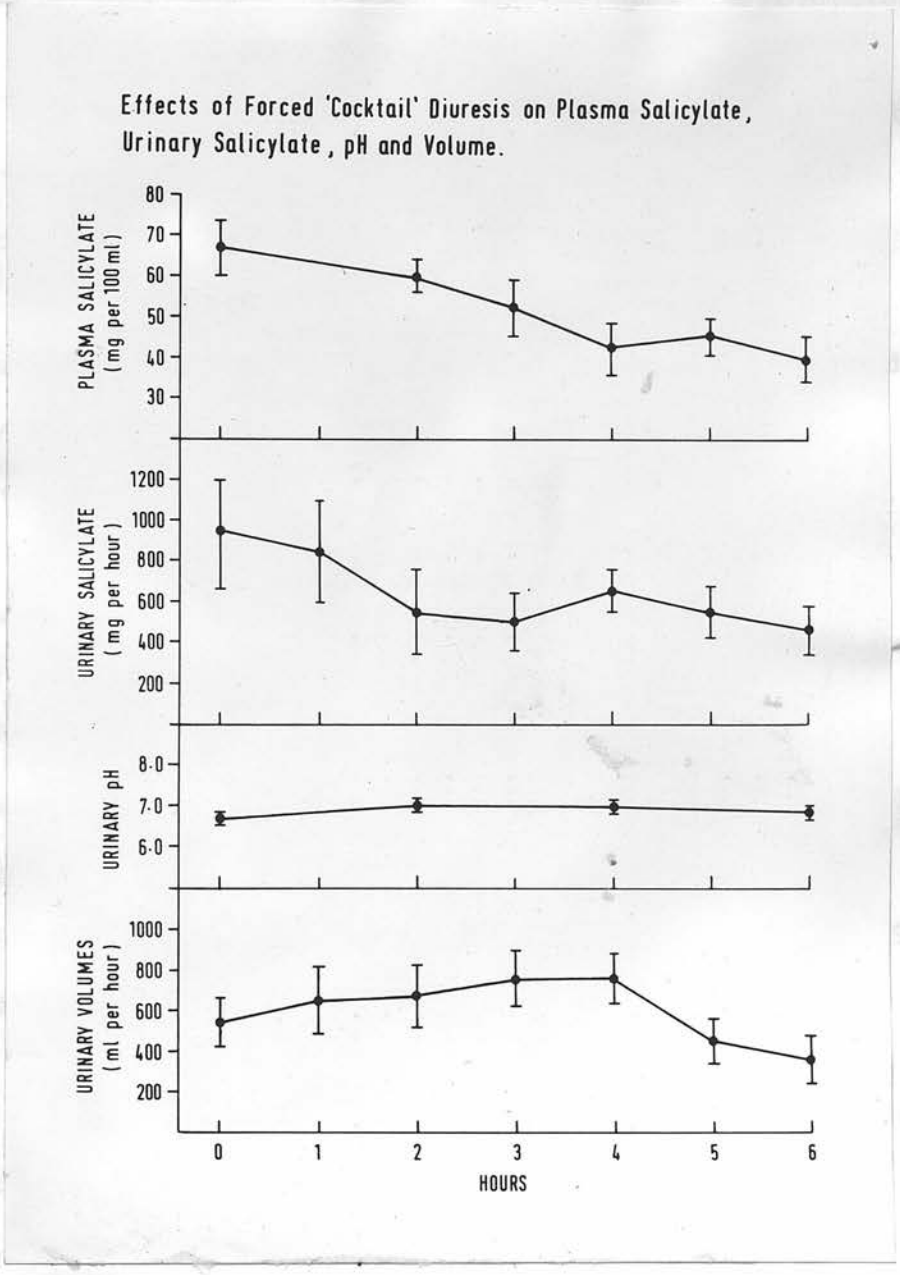

Figure 42.

Changes in mean values (± S.E.M.) of plasma and urinary salicylate, urinary pH and urine volumes in 13 patients treated with forced "cocktail" diuresis.

Changes in Acid-Base Status Relative to Changes in Salicylate

Results are shown in Table LIV and Fig. 43.

Of the six patients who were alkalotic before the start of treatment, four, 72, 76, 79 and 83, had a normal arterial pH during the course of treatment. The other two patients, 82 and 84, remained mildly alkalotic, but less so than at the start of treatment. Patient 75, who was initially acidotic, regained a normal pH; all the other patients continued with normal pH levels.

In all patients there was improvement in the levels of arterial pCO_2 and standard bicarbonate and in one patient 75 the pCO_2 became normal.

These improvements in acid-base status occurred as the treatment continued and as the plasma salicylate progressively fell.

Changes in Plasma Potassium and Urinary Potassium Relative to Changes in Arterial and Urinary pH.

Results are shown in Tables LIII and LV and in Fig. 44.

During the initial six hour period of treatment only two patients, 72 and 83, developed mild hypokalaemia and seven patients, 73, 74, 75, 79, 80, 81 and 82, showed slight increases in the plasma potassium. The mean values of plasma potassium plotted in Fig. 44 remained in normal limits. It is of interest to note that a number of the patients, who had plasma potassium levels done subsequent to the main diuresis period, did show significant reductions in the blood levels but with the exception of patient 72 the hypokalaemia was not severe. No patient showed any clinical

TABLE LIV

PATIENTS		ARTERIAL BLOOD GASES					
		pH		pCO_2 (mm/Hg)		Standard Bicarbonate (mEq per litre)	
		Peak Level	Lowest Level	Peak Level	Lowest Level	Peak Level	Lowest Level
MALES	72	7.48	7.45	28.0	22.0	20.0	20.0
	73	7.42	7.39	31.0	31.0	22.0	21.0
	74	7.42	7.40	34.0	30.0	23.0	21.5
	75	7.44	7.35	47.0	22.0	22.0	21.0
	76	7.46	7.42	25.0	20.0	20.0	20.0
	77	7.44	7.41	23.0	20.0	22.5	19.0
	78	7.42	7.40	24.0	21.0	24.0	19.0
FEMALES	79	7.53	7.43	28.0	16.0	23.0	19.0
	80	7.49	7.43	23.0	20.0	22.0	19.0
	81	7.42	7.39	26.0	21.0	21.0	18.0
	82	7.50	7.46	19.0	17.0	20.5	20.0
	83	7.47	7.43	22.0	19.0	22.0	20.0
	84	7.50	7.48	30.0	20.0	25.0	22.5

Acid-base changes during the period of observation in 13 patients treated with forced "cocktail" diuresis.

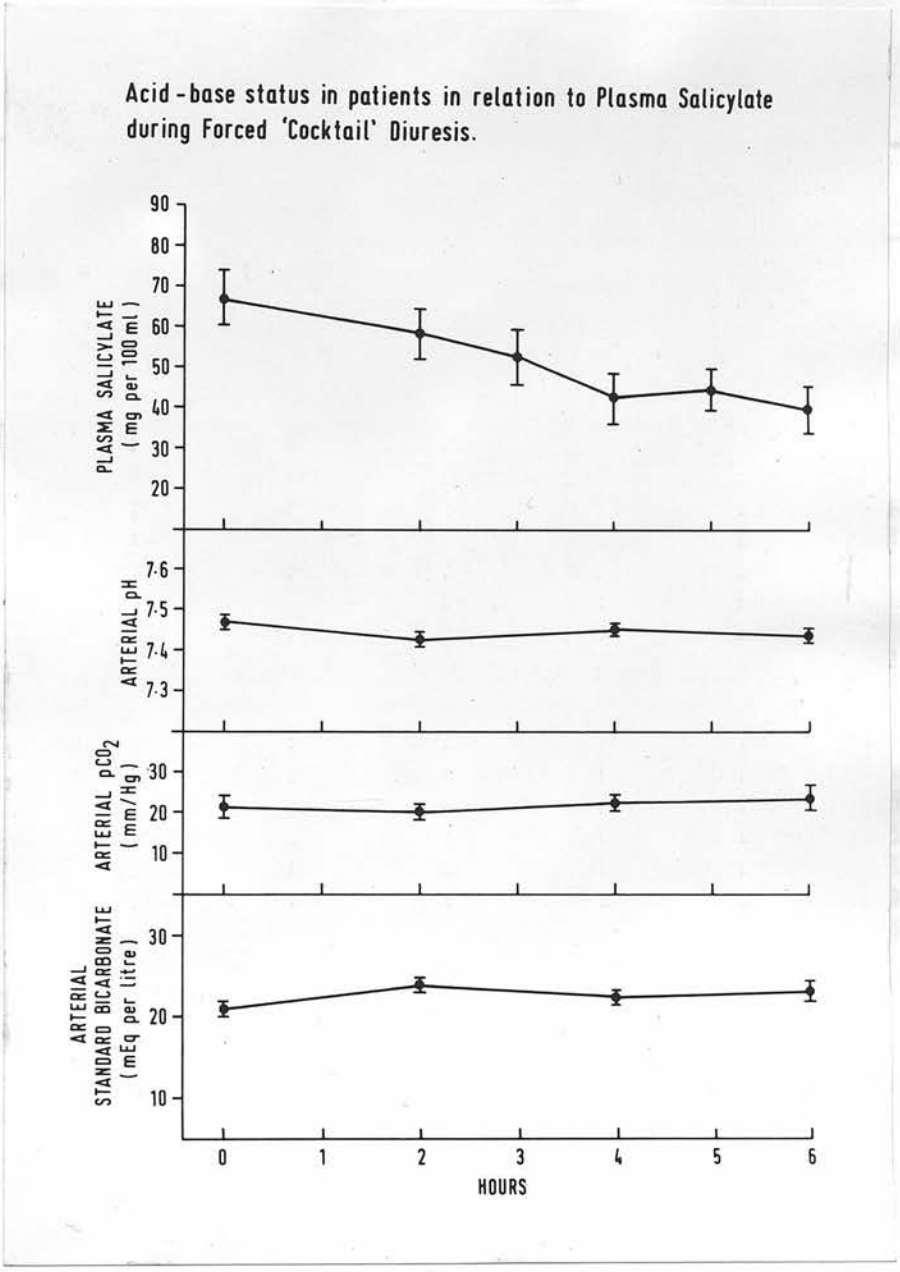

Figure 43.

Changes in mean values ($\pm$ S.E.M.) of plasma salicylate in relation to mean values (- S.E.M.) arterial pH, pCO_2 and standard bicarbonate in 13 patients treated with forced "cocktail" diuresis.

TABLE LV

PATIENTS		PLASMA POTASSIUM (mEq per litre)						
		Time (Hours)						
		Pretreatment						
		0	3	6	8	12	16	24
MALES	72	3.6	3.1	3.1		2.9		
	73	4.0	4.2	5.4		3.3		4.4
	74	3.8	4.2	4.4		3.6	3.5	3.2
	75	4.2	3.6	4.4			3.6	3.6
	76	4.4	4.3	4.0			3.4	4.1
	77	4.1	4.0	4.0			4.0	
	78	3.9	3.5	3.7			3.3	3.2
FEMALES	79	3.9	3.9	4.6				3.4
	80	4.3	4.4	4.4		3.2		3.3
	81	4.2	4.3	4.7		3.4		4.3
	82	3.8	3.9	5.0				3.2
	83	3.6	3.8	3.4			3.6	4.0
	84	4.2	3.6	3.6			3.2	4.3

Changes in plasma potassium in 13 patients treated with forced "cocktail" diuresis.

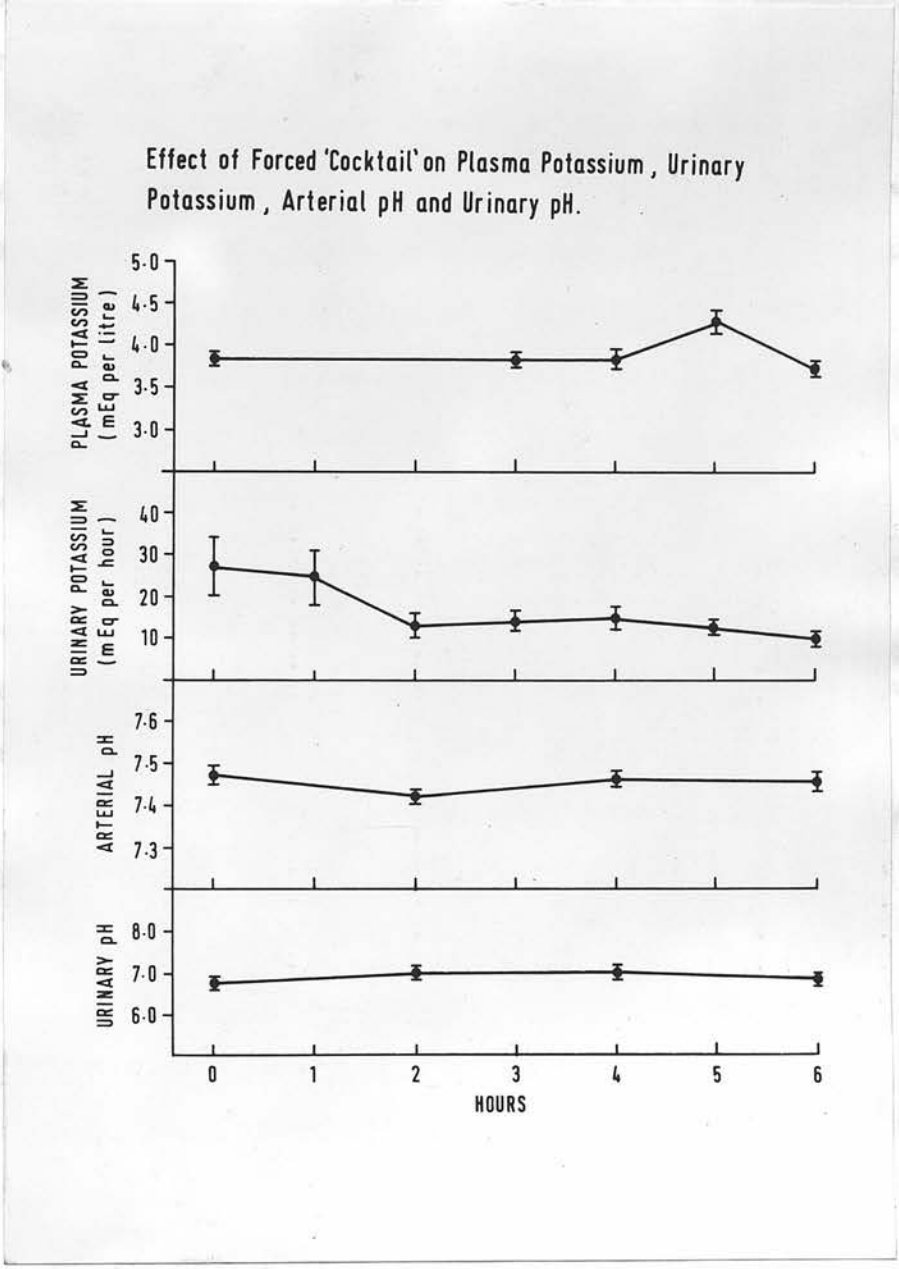

Figure 44.

Changes in mean values (± S.E.M.) of plasma and urinary potassium, arterial pH and urinary pH in 13 patients treated with forced "cocktail" diuresis.

evidence of hypokalaemia or tetany and all made an uneventful recovery.

After an initial peak loss of 25 mEq. of potassium per hour (Fig. 44) the mean urinary losses of this cation stabilised at approximately 15 mEq. per hour. The total losses of potassium in the urine are shown in Table LIII. The range was 65.0 to 161.0 mEq. with an average loss of 96.0 mEq.

There was no apparent relationship between the recorded levels of plasma and urinary potassium levels and changes in the arterial and urinary pH, which remained relatively steady throughout. It is important to note that, despite the reduction in the amount of alkali given in this regime, alkalinising effect on the urine was demonstrated in this group of patients. The average urinary pH remained about 7.0 and the highest level reached was 7.9.

Changes in Plasma Potassium, Magnesium, Calcium and Inorganic Phosphate in Relation to Arterial pH and P.C.V.

Results are shown in Tables LVI, LVII, LVIII and LIX and in Fig. 45.

The plasma magnesium tended to fall in all the eight patients studied. In only one patient, 80, did moderate hypomagnesaemia develop. This was transient and had spontaneously returned to normal after a further six hours. The total urinary excretion of magnesium over the initial six hours of treatment was small (Table LIII) and ranged from 4.0 to 30.0 mg. (mean 15.3 mg.) in six of the patients.

TABLE LVI

PATIENTS		PLASMA MAGNESIUM (mg. per 100 ml.)			
		Time (Hours)			
		Pretreatment			
		0	3	6	12
MALES	74	2.40	2.90	2.45	2.10
	75	2.70	2.50	1.95	2.20
	76	2.75	2.10	2.40	2.60
	77	2.45	2.25	2.00	2.10
FEMALES	79	2.95	2.80	2.25	2.60
	80	2.30	2.00	1.40	1.70
	82	2.45	1.90	1.96	
	83	2.25	1.90	2.10	2.35

Changes in plasma magnesium in 8 patients treated with forced "cocktail" diuresis.

TABLE LVII

PATIENTS		PLASMA CALCIUM (mg. per 100 ml.)				
		Time (Hours)				
		Pretreatment 0	3	6	12	24
MALES	72	8.7	8.5	7.8		
	74	8.0	7.4	7.4	7.4	8.8
	75	11.0	11.0	9.0	7.4	8.4
	76	10.9	9.8	7.4		8.6
	77	10.7	7.8	8.4	8.8	
	78	9.7	9.2	7.9	8.7	
FEMALES	79	9.9	10.5	8.0		9.2
	80	10.7	9.5	7.0		8.4
	81	8.6	6.7	7.0	7.0	7.6
	82	10.5	7.7	7.7		
	83	10.5	10.3	8.8		9.7
	84	9.9	8.9	8.2		

Changes in plasma calcium in 12 patients treated with forced "cocktail" diuresis.

TABLE LVIII

PATIENTS		PLASMA INORGANIC PHOSPHORUS (mg. per 100 ml.)				
		Time (Hours)				
		Pretreatment 0	3	6	12	24
MALES	74	3.8		3.2		
	76	3.9	3.8		2.6	
	77	3.8		2.8		
FEMALES	79	5.8	5.5	2.8	2.9	2.2
	80	2.4	3.0	1.1		1.9
	82	3.5		3.0		
	83	3.2	3.4	2.2		2.1

Changes in plasma inorganic phosphorus in 7 patients treated with forced "cocktail" diuresis.

TABLE LIX

		PACKED CELL VOLUME (%)						
PATIENTS		Time (Hours)						
		Pretreatment						
		0	2	4	6	12	16	24
MALES	72	46		44	42	37		42
	73	54	51		44			
	75	45	46	44	45	42		43
	76	42						
	77	42		37	34			
	78	54		47	45		43	
FEMALES	79	41			42	45	46	
	80	49		41	39		39	39
	83	45			42			
	84	46		40	40		44	

Changes in PCV in 10 patients treated with forced "cocktail" diuresis.

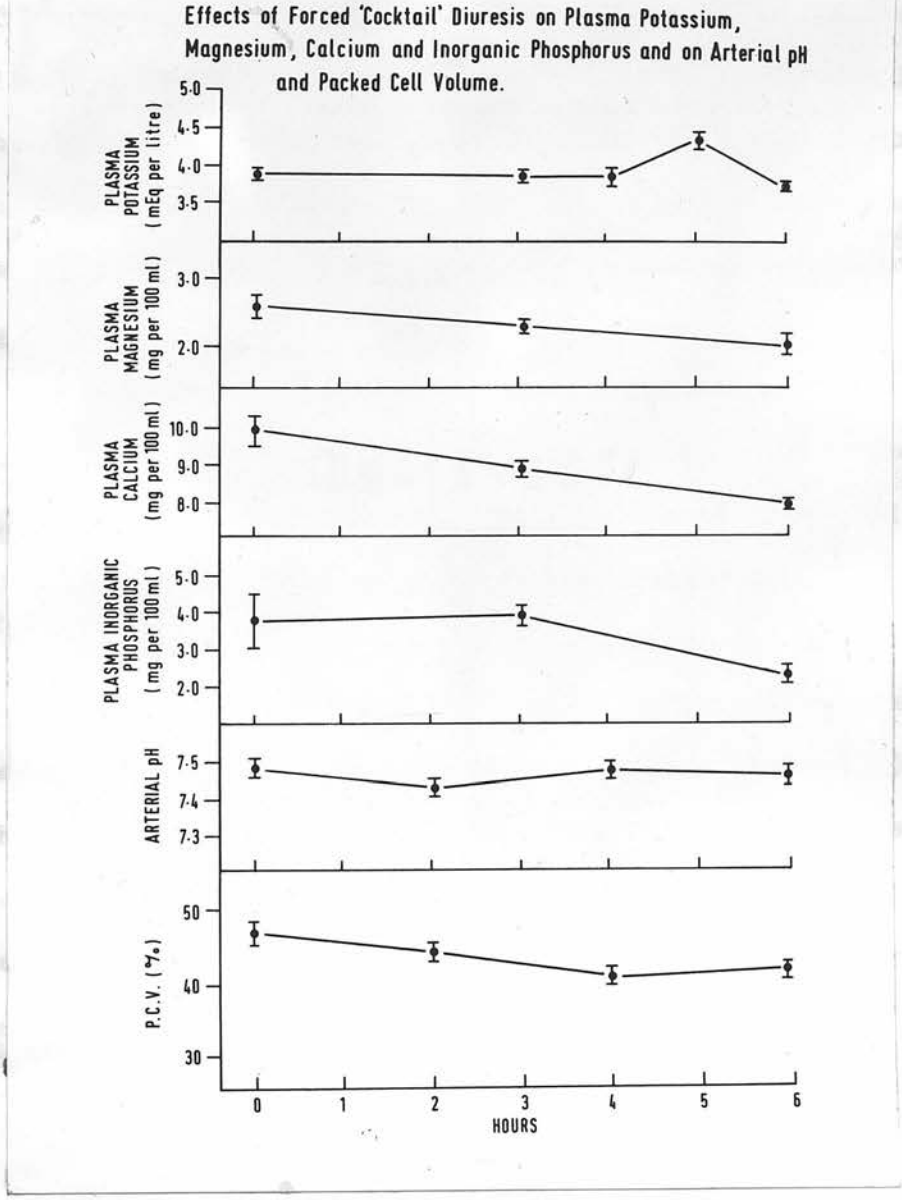

Figure 45.

Changes in mean values (± S.E.M.) of plasma potassium, magnesium, calcium and inorganic phosphorus, arterial pH and P.C.V. in patients treated with forced "cocktail" diuresis.

In the 12 patients, in whom the plasma calcium was monitored, eight developed hypocalcaemia within the first six hours of treatment, but within 24 hours the plasma calcium levels had risen spontaneously and in most cases were within the normal range. The values for urinary excretion of calcium in the first six hours in six patients are shown in Table LIII. As with magnesium, these were low and ranged from 23.0 to 40.0 mg. with an average of 34.6 mg.

Measurements of plasma inorganic phosphorus were made in six patients (Table LVIII). Only one, patient 80, developed significant hypophosphataemia. Within 24 hours this level had risen considerably without any phosphate replacement.

The falls in mean values of plasma magnesium, calcium and inorganic phosphorus (Fig. 45) all occurred during the first six hours. Similar changes occurred in the P.C.V. (Table LIX). The mean values are also plotted in Fig. 45. At six hours the reduction in P.C.V. was 11 per cent, in plasma magnesium 15 per cent, plasma calcium 20.5 per cent and inorganic phosphorus 42 per cent. No significant change was observed in arterial pH or plasma potassium.

Changes in Plasma and Urinary Sodium

Levels of plasma sodium were measured in all the 13 patients during the first six hours of treatment (Table LX). There were no significant changes in the plasma levels in 11 patients. In two, 73 and 79, who were slightly hyponatraemic before treatment, the plasma levels rose to normal within 2-4 hours and thereafter

TABLE LX

PATIENTS		PLASMA SODIUM (m.Eq. per litre) Time (Hours) 0	2	4	6
MALES	72	138	136	137	138
	73	133	132	140	146
	74	147	145	143	145
	75	139	140	136	138
	76	140	142	136	137
	77	135	138	136	140
	78	137	140	137	136
FEMALES	79	132	142	140	138
	80	141	138	136	142
	81	138	136	138	138
	82	140	140	136	138
	83	138	139	136	136
	84	142	140	140	142
Mean Values		138	139	138	140

Changes in plasma sodium in 13 patients treated with forced "cocktail" diuresis.

the levels were maintained. Urinary excretion of sodium during the first six hours varied considerably in these patients ranging from 58 to 316 mEq. (mean 162.9 mEq.).

Fluid Balance

Results are shown in Table LIII.

As in the other groups of patients treated there was a calculated fluid deficit varying in individual cases from 3.5 to 11.1 litres (mean 5.9 litres). All of the patients achieved a brisk diuresis and none were clinically severely dehydrated. A number of patients, however, had marked features of sweating and hyperpnoea and these features were particularly marked in patients 73, 78 and 82, who were estimated to have the greatest fluid deficits.

Discussion

Forced "cocktail" diuresis was a very effective means of reducing the plasma salicylate. The mean half excretion rate for salicylate was only slightly longer than that found with forced alkaline diuresis. The urine flow per minute achieved by forced "cocktail" diuresis was similar to that with forced saline-laevulose and forced alkaline diureses. The increased recovery of salicylate, therefore, compared with forced water diuresis, was almost certainly again associated with the relative alkalinisation of the urine which occurred. The urinary pH was stabilised above 7.0 for most of the peak diuresis, but in none of the patients did this rise above 8.0, which was regarded by

Cumming et al. (1964) as a danger level and indicative of over-enthusiastic bicarbonate administration. Also as the urine became more alkaline so the amounts of free salicylate excreted would be increased with more reduction in the toxic effects of the overdosage.

The acid-base changes which occurred during the course of this treatment, were very reassuring. In both the patients who initially were alkalotic and in one who was acidotic, there was a general trend for the arterial pH to return to a normal value. These trends continued throughout the period of treatment and it would therefore seem that in this regime, the amount of bicarbonate infused was sufficient to promote excretion of the salicylate without producing a dangerous metabolic alkalosis. It is probable that the improvements in arterial pH were related to the removal of salicylate rather than any more direct effects of the administered bicarbonate. The improvements in the arterial pCO_2 and standard bicarbonate levels also were greater than with the other regimes, which lends support to the supposition that the improvements in arterial blood gases were related to the reduction in plasma salicylate, particularly free salicylate.

Hypokalaemia was not found to be a problem in this group of patients. Low levels of plasma potassium were found in a number of patients, but these were not severe and there were no clinical features to suggest hypokalaemia in any of the patients. For these reasons, the changes in plasma potassium levels were not hazardous. The results indicated, however, that hypokalaemia may develop after the main period of diuresis has passed. It may therefore be necessary to continue potassium supplements for up to

24 hours after the start of diuresis therapy. In most patients it is possible to give adequate oral potassium supplements after about 6 hours and so any dangers, which may exist from intensive intravenous potassium administration, can be avoided. In this group of patients there were greater losses of potassium in the urine than with forced alkaline diuresis. A likely explanation is that because of the smaller amounts of bicarbonate infused and the reduced tendency to metabolic alkalosis with forced "cocktail" diuresis, there is a reduced cellular uptake of potassium. Any surplus of potassium given as supplements, therefore, will be excreted through the kidneys and, provided an adequate urine flow has been established, there is no hazard in the treatment.

As with changes in plasma potassium, hypomagnesaemia was not a prominent feature in these patients. As the urinary excretion of magnesium over the initial six hours of treatment was low, it may be assumed that no great shifts from the extracellular to the intracellular compartments were occurring with this cation.

Hypocalcaemia, however, was found in over 60 per cent of the patients studied. The hypocalcaemia was of a significant degree, but less severe than with the other regimes used in this investigation. It was a rather transient finding and within 24 hours the plasma levels had recovered spontaneously to normal values. The urinary excretion of calcium in the first six hours was not very great and was insufficient to explain the falls in plasma calcium. These more probably resulted from two other mechanisms; either as an effect of haemodilution or as a result of cellular and bone uptake of calcium ions in response to

alterations in acid-base state. From the changes in the packed cell volume, there was a suggestion that haemodilution may have been a significant factor in this group of patients. If a correction factor is introduced for the percentage fall in packed cell volume in the course of the six hour period the mean plasma calcium levels remain within the normal range. It is possible, therefore, that no true hypocalcaemia existed, but in the absence of more detailed studies on this aspect it is perhaps more appropriate to assume that all three factors, urinary excretion, haemodilution and ion shift, contributed to the levels of plasma calcium which were found.

A number of measurements were made of plasma inorganic phosphorus during the initial six hour period. Only one patient developed significant hypophosphataemia and again showed a spontaneous recovery. The mean levels of plasma inorganic phosphorus at no time fell below the lower limits of the normal range. It is of interest to note that in one patient only, patient 80, were hypomagnesaemia and hypocalcaemia and hypophosphataemia demonstrated simultaneously. The falls in these elements seemed to be related and in this patient also there was a considerable reduction in the packed cell volume. It is likely therefore that in this patient the reduction in levels of magnesium, calcium and inorganic phosphorus was largely due to haemodilution.

None of the patients in this group showed any features of tetany. This was not surprising in the light of the results noted in the previous groups of patients. With forced "cocktail"

diuresis there was less tendency for metabolic alkalosis and hypomagnesaemia was not demonstrated. Marked hypocalcaemia did occur, although in this case haemodilution may have been the most important cause. Even if this was not so, the absence of tetany may possibly be explained on the basis of relative increase in ionised calcium as a result of competition between salicylate and calcium for protein-building sites as has been discussed previously. An alternative explanation, is suggested by the results of the plasma inorganic phosphorus. The degree of ionisation of calcium is influenced by plasma phosphate concentration (Merrill, 1956). For this reason, the fall in the level of plasma phosphate simultaneous with the development of hypocalcaemia would tend to increase the ionised fraction of plasma calcium and to obviate the occurrence of tetany. The number of measurements on plasma inorganic phosphorus was limited and so there must be reservations about any conclusion drawn from these figures. It is interesting nevertheless, to speculate that similar changes in plasma phosphate may have occurred in the previous groups of patients treated with other regimes of therapy and may, therefore, have been a factor in preventing tetany.

As in all the other groups of patients which have been studied, considerable fluid deficits were found in these patients. There seemed to be a relationship between the intensity of clinical features observed, in particular sweating and hyperpnoea, and the degree of fluid deficit found. There is little doubt that the deficits were due to the marked increase in insensible fluid loss, which occurs in severe acute salicylate poisoning, as all of the patients established a good urinary flow within two hours of

starting the diuresis therapy.

Conclusion

Forced "cocktail" diuresis produced a satisfactory reduction of the plasma salicylate and a good urinary recovery of salicylate. Hypokalaemia was not a serious problem. Similarly hypomagnesaemia scarcely occurred with these patients and, although hypocalcaemia was observed, haemodilution was perhaps an important factor and calcium deficits may not have occurred to any significant degree. Although there was a general trend towards reduction in plasma inorganic phosphorus, true hypophosphataemia was demonstrated in only one patient and this was not sustained. Together with the improvement in levels of plasma salicylate, the acid-base status of all patients, irrespective of what the initial arterial pH level was, improved and in most cases the arterial pH returned to normal. The amount of bicarbonate infused in the therapy did not provoke significant degrees of metabolic alkalosis. Forced "cocktail" diuresis as described, is therefore a safe, yet effective method of treatment for patients with severe acute salicylate overdosage. It is a suitable regime for patients, in whom the acid-base disturbance results in systemic alkalosis and also for patients, who are acidotic.

COMPARISON BETWEEN THE EFFECTS OF FORCED ORAL FLUIDS, FORCED SALINE-LAEVULOSE DIURESIS, FORCED ALKALINE DIURESIS AND FORCED "COCKTAIL" DIURESIS

The results for these four major regimes have been described in detail on an individual basis, but in order to assess the effectiveness and dangers of the different regimes, it is necessary to compare the relative changes, which were found.

Clearance of Salicylate

The mean clearance values for salicylate during the six hour period following the commencement of treatment was calculated from the conventional clearance formula $\frac{UV}{P}$. The mean clearance values of salicylate for the four different groups were calculated from the mean urinary volume (ml. per minute), the mean plasma salicylate (mg. per ml. plasma) and the mean urinary salicylate (mg. per ml. urine) before treatment and at hourly intervals up to six hours after starting treatment. The results are plotted in Fig. 46. For both oral fluids and saline-laevulose diuresis, the clearance value of salicylate fell as the diuresis continued. In contrast, the clearance of salicylate with forced alkaline and forced "cocktail" diuresis had a tendency to rise as the diuresis proceeded. The clearance of salicylate with forced alkaline was rather better than with forced "cocktail" diuresis the average clearance of salicylate in the latter being 20 ml. per minute and in the former 25 ml. per minute. A similar comparison was found for the mean half excretion times for salicylate for the four regimes. These are shown in Table LXI.

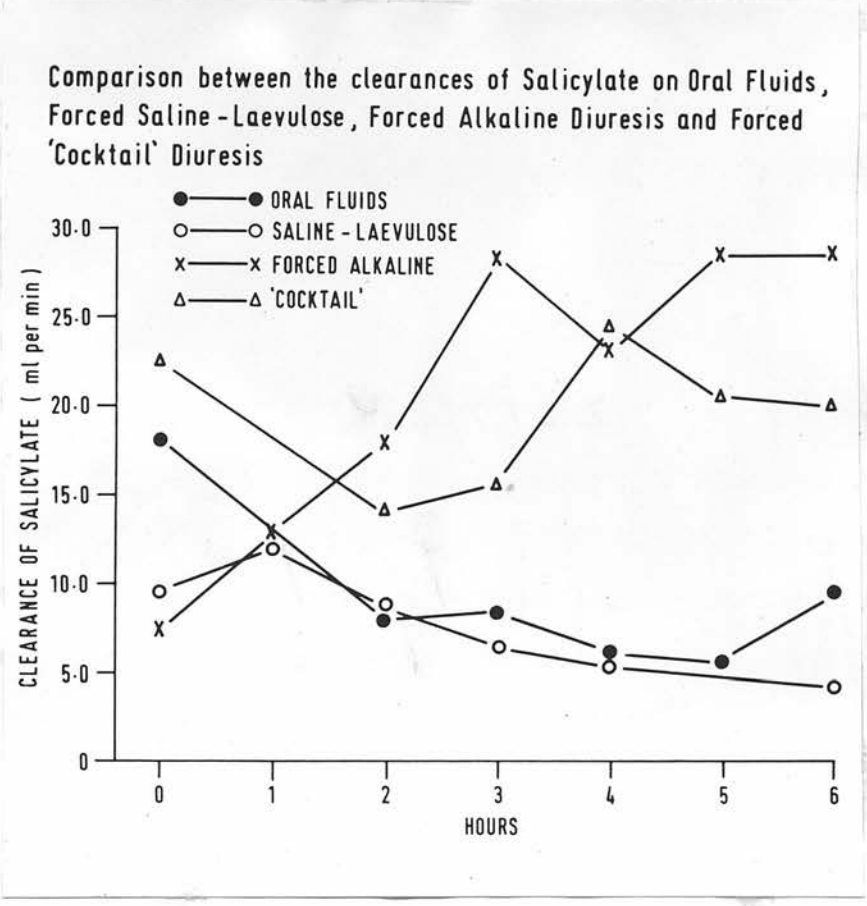

Figure 46.

Plots of the mean clearance values of salicylate with the four main types of treatment studied.

TABLE LXI

REGIME	Mean Half Excretion Time for Salicylate (Hours)
Forced Oral	22.0
Forced Saline-Laevulose	10.0
Forced Alkaline	5.0
Forced "Cocktail"	6.7

The mean half excretion times for salicylate calculated for the patients treated with forced oral fluids, forced saline-laevulose diuresis, forced alkaline diuresis with standard potassium supplements and forced "cocktail" diuresis.

Again forced alkaline diuresis was the best method for removing salicylate. Forced "cocktail" diuresis, however, was a close second and both these methods were clearly superior to both oral fluids and saline-laevulose diuresis. These results in respect of changes in salicylate levels corresponded well to the observations made on the clinical progress of the patients. With forced alkaline and forced "cocktail" diureses the patients obtained rapid relief of symptoms of salicylism, but with the other two types of treatment symptoms tended to persist.

Clearances of Potassium

The clearance of potassium was calculated in a similar way to the clearance of salicylate for the four different regimes. The results are plotted during the first six hour period of treatment in Figure 47. Before treatment for oral fluids, saline-laevulose diuresis and forced "cocktail" diuresis the high levels of potassium clearance almost certainly can be explained on the basis of collections of urine not representing an acurate one hour period. The clearance values of potassium were similar for the four regimes of treatment. The highest clearance of potassium was with forced "cocktail" diuresis and averaged 70 ml. per minute. That for forced saline-laevulose diuresis was 60 ml. per minute, for forced alkaline diuresis, 55 ml. per minute, for forced oral fluids was 50 ml. per minute. The reason for the relatively low clearance of potassium with forced alkaline diuresis was probably related to the administration of large amounts of bicarbonate in that regime, which would result in a large cellular uptake of

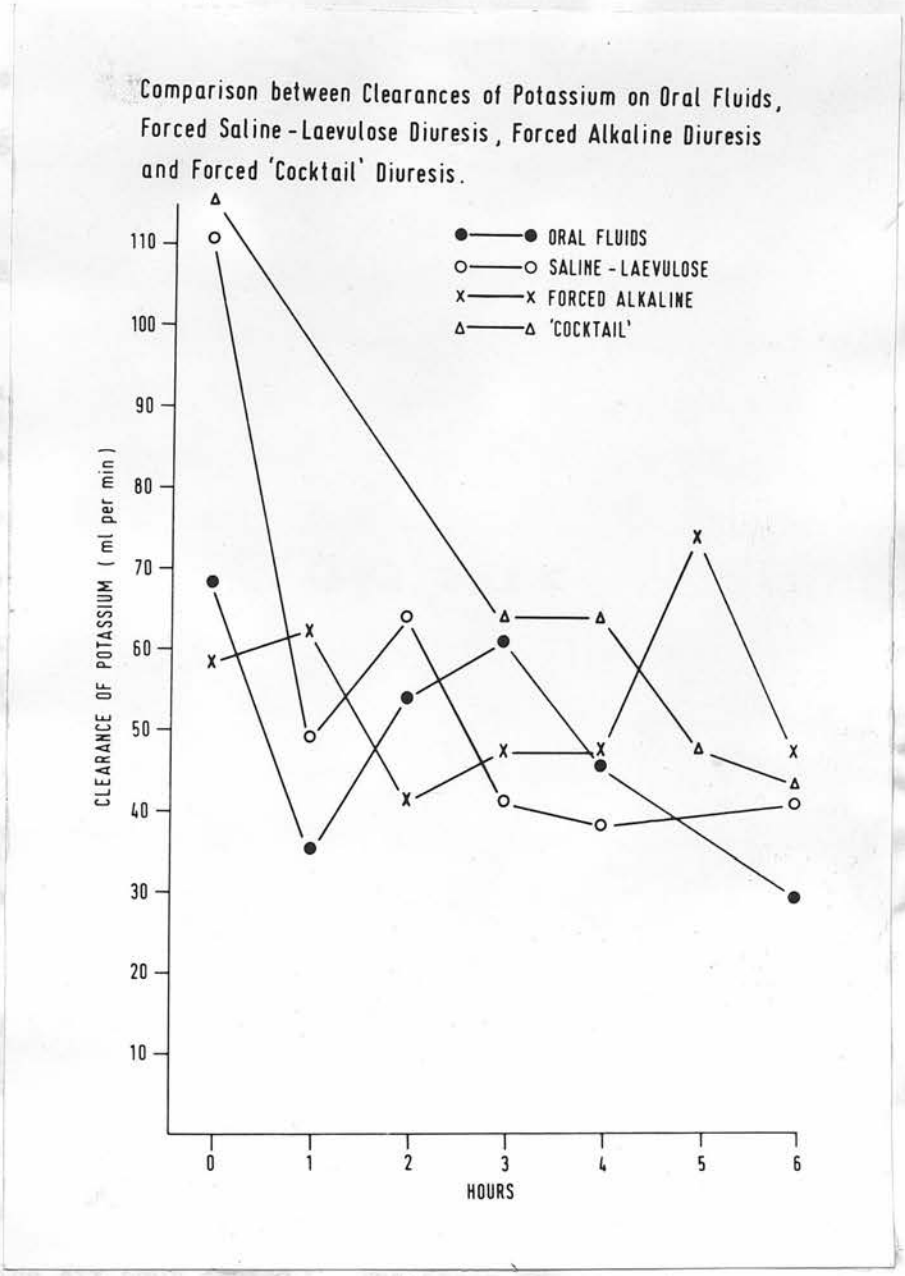

Figure 47.

Plots of the mean clearance values of potassium with the four main types of treatment studied.

potassium from the extracellular fluids. The reduced clearance of potassium with forced oral fluids can be readily explained on the basis of a lower urine flow compared with the other three regimes.

Changes in Plasma Potassium, Magnesium and Calcium

The changes in mean values are plotted in Figure 48. The least change in plasma potassium in the first six hours of treatment occurred with the forced "cocktail" diuresis and the greatest changes were found, when using forced alkaline diuresis. The other two regimes were intermediate in their effects on plasma potassium. Significant and at times severe levels of hypokalaemia were found from the third hour onwards with forced alkaline diuresis and to a lesser extent with forced oral fluids. In contrast, the levels of plasma potassium remained normal when using forced "cocktail" diuresis.

Similar findings were obtained when the four regimes were compared in respect of plasma magnesium. Forced "cocktail" diuresis did not cause any significant hypomagnesaemia, whereas forced alkaline diuresis was associated with marked falls in plasma magnesium from the third hour of treatment until the end of the six hour period. The other two regimes were again intermediate in effect, though in this case, forced saline-laevulose was rather similar to forced alkaline diuresis and forced oral fluids similar to forced "cocktail" diuresis.

With all the four types of treatment the plasma calcium levels fell during the second half of the main diuresis period.

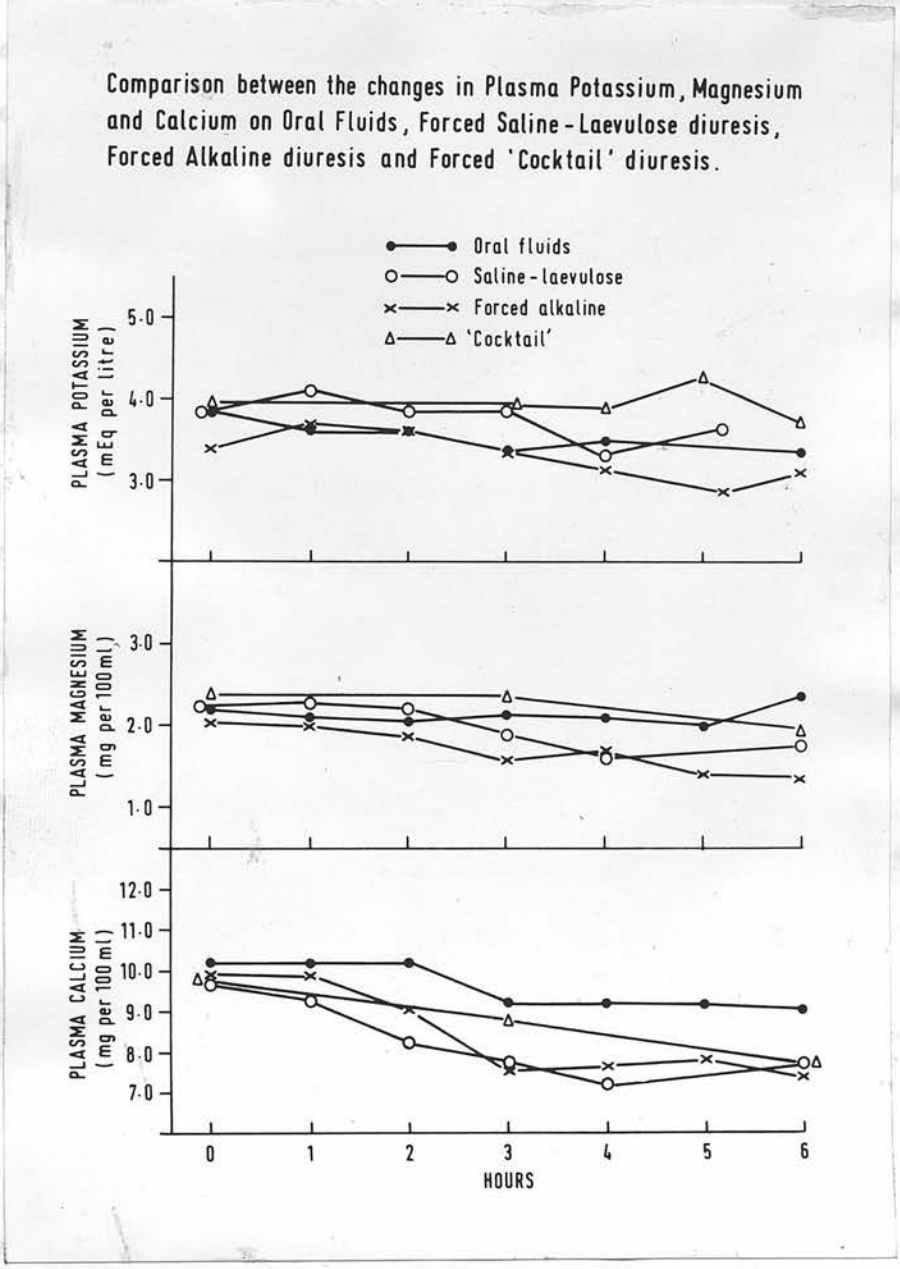

Figure 48.

Comparison between the mean changes in plasma potassium, magnesium and calcium, which occurred with the four regimes of therapy.

The least change was caused by forced oral fluids and forced "cocktail" diuresis. The changes with forced alkaline and forced saline-laevulose diuresis were more severe, but it should be noted that at the end of the six hour period there was little difference between the levels of plasma calcium in the three intravenous infusion regimes. Haemodilution, however, was probably an important factor in the hypocalcaemia with forced "cocktail" diuresis but only to a small degree with forced saline-laevulose and forced alkaline diuresis. If the plasma calcium, in the case of forced "cocktail" diuresis, was corrected for this degree of haemodilution, the levels were within the normal range.

Changes in Urinary Volume, Arterial pH, Urinary pH and P.C.V.

The results are plotted for the mean values over the initial six hours of treatment in Fig. 49.

All three regimes in which similar infusion rates were given resulted in similar urinary flows, and from this point of view they were highly comparable. The urine flow with forced oral fluids as had been expected was considerably less than with the other three regimes.

In terms of arterial pH, only forced alkaline diuresis caused a dramatic change. With this form of treatment severe degrees of metabolic alkalosis were produced, which were perhaps all the more important as they occurred over short periods of time. The other three regimes caused much less changes in H^+ concentration and the pH values remained more or less within the normal range.

Regarding urinary pH, forced alkaline and forced "cocktail"

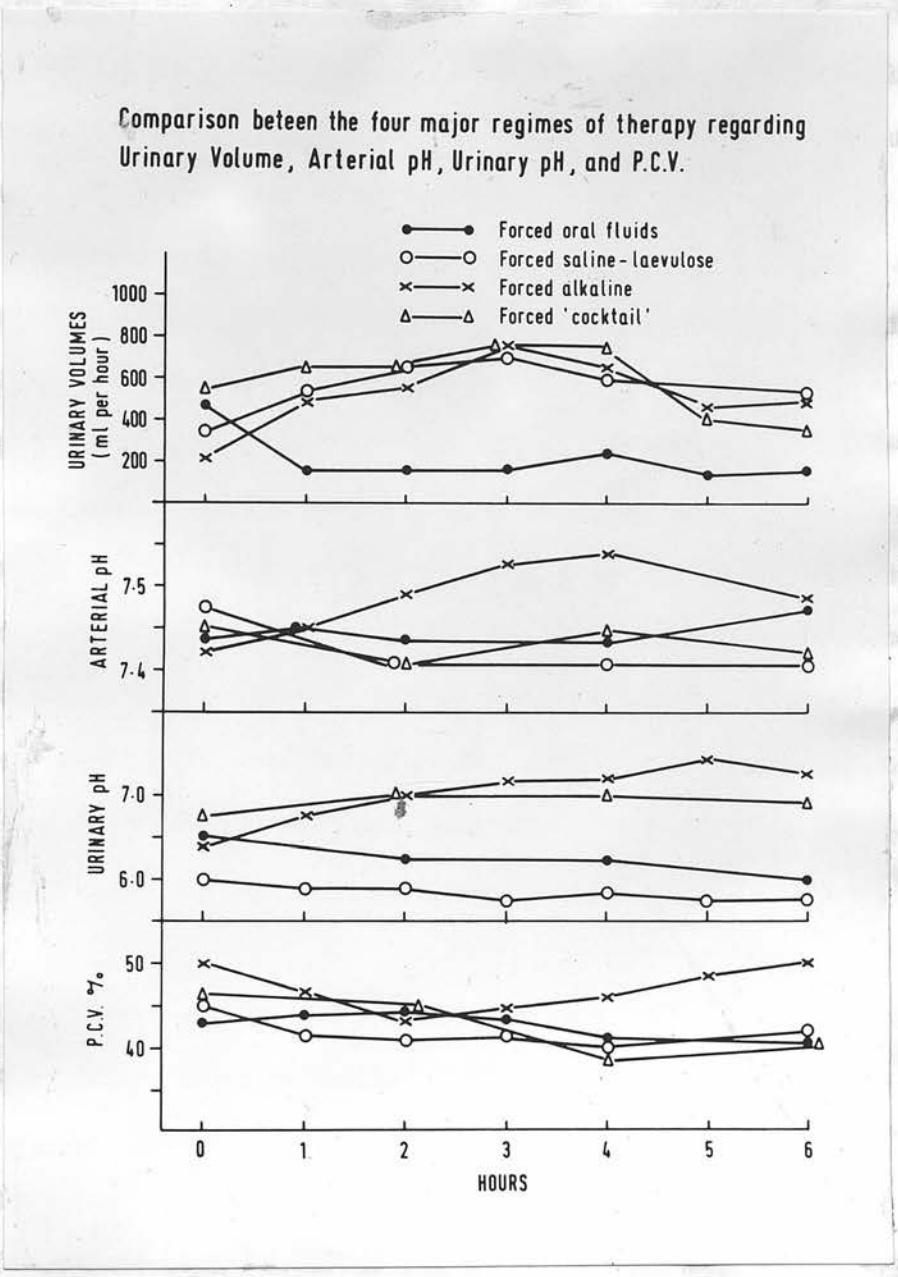

Figure 49.

Comparison between the mean changes in urinary volumes, arterial pH and P.C.V., which occurred with the four forms of treatment.

diureses caused a significant degree of alkalinisation of the urine which was rather more marked with the former. Forced saline-laevulose and forced oral fluids failed to achieve this beneficial effect and indeed with these two treatments the urine tended to become more acid.

The changes in packed cell volume noted with forced "cocktail", forced saline-laevulose and oral fluids were relatively similar. All of them showed a reduction, the nadir of the curve occurring approximately four hours after starting treatment. With forced alkaline diuresis the packed cell volume fell earlier at two hours, but thereafter it showed a steady and progressive increase to the end of the six hour period. As the main falls in plasma potassium, magnesium and calcium occurred between four and six hours after starting treatment haemodilution may have been a factor in all the regimes, with the exception of forced alkaline diuresis.

Fluid Deficit

The calculated fluid balance at the end of the total diuresis period in all cases indicated the presence of a significant fluid deficit. There were considerable variations in severity of this but it was a uniform and regular finding. The causes of this fluid deficit have been discussed and it would seem likely that quite apart from any factor of initial dehydration due to factors such as vomiting the main cause of the fluid deficit is increased insensible water loss as a result of increased sweating and hyper-ventilation. Throughout the study there was impression that the magnitude of the estimated fluid deficit was directly related to

the severity of the poisoning. In order to test out this suggestion the relationship between the estimated fluid deficit and the peak plasma salicylate level in 33 consecutive severely poisoned patients was calculated (Figure 50). A significant relationship was found ($r = 0.72$; $p = < .001$). The state of the fluid balance, therefore, will provide an additional means of assessing patients with severe salicylate poisoning. It is, of course, a retrospective means of assessment; but for purposes of research studies may be of some value.

Conclusion

Experts agree that the treatment of patients with severe acute salicylate poisoning should be primarily directed to increasing the removal rate of the salicylate. There is great controversy, however, about the most appropriate method of achieving this. The fact that all the patients studied had significant fluid deficits makes treatment with one or other method of forced iuresis the most rational form of treatment, in so far as these regimes will correct the initial dehydration and will also compensate for any continued losses of fluid as a result of sweating and hyperventilation. It is difficult, if not impossible, to assess these losses on a clinical basis and if such regimes as peritoneal dialysis, exchange transfusion, ion exchange resin or even haemodialysis are used, this factor may be overlooked.

Forced diuresis therapy for the treatment of patients with acute salicylate poisoning, therefore, must remain the most

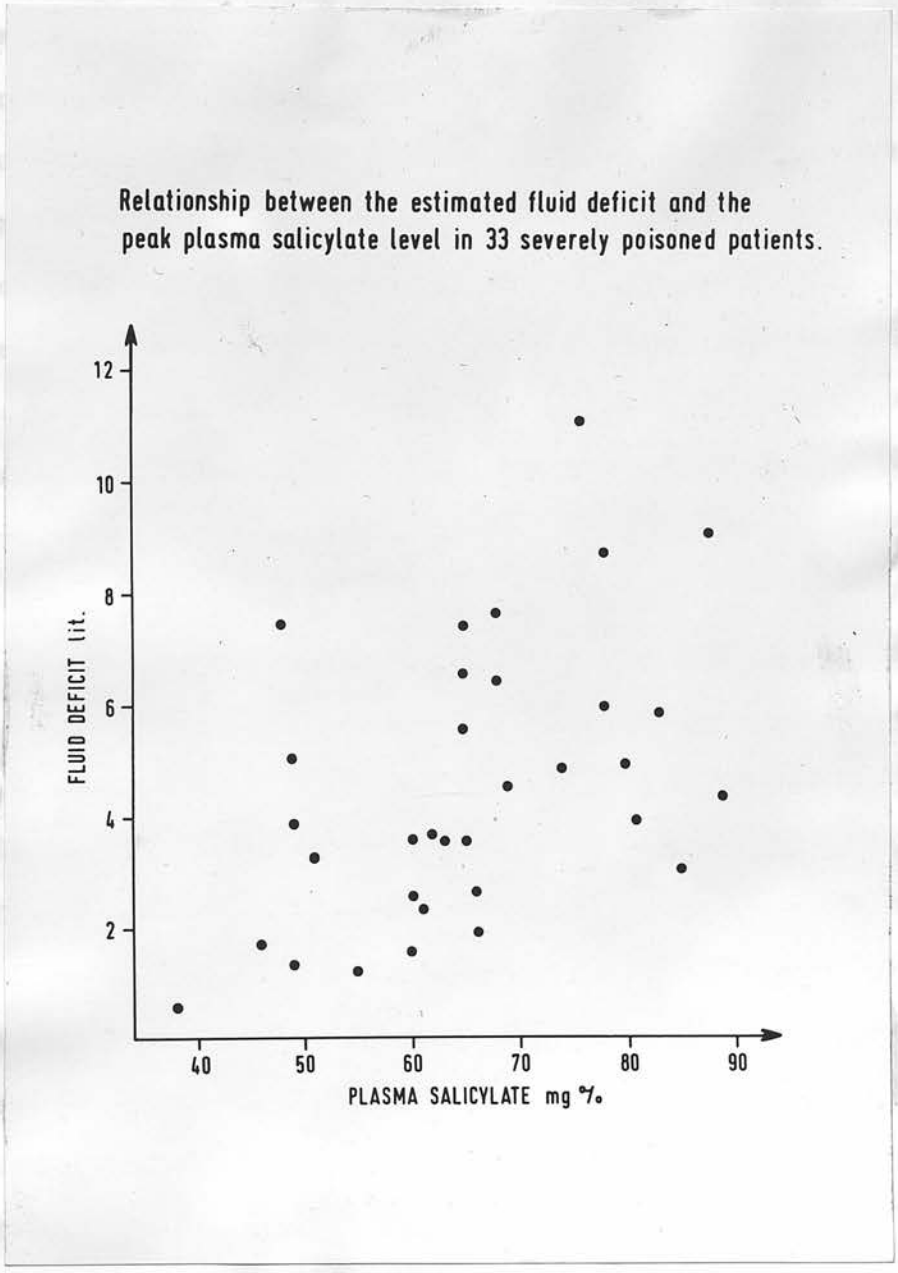

Figure 50.

Relationship between the estimated fluid deficit and the peak plasma salicylate level in 33 patients with severe salicylate poisoning.

attractive form of treatment. As has been explained, the vast majority of patients with this poisoning are in the younger age groups and it is quite exceptional to encounter patients who have sufficiently severe renal, cardiac or respiratory disorders to prevent the safe and effective use of this treatment. No matter how elaborate and effective the artificial means of removing salicylate are, or how expertly they are used, none of them can compare with healthy kidneys. The patients own normal kidneys are also much more efficient in regulating the excretion and conservation of fluids and electrolytes and in the maintenance of acid-base balance.

In this series of investigations several different regimes of forced diuresis have been studied in some detail. A method has been developed which is a modification of that advocated by Dukes et al. (1963). This has been called, for simplicity, forced "cocktail" diuresis. It is both effective and safe and is, therefore, suitable not only for use in major hospitals, where there is readily available, adequate biochemical and medical expertise, but also in small hospitals, where facilities for close biochemical monitoring of patients is limited. The regime of forced "cocktail" diuresis although marginally less effective than forced alkaline diuresis in reducing the plasma salicylate level has the great advantage of causing insignificant changes in acid-base balance and in plasma potassium and magnesium. It is probable also that any changes found in plasma calcium are of little importance. This regime, therefore, may be used safely with the minimum of biochemical monitoring, although clearly, where this is available, it would be desirable that it should be done.

A further important advantage of the regime is that it is effective for even very severely poisoned patients. Hence it provides a suitable alternative form of treatment to the use of the artificial kidney and will thereby reduce the burden on the use of that machine. Acute salicylate poisoning is sufficiently common for this consideration to be important. Only where there is a direct contra-indication to the use of forced diuresis, such as the presence of renal failure, severe cardiovascular disorder and pulmonary oedema should there be resort to the use of the artificial kidney or some other artificial means of removing salicylate from the body. On rare occasions when the patient is very severely poisoned or is not responding to forced "cocktail" diuresis at a sufficiently satisfactory rate, the method may be effectively combined with either peritoneal dialysis or haemodialysis itself. In this way a maximum intensity treatment is achieved.

Because of the admission arrangements to the Poisoning Treatment Centre, Royal Infirmary, Edinburgh, the results given in this report refer to observations made on older children and adults. The regimen of forced "cocktail" diuresis, therefore, applies to these groups of patients only. On the other hand, the metabolic disturbances in infants and young children are basically the same, although the metabolic acidosis may be more extreme and may appear earlier. The principles of treatment are similar and with appropriate adjustments in quantity to suit the size and age of the patient a regime of forced "cocktail" diuresis could also be devised for paediatric use.

Little reference has been made to the psychiatric management of patients with acute salicylate poisoning. In older children above the age of 12 and in adults the great majority of patients are suffering from intentionally self-administered poisoning. Some of these seriously wish to die and so are truly attempting suicide, but the great majority are suffering from self-poisoning described by Kessel (1965). The precipitating factor is usually some crisis situation, which in expert hands, can often be relieved quickly and satisfactorily. The various factors, which require consideration in the psychiatric management of these patients, are complex and beyond my scope as a physician. Suffice it to comment that any patient, who has intentionally taken an overdosage of any toxic substance, must be given the benefit of expert psychiatric advice as a matter of urgency. Failure to provide this, is failure to manage the patient adequately.

ACKNOWLEDGEMENTS

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The modern management of patients with severe poisoning and the intensity of investigation such as has been described in this thesis must, of necessity, involve closely integrated team-work. I am therefore very grateful to the many members of the medical and nursing staff of the Poisoning Treatment Centre, who have helped me so generously with the collection of samples and the general care of the patients. In particular I should like to thank Drs. A.T. Proudfoot and A.G. Fraser for their assistance and for valuable discussions together.

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I should like to express my appreciation to Professor J.A. Strong for the helpful discussion we had together regarding

certain of the metabolic considerations, which emerged from the results.

I am grateful to E. & S. Livingstone Ltd., Edinburgh for their permission to reproduce Figure 1 from their book "Treatment of Common Acute Poisonings". I also thank J. & A. Churchill, London, and Dr. H. Campbell for their kind permission to reproduce Figures 4, 6, 7 and 8 from their publication, "Salicylates - An International Symposium.".

Finally I should also like to express my gratitude to Miss N. Collins for her patience and care in typing the manuscript.

REFERENCES

ABRAMSON, E. and ARKY, R. (1966). "Diabetic Acidosis with Initial Hypokalaemia. Therapeutic Implications". J. Am. med. Ass. 196, 401.

ALEXANDER, J.K., SPALTER, H.J. and WEST, J.R. (1955). "Modification of the Respiratory Response to Carbon Dioxide by Salicylate." J. Clin. Invest. 34, 533.

ANDERSON, J.A., LEE, H.A. and STROUD, C.E. (1965). "Haemodialysis in Infants and Small Children." Brit. med. J. 1, 1405.

ARNOLD, F.J., HODGES, J.B., BARTA, R.A., SPECTOR, S., SUNSHINE, I. and WEDGEWOOD, R. (1959). "Evaluation of the Efficacy of Lavage and Induced Emesis in Treatment of Salicylate Poisoning". Pediatrics 23, 286.

BARNETT, H.L., POWERS, J.R., BENWARD, J.H. and HARTMANN, A.F. (1942). "Salicylate Intoxication in Infants and Children". J. Pediat. 21, 214.

BEAUMONT, J.L., WILLIE, A. and LENEGRE, J. (1955). "Influence de l'Acide Acetyle salicylique sur l'Hemostase". Bull. Soc. Med. Hop. Paris 71, 1077.

BEN-ISHAY, D. (1964). "Aminoaciduria Induced by Salicylates". J. Lab. clin. Med. 63, 924.

BERGSTROM, W.H. (1956). "The Skeleton as an Electrolyte Reservoir". Metabolism 5, 433.

BERLINER, R.W. and KENNEDY, T.J. (1948). "Renal Tubular Secretion of Potassium in the Normal Dog". Proc. Soc. Exper. Biol. and Med. 67, 542.

BERLINER, R.W., KENNEDY, T.J. and ORLOFF, J. (1951). "Relationship between Acidification of the Urine and Potassium Excretion". Amer. J. Med. 11, 274.

BERMAN, L.B., JEGHERS, H.J., SCHREINER, G.E. and PALLOTTA, A.J. (1956). "Haemodialysis, Effective Therapy for Acute Barbiturate Poisoning". J. Amer. med. Ass. 161, 820.

BEVERIDGE, G.W., FORSHALL, W., MUNRO, J.F., OWEN, J.A. and WESTON, I.A.G. "Acute Salicylate Poisoning in Adults". Lancet, 1, 1406.

BRACEY, D.W. (1951). "Acute Renal Failure. Two Cases Treated by Decapsulation and Peritoneal Dialysis". Brit. J. Surg. 38, 482.

BREAKEY, B.H., WOODRUFF, M.W. and REUS, W.F. (1961). "The Adaptability of the Kolff Twin Coil Artificial Kidney for Dialysis in Infancy". J. Urol. 86, 304.

BRIGGS, A.P. and FINDLEY, T. (1967). "Normal Acid-Base Regulations and Derangements in Fixed Anion Acidosis". Metabolism 16, 697.

BRODIE, B.B., UDENFRIEND, S. and COBURN, A.F. (1944). "Determination of Salicylic Acid in Plasma". J. Pharmacol. exp. Ther. 80, 114.

BROWN, S.S., CAMERON, J.C. and MATTHEW, H. (1967). "Plasma Salicylate Levels in Acute Poisoning in Adults". Brit. med. J. 1, 738.

BRUTON, O.C. (1958). "Exchange Transfusion for Acute Poisoning". U.S. Armed Forces M.J. 9, 1128.

CAMPBELL, E.J.M. and MACLAURIN, R.E. (1958). "Acute Renal Failure in Salicylate Poisoning." Brit. med. J. 1, 503.

CLARK, L.C., FINLEY, S.C., DAVIS, S.R. and FINLEY, W.H. (1961). "The Removal of Salicylate from the Blood by an Anion Exchange Resin". Amer. J. Dis. Child. 102, 605.

CLEMMESEN, C. and NILSSON, E. (1961). "Therapeutic Trends in the Treatment of Barbiturate Poisoning. The Scandinavian Method". Clin. Pharmacol. Ther., 2, 220.

COOKE, R.E., SEGAR, W.E., CHEEK, D.B., CORILLE, F.E. and DARROW, D.C. (1952). "The Extrarenal Correction of Alkalosis Associated with Potassium Deficiency". J. Clin. Invest. 31, 798.

CRAIG, J.O., FERGUSON, I.C. and SYME, J. (1966). "Infants, Toddlers and Aspirin". Brit. med. J. 1, 757.

CUMMING, G. (1961). "The Medical Management of Acute Poisoning". p. 85, Cassell, London.

CUMMING, G., DUKES, D.C. and WIDDOWSON, G. (1964). "Alkaline Diuresis in Treatment of Aspirin Poisoning". Brit. med. J. 2, 1033.

CURRY, J.S. (1965). "Symposium - Identification of Drugs and Poisons". p. 46, London.

DAVIS, P.L. and SMITH, P.K. (1951). "Relation of the Rate of Excretion of Salicylate to Urinary Acidity". Arch. internat. pharmacodyn. 86, 303.

DONE, A.K. (1960). "Salicylate Intoxication: Significance of Measurements of Salicylate in Blood in Cases of Acute Ingestion". Pediatrics 26, 800.

DONE, A.K. (1963). "Ontogenetic Studies of Salicylate Intoxication" in Salicylates. An International Symposium. Boston, Little, Brown, p.260.

DONE, A.K. (1965). "Salicylate Poisoning". J. Am. Med. Ass., 192, 770.

DONE, A.K. and OTTERNESS, L.J. (1956). "Exchange Transfusion in the Treatment of Oil of Wintergreen (Methyl Salicylate) Poisoning." Pediatrics, 18, 80.

DOOLAN, P.D., MURPHY, W.P., WIGGINS, R.A., CARTER, N.W., COOPER, W.C., WATTEN, R.H. and ALPEN, E.L. (1959). "An Evaluation of Intermittent Peritoneal Lavage". Am. J. Med. 26, 831.

DOOLAN, P.D., WALSH, W.P., KYLE, L.H. and WISHINSKY, H. (1951). "Acetyl salicylic Acid Intoxication. A Proposed Method of Treatment." J. Am. Med. Ass. 146, 105.

DUKES, D.C., BLAINEY, J.D., CUMMING, G. and WIDDOWSON, G. (1963). "The Treatment of Severe Aspirin Poisoning". Lancet, 2, 329.

DUVAL, M. and LEVEAU, J. (1962). "A propos d'un Cas d'Intoxication par l'Acide Acetyl salicylique Traité par le THAM." Arch. Francaise de Pediatrie 19, 795.

EICHENHOLZ, A., MULHAUSEN, R.O., ANDERSON, W.E. and MACDONALD, F.M. (1962). "Primary Hypercapnia: A Cause of Metabolic Acidosis." J. Appl. Physiol. 17, 283.

EICHENHOLZ, A., MULHAUSEN, R.O. and REDLEAF, P.S. (1963). "Nature of Acid-Base Distrubance in Salicylate Intoxication". Metabolism 12, 164.

ELKINGTON, J.R., SINGER, R.B., BARKER, E.S. and CLARK, J.R. (1955). "Effects in Man of Acute Experimental Respiratory Alkalosis and Acidosis on Ionic Transfers in the Total Body Fluids". J. Clin. Invest. 34, 1671.

ELLIOT, G.B. and CRIGHTON, J.U. (1960). "Peritoneal Dialysis in Salicylate Intoxication". Lancet 2, 840.

"Emergency Treatment in Hospital of Cases of Acute Poisoning" Central Health Services Council (1962). H.M.S.O., London.

ERGANIAN, J.A., FORBES, G.B. and CASE, D.M. (1947). "Salicylate Intoxication in the Infant and Young Child". J. Pediat. 30, 129.

ETTELDORF, J.N., DOBBINS, W.T., SUMMIT, R.L. RAINWATER, W.T. and FISCHER, R.L. (1961). "Intermittent Peritoneal Dialysis Using 5 per cent Albumin in the Treatment of Salicylate Intoxication in Children. J. Pediat. 58, 226.

ETTELDORF, J.N., MONTCALVO, J.M., KAPLAN, S. and SHEFFIELD, J.A. (1960). "Intermittent Peritoneal Dialysis in the Treatment of Experimental Salicylate Intoxication". J. Pediat. 56, 1.

FEUERSTEIN, R.C., FINBERG, L. and FLEISHMAN, E. (1960). "The Use of Acetazolamide in the Therapy of Salicylate Poisoning". Pediatrics 25, 215.

FISKE, C.H. and SUBBARROW, Y. (1925). "The Colorimetric Determination of Phosphorus". J. Biol. Chem. 66, 375.

FORLAND, M. and PULLMAN, T.N. (1963). "Electrolyte Complications of Drug Therapy". Med. Clin. N. Amer. 47, 113.

FREIER, S., NEAL, B.W., NISBET, H.I.A., REES, G.J. and WILSON, F. (1957). "Salicylate Intoxication Treated with Intermittent Positive-Pressure Respiration". Brit. med. J. 1, 1333.

FRICK, P.G. (1956). "Haemorrhagic Diathesis with Increased Capillary Fragility Caused by Salicylate Therapy". Am. J. med. Sci. 231, 402.

GAMBLE, J.L. and ROSS, S.G. (1925). "The Factors in the Dehydration following Pyloric Obstruction". J. Clin. Invest. 1, 403.

GAULTIER, M., FOURNIER, E., GERVAIS, P. and BIGNON, J. (1963). "Les Indications du THAM dans le Traitement des Intoxications Aigues". Therapie, 18, 849.

GHOSE, R.R. and JOEKES, A.M. (1964). "Treatment of Severe Aspirin Poisoning without Dialysis". Lancet, 1, 1409.

GHOSE, R.R. (1967). "The Significance of Acid-base Measurements in the Management of Salicylate Intoxication". Post grad. med. J. 43, 454.

GITELMAN, H.J. (1967). "An Improved Automated Procedure for the Determination of Calcium in Biological Specimens". Analyt. Biochem. 18, 521.

GOLDSTEIN, A. (1949). "Interactions of Drugs and Plasma Proteins". Pharmacol. Rev. 1, 102.

GOODMAN and GILMAN, (1965). "The Salicylates" in The Pharmacological Basis of Therapeutics. p. 327. The Macmillan Company, New York.

GRAHAM, J.D.P. (1967). "Poisoning in the Home". Brit. med. J. 1, 157.

GRANVILLE-GROSSMAN, K.L. and SERGEANT, H.G.S. (1960). "Pulmonary Oedema due to Salicylate Intoxication". Lancet, 1, 575.

GREER, H.D., WARD, H.P. and CORBIN, K.B. (1965). "Chronic Salicylate Intoxication in Adults". J. Amer. Med. Ass., 193, 555.

GROSS, H. and GREENBERG, L.A. (1948). "The Salicylates" p. 99, New Haven.

GUTMAN, A.B., Yü, T.E. and SIROTA, J.H. (1955). "A study by Simultaneous Clearance Techniques of Salicylate Excretion in Man. Effect of Alkalinisation of the Urine by Bicarbonate Administration". J. clin. Invest. 34, 711.

HANNA, S., HARRISON, M., MacINTYRE, I. and FRASER, R. (1960). "The Syndrome of Magnesium Deficiency in Man." Lancet 2, 172.

HARVIE, F.H. and SINGER, R.B. (1955). "Salicylate Poisoning". Amer. J. Diseases Children, 89, 149.

HETZEL, B.S., CHARNOCK, J.S. and LANDER, H. (1959). "Metabolic Effects of Salicylate in Man". Metabolism 8, 205.

HEYMANN, S. JAVETT, S.N. and RANDOLPH, A.M. (1954). "Salicylate Overdosage and Intoxication in Infants and Young Children". S. African Med. J. 28, 1092.

HICKMAN, R.O. and SCRIBNER, B.H. (1962). "Application of the Pumpless Haemodialysis System to Infants and Children". Trans. Am. Soc. Artificial Internal Organs. 8, 309.

HOFFMAN, W.S. and NOBE, C. (1950). "The Influence of Urinary pH on the Renal Excretion of Salicyl Derivatives During Aspirin Therapy." J. Lab. and Clin. Med. 35, 237.

ISRAELS, S. and DAVIES, H. (1961). "The Effects of Tris-Hydroxymethylaminomethane (THAM) on Renal Excretion of Salicylate." Amer. J. Dis. Child. 102, 744.

102, 512.

JAMES, J.A., KIMBELL, L. and READ, W.T. (1962). "Experimental Salicylate Intoxication 1. Comparison of Exchange Transfusion, Intermittent Peritoneal Lavage and Haemodialysis as Means for Removing Salicylate". Pediatrics 29, 442.

JORGENSEN, H.E. and WIETH, J.O. (1963). "Dialysable Poisons, Haemodialysis in the Treatment of Acute Poisoning". Lancet 1, 81.

KAPLAN, S.A. and DEL CARMEN, F.T. (1958). "Experimental Salicylate Poisoning: Observations on the Effects of Carbonic Anhydrase Inhibitor and Bicarbonate". Pediatrics 21, 762.

KAPLAN, E.H., KENNEDY, J. and DAVIS, J. (1954). "Effects of Salicylate and other Benzoates on Oxidative Enzymes of the Tricarboxylic Acid Cycle in Rat Tissue Homogenates". Arch. Biochem. 51, 47.

KENNEDY, A.C., LINTON, A.L., LUKE, R.G., RENFREW, S. and DINWOODIE, A. (1964). "The Pathogenesis and Prevention of Cerebral Dysfunction During Dialysis." Lancet, 1, 790.

KESSEL, N. (1965). "Self-poisoning". Brit. med. J. 2, 1265.

KRAMER, W. (1963). "From Reanimation to Deanimation (Intravital Death of the Brain During Artificial Respiration)". Acta Neurologica Scand. 39, 139.

LEIKIN, W.L. and EMMANOUILIDES, G.C. (1960). "The Use of Exchange Transfusion in Salicylate Intoxication". J. Pediatrics, 37, 715.

LIPMAN, B.L., KRASNOFF, S.O. and SCHLESS, R.A. (1949). "Acute Acetylsalicylic Acid Intoxication". Am. J. Diseases Children. 78, 477.

LOCKET, S. (1957). "Clinical Toxicology". p. 317, St. Louis.

MACDONALD, R.P. (1965). "A Simple Method of Measurement of Plasma Salicylate". Stand. Meth. clin. Chem. 5, 237.

MACKAY, R.J. (1961). "Comparison of Current Methods for Removing Salicylate". Am. J. Dis. Child. 102, 513.

McLAUGHLIN, G.E. (1965). "Salicylate Intoxication". J. Am. Med. Ass. 194, 571.

MACPHERSON, C.R., MILNE, M.D. and EVANS, B.M. (1955). "The Excretion of Salicylate". Brit. J. Pharmacol. 10, 484.

MATTHEW, H. and LAWSON, A.A.H. (1966). "Acute Barbiturate Poisoning - A Review of Two Years Experience". Quart. J. Med. 35, 539.

MATTHEW, H. and LAWSON, A.A.H. (1967). "Treatment of Common Acute Poisonings". E. & S. LIVINGSTONE, EDINBURGH.

MATTHEW, H., MACKINTOSH, T.F., TOMPSETT, S.L. and CAMERON, J.C. (1966). "Gastric Aspiration and Lavage in Acute Poisoning". Brit. med. J. 1, 1333.

MERRILL, J.P. (1956). "Electrolyte Changes in Renal Failure". Metabolism 5, 419.

MILNE, M.D. (1963). "The Excretion of Salicylate and its Metabolites". in Salicylates - An International Symposium. Churchill, London.

MONTANI, S. and PERRET, C. (1963). "Treatment of Barbiturate Poisoning Based on 271 Cases". Schweiz. med. Wschr. 93, 692.

MOOREHEAD, J.F., EDWARDS, E.C. and GOLDSMITH, H.J. (1965). "Haemodialysis of Three Children and One Infant with a Haemolytic-Uraemic Syndrome". Lancet 1, 570.

MORRIS, N. and GRAHAM, S. (1931). "Value of Alkali in Salicylate Therapy". Arch. Dis. Childh. 6, 273.

MYERS, E.N., BERNSTEIN, J.M. and FOSTIROPOLOUS G. (1965). "Salicylate Ototoxicity". New Eng. J. Med. 273, 587.

NAHAS, G.G. and LIGOU, T.C. (1959). "Etude Experimentale du Tamponnement de l'Acidose Aigue par le THAM". Presse Medicale 67, 1735.

OLIVER, T.K. and DYER, M.E. (1960). "The Prompt Treatment of Salicylism with Sodium Bicarbonate". Am. J. Diseases Children 99, 553.

PARSONS, F.M. (1963). "The Use of the Artificial Kidney in Salicylate Poisoning". in Salicylates: An International Symposium. p. 281. Churchill, London.

POLSON, C.J. (1959). "Poisoning by Salicylates". in Clinical Toxicology p. 173, English Universities Press Ltd., London.

PRESCOTT, L.F. (1965). "Effects of Acetylsalicylic Acid, Phenacetin, Paracetamol and Caffeine on Renal Tubular Epithelium". Lancet, 2, 91.

PULLEN, H., DOIG, A. and LAMBIE, A. (1967). "Intensive Intravenous Potassium Replacement Therapy". Lancet, 2, 809.

QUICK, A.J. and CLESCERI, L. (1960). "Influence of Acetylsalicylic Acid and Salicylamide on the Coagulation of Blood". J. Pharmacol. 128, 95.

RANGNO, R., GOURLEY, B. and ISRAELS, S. (1962). "The Mechanism of Action of Organic Buffers on Salicylate Excretion by the Kidney". J. Pediat. 61, 279.

RADEBOUGH, J.F. and EMERY, J.O. (1957). "Salicylate Poisoning: Treatment with Replacement Transfusion". J. Maine Med. Ass. 6, 437.

RAPAPORT, S. and GUEST, G.M. (1945). "The Effect of Salicylates on the Electrolyte Structure of Blood Plasma. 1. Respiratory Alkalosis in Monkeys and Dogs after Sodium and Methyl Salicylate; the Influence of Hypnotic Drugs and of Sodium Bicarbonate on Salicylate Poisoning". J. Clin. Invest. 24, 759.

RAPPAPORT, A.E., NIXON, C.E. and BARKER, W.A. (1945). "Fatal Secondary Toxic Thrombocytopenic Purpura due to sodium Salicylate, Report of Case". J. Lab. Clin. Med. 30, 916.

REA, W.J. and ROBERTSON, W.O. (1963). "Serum Salicylate Levels. Their Importance in Predicting Toxicity". Ohio State Med. J. 1, 681.

RENTSCH, J.B. and MARSH, S.B. (1959). "Two Cases of Salicylate Intoxication Successfully Treated by Exchange Transfusion". Am. J. Diseases Children 98, 778.

RILEY, H.D. and WORLEY, L. (1956). "Salicylate Intoxication". Pediatrics 18, 578.

ROBIN, E.D., DAVIS, R.P. and REES, S.B. (1959). "Salicylate Intoxication with Special Reference to the Development of Hypokalaemia". Amer. J. Med., 1, 869.

ROBIN, E.D. and HUME, D. (1959). "Artificial Ablation of the Anterior Hypothalamus and the Effects of Salicylates on Ventilation". Am. J. Med. 1, 875.

ROBINSON, J.R. (1961). "Fundamentals of Acid-Base Regulation". Springfield, Ill., Charles C. Thomas.

ROUTH, J.I. and DRYER, R.L. (1961). "Colorimetric Measurement of Plasma Salicylate". Stand. Meth. Clin. Chem. 5, 237.

RUSHTON, D.G. (1963). "Post-mortem Appearances in Salicylate Poisoning" in Salicylates - an International Symposium. p. 253, Churchill, London.

SCHREINER, G.E., BERMAN, L.B., GRIFFIN, J. and FEYS, J. (1955). "Specific Therapy for Salicylism". New. Eng. J. Med. 253, 213.

SCHWARTZ, R., FELLERS, F.X., KNAPP, J. and YAFFE, C. (1959). "The Renal Response to Administration of Acetazolamide during Salicylate Intoxication". Pediatrics 23, 1103.

SCHWARTZ, R. and LANDY, G. (1965). "Organic Acid Excretion in Salicylate Intoxication". J. Pediat. 66, 658.

SCOTT, J.T., DENMAN, A.M. and DORLING, J. (1963). "Renal Irritation Caused by Salicylates". Lancet, 1, 344.

SEFTEL, H.C. and KEW, M.C. (1966). "Early and Intensive Potassium Replacement in Diabetic Acidosis". Diabetes, 15, 694.

SEEGAR, W.E. (1961). "Comparison of Current Methods of Removing Salicylate." Am. J. Dis. Child. 102, 514.

SEEGAR, W.E. and HOLLIDAY, M.A. (1958). "Physiological Abnormalities of Salicylate Intoxication". New Eng. J. Med. 259, 1191.

SEEGAR, W.E. GIBSON, R.K. and RHEMY, R. (1961). "Peritoneal Dialysis in Infants and Small Children". Pediatrics, 27, 603.

SELDINGER, S.I. (1953). "Catheter Replacement of the Needle in Percutaneous Arteriography". Acta Radiol. 39, 368.

SIGGAARD-ANDERSEN, O. (1962). "Acute Experimental Acid-Base Disturbances in Dogs. An Investigation of the Acid-Base and Electrolyte Content of Blood and Urine". Scand. J. Clin. Lab. Invest. 14, 598.

SINGER, R.B. (1954). "The Acid-Base Disturbance in Salicylate Intoxication". Medicine 33, 1.

SMITH, J.M. and MACKINNON, J. (1951). "Aetiology of Aspirin Bleeding". Lancet, 2, 569.

SMITH, M.J.H. and TALBOT, J.M. (1950). "Estimation of Plasma-Salicylate Levels". Brit. J. exp. Path. 31, 65.

SMITH, M.J.H. and IRVING, J.D. (1955). "The Effect of Salicylate on the Passage of a Barium Meal in the Rat". Brit. J. Radiol. 28, 39.

SMITH, MJH. (1959). "The Effects of Salicylate on the Metabolism of Acetate in the Rat". J. Biol. Chem. 234, 144.

SMITH, M.J.H. (1966). "Toxicology" in The Salicylates p. 262. Interscience Publishers, London.

SMITH, M.J.H. and Smith, P.K. (1966). "The Salicylates" p. 272, Interscience Publishers, London.

SMITH, P.K., GLEASON, H.L., STOLL, C.G. and OGORZALEK, S. (1946). "Studies on the Pharmacology of Salicylates". J. Pharmacol. Exptl. Therap. 87, 237.

SPECTOR, S. and McKHANN, C.F. (1948). "Respiratory Acidosis and Alkalosis in Children". J. Pediat. 32, 227.

SPECTOR, S. (1958). "Management of Acute Aspirin Poisoning in Children". Quart. Rev. Pediatrics, 13, 179.

STRAUSS, J. and NAHAS, G.G. (1960). "Use of Amine Buffer in the Treatment of Acute Salicylate Intoxication". Proc. Soc. Exper. Biol. and Med. 105, 348.

STRAUSS, J., NAHAS, G.G. and CLARK, H. (1961). "Action du Tri-hydroxy-methyl-amino methane (THAM) dans le Traitement de l'Intoxication Aigue par le Salicylate". Am. J. Dis. Child. 102, 770.

SUMMITT, R.L. and ETTELDORF, J.N. (1964). "Salicylate Intoxication in Children - Experience with Peritoneal dialysis and Alkalinisation of the Urine". J. Pediat. 64, 803.

TENNEY, S.M. and MILLER, R.M. (1955). "The Respiratory and Circulatory Actions of Salicylate". Am. J. Med. 19, 498.

THIN, C.G. and THOMSON, P.A. (1967). "Estimation of Calcium and Magnesium in Serum and Urine by Atomic Absorption Spectrophotometry". J. Clin. Path. 20, 280.

THOMSON, T.J. and ALSTEAD, S. (1960). "Treatment of Acute Poisoning". Brit. med. J. 2, 726.

TO-DAY'S DRUGS. "Treatment of Acute Poisoning - 1". Brit. med. J. 2, 927.

TRINDER, P. (1954). "Rapid Determination of Salicylate in Biological Fluid". Biochem. J. 57, 301.

T'SAI FAN YÜ and GUTMAN, A.B. (1959). "The Effects of Salicylate on Kidney Function". J. clin. Invest. 38, 1298.

VALLEE, B.L., WACKER, W.E.C. and ULMER, D.D. (1960). "The Magnesium - Deficiency Tetany Syndrome in Man". New Engl. J. Med. 262, 155.

von WEISS, J.F. and LEVER, W.F. (1964). "Percutaneous Salicylic Acid Intoxication in Psoriasis". Arch. Derm., 90, 614.

WHANG, R. and REYES, R. (1967). "The Influence of Alkalinisation on the Hyperkalaemia and Hypermagnesaemia in Uraemic Rats". Metabolism, 16, 941.

WHITTEN, C.F., KESAREE, N.M. and GOODWIN, J.F. (1961). "Managing Salicylate Poisoning in Children. An Evaluation of Sodium Bicarbonate Therapy". Am. J. Dis. Childh. 101, 178.

WILLIAMS, T.F., WINTERS, R.W., CLAPP, J.R., HOLLANDER, W. and WELT, L.G. (1958). "Effects of 2, 4 Dinitrophenol on Respiration in the Dog." Am. J. Physiol. 193, 181.

WINTERS, R.W., LOWDER, J.A. and ORDWAY, N.K. (1958). "Observations on the Plasma Carbon Dioxide Tension During Recovery from Metabolic Acidosis". J. Clin. Invest. 37, 640.

WINTERS, R.W., WHITE, J.S., HUGHES, M. and ORDWAY, N.K. (1959). "Distrubances of Acid-Base Equilibrium in Salicylate Intoxication". Pediatrics 23, 260.

WINTERS, R.W. (1963). "Acid-Base Disturbances, and the Treatment of Salicylate Intoxication" in Salicylates. An International Symposium. p. 270, Boston, Little, Brown.

YOSHIDA, T., METCOFF, J. and KAISER, E. (1961). "A Metabolic Lesion in Salicylate Intoxication". Amer. J. Diseases Children, 102, 511.