STUDIES ON THE CLINICAL PHARMACOLOGY OF SODIUM SALICYLATE

by

WILLIAM A. PARKER

M.B., Ch.B., F.R.F.P.S.G.

Assistant in Materia Medica, Glasgow University.

THESIS for the DEGREE of M.D. of GLASGOW UNIVERSITY

SEPTEMBER, 1947.

From the University Department of Materia Medica and Therapeutics, and Stobhill Hospital, Glasgow.

ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

TABLE OF CONTENTS

PREFACE

Sodium salicylate is used daily in many hospitals and yet there is widely varying opinion as to the form of administration and dosage in which this drug should be used. One had many discussions with colleagues in this hospital about methods of administration, and about the mode of action of sodium salicylate in producing its toxic manifestations, especially the so called 'acidosis'. Some of my colleagues ignored the milder toxic effects of the drug as merely indicating therapeutic concentration in the plasma, while others discontinued the drug at their appearance. Most used alkali concurrently with sodium salicylate, traditionally rather than rationally, and little was known of the factors governing excretion of this drug.

In an attempt to throw light on some of these problems, this work was undertaken in the wards of the late Professor Morris at Stobhill Hospital, with the exception of the animal experiments which were carried out in the Materia Medica Department of the University of Glasgow.

In May, 1947, at Aberdeen, a paper on part of this work was presented to the Association of Physicians of Great Britain and Ireland.

I must record my debt to the late Professor Noah Morris, whose advice, constant encouragement, and critical interest made this thesis possible.

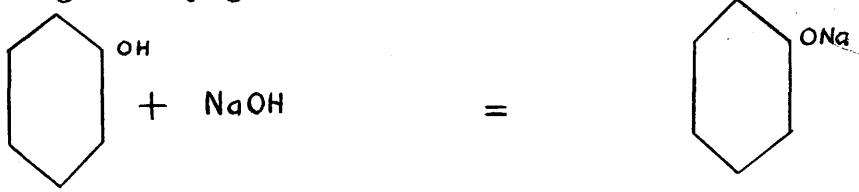
I am indebted to Dr.J.D.P.Graham of the Materia Medica Department of Glasgow University for his help with the animal experiments, and to Mr.A.McCutcheon of the Biochemistry Department of Stobhill Hospital for his willing assistance at all times.

HISTORICAL INTRODUCTION

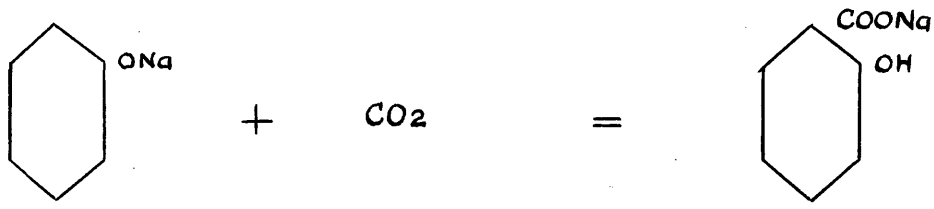
1. The Evolution of Sodium Salicylate.

Willow Bark (Salix Alba) has antipyretic properties which were known for many years before any investigation of its active principles was undertaken. The analytical chemist Leroux in 1827 was the first to discover that it yielded a bitter glucoside called salicin. Some eleven years later in 1838 Piria made salicylic acid from salicin and this was followed by the preparation of salicylic acid from oil of gaultheria (oil of wintergreen) by Cahours in 1844. It was not until 1860 that the synthetic manufacture of salicylic acid from phenol was accomplished by Kolbe and Lautemann, a link in its manufacture being the preparation of sodium salicylate.

Sodium salicylate is now prepared industrially by the reaction of CO_2 with sodium phenoxide (Kolbe's Reaction). Pure phenol is treated with caustic soda solution and the resulting phenoxide evaporated to dryness. The dry powder is heated to 120-140°C in an atmosphere of CO_2 at 100 lb/sq.metre pressure, as long as any gas is absorbed.



Phenol + Caustic Soda = Sodium Phenoxide



Sodium Phenoxide + Carbon dioxide = Sodium Salicylate

2. Sodium Salicylate in Medicine.

Maclagan of Dundee in 1876 introduced salicin into medicine for the first time in the treatment of rheumatic fever and gave the opinion that it exerted a curative action. Although sodium salicylate had been used by Buss (1875), and others as an antipyretic, the credit of first using and recognising the value of sodium salicylate in rheumatic fever must go to Stricker (1876) who was working in Traube's Clinic. Broadbent (1876) in the same year was impressed with its effects in this condition and advocated what in those days was a comparatively large dose, namely 7½ to 20 grs. hourly. Clarke (1906) was enthusiastic about its use and stated that it offered protection to the heart in rheumatic fever. Lees (1908) declared that sodium salicylate was as truly antirheumatic as quinine was antimalarial and mercury antisyphilitic.

Since the early enthusiastic reports many workers have doubted the specificity of sodium salicylate in rheumatic fever, and many have denied that it has any significant effect

on the course of the disease or any influence on the cardiac lesions. The opposite view has been revived with each introduction, or reintroduction of a particular regimen of administration of sodium salicylate, and has been followed by adversely critical opinion.

All agree, however, that the effect of the drug on the pyrexia and the joint pains of rheumatic fever, and its general improvement of the physical comfort of the patient is unequivocal. The pharmacological actions of sodium salicylate have been widely studied, and yet there remain many outstanding problems associated with its administration, absorption, distribution in the body, excretion and toxicity. Previous work on these problems is reviewed in the relevant sections of the following pages, together with some personal investigations which have in the greater part been based on practical problems arising from the clinical exhibition of the drug.

CHAPTER I.

THE ORAL ADMINISTRATION OF SODIUM SALICYLATE

The most common route used for the administration of sodium salicylate is by the mouth because the drug is readily absorbed from the upper gastro-intestinal tract. Broadbent (1876) recommended 7½ to 20 grains hourly in the treatment of rheumatic fever, while Hanzlik (1926) recommended 15 grains with an equal quantity of sodium bicarbonate every hour, or alternately 15 grains with bicarbonate three times a day whether symptoms be present or not. Morris & Graham (1931) and Findlay (1931) usually employed 15 grains four hourly or occasionally hourly in children with successful results. Goodman and Gilman (1941) recommended 5 to 15 grains repeated every three or four hours, or if intensive medication was required 15 grains hourly until toxic symptoms ensued. Numerous other authors have recommended oral administration varying between hourly and four hourly, all of which were apparently successful. In considering frequency of administration, the rate of absorption and excretion of the drug should be considered. This is reflected by the concentrations in the plasma over a period following

administration of a single dose. Smith et al (1946) showed that after single 2 gm. doses of sodium salicylate to normal adults peak plasma concentrations were obtained two hours after administration and the plasma levels fell slowly thereafter over the next six hours studied.

A. The Frequency of Administration and Dosage.

It was considered worth while to investigate the rise and fall of plasma levels following various single doses of sodium salicylate, in order to assess the time taken to attain maximum concentration, and to assess the rate of fall of plasma levels after the peak concentration had been reached. Four groups of individuals were studied, each group consisting of four convalescent patients. All were given their respective doses of sodium salicylate dissolved in two ounces of water from two to two and a half hours after their last meal. These patients were adults from whom venous blood was obtained for the estimation of plasma salicylate content at the times indicated below. The average plasma levels are given for each group of patients in mgms.% in Table I. Of these patients Group I. received 5 grains of sodium salicylate, while Group II. received 10 grains of salicylate. Group III. received 15 grains and Group IV. 100 grains.

TABLE I.

GROUP	15 min.	30 min.	1 hr.	2hrs.	3hrs.	4hrs.	8hrs.
I.	-	-	3.5	3.1	1.5	0.6	Nil
II.	-	-	3.5	4.2	2.6	2.0	0.3
III.	-	-	4.2	9.3	6.4	5.2	2.4
IV.	16.3	21.1	28.1	31.7	30.1	28.3	18.1

It will be seen that the maximum plasma levels occurred 2 hours after administration except in Group I. where the maximum level was apparent after 1 hour, but in this case where the dosage was 5 grs., the difference in concentration at one and two hours is very small. Thus with the exception of very small dosage, it appears that the maximum plasma levels occur two hours after administration. This, however, did not necessarily mean that four hourly dosage could not produce a steady plasma level, so it was decided to examine the daily plasma levels produced in the same group of patients by two hourly and then by four hourly dosage.

Four adult patients were selected, of the same age group, who had no determinable gastric or renal upset. They were given 10 grs.Sodium salicylate with 10 grs.Sodium

bicarbonate at two hourly intervals day and night for seven days. Plasma levels were estimated daily, immediately before the midday dose of the drug. Four days later when plasma levels had returned to zero this was repeated, with the difference that 20 grs.Sodium salicylate with 20 grs.Sodium bicarbonate were administered four hourly. The average plasma levels for the group are shown in Table 2.

TABLE 2

	1	2	3	4	5	6	7
10 grs.every two hours,	28.4	25.7	24.1	24.8	23.4	27.0	25.2
20 grs.every four hours,	15.8	29.9	21.8	23.7	22.7	25.8	26.0

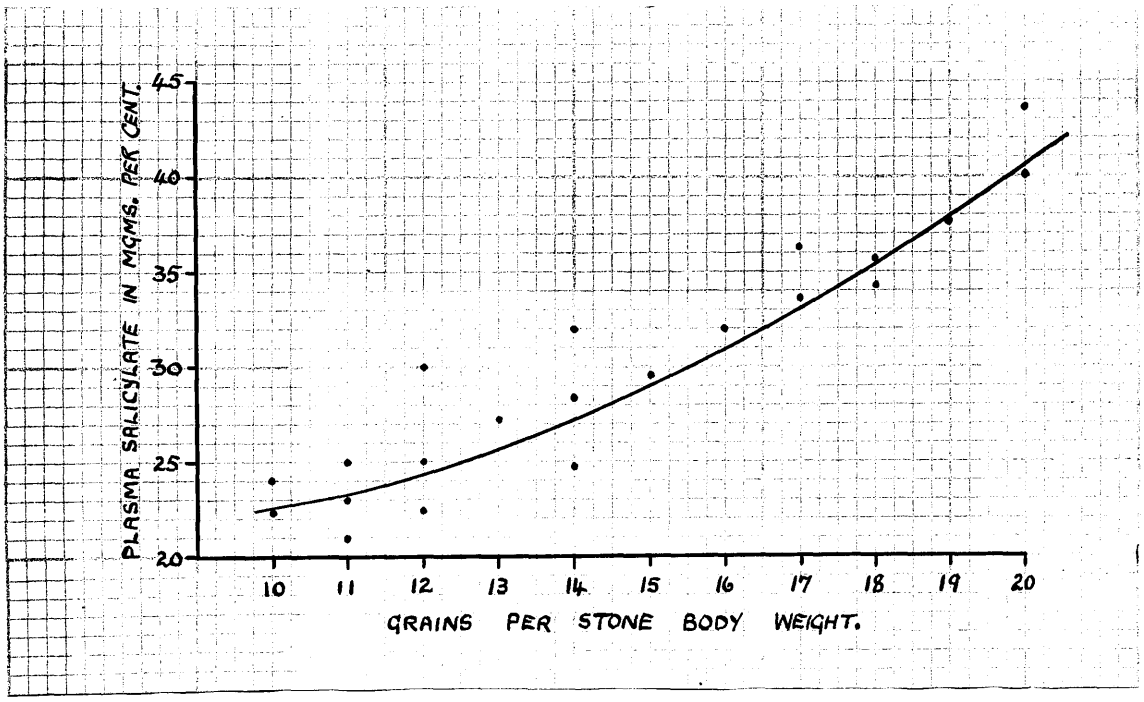
There is no significant difference, showing that although maximum plasma levels occur two hours after single doses of sodium salicylate, four hourly continued dosage will maintain plasma levels adequately.

During the treatment of patients suffering from rheumatic fever it had been observed that there was much variation in the plasma levels of patients on similar dosage of sodium salicylate. It was difficult to assess the dose of the drug which would be required to produce a given plasma level

in the individual, and the dose was usually adjusted by trial and error. Taran and Jacobs (1945) stated that 1.5 grs.per lb. body weight in children was sufficient to raise the plasma level to 35-40 mgms.%, while Manchester (1946)[1] believed Sodium salicylate 12 gms. with Sodium bicarbonate 8 gms. daily, would produce an average plasma level of 37 mgms.% in young adults. It would seem logical to correlate dose with body weight rather than age in this instance, although Goodman and Gilman (1941) stated that children required larger doses than those calculated from age and weight.

Twenty-one patients were studied in this series. Some were being treated for rheumatic fever, and others were convalescents. In order that the plasma levels should approximate to maximal levels, the last three plasma levels of the first week of treatment were assessed and the average figure determined. All patients received Sodium salicylate alone. Average plasma levels are shown against dose in grains per stone body weight in Fig.1.

FIGURE 1



It is seen that there is reasonable variation in the plasma levels of different individuals when dose is related to body weight, but that there is a general correlation between them. Above a plasma level of 25 mgms.% there is a sharper rise in plasma concentration for each increase in dosage, showing that relatively small increases in dose above 14 grains per stone body weight can be attended by marked rise in plasma levels.

B. The Effect of Sodium Bicarbonate on Plasma Levels when administered with Sodium Salicylate.

There are conflicting views held by different workers on the effect produced by the coincident administration of sodium bicarbonate with sodium salicylate. Lees (1908) claimed that the administration of sodium bicarbonate with salicylate modified and prevented the symptoms of salicysm while Meara (1910) believed that the use of alkalis together with salicylate was dictated more by tradition than by rationale. Hanzlik, Scott and Thoburn (1917) found that the administration of approximately equal doses of bicarbonate and salicylate did not prevent the symptoms of salicylism, a view with which Delore (1925) did not agree. Morris and Graham (1931) stated that when alkali was combined with salicylates toxic symptoms were less frequent, even though more salicylic ion was circulating in the blood. They considered that the addition of alkali increased the salicylate content of the blood from two to four times. More recently Smull, Wegria and Leland (1944) found that sodium bicarbonate given in conjunction with sodium salicylate orally, produced lower serum levels of salicylate than sodium salicylate administered alone, as did Smith et al. (1946). This was not confirmed by Huntingdon et al (1946) who found that patients on 60 grains per day of sodium salicylate showed no lower levels

with the addition of bicarbonate, admitting however that their observation period was short. Finally Jager and Alway (1946) claimed that higher doses of sodium salicylate were required in adults and children when alkali was added, to maintain a therapeutic level of 35 mgms.%.

During the present investigations it had been noted on several occasions that the withdrawal of sodium bicarbonate from patients on salicylate therapy was attended by higher plasma levels. This occurrence was then studied further.

(1) The effect of the addition of sodium bicarbonate to single doses of sodium salicylate was assessed on the group of patients on whom plasma levels resultant from a single dose of 100 grains of sodium salicylate alone (Table 1, Gp.IV.) had already been obtained. In this instance under similar conditions these patients were given 100 grs.Sodium salicylate with 200 grs.Sodium bicarbonate. The resultant plasma levels were obtained as described previously and for comparison are shown in Table 3, together with those obtained with sodium salicylate alone.

TABLE 3

Time After Administration	Average Plasma Levels in mgms.%	
	Sodium Salicylate alone	Sodium Salicylate with Bicarbonate
15 min.	16.3	8.9
30 min.	21.1	18.6
1 hr.	28.1	25.6
2 hrs.	31.7	28.9
3 hrs.	30.1	27.1
4 hrs.	28.3	21.7
8 hrs.	18.1	9.2

These figures show that with single doses the concentrations reached are comparable (within 3 mgms.%) at the maximum which occurs at the same time, two hours after administration. After the peak levels the plasma concentration tends to fall away more rapidly with alkali. Lester et al (1946) using acetyl-salicylic acid found that with alkali the same maximum concentration was reached but much earlier, a fact which led them to the conclusion that bicarbonate markedly increased the rate of absorption. It would appear from the observations shown here that bicarbonate increases the rate of

elimination of sodium salicylate (a deduction further studied in Chapter V.) but has little or no effect on absorption.

(2) Another two patients were studied while receiving continuous four hourly doses. Sodium salicylate was given alone for several days and then sodium bicarbonate was added. This was repeated over periods of 40 and 30 days respectively. The fluid intake was stabilised at 60 ozs. daily, both patients receiving the same ward diet, being confined to bed. Plasma levels were estimated daily at the same time each day, blood being withdrawn by venipuncture for this purpose. Dosage and plasma levels are shown on figures 2 and 3.

It was found that when sodium salicylate was given alone the plasma levels tended to rise rapidly and reached a higher level at all times than when alkali was administered concurrently. The addition of bicarbonate produced an appreciable daily fall in the levels until after several days the plasma level was over 10 mgms.% lower, at which level it was maintained. It was also noted that earlier high levels with sodium salicylate alone tended to fall but not so rapidly as with the addition of alkali. The levels with both salicylate alone, and with alkali, were markedly lower on repetition of the doses at later dates than at the start of the period

studied, indicating that on continued dosage with or without alkali plasma levels tend to fall. It would seem that a larger dose of salicylate would be required to maintain the plasma levels after a period of continued administration.

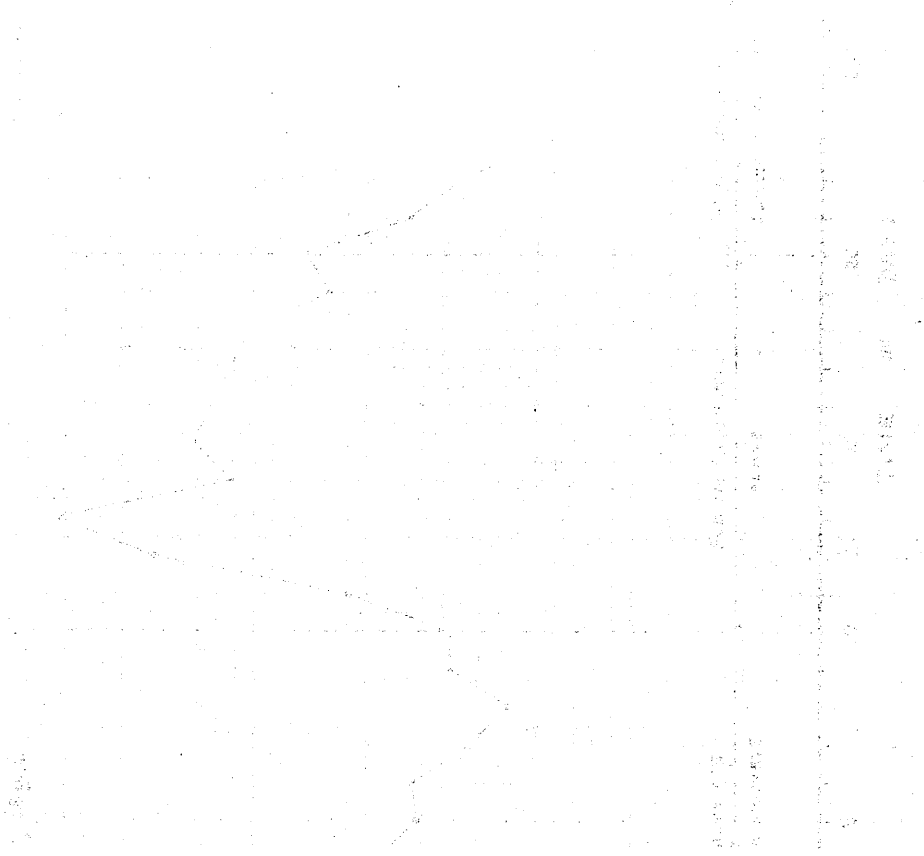


FIGURE 2

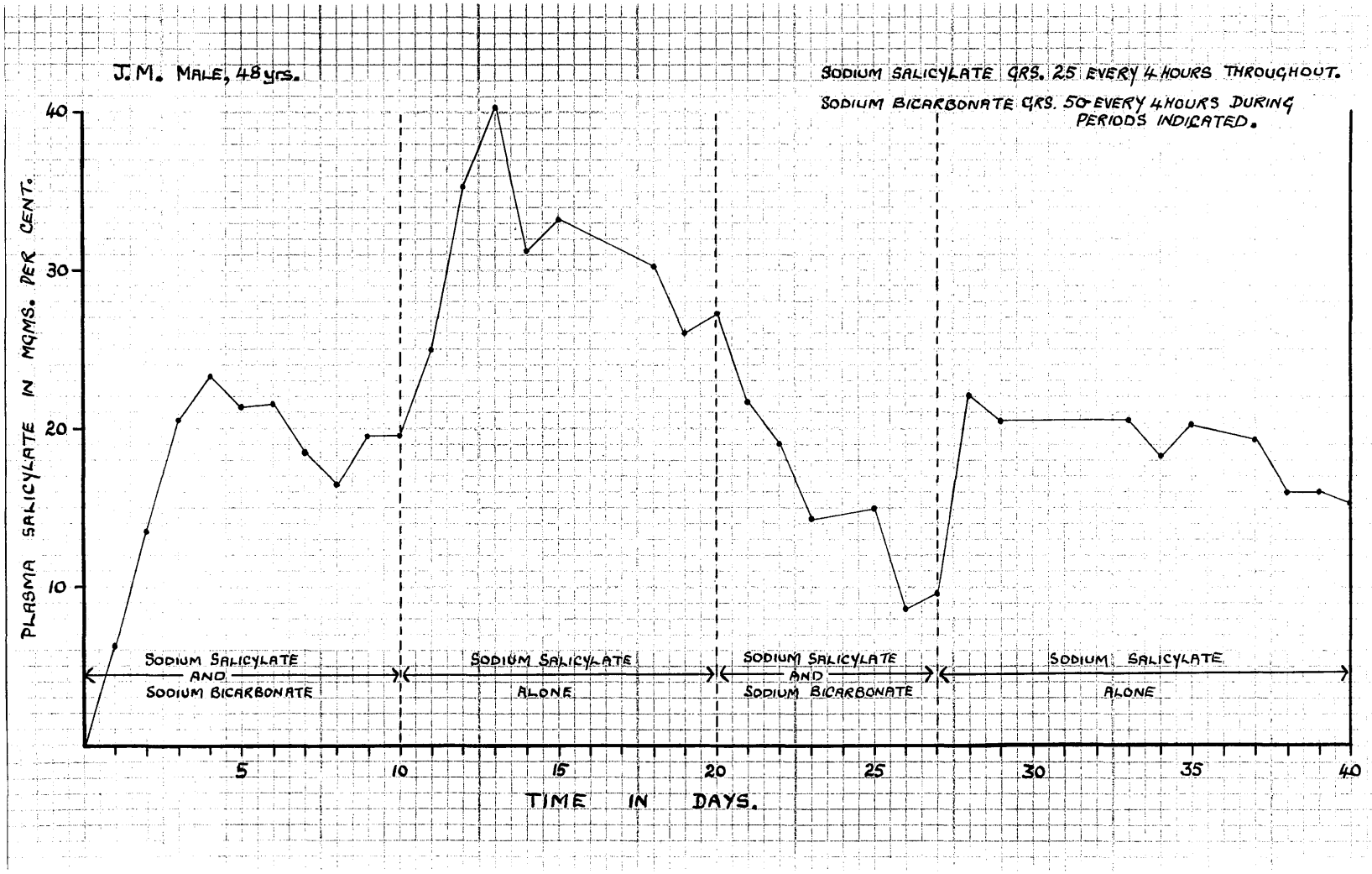
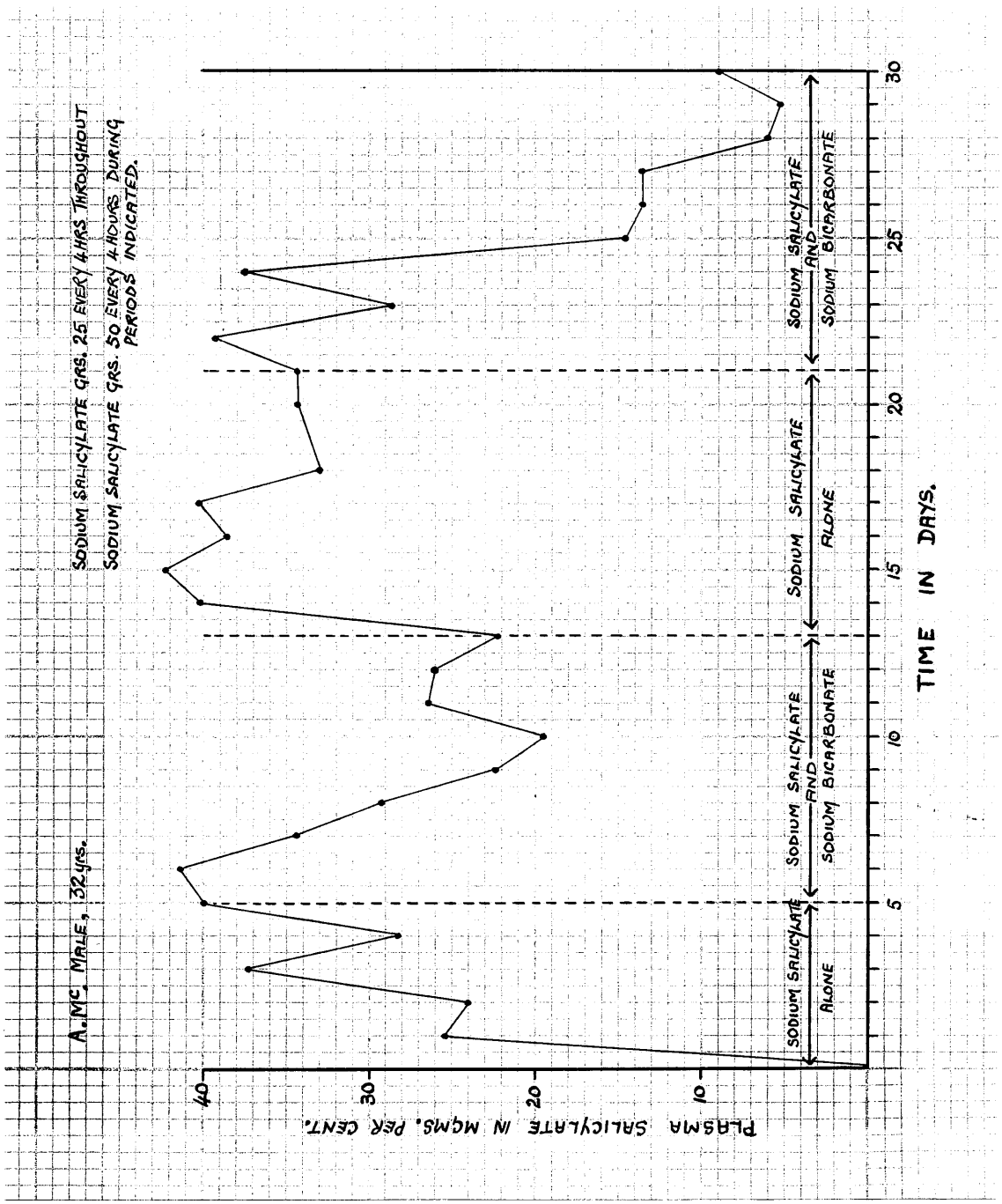
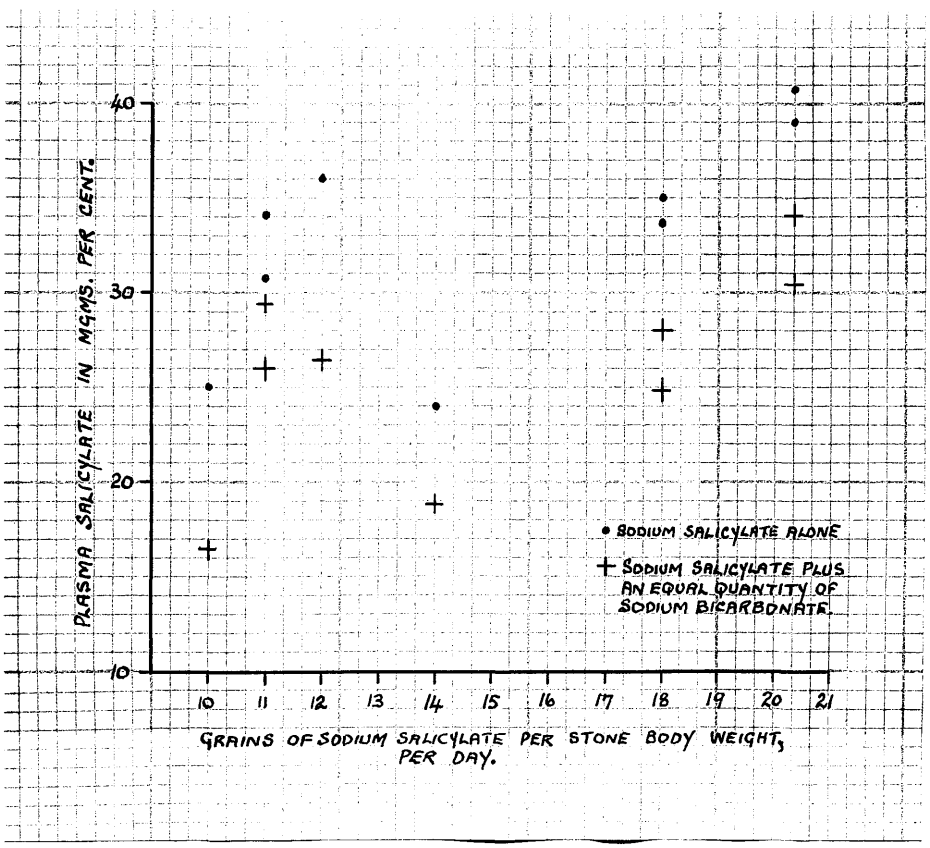

J. M. MALE, 48 yrs.
SODIUM SALICYLATE GRS. 25 EVERY 4 HOURS THROUGHOUT.
SODIUM BICARBONATE GRS. 50 EVERY 4 HOURS DURING PERIODS INDICATED.
PLASMA SALICYLATE IN MGMS. PER CENT.
40
30
20
10
SODIUM SALICYLATE AND SODIUM BICARBONATE
SODIUM SALICYLATE ALONE
SODIUM SALICYLATE AND SODIUM BICARBONATE
SODIUM SALICYLATE ALONE
5
10
15
20
25
30
35
40
TIME IN DAYS.

FIGURE 3


A. MC. MALE, 32 yrs.
SODIUM SALICYLATE GRS. 25 EVERY 4 HRS. THROUGHOUT
SODIUM SALICYLATE GRS. 50 EVERY 4 HOURS DURING PERIODS INDICATED.
PLASMA SALICYLATE IN MGMS. PER CENT.
40
30
20
10
5
10
15
20
25
30
TIME IN DAYS.
SODIUM SALICYLATE ALONE
SODIUM SALICYLATE AND SODIUM BICARBONATE
SODIUM SALICYLATE ALONE
SODIUM SALICYLATE AND SODIUM BICARBONATE

The opportunity was taken to demonstrate still further the effects of addition of alkali. Nine patients who were receiving sodium salicylate alone had their plasma levels assessed daily for three days and then an equal quantity of bicarbonate was added. Plasma levels were then obtained for another three days. Plasma levels were plotted against dose per grain body weight and shown in Figure 4.

FIGURE 4



These results serve to illustrate that irrespective of dose of sodium salicylate the addition of bicarbonate produces a lower plasma level.

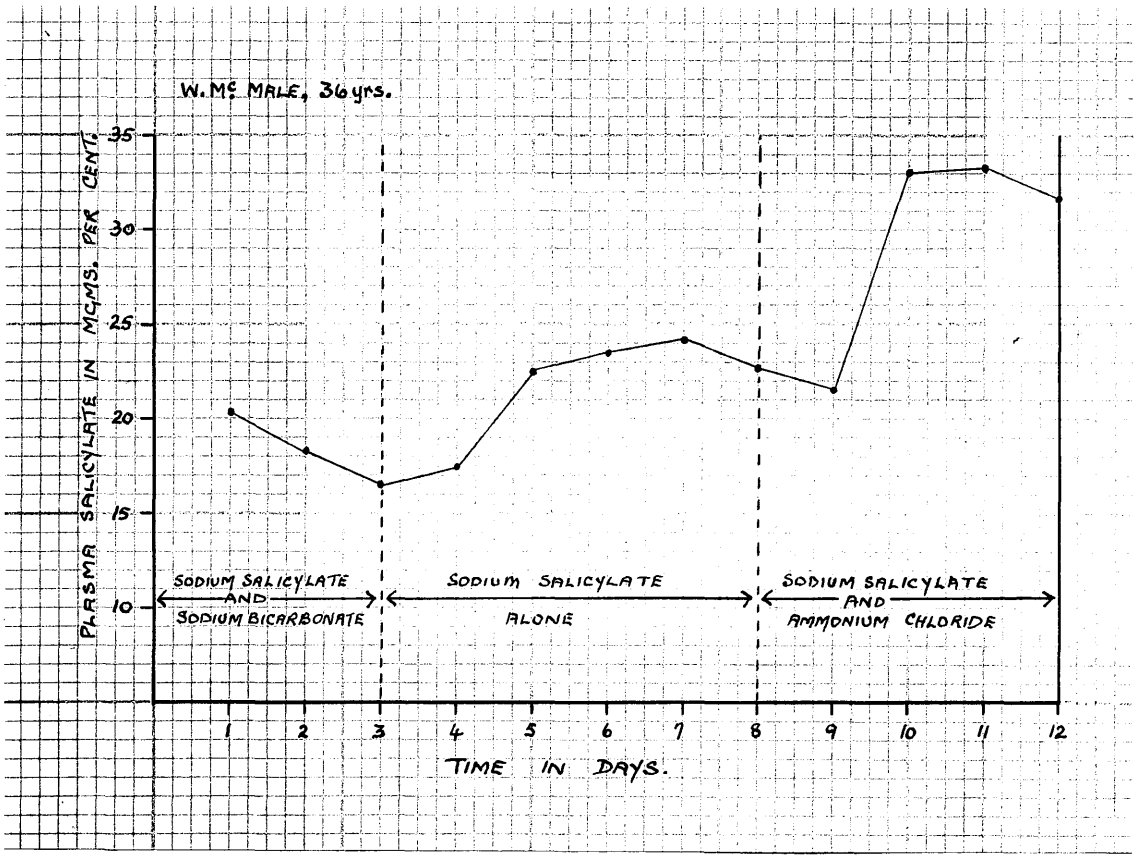
C. The Effect of Ammonium Chloride on the Plasma Levels when Administered with Sodium Salicylate.

It now appeared logical to postulate that an acid salt administered with sodium salicylate might have an opposite effect to an alkaline salt, thereby increasing the plasma level. The effect of an acid salt, namely ammonium chloride, on the metabolism of salicylates has been noted by Smith et al (1946). Using multiple doses on convalescent patients for 48 hours, they showed that an acid salt administered concurrently with sodium salicylate produced higher plasma levels towards the end of the period, than when sodium salicylate was administered alone or with alkali. Caravati and Cosgrove (1946) found that Ammonium Chloride 4 gms. daily increased the plasma salicylate levels. Here two convalescent patients were studied over a longer period than that of Smith et al (1946).

W.Mc. 30 grs.of Sodium Salicylate with 30 grs.of Sodium Bicarbonate were administered four hourly night and day until the plasma level had reached a maximum on this dosage. For the next five days the patient was given Sodium salicylate grs.30

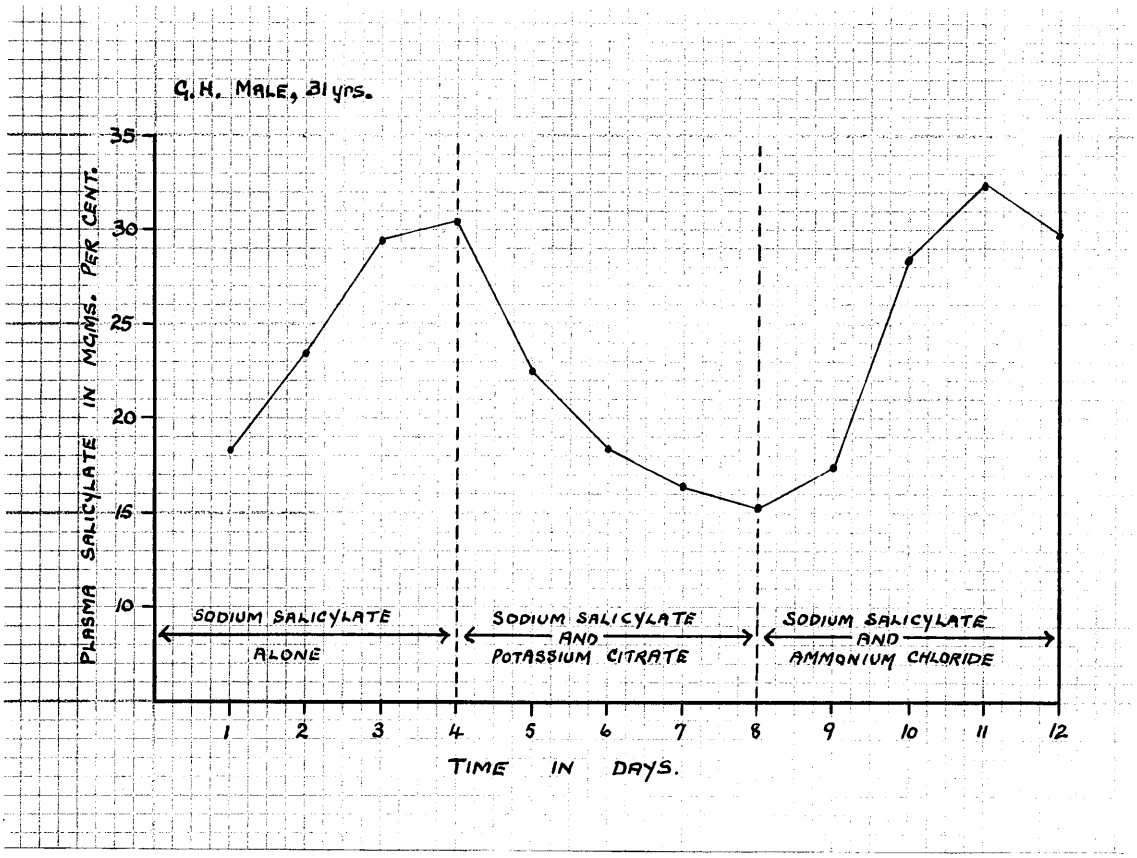
alone, followed by another four days receiving Sodium Salicylate grs.30 and Ammonium Chloride grs.15 all four hourly. Plasma levels were obtained daily at 11 a.m., and are shown in Figure 5.

FIGURE 5



G.H. This patient was given Sodium salicylate grs.25 four hourly at the start of the investigation until the plasma levels were reaching a peak, then Sodium salicylate grs.25 and Potassium citrate grs.60 were given every four hours for four days. For another four days he received Sodium salicylate grs.25 and Ammonium chloride grs.15 four hourly. Plasma levels were obtained daily at 11 a.m. and are shown in Figure 6.

FIGURE 6



Both patients show highest levels while receiving the acid salt concurrently with Sodium salicylate, the lowest levels with alkali and intermediate levels with Sodium salicylate alone. The plasma levels with alkali were slightly more than half those attained with the acid salt.

This effect was demonstrated in yet another manner in a further two convalescent patients. These patients received 25 grs.of Sodium salicylate together with 25 grs.of Sodium bicarbonate throughout, but for a period were given in addition grs.15 of Ammonium chloride every four hours. The plasma levels are shown in figures 7 and 8.

FIGURE 7

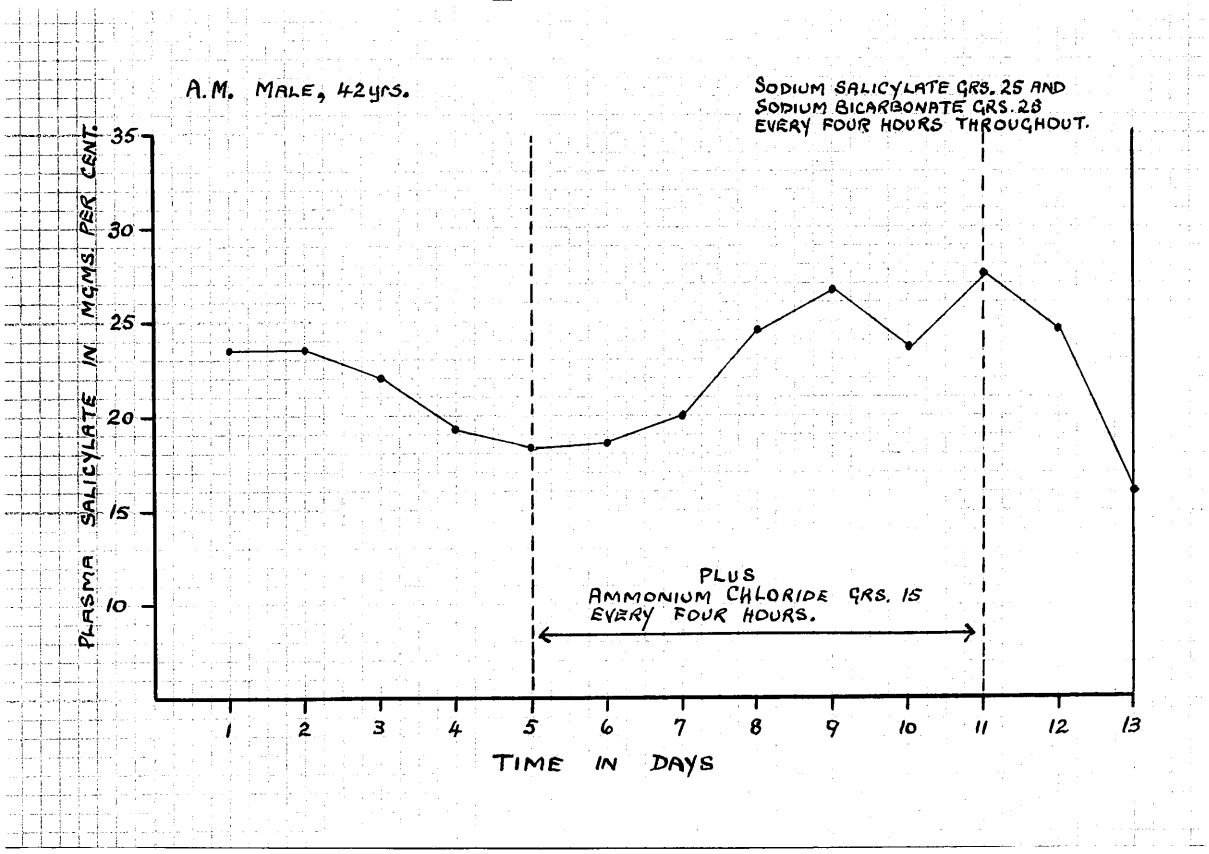
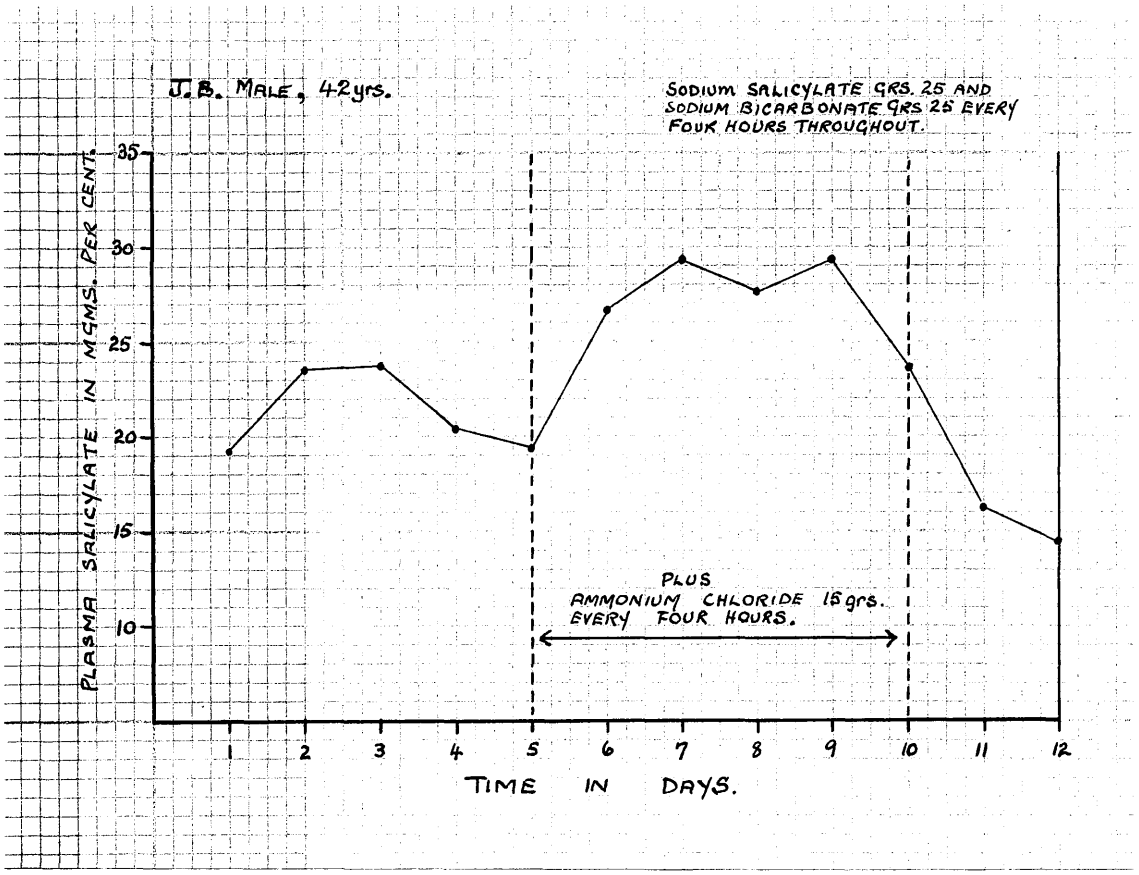


FIGURE 8



With the administration of Ammonium chloride the plasma levels rose in both cases but not to the same extent as they would have risen had Ammonium chloride been administered without the presence of bicarbonate (Figs.5 and 6). Apparently, then, minimal plasma levels are obtained with the addition of bicarbonate, maximal levels with an acid salt, and intermediate

levels with Sodium salicylate alone. A balance is struck when an alkaline and acid salt are administered together with salicylate.

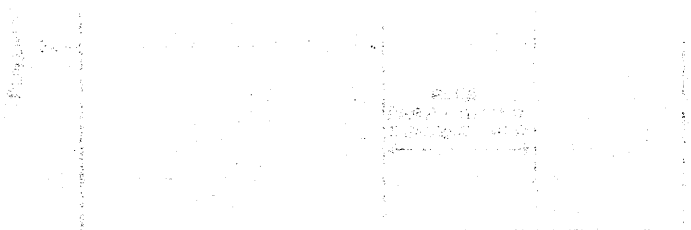
D. The Effect of Para-aminobenzoic Acid on Plasma Salicylate Levels when Administered with Sodium Salicylate.

Until recently p-aminobenzoic acid has only been studied from the viewpoint of its anti-sulphonamide properties, and as a result of these properties, has been considered to be one of the components of the Vitamin B complex. It has been said to be a true vitamin when given in small doses, as well as bacteriostatic when given in large doses. According to Ansbacher (1944) p-aminobenzoic is a detoxified aniline, allied to the series of anaesthetics of which novocain is one, being a benzoic acid derivative, and is widely distributed in tissue fluids and in nature, its richest source being yeast. Tierney (1946) has demonstrated the innocuousness of p-aminobenzoic acid in large doses in the treatment of tsutsugamushi disease using 8 gms. initially and 3 gms. every two hours, while Benda et al (1946) using the drug intravenously found that it was free from any sign of toxicity.

Using p-aminobenzoic acid empirically in the treatment of rheumatic fever Dry et al (1946) found that its

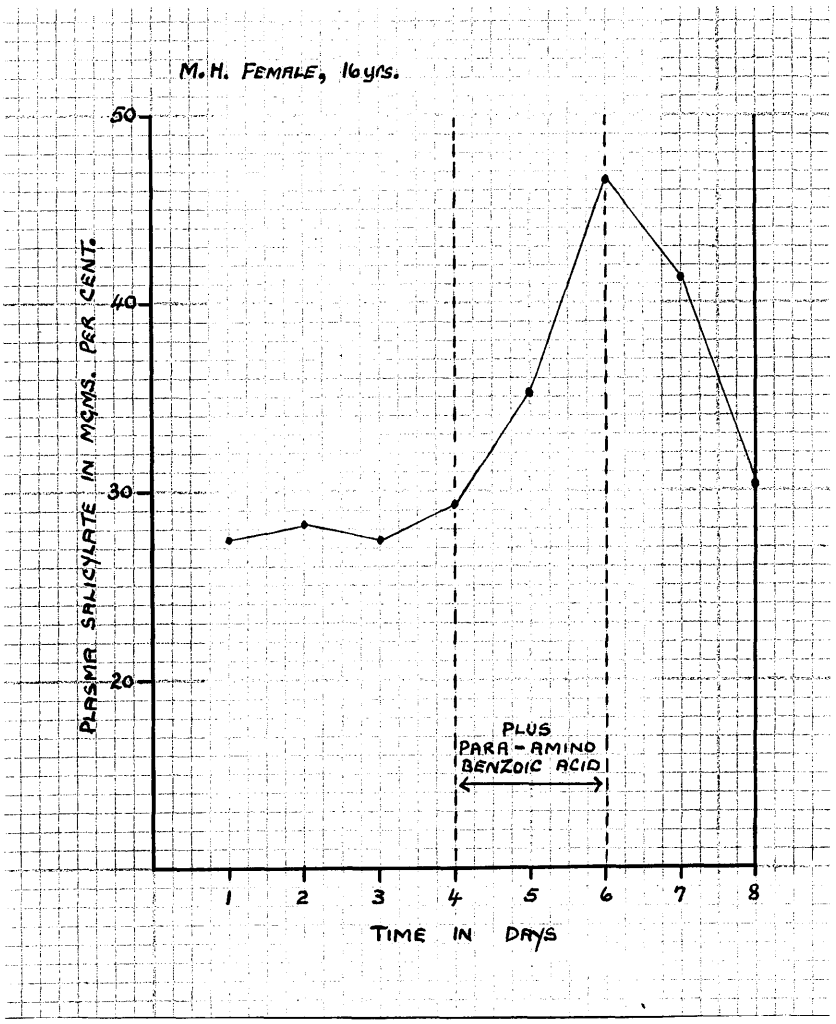
administration concurrently with sodium salicylate and bicarbonate raised the plasma level of salicylate. This they consider to be of importance since in view of the conclusions of Coburn (1943) that a therapeutic level of not less than 35.0 mgms.% is necessary in rheumatic fever, the assurance of adequate quantities of salicylate in the blood must be of importance. They think that inadequate levels may be directly related to those instances in which the therapeutic response in rheumatic fever is inadequate and in which relapses occur.

In view of these statements it was necessary to confirm the finding of higher salicylate plasma levels with the use of p-aminobenzoic acid. The same high doses as used by Dry et al (1946) were repeated in view of the reported absence of toxicity.



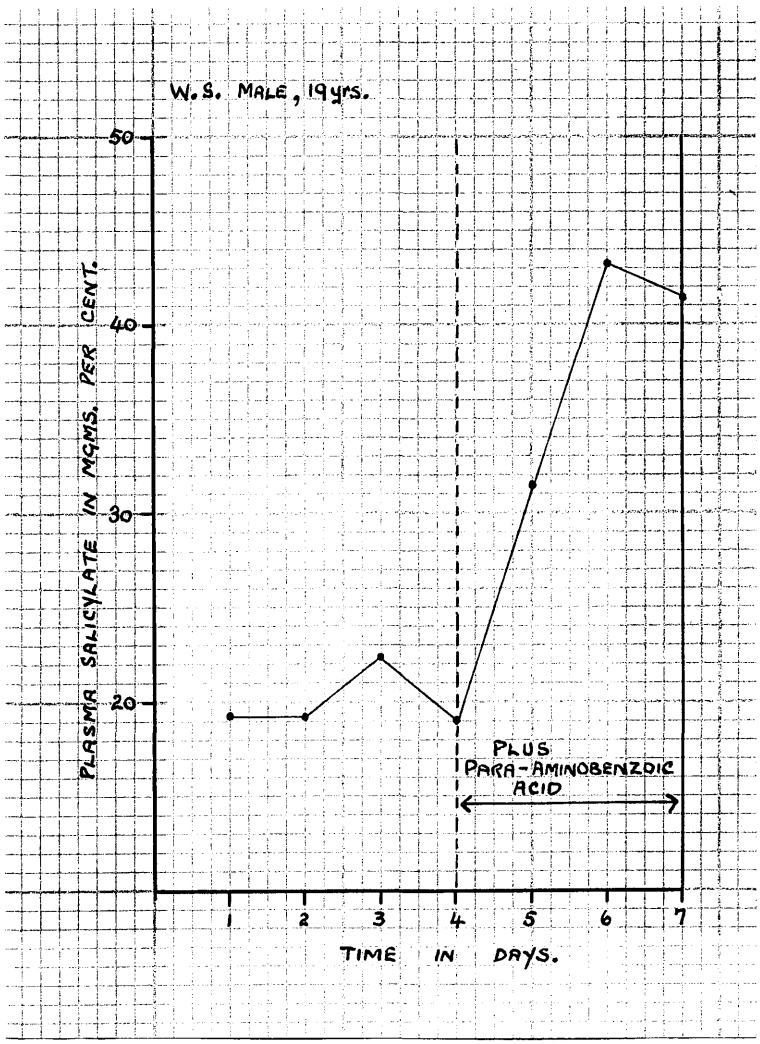
M.H. Female aged 16 years. Rheumatic fever. This patient was being given as a routine Sodium salicylate grs.30 with Sodium bicarbonate grs.30 four hourly. Plasma levels were taken for several days and then p-aminobenzoic acid administered concurrently for two days in the dose of 2 gms.every four hours. Plasma levels were obtained during this period and subsequently for two days.

FIGURE 9



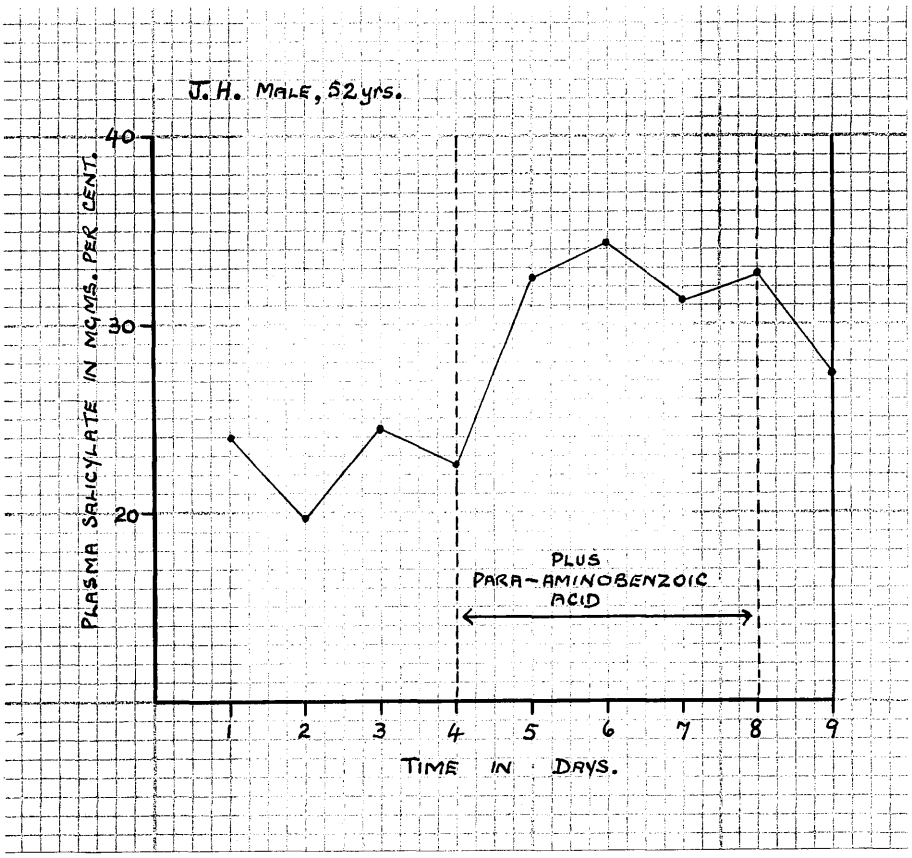
W.S. Male, 19 years. Rheumatic fever. This patient received Sodium salicylate grs.30 with an equal quantity of bicarbonate throughout but during the last three days received in addition p-aminobenzoic acid in the dose of 24 gms. daily in divided four hourly doses.

FIGURE 10



J.H. Male, 52 years. Convalescent Hemiplegia. As a control this patient was given Sodium salicylate alone, grs.20 every four hours for several days and then the addition of p-aminobenzoic acid 2 gms.four hourly was made for four days.

FIGURE 11



Laboratory investigation had shown that p-aminobenzoic acid in no way affected the estimation of plasma salicylate when present in the plasma.

It is shown in Figs.9-11 that p-aminobenzoic acid has the effect of raising the plasma levels when administered with sodium salicylate, and that the effect is most marked when bicarbonate is being given at the same time. No toxic symptoms attributable to p-aminobenzoic acid were noted during the dosages given here although there was an increase in the toxic manifestations of salicylate as the plasma levels rose. It would seem that p-aminobenzoic acid produces a similar effect on the plasma level as ammonium chloride. The mechanism of this effect will be further discussed in Chapter V.

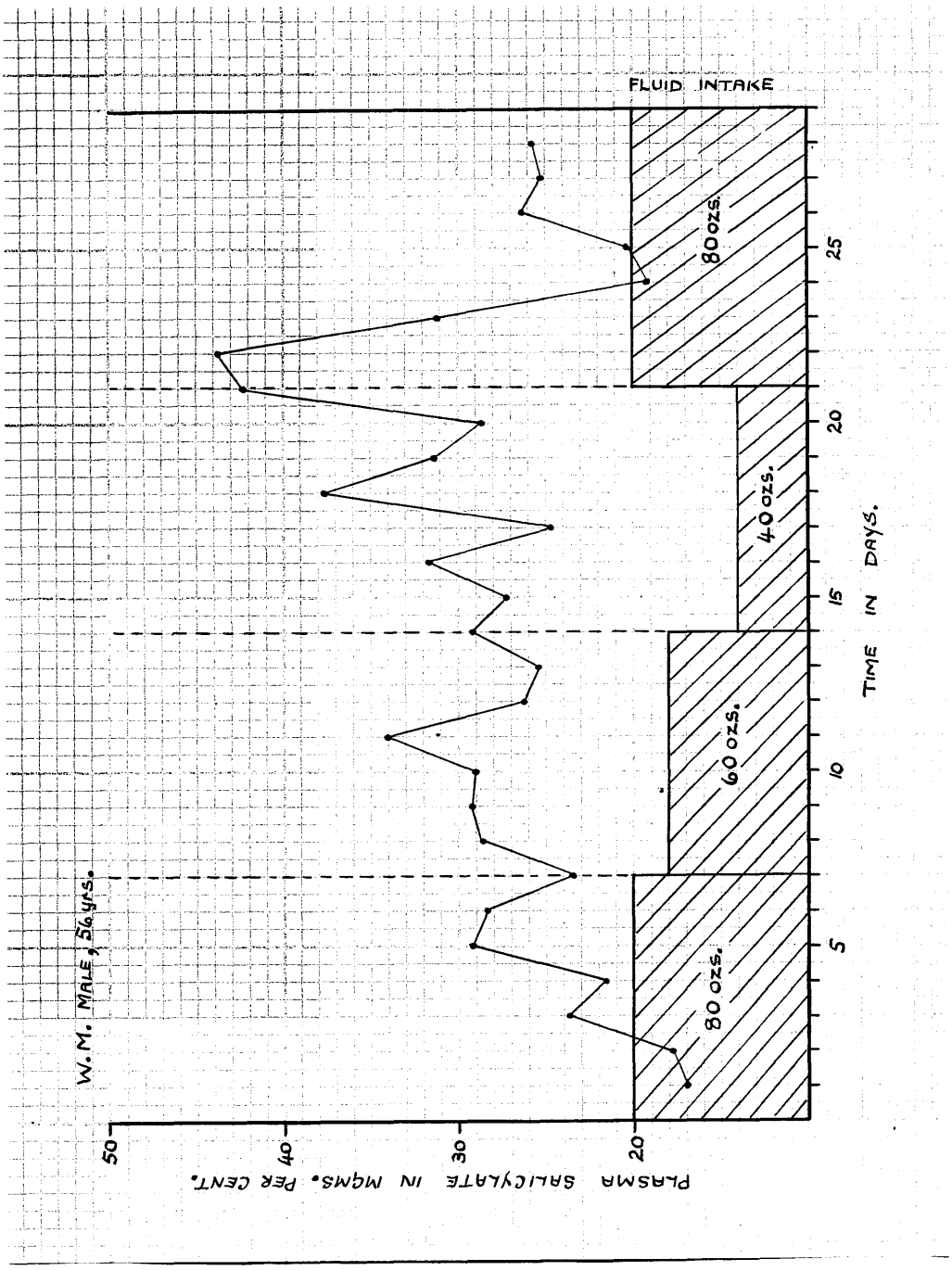
E. The Effect of Fluid Intake on Plasma Levels with Fixed Doses of Sodium Salicylate.

The effect of varied fluid intake on plasma levels of salicylate has apparently not been previously studied. That fluid intake might be diminished during salicylate intoxication is evident especially in the presence of nausea. Vomiting, a common feature of salicylate toxicity, would aggravate the condition even further. Diminished fluid intake, together with dehydration is described as a feature of salicylate intoxication in children by Erganian et al (1947).

An attempt is made to assess the effect of large and small fluid intakes on adults. The results obtained from

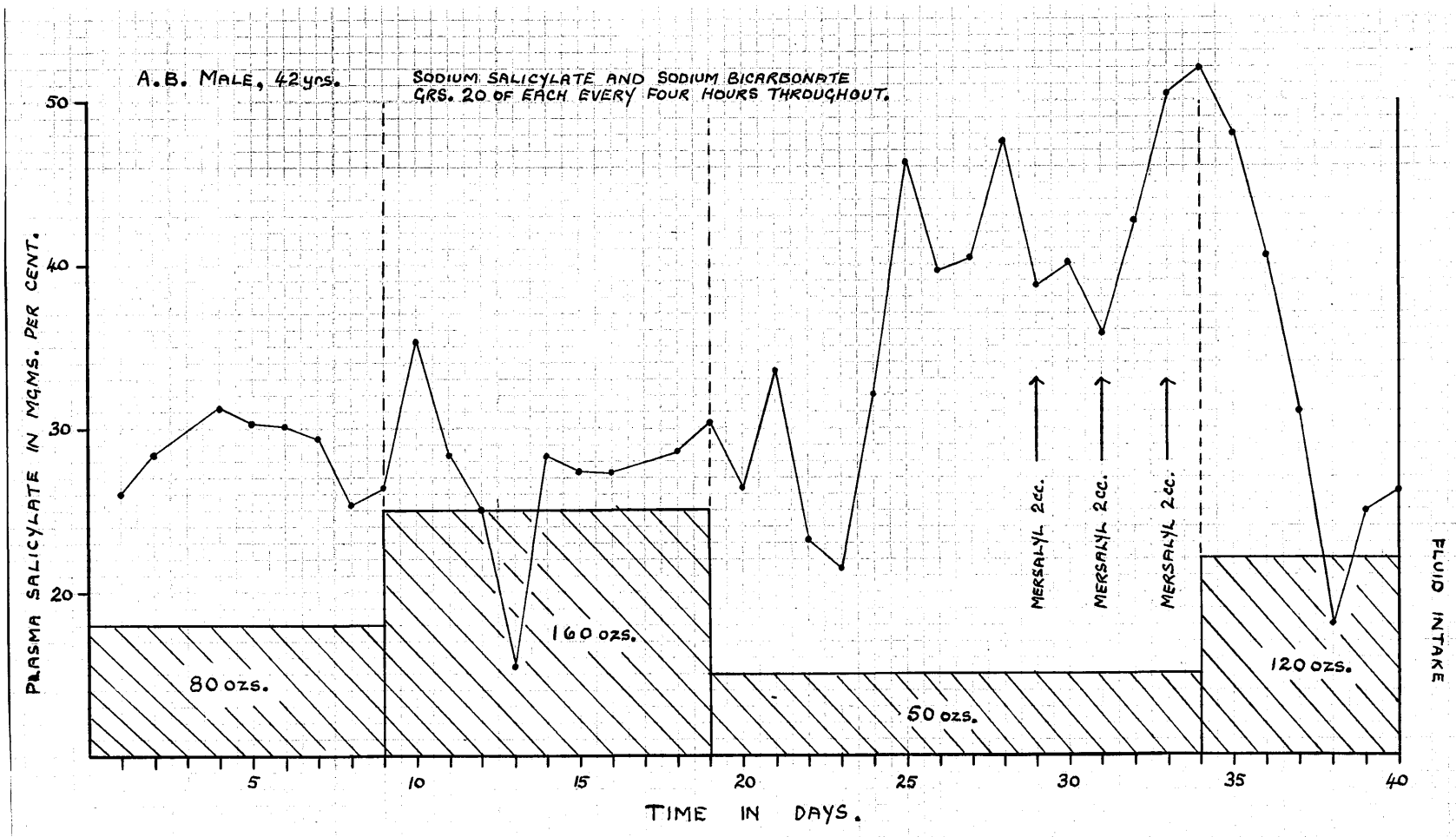
alteration of fluid intakes in four adults are presented in detail.

FIGURE 12



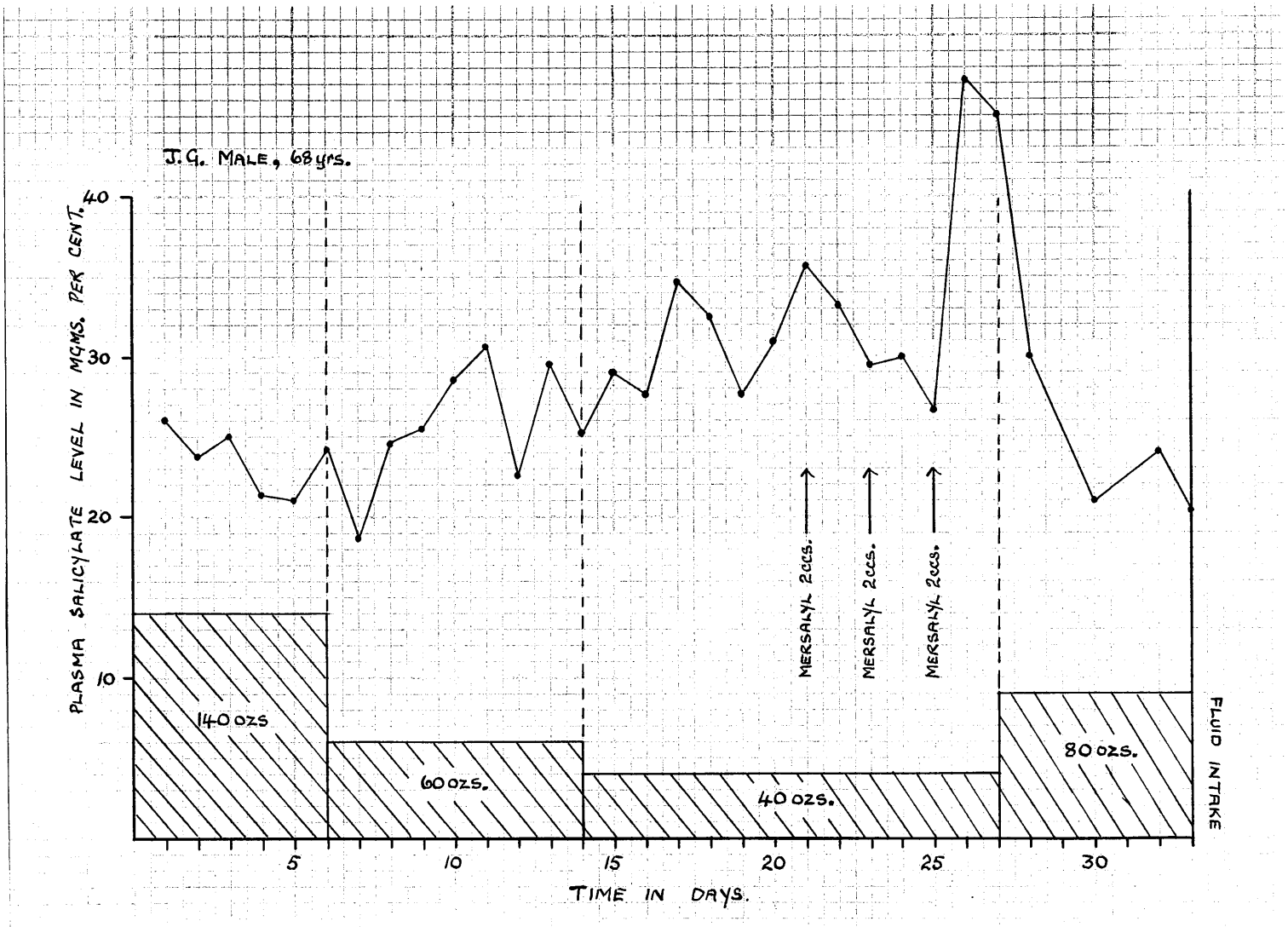
W.M. Hemiplegia, aged 56 years, without renal or gastric involvement was given Sodium salicylate grs.20 with Sodium bicarbonate grs.20 throughout the 28 days while under observation every four hours. For seven day consecutive periods he was allowed an exact fluid intake of 80, 60, 40, 80 ozs.daily and plasma levels ascertained daily at 11 a.m.

FIGURE 13



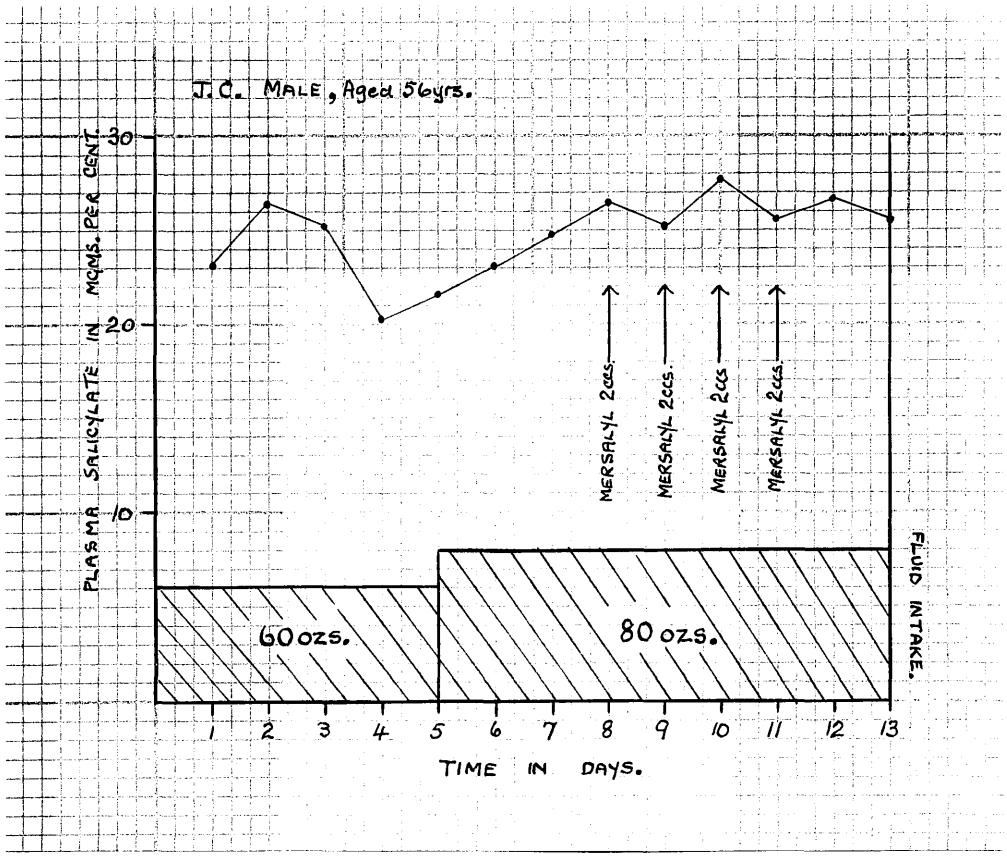
A.B. Male, aged 42 years, with Chronic Rheumatoid Arthritis. Doses and Fluid Intake as shown in the figure. With the first intramuscular injection of mersalyl there was a 50% increase in urinary output but no increase with the subsequent two injections. The plasma level rose to 52.1 mgms.% on day 34 and was associated with some mental confusion, hyperventilation, nausea, and general malaise, so the fluid intake was immediately raised.

FIGURE 14



J.G. Male, aged 68 years, with Hemiplegia. Grains 25 of Sodium Salicylate with an equal quantity of bicarbonate administered every four hours throughout.

FIGURE 15



J.C., Male, aged 56 years, convalescent from fibrositis, received grs.25 of Sodium Salicylate with an equal quantity of sodium bicarbonate four hourly throughout.

It will be seen from the presented data that there is little effect on the plasma levels while the fluid intake remains above 50 ozs.per day. Variation of the fluid intake above this amount may produce a temporary upset in the plasma level but this settles within a few days (Figure 13). The

first three cases show that when the fluid intake is reduced below 50 ozs. there is a marked rise in plasma levels on each occasion, although this effect may be delayed for two to three days. Resumption of an adequate fluid intake when the levels have reached a maximum leads to a speedy return of the plasma level to a normal level. The use of a mercurial diuretic in the presence of an established low fluid intake further increases the plasma level (Figures 13 and 14) but in the presence of an adequate fluid intake has no determinable effect although diuresis was greater (Figure 15) indicating that the mercurial diuretic is producing its effects by aggravating the fluid loss and not by interfering with renal excretion of salicylate.

It would appear then that as the body fluid decreases the plasma level rises if the administration of salicylate is continued, and this rise can be marked. These results have been shown in adults but it is likely that in children in whom dehydration is an early feature of salicylate toxicity, such toxicity may be aggravated greatly by lack of fluid. It is apparent also that administration of adequate fluid will do much to relieve the situation especially if (Figures 2, 3 and 4) it is combined with bicarbonate administration.

F. The Effect of Exercise on the Plasma Salicylate Level.

It is quite common in the treatment of sub-acute and chronic rheumatism to allow the patient to be ambulant while receiving salicylate therapy. This is the rule of Robertson et al (1946) who believes in the therapeutic value of early physical activity in the rheumatic fever cases he treats. It was thought of interest to find if the plasma level would be altered by the exercise to which such patients might be subject.

Five patients all of whom were convalescent were given 75 grs.of Sodium Salicylate in three ounces of water some three hours after their last meal and were confined to bed with minimal movement. Exactly 2 hours later the plasma level was ascertained. Two days later when the plasma levels had again returned to zero the experiment was repeated with the difference that on this occasion after taking the drug the patients went out and either walked or played in the hospital grounds, but in any event kept active for two hours after which their plasma levels were again obtained.

TABLE 4

Patient	Plasma levels in mgms.%	
	Without Exercise	With Exercise
1	19.0	17.6
2	19.7	22.5
3	21.3	26.3
4	18.6	18.0
5	21.4	17.2
Average	20.0	20.3

The plasma levels are shown in Table 4 from which it will be seen that there was individual variation but no significant difference in the group. Thus it appears that ordinary physical activity has no significant effect on the plasma levels.

G. Variation in Plasma Levels from Inaccurate Dosage, and Deterioration of Mixture.

The standard method of dispensing sodium salicylate in this hospital was in a mixture containing sodium bicarbonate, the combined doses of both ingredients being carried in $\frac{1}{2}$ oz. of water. In general this meant quite an amount of sediment of undissolved sodium bicarbonate lying in the bottles before administration.

Earlier it had been noted that plasma levels varied

markedly on fixed doses of sodium salicylate and bicarbonate dispensed in this way and administered to a patient. The possibilities were, as all patients were receiving the drug:

1. Irregular administration.
2. Inaccurate dispensing.
3. Inaccurate measurements in the ward.
4. Inadequate shaking of the bottle before administration.
5. Deterioration of the mixture on standing.

A careful investigation eliminated the first three of these possibilities.

Inadequate shaking of the bottle. Several bottles containing 12 ozs.of a mixture of grains 30 of sodium salicylate and grains 30 of sodium bicarbonate to the ½ oz. were selected. These were measured into single doses accurately but only after the usual amount of shaking of the bottle done in the ward. All sediment was allowed to settle between each measurement. The doses were then suitably diluted and the salicylate content measured using the method described for plasma. It was found that the initial 12 doses removed from each bottle contained 95 to 120 per cent of the required amount of salicylate, while the last 12 doses contained only 70 to 95 per cent of the expected total salicylate content. This indicated that inadequate

shaking gave a marked error probably from uneven distribution of undissolved bicarbonate. It also showed that towards the end of a bottle patients were receiving greater amounts of bicarbonate than during the first few doses, a fact which would affect plasma levels by influencing the excretion of salicylate in the urine (see Chapter V.).

Deterioration. After three weeks mixtures of sodium salicylate and bicarbonate yielded up to 10 per cent less salicylate as estimated by analysis before and after this period.

For all experiments and patients observed in this thesis, when the oral route was used sodium bicarbonate was dispensed in a separate bottle and solutions of sodium salicylate were freshly prepared. In this way the amounts of sodium salicylate administered were accurate.

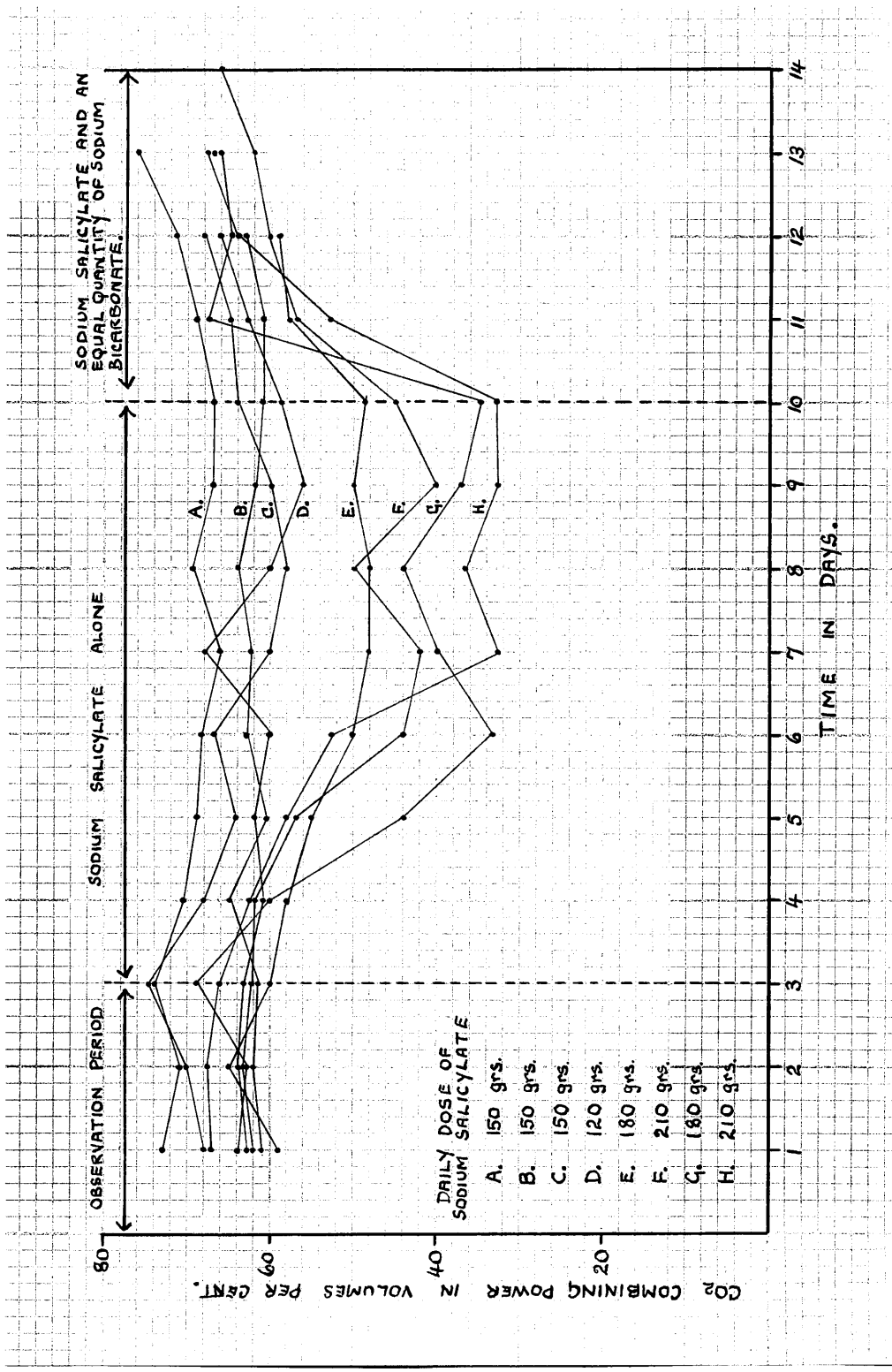
H. The Effect of Sodium Salicylate on the CO_2 Combining Power of the Plasma.

Many workers have reported alterations in the alkali reserve of the blood on large doses of salicylate. Johnson (1930), Odin (1932), Morris & Graham (1931), Dodd et al (1937), Fashena & Walker (1944), Ryder et al (1945), Manchester (1946), Erganian et al (1947), and others have noted a fall in the CO_2

combining power with salicylate therapy. Most of the above workers noted that the addition of sodium bicarbonate prevented or reduced the effect on the CO_2 combining power. In this series eight patients were given sodium salicylate in varying doses every four hours by mouth for seven days, followed by the addition of sodium bicarbonate for further periods. The CO_2 combining powers were estimated daily before and during the administration of the drugs by the method of Van Slyke and Cullen (1917). These are shown with the relevant data in Figure 16. All the patients shown were adult males.

It will be seen that in the majority of cases the CO_2 combining power fell with the administration of sodium salicylate alone. The fall appeared to be more marked as the dose of sodium salicylate increased, but in no case shown in Figure 16 was there a severe enough reduction in the CO_2 combining power to warrant stopping the drug. It is interesting that the lowest figures are shown on the third or fourth day of salicylate therapy, and that in all cases where the CO_2 combining power was low the addition of bicarbonate restored the values rapidly. The lowest plasma salicylate concentration at which a significant fall in the CO_2 combining power was first noted was 25.8 mgms.% and the average figure 34.8 mgms.%.

FIGURE 16


CO2 COMBINING POWER IN VOLUMES PER CENT.
80
60
40
20
TIME IN DAYS.
1
2
3
4
5
6
7
8
9
10
11
12
13
14
OBSERVATION PERIOD
SODIUM SALICYLATE ALONE
SODIUM SALICYLATE AND AN EQUAL QUANTITY OF SODIUM BICARBONATE.
A.
B.
C.
D.
E.
F.
G.
H.
DAILY DOSE OF SODIUM SALICYLATE
A. 150 grs.
B. 150 grs.
C. 150 grs.
D. 120 grs.
E. 180 grs.
F. 210 grs.
G. 180 grs.
H. 210 grs.

Summary.

Various factors which can affect the plasma concentration of salicylate with oral administration have been demonstrated, all of which may have a practical application in salicylate therapy. The effect of varying oral dosage of salicylate on the CO_2 combining power has also been shown.

APPENDIX:

METHOD OF ESTIMATION OF PLASMA SALICYLATE.

Until 1944 extensive studies on the absorption of sodium salicylate and resultant plasma levels were handicapped as there was no satisfactory method of measuring the salicylate content of the plasma which could be performed frequently and accurately in the hospital laboratory. In 1944, however, Brodie, Udenfriend and Coburn published a comparatively simple but accurate method for the determination of salicylate in the plasma. This method depends on the salicylate in a quantity of plasma coming into equilibrium with ethylene dichloride in the presence of acid, and later into equilibrium with ethylene dichloride and water. A colour can be developed in the water with an iron salt and measured photoelectrically. By calibration

with known quantities of salicylate accurate estimations of plasma salicylate are obtained. This method was accurate in these estimations to within +5% or -5%.

It was found that a greater sensitivity was required in measuring plasma levels below 10 mgms.% and for this purpose the following modification was introduced. A larger volume of plasma namely 4 ccs. was made acid with 2 ccs. of 6N HCl with the addition of 3 ccs. of distilled water and the method proceeded with as described. A calibration curve was prepared for the new quantities. With this modification it was possible to detect and measure quantities down to 0.4 mgms.% accurately.

This method necessitated several hours to carry through, so frequently it was found necessary to collect a number of specimens for several days before estimation. A careful check showed that storage of the plasma at room temperature or refrigeration of whole blood for periods up to one week made no appreciable difference to the readings.

CHAPTER II.

THE RECTAL ADMINISTRATION OF SODIUM SALICYLATE

In an attempt to reduce the gastric disturbances which are well known with oral administration of sodium salicylate in adequate dosage many workers have used sodium salicylate administration per rectum with varying success in the treatment of rheumatic fever.

Heyn (1912) gave sodium salicylate, 120 to 240 grains in 6 ozs. of starch water into the rectum. There was relief from joint pains and a marked reduction in temperature. Judging from ether extracts of the stools he found maximum absorption occurred during the first 12 hours after administration. He considered gastric disturbances were avoided and therapeutic results obtained showing the rectal route to be preferable to the oral one. Irving (1923) had similar experiences in children where he employed a dose of 1 to 3 grains per pound body weight noting that children complained of headache and tinnitus within 15 to 45 minutes of the installation of the sodium salicylate. Blume & Nohara (1933) compared the level of the salicylate in the blood and the quantity of salicylate excreted in the urine of rabbits after oral and rectal administration. They found a slightly higher blood salicylate

content after rectal administration than when the drug was given by mouth, but a similar amount was excreted in the urine no matter which method of administration was used. They decided that absorption was more rapid when the drug was administered per rectum as the solution came immediately into contact with a larger area of mucosa from which absorption could take place. Velasquez (1939) obtained satisfactory results with an isotonic solution of sodium salicylate (23.2 gms.per litre). He too considered that since gastric disturbances are thereby avoided, the rectal route is preferable to the oral one. Mackenzie (1943), comparing the oral and rectal administration of sodium salicylate by estimating urinary salicylate, decided that excretion was more rapid when the drug was given by the mouth, but that absorption was similar by both routes. He thought that salicylate enemata could if necessary replace the oral administration of the drug. However, Huntingdon et al (1946), using 50 grains sodium salicylate per rectum in 1 oz. of water at four hourly intervals were unable to obtain a serum level of salicylate above 7 mgms % and decided that the absorption of sodium salicylate from the rectum was poor.

The majority of workers have compared the rectal and oral route by examination of excretion of salicylate or by

therapeutic and toxic effect, methods which are indirect and which tend to inaccuracy.

Technique used in the following investigation. The sodium salicylate was dissolved in three ozs. of water and run into the rectum after an evacuating enema had been returned. The tubing with catheter was then washed through into the rectum with a further one oz. of water. All fluids were administered at body temperature.

A. Comparison of Plasma Levels with Oral and Rectal Administration:

As a preliminary to the treatment of rheumatic fever by the rectal route with sodium salicylate, the oral and rectal routes were compared in five patients. These patients were given 100 grains of sodium salicylate in five ozs. water orally some $2\frac{1}{2}$ hours after the last meal. Plasma levels of salicylate were obtained at 15 mins., 30 mins., 1 hour, 2 hours, 4 hours, 8 hours and 24 hours after administration of the drug. Several days later when all salicylate had been excreted, the same dose in the same quantity of water, was given to the same patient but this time rectally. No difficulty was experienced by the patient in retaining the salicylate enema which was administered at body temperature.

Figure 17 shows the plasma salicylate levels obtained

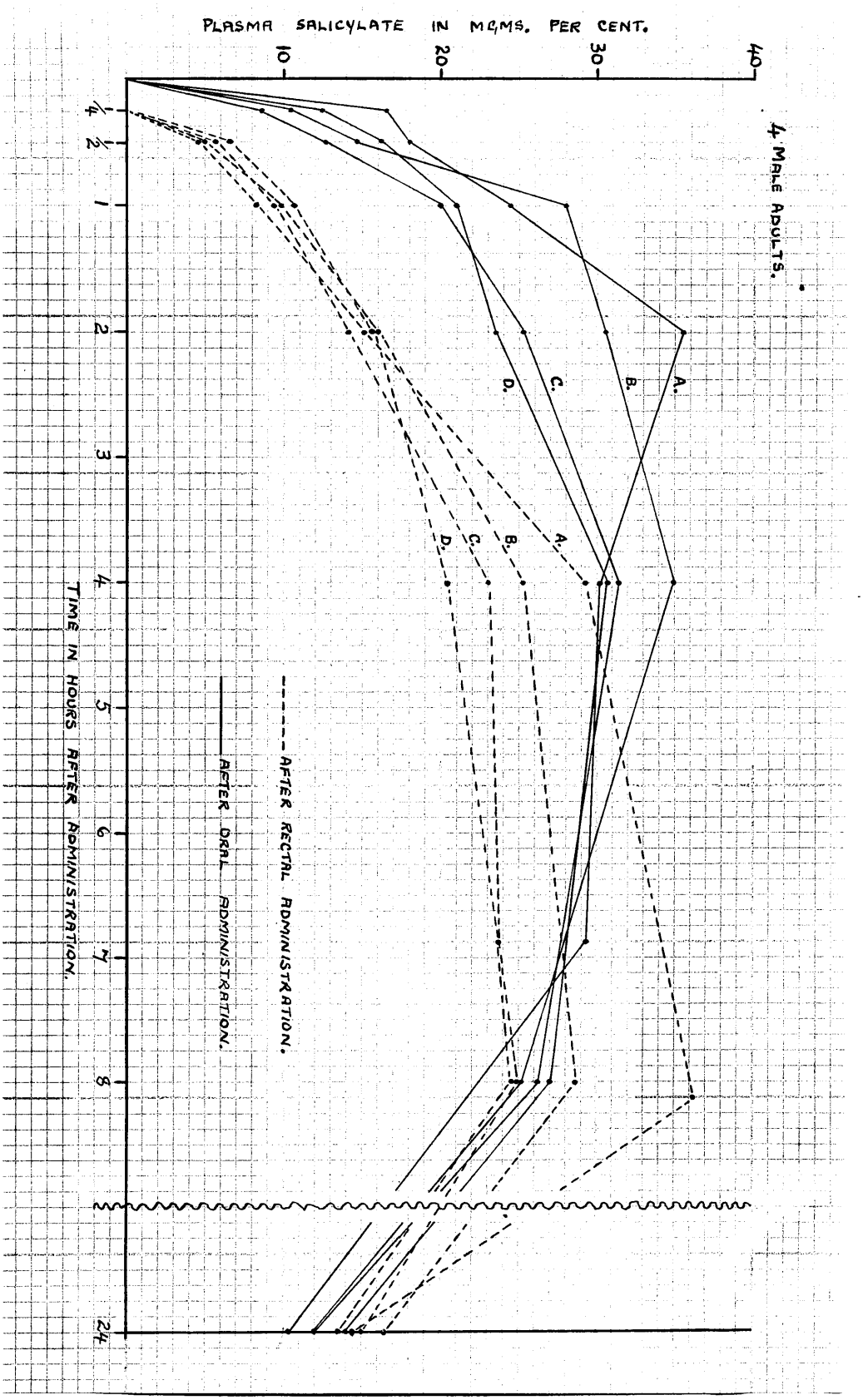

PLASMA SALICYLATE IN MGMS. PER CENT.
10
20
30
40
4 MALE ADULTS.
A.
B.
C.
D.
A.
B.
C.
D.
AFTER RECTAL ADMINISTRATION.
AFTER ORAL ADMINISTRATION.
¼
½
1
2
3
4
5
6
7
8
24
TIME IN HOURS AFTER ADMINISTRATION.

FIGURE 17.

by rectal and oral administration of sodium salicylate in this manner.

It will be seen that the peak plasma levels obtained with the oral route tend to occur at either the second or fourth hours, while with rectal administration the peak plasma levels occur at the eighth hour. This is taken to indicate that the absorption from the rectal mucosa is slower than from the mucosa of the upper gastro-intestinal tract. Apparently the peak plasma levels from oral administration tend to be slightly higher than those obtained with rectal installation. This might be explained by the fact that with rectal salicylate, excretion has been going on for at least four hours longer than with the oral route before maximum plasma concentrations are reached. The rate of elimination of salicylate judged by the fall in plasma levels after peak concentrations have been attained are comparable.

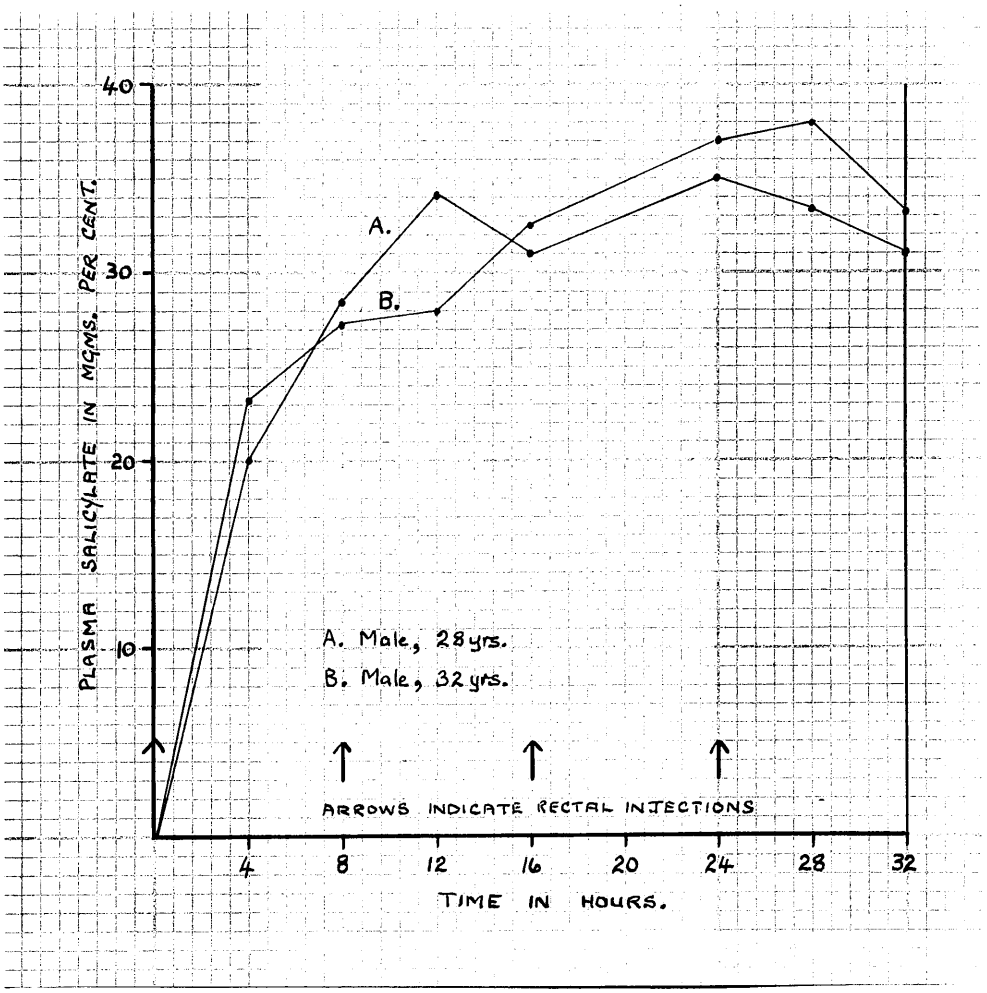
B. Frequency of Administration:

From the above experiment it appeared that rectal absorption was adequate and that eight hourly rectal installations of sodium salicylate might be adequate in maintaining plasma levels of salicylates.

(1) A further two patients were given 60 grains of sodium salicylate in three ozs. of water rectally every eight hours and

the plasma levels were estimated every four hours except during the night, over a period of 32 hours. The results are shown in Figure 18, where it may be seen that the plasma levels were maintained satisfactorily over the period studied.

FIGURE 18.



(2) Larger doses of sodium salicylate were used for the following patients. These patients received 75 grains of sodium

salicylate in three ozs. of water by the rectal route every eight hours and a study made of plasma levels, toxic symptoms, and bowel movements over a period of seven days. These results are shown in Figure 19, and Table 5.

FIGURE 19.

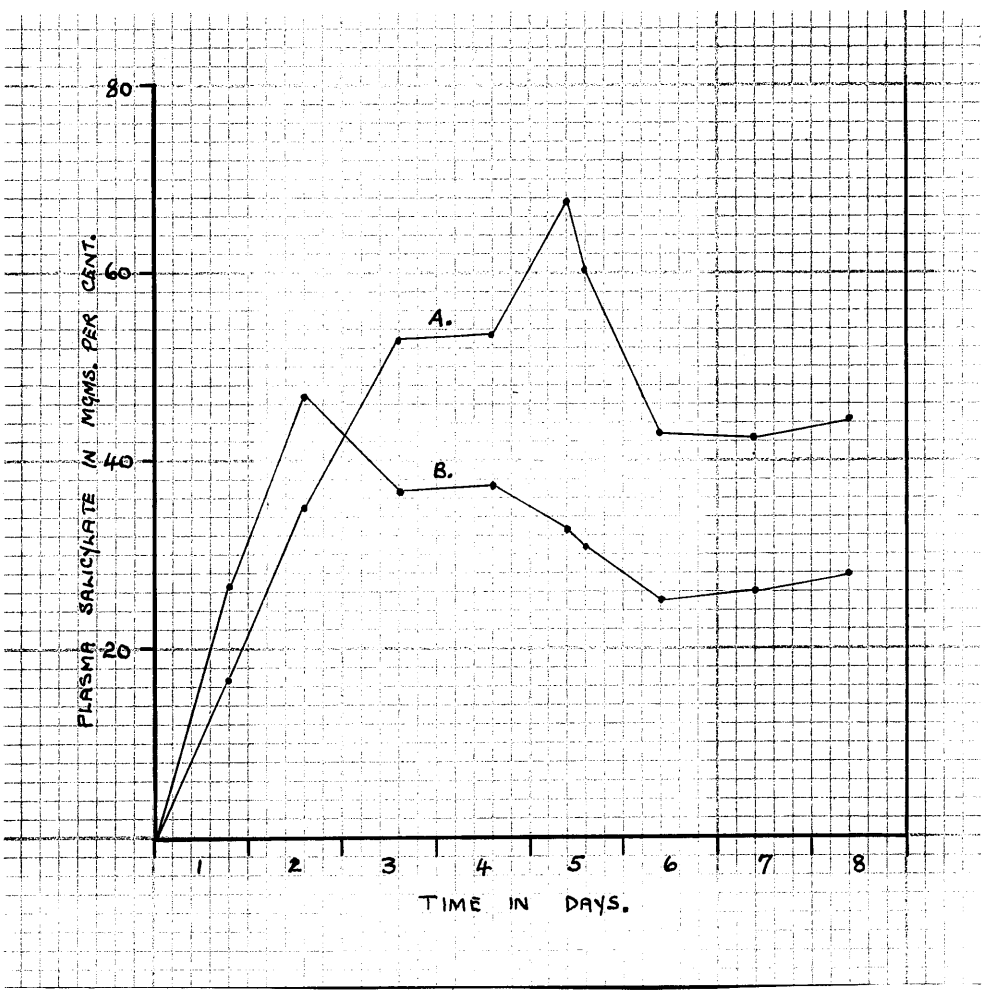


TABLE 5.

Rectal Administration of Sodium Salicylate was given in three ozs. water every 8 hours commencing on 1st. day at 9 a.m.

A = Male adult, 36 years. Weight 7 st. 7 lbs.

B = Male adult, 42 years. Weight 10 st. 2 lbs.

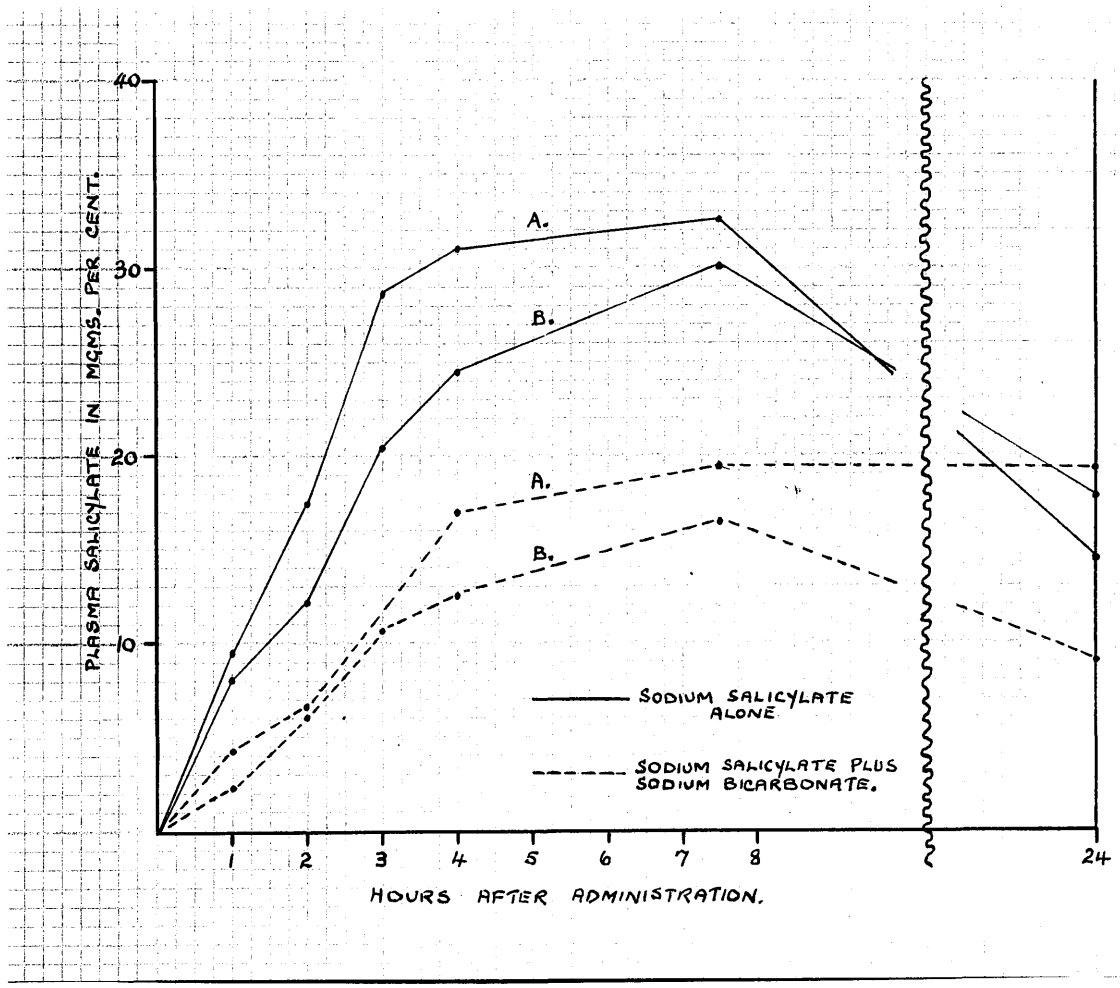
Day of Therapy	Toxic Manifestations	Bowel Movements
B. 1.	Nil.	Enema before start.
2.	Tinnitus.	Soft stool 6 a.m.
3.	Tinnitus, deafness and nausea slight.	Soft stool 9 a.m. Soft stool 10 p.m.
4.	Tinnitus, deafness, hyperventilation with no nausea.	Soft stool 7 a.m.
5.	Tinnitus, hyperventilation slight.	Normal stool 8 a.m.
6.	Tinnitus only.	No motion.
7.	Tinnitus.	Normal stool 7 a.m.
8.	Tinnitus.	Soft stool 8 a.m.
A. 1.	Nil.	Enema before start.
2.	Tinnitus, deafness.	3 soft stools 6 a.m., 1 p.m., 4 p.m.
3.	Tinnitus, deafness, nausea.	Normal motion 8 a.m.
4.	Tinnitus, deafness, nausea, vomited once. Loss of appetite, marked perspiration, hyperventilation.	No motion.
5.	Vomited in the morning twice, grs. 60 sodium bicarbonate 4 hourly orally, from 10 a.m. By evening, tinnitus only. Appetite good.	Soft stool 8 a.m. and 7 p.m.
6.	Tinnitus and slight deafness only. Bicarbonate discontinued 4 p.m.	Soft stool 7 a.m.
7.	Tinnitus only.	No motion.
8.	Tinnitus.	Soft stool 7 a.m.

It has been shown that high plasma levels were obtained in both cases with the usual manifestations of toxicity including gastric disturbances. The addition of oral sodium bicarbonate gr. 60 four hourly on the fifth day to patient A. reduced the plasma level by over 19.2 mgms. % within 21 hours, while in the same period patient B. who was not given bicarbonate had a fall of plasma level of only 6.0 mgms. %. From this it is concluded that the oral administration of sodium bicarbonate to a patient receiving rectal installations of salicylate produces lower plasma levels in the same way as a patient on oral salicylate. This is further evidence showing that sodium bicarbonate orally influences elimination rather than absorption of sodium salicylate. It will be seen that there was no marked upset in bowel action with the frequent rectal administrations of sodium salicylate which the patients had no difficulty in retaining, and during which they experienced no rectal discomfort. Widely different levels were experienced on continued dosage of the same amounts in the two patients, although plasma levels in both cases were adequate on 8 hourly enemata. This also indicates that a close watch should be kept on plasma levels when patients are receiving high rectal doses of salicylate.

C. The Concurrent Administration of Alkali:

The following two cases demonstrate the effect of sodium bicarbonate when administered rectally with an equal quantity of sodium salicylate. In the same manner as previously described, the two patients were given 100 grs. of sodium salicylate alone per rectum and at a later date the same dose was administered again, this time with the addition of an equal quantity of sodium bicarbonate.

These results are shown in Figure 20.



It will be seen that the maximum plasma concentrations obtained with the addition of bicarbonate are significantly lower than with salicylate alone, although the maximum level occurred at the same time with both. This is taken to be evidence showing that the addition of bicarbonate to sodium salicylate by the rectal route interferes with the absorption of sodium salicylate.

D. The Treatment of Rheumatic Fever:

It was decided to treat two cases of rheumatic fever by rectal salicylate administration throughout. A short summary of both case records with the plasma levels obtained follows.

Case I. J.H., male, 26 years of age, admitted Stobhill Hospital 12.12.46, with flitting arthritis involving knees, ankles, wrists and shoulders which had been present for three weeks. Temperature 100°F, Pulse Rate 94/min., Respiration 22/min. There was no cardiac enlargement, arrythmia or bruits. Hb. 13.4 gms %. E.S.R. 94 mm in first hour, 105 in second hour. W.B.C. 8,000/cu.mm. R.B.C. 4.5 million. B.P. 120/60. No radiological evidence of bone abnormality was detected.

Rectal sodium salicylate administration was commenced on 14.12.46 with the dose of 60 grs. in three ozs. water every eight hours.

Progress and Plasma Levels

	Plasma Levels	
15.12.46	13.6 mgms %	Less arthralgia. Temp. normal. Tinnitus.
16.12.46	14.3 mgms %	No joint pains. Tinnitus and slight deafness. Pulse Rate 72/min.
17.12.46	26.6 mgms %	Persistent tinnitus and deafness. E.S.R. 65/1st.hour. 86/2nd.hour.
18.12.46	23.6 mgms %	Deeper respiration, some sweating but comfortable.
19.12.46	32.1 mgms %	Sod.Bic. gr. 60 orally t.i.d., after attack of nausea.
20.12.46	28.0 mgms %	Respiration normal, no nausea. Sod.bic. discontinued.
28.12.46	28.2 mgms %	
8.1.47	28.0 mgms %	
10.1.47	Salicylate discontinued.	
12.1.47	No further symptoms. Allowed up slowly. Hb. 14.5 gms %. E.S.R. 3/1st.hr. 12/2nd.hr. W.B.C. 9,000. R.B.C. 4.75 million. B.P. 125/75.	

Discharged 21.1.47. Reviewed 20.2.47 - no abnormality or complaint.

The patient shows remarkably steady levels on rectal salicylate. He had an uneventful recovery with all clinical signs disappearing by the fourth day of treatment except for a raised E.S.R. The patient had no difficulty with defaecation, passing a daily motion before the morning enema and an occasional small soft stool during the afternoon. There was no rectal irritation or difficulty in retaining the salicylate enemata.

Case II. J.C., male, aged 12 years. Admitted to Eastern District Hospital on 4.9.46 with flitting arthritis involving the ankles, wrists, knees and elbows for 12 days previously. Sore throat three weeks previously. No previous history of rheumatism.
Investigation: Temperature 101°F., Pulse Rate 140/min., Respiration 24/min., W.B.C. 10,000/cu. mm., Hb. 13 gms %. R.B.C. 4,000,000. E.S.R. 86/1st.hr., 102/2nd.hr. Moderate cardiac enlargement with an apical systolic conducted bruit. No diastolic murmur. E.C.G., P.R. interval .25 sec.

Starting 6.9.46 rectal sodium salicylate was administered 40 grs. in two ozs. water in 8 hourly enemata, - 11 p.m., 7 a.m., 3 p.m. daily.

	Plasma Levels	
7.9.46	22.6 mgms %	E.S.R. 90/1st.hr. Joint pains less severe. Pulse Rate 140/min.
8.9.46	36.5 mgms %	Tinnitus, deafness, sweating. No joint pains. Pulse Rate 120/min.
9.9.46	42.1 mgms %	Tinnitus, deafness, slight nausea. Normal temperature. Pulse Rate 120/min.
10.9.46	39.8 mgms %	
14.9.46	42.0 mgms %	E.S.R. 88/1st.hour. Pulse Rate 110/min. Tinnitus and deafness only.
18.9.46	38.6 mgms %	
21.9.46	42.5 mgms %	Slight nausea.
26.9.46	36.4 mgms %	E.S.R. 42/1st.hour. No nausea. Tinnitus and deafness persisted throughout from this time.
28.9.46	38.2 mgms %	
6.10.46	30.6 mgms %	E.S.R. 28/1st.hour. Pulse Rate 90/min.
10.10.46	32.6 mgms %	
15.10.46	30.8 mgms %	E.S.R. 15/1st.hour. Pulse Rate 78/min. E.C.G. P.R. interval .18 sec.
21.10.46	28.6 mgms %	E.S.R. 8/1st.hour. Pulse Rate 82/min.
28.10.46	29.6 mgms %	E.S.R. 5/1st.hour. Pulse Rate 82/min.
4.11.46	26.6 mgms %	E.S.R. 5/1st.hour. Pulse Rate 78/min.
5.11.46	Rectal salicylate discontinued.	
7.11.46	No further symptoms. Allowed up slowly.	
18.11.46	Hb. 14 gms %, W.B.C. 9,000/cu. mm. R.B.C. 4.5 million. E.S.R. 4/1st.hour, 12/2nd.hour. No cardiac enlargement but a conducted bruit systolic in time. Discharged.	
28.11.46	No further symptoms.	

This case also shows an uneventful recovery. The plasma levels were well maintained and only minor toxic manifestations were seen.

Thus both patients showed remarkably steady levels throughout with clinical improvement within 48 hours and both appeared well on discharge and during a short follow-up period. There was no upset in bowel rhythm or rectal irritation during treatment.

Conclusions.

The rectal absorption of sodium salicylate is slower than with oral administration but adequate plasma levels may be maintained by 8 hourly rectal enemata of sodium salicylate alone with full therapeutic results in rheumatic fever. The technique of administration is simple and this form of administration is well tolerated with little upset in bowel rhythm. The addition of sodium bicarbonate rectally decreases the absorption of sodium salicylate markedly while if given concurrently by the mouth facilitates the elimination of salicylate. The effect of rectal administration on the gastric manifestations of salicylate toxicity are discussed in Chapter VI.

CHAPTER III.

THE INTRAVENOUS ADMINISTRATION OF SODIUM SALICYLATE

Coburn (1943) reintroduced the intravenous treatment claiming that in rheumatic fever speedier control of the disease with a fall in incidence of cardiac damage, was possible with this route. His reason for using the intravenous route was to produce and maintain plasma levels above 35.0 mgms %, which he considered the minimum therapeutic level in rheumatic fever. He advocated up to ten days intravenous therapy using 10 gms. of sodium salicylate as a 1% solution, or 20 gms. as a 2% solution, in normal saline, over a period of eight hours daily. This he then followed by high oral doses to maintain the high plasma levels so produced.

Earlier workers, Mendel (1905), Matta (1916), Gilbert et al. (1921), Lutembacher (1921), Lesné (1922), and Carnot and Blamoutier (1925) had all used and recommended the intravenous route for the administration of sodium salicylate. Hanzlik (1926) reviewing all the previous work found that the claims that were made were "unsupported by a single iota of evidence".

Since Coburn's work many others have criticised this method of administration mainly on the grounds that therapeutic efficiency of sodium salicylate was not improved, among them

Ball (1945), McEachern (1945), Warren et al. (1945), and Wégria and Smull (1945) on two occasions. Taran and Jacobs (1945) claimed that the intravenous route was hazardous. In a recent well controlled study of 186 cases of rheumatic fever Warren et al. (1946) after a follow up period of three years found that intravenous therapy offered no advantage over oral therapy. Jager and Alway (1946) however supported Coburn's views. Manchester (1946)(1) noted that within 48 hours salicylate levels in the plasma with oral therapy exceeded those from intravenous therapy except during and immediately after an intravenous injection. But Manchester (1946)(2) nevertheless believes in the therapeutic efficiency of intravenous sodium salicylate in controlling cardiac damage.

It appears logical to assume that if intravenous therapy is to supersede oral therapy even in the first few days of the treatment of rheumatic fever, the intravenous route must produce higher plasma levels of salicylate than the oral route. This was the prime reason that led Coburn (1943) to reintroduce this form of administration.

(A) The Comparison of Plasma Levels following Oral and Intravenous Administration of Sodium Salicylate:

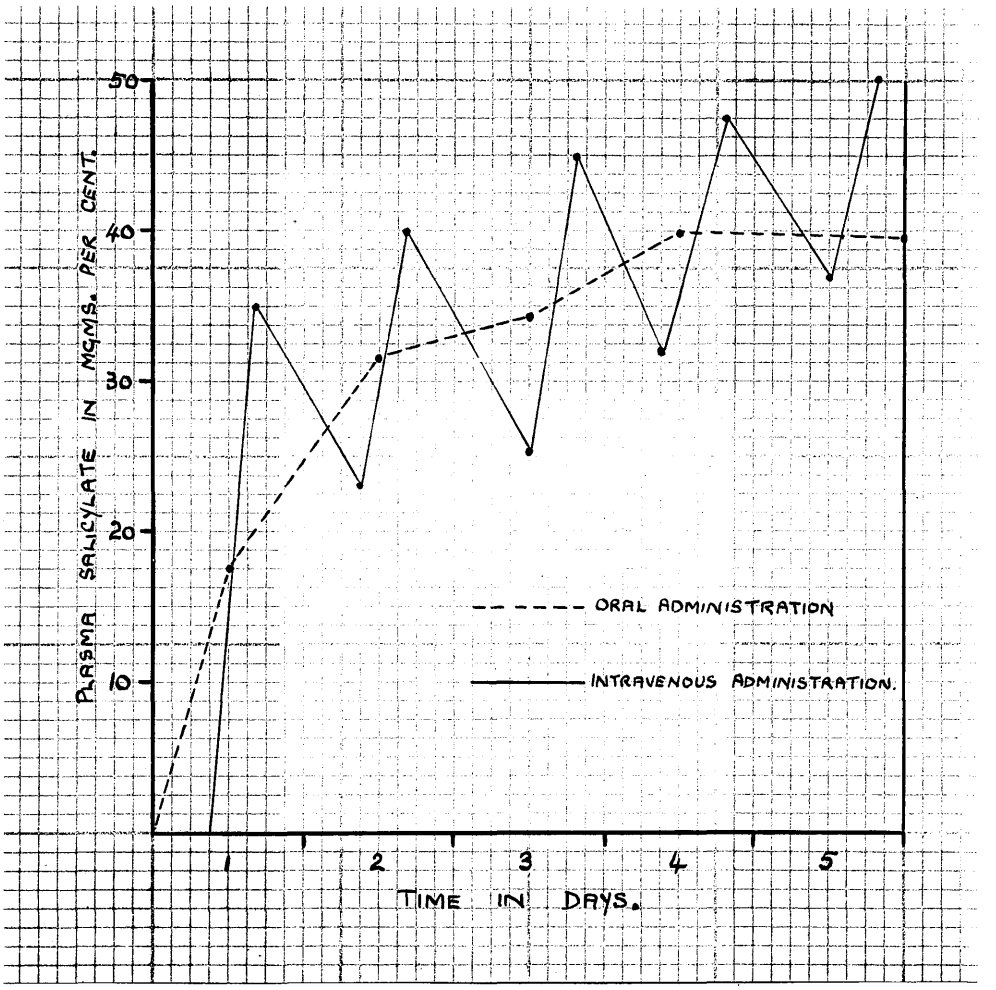
To compare the plasma salicylate concentrations from oral and intravenous therapy, five male adults were given 10 gms.

of sodium salicylate in 1,000 ccs. of normal saline over eight hour periods for several days. Some days later when all salicylate had been excreted as determined by examination of the urine, the same patients were given 10 gms. of sodium salicylate orally in divided four hourly doses daily. With oral administration plasma salicylate levels were obtained daily immediately prior to the administration of one of the four hourly doses, and with intravenous therapy daily, both before and after each intravenous injection.

The plasma levels obtained in this manner have been shown as the average plasma levels for this group of patients first with oral administration and then with intravenous therapy in Figure 21.

It will be seen from Figure 21 that marked peaking occurred immediately after the intravenous injection but by the next morning the plasma levels had fallen considerably. The plasma levels with oral therapy were steady, and compared favourably with those obtained from intravenous therapy, apart from the peak concentrations immediately after the intravenous injection which lasted for a short period only. Oral administration concentrations were consistently higher than the concentrations found before the intravenous injection. Random plasma estimations taken after the intravenous injections and before the succeeding one

FIGURE 21.


50
40
30
20
10
PLASMA SALICYLATE IN MGMS. PER CENT.
ORAL ADMINISTRATION
INTRAVENOUS ADMINISTRATION.
1
2
3
4
5
TIME IN DAYS.

showed that the fall in plasma concentration is rapid immediately after the injection indicating that the peak concentration after the injection is of short duration.

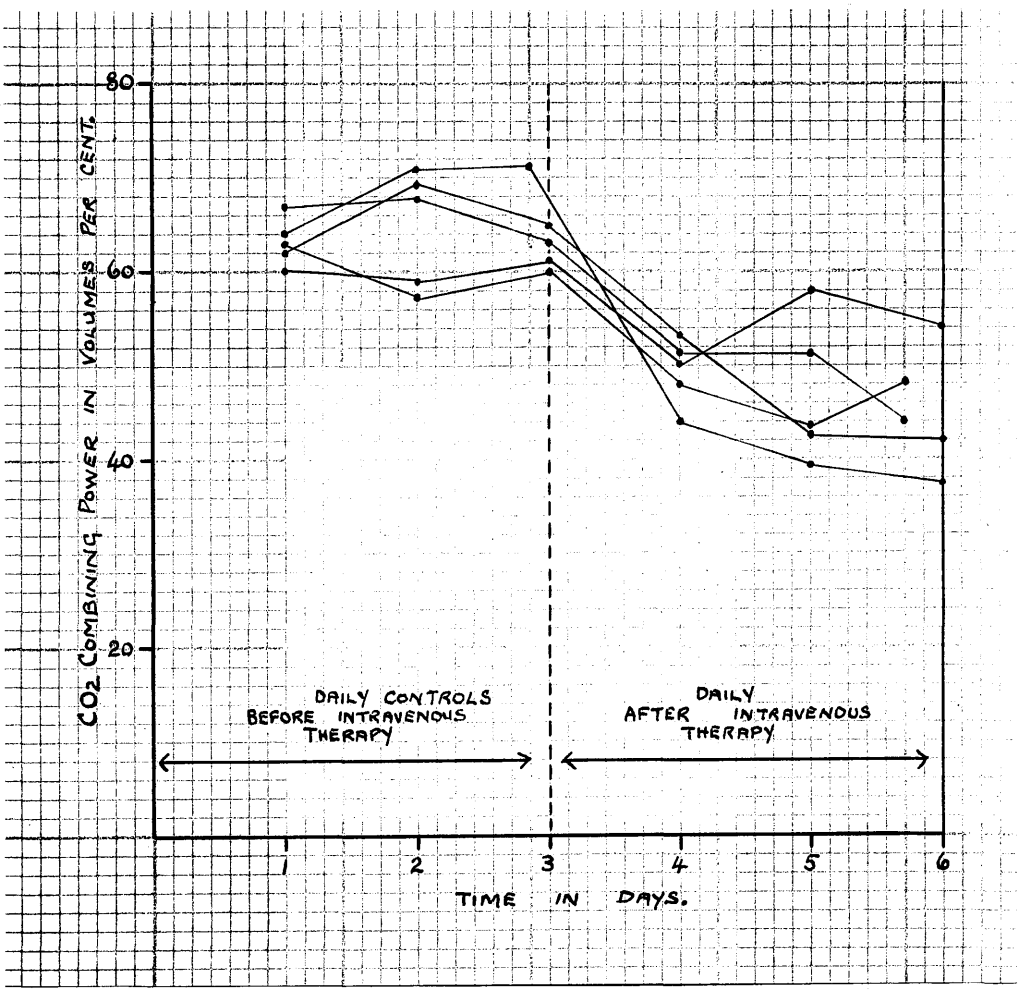
(B) The effect of Intravenous Administration of Sodium Salicylate on the CO_2 Combining Power:

Intravenous injection of 10 gms. of sodium salicylate leads to a marked drop in the CO_2 combining power. The CO_2 combining powers in 5 patients who were receiving 10 gms. of sodium salicylate daily in normal saline were estimated daily. A short control period was observed and all results are shown in Figure 22.

The fall in CO_2 combining power with the daily administration of 10 gms. of sodium salicylate intravenously compares unfavourably with the fall obtained with an equivalent amount given orally as shown in Fig.16.

However it was noted that in two cases the coincident administration of intravenous sodium lactate prevented this fall in CO_2 combining power. The sodium lactate was given as an M/6 solution in the normal saline in which the sodium salicylate was administered. This might be an indication for the use of concurrent sodium lactate administration when sodium salicylate is being given intravenously, but the mechanism of its action in preventing the reduction in CO_2 combining power was not studied.

FIGURE 22.


80
60
40
20
CO2 Combining Power in Volumes Per Cent.
DAILY CONTROLS BEFORE INTRAVENOUS THERAPY
DAILY AFTER INTRAVENOUS THERAPY
1
2
3
4
5
6
TIME IN DAYS.

The Toxic manifestations with intravenous salicylate were observed in several cases and are discussed in Chapter VI. These toxic effects, with the exception of vomiting, were at least as frequent as when the same quantity of the drug was given orally, and in several cases the individual toxic effects were more severe.

Conclusions.

In the light of the above observations there appears little to commend intravenous therapy as being a better mode of administration than oral therapy. The technique is more difficult and is resented by patients, as an eight hour immobilisation of a limb when arthralgia is present can be very painful. The above observations, that just as effective plasma levels can be obtained with oral administration, that more marked reductions in CO_2 Combining Power take place, and that toxic effects are at least as frequent and severe, led this worker to abandon the intravenous route as a method of sodium salicylate therapy. This work would tend to support the observations of Hanzlik (1926), and others, that intravenous salicylate therapy offers few, if any, advantages over oral administration of the drug.

CHAPTER IV.

THE DISTRIBUTION OF SALICYLATE IN THE BODY FLUIDS

Jacoby (1908) was the first to indicate that salicylate could be bound by the plasma proteins. Basing his conclusions on observations on the serum of rabbits, he stated that binding occurred only in vivo, and could not be produced in vitro. However this in vitro binding has since been produced by others. Coquonin (1922) found that dialysing salicylated serum against physiological saline free from salicyl gave an even distribution of salicyl after sufficient time. However, Chabanier et al. (1923) were able to show that serum containing sodium salicylate lost practically none of the salicylate to isotonic saline, while serum dialysed against saline containing salicylate rapidly gained more salicylate with its virtual disappearance from the saline, indicating the peculiar affinity for the salicylate of plasma. Van Leeuwem and Drzimal (1924) showed that serum from asthmatics bound salicylate more than did normal serum.

As Davis (1943) has shown with sulphonamide, the distribution of a drug in body fluids should be analysed in terms of binding to protein. Lester et al. (1946) working with animals found the statement of Reinhold et al. (1944) "that

sulphonamide so bound in a protein-sulphonamide complex appears to be in equilibrium with the free sulphonamide and plasma proteins and that the penetration of sulphonamides into erythrocytes and other cells, and into the C.S.F. and other body fluids including the glomerular filtrate is confined to the ultrafiltrable portion" is equally applicable to salicylate. Lester et al. (1946) showed, moreover, that the results obtained by ultrafiltration and dialysis were comparable.

In view of the statement of Coburn (1943) that better therapeutic results were obtained in rheumatic fever at a concentration of salicylate in the plasma over 35.0 mgms. %, and the possibility that it is the dialysable or free salicylate fraction in the plasma which controls concentration in the body fluids, it was of interest to ascertain if the free salicylate was significantly of greater proportion at this total plasma salicylate level. Or, to ascertain if there was a total plasma salicylate concentration above which the free salicylate increased rapidly, thus giving rise to greater concentration in the body fluids, with a possible bearing on the therapeutic results. This investigation falls into two parts, firstly, the determination of free and bound salicylate in the plasma and its variation with plasma protein concentration, and secondly, the determination of the relationship between the free salicylate

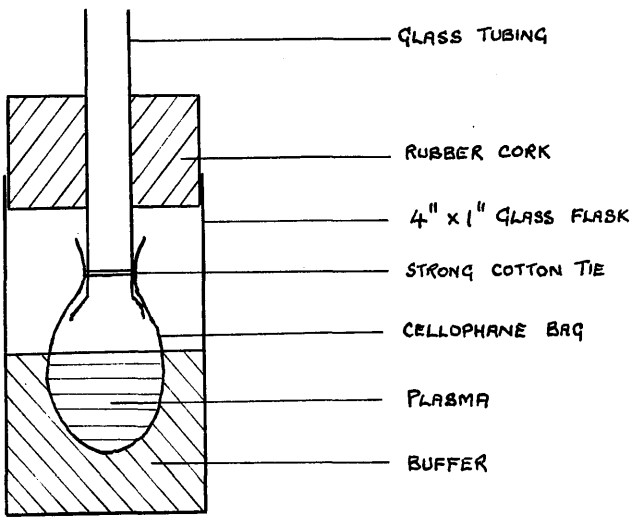
in the plasma and the body fluids.

A. The determination of bound and free salicylate in the plasma and its variation with plasma protein concentration:

Methods used.

(a) 2 ccs. of the plasma containing the salicylate were dialysed at room temperature(1), in a cellophane bag(2), against 5 ccs. of buffer(3). Dialysis was carried on for 24 hours at which time equilibrium was obtained as further dialysis gave no increase in the concentration of salicylate in the buffer. A solute which can traverse the membrane will, if there is no other restraining force, diffuse through it until the concentrations in the two media are identical(4). The restraining force in this instance is plasma protein to which bound salicylate is attached and to which the membrane is not permeable, the unbound or free salicylate being diffusable.

FIGURE 23.



Thus the concentration of free salicylate in the plasma is found by multiplying the concentration in the buffer by the total water in the system divided by the plasma water(5). The difference between the free salicylate and the total salicylate(6) was taken to be the amount of the bound drug. The effects of Donnan equilibrium were neglected(7).

(b) The total plasma proteins were estimated by the Dipping Refractometer (Zeiss).

1. Lester et al. (1946) and Davis (1943) have shown that temperature exerts no appreciable effect on the magnitude of the binding.

2. The cellophane used in these experiments was manufactured and supplied by British Cellophane, Ltd.

3. The buffer used was that of Davis (1943) designed to simulate body fluids and prevent interference with dialysis of plasma by pH, and was 0.15 M NaCl in 0.01 M Sodium phosphate adjusted to pH 7.4 (25°C.).

4. Peters (1935).

5. Plasma water was taken to be total plasma volume as used in the experiments, as the factor for conversion of plasma volume to plasma water is small - Davis (1943). It is dependent on concentration of plasma protein, and for example, at a plasma protein concentration of 5.94 gms.% the factor is 0.955.

6. Estimated by the method of Brodie et al. (1944) on a sample of the plasma before dialysis.

7. In so doing the precedent of Davis (1943) is followed. In the estimation of an unbound drug any error caused will be in the direction of underestimating the binding.

Technique.

1. A number of individual plasmas was obtained freshly from patients. These plasmas were divided into portions and

to each portion was added a measured quantity of sodium salicylate in order that the range 10 to 60 mgms. % which might be expected during salicylate therapy was covered in each plasma. After thorough shaking, the plasmas were left at room temperature for two hours. The total salicylate content and the free and bound salicylate were then estimated.

2. Plasmas were obtained from patients on salicylate therapy, and total, free, and bound salicylate estimated.

3. The plasma proteins were estimated from eight patients receiving salicylate therapy, and on four of the plasmas used in 1. for the in vitro experiments. In all these plasmas, total salicylate levels above and below 25.0 mgms.% had been obtained with the free and bound salicylate. From individual curves the bound salicylate at a total concentration of 25.0 mgms.% were obtained in each plasma and could be related to the plasma protein concentration.

In this way dialysis was carried out some 68 times including 20 in vitro estimations over a range of 10 to 60 mgms.% on fresh plasma. All estimations of free salicylate were then plotted against total salicylate and have been shown in Fig.24,

while bound salicylate was plotted against total salicylate and shown in Fig.25. From 3. above the amount of bound salicylate at a total level of 25.0 mgms.% was plotted against the plasma proteins and is shown in Fig.26.

In Figure 24, it is shown that as the total salicylate in the plasma increases, so does the unbound or free salicylate. The increase in free salicylate, however, is proportionately greater as the total salicylate rises.

In Figure 25 it will be seen that as the total salicylate in the plasma rises, so does the bound salicylate. The increase in bound salicylate, however, becomes proportionately less as the total level rises. The curve tends to flatten out above a total salicylate concentration of 40.0 mgms.% although there is not enough evidence to show that a maximum binding has been reached at the total levels shown.

Figure 26. It appears that the binding of salicylate by protein increases with increase in concentration of protein. The effect is not marked, as from the figure it may be calculated that at a level of 25.0 mgms.% there is an increase in binding of salicylate of 3 mgms.% for each gram % increase in the protein concentration of the plasma. There also appears to be individual variation.

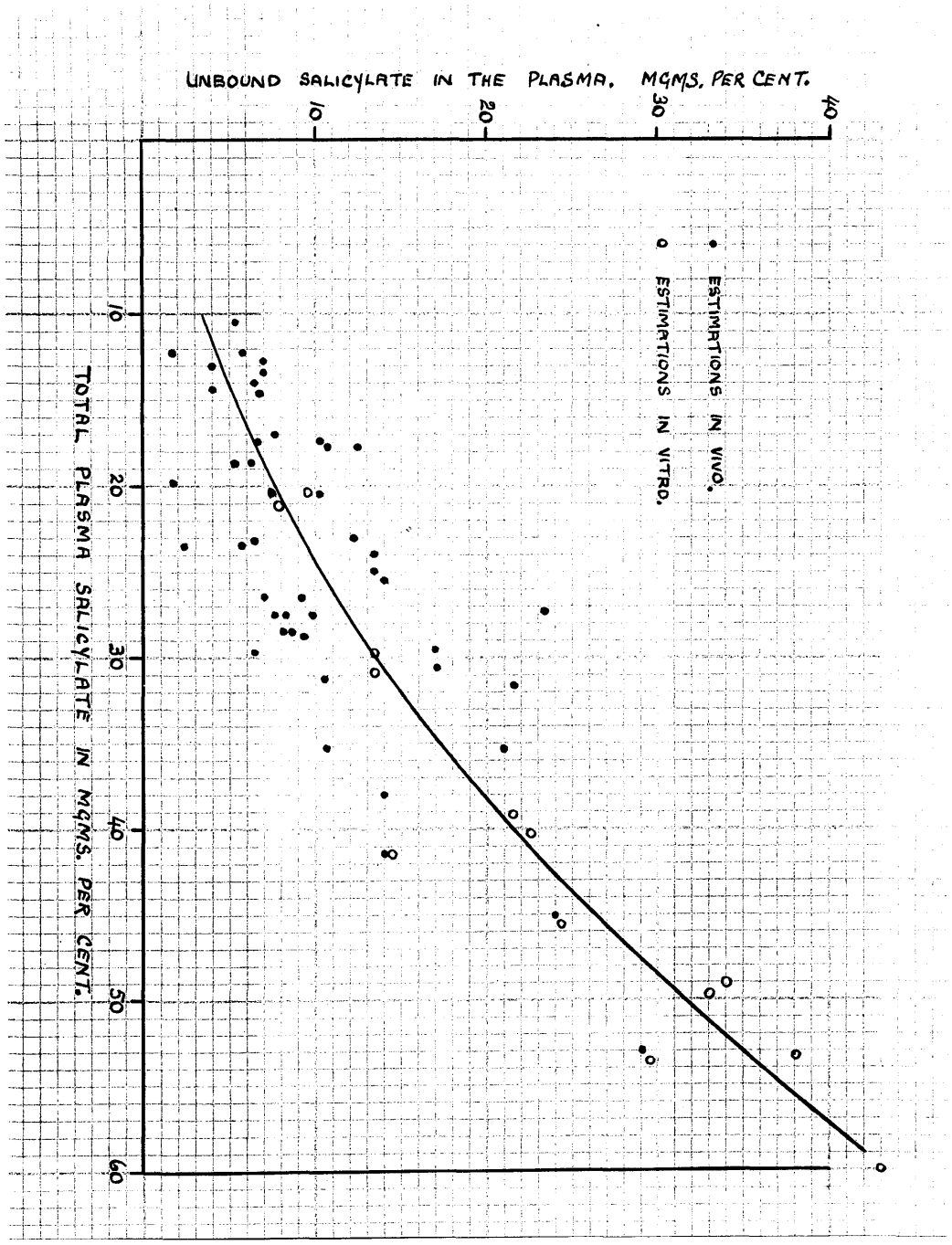

UNBOUND SALICYLATE IN THE PLASMA. MGMS. PER CENT.
10
20
30
40
• ESTIMATIONS IN VIVO.
o ESTIMATIONS IN VITRO.
10
20
30
40
50
60
TOTAL PLASMA SALICYLATE IN MGMS. PER CENT.

FIGURE 24.

FIGURE 25.

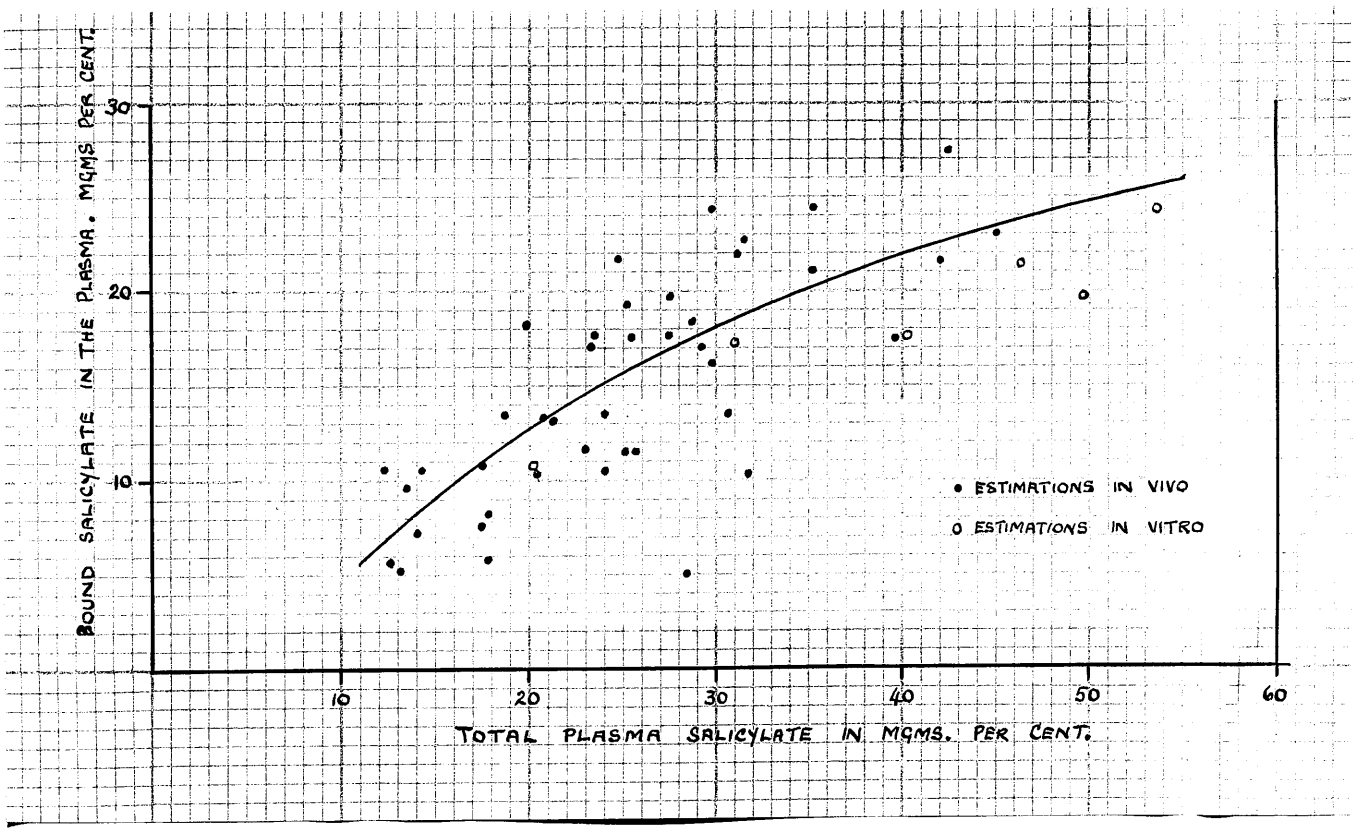
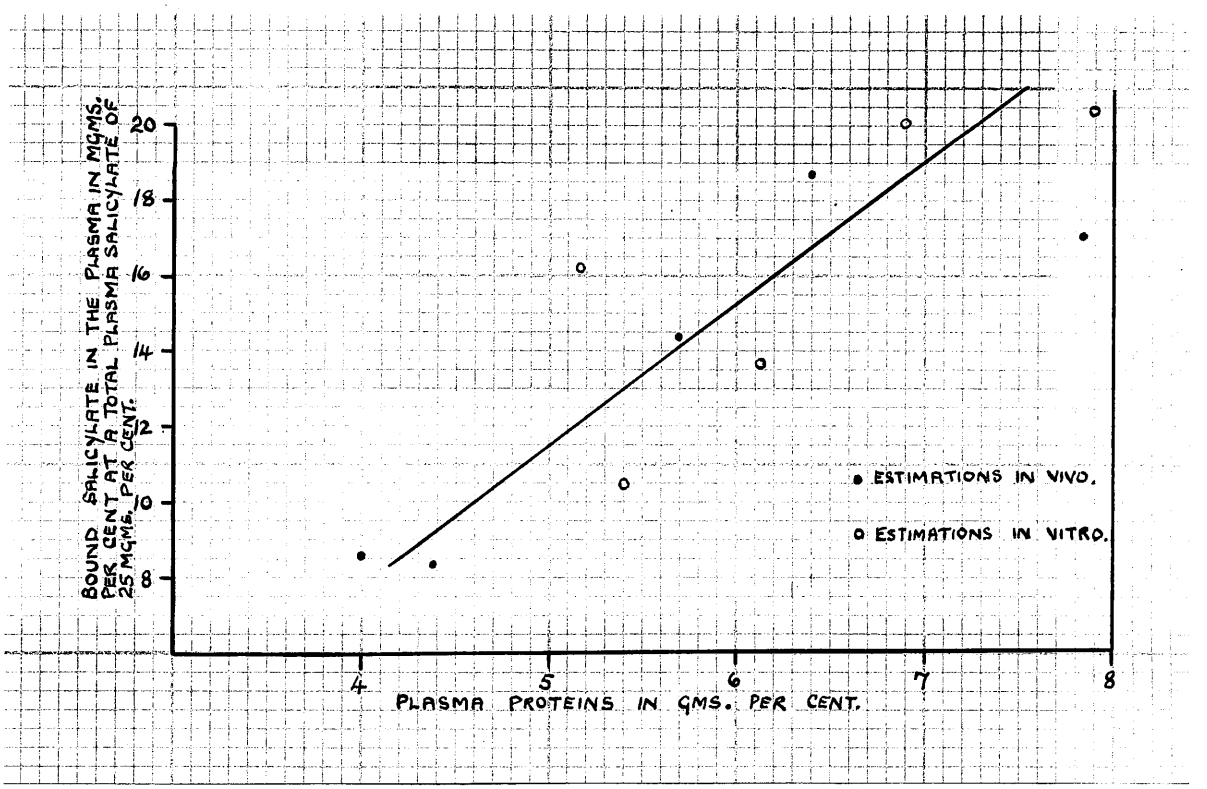

BOUND SALICYLATE IN THE PLASMA. MGMS PER CENT.
30
20
10
10
20
30
40
50
60
TOTAL PLASMA SALICYLATE IN MGMS. PER CENT.
• ESTIMATIONS IN VIVO
o ESTIMATIONS IN VITRO

FIGURE 26.


BOUND SALICYLATE IN THE PLASMA IN MGMS. PER CENT AT A TOTAL PLASMA SALICYLATE OF 25 MGMS. PER CENT.
20
18
16
14
12
10
8
4
5
6
7
8
PLASMA PROTEINS IN GMS. PER CENT.
• ESTIMATIONS IN VIVO.
o ESTIMATIONS IN VITRO.

B. The Distribution of salicylate in other body fluids:

Employing dogs and rats Lester et al. (1946) found strong evidence that at equilibrium, salicylate is distributed throughout the non-protein extra-cellular water in a concentration equal to that in the water of the red cells, and the ultrafiltrate of plasma. With C.S.F. in animals, they found that the salicylate concentration 8 hours after intravenous injection of the drug, was much lower than that of the ultrafiltrate of plasma, deducing that it took many hours for the C.S.F. to come into equilibrium.

Smith et al. (1946) found that the amount of salicylate in the red cells was low but of the same magnitude as might be expected if the cell membrane was freely permeable to the salicylate contained in the plasma filtrate. Coburn (1943) was of the opinion that the amount of salicylate contained in the red cells was negligible and Hanzlik (1926) that the amount in the sweat was negligible.

In this investigation the salicylate concentrations were obtained on various body fluids - the water of the red cells, C.S.F., sweat, and pleural fluid from patients undergoing salicylate therapy. Where special calculations were involved the method is subscribed. In most instances the free salicylate was estimated in the plasma by dialysis, after total

plasma salicylate had been determined, and only in two instances indirectly, from the curve of Figure 24.

The results which were obtained are shown in Tables 6 to 9.

TABLE 6.

	Haemato-crit Reading for R.B.C. %	Total Salicylate in Plasma mgms.%	Total Salicylate in Whole Blood mgms.%	Salicylate Concentration for R.B.C. mgms.% (1)	Salicylate Concentration for Water of R.B.C. mgms.% (2)	Free Salicylate in Plasma mgms.%
In Vitro	49	75.2	53.0	29.9	39.8	40.2
	49	40.2	29.8	18.9	25.2	20.3 (3)
	45	25.6	19.4	11.7	15.6	10.2
In Vivo	42	24.7	19.8	10.7	14.2	10.8
	44	37.6	31.8	24.4	32.5	16.8
	47	29.4	22.4	14.7	19.6	15.6
	30	62.4	49.8	20.4	27.2	30.6

TABLE 7.

Haemato-crit Reading for R.B.C. %	Total Salicylate in the Plasma mgms.%	Total Salicylate in Whole Blood mgms.%	Salicylate Concentration for R.B.C. mgms.%	Salicylate Concentration for Water of R.B.C. mgms.%	Free Salicylate in Plasma mgms.%	Total Salicylate in C.S.F. (4) mgms.%
47	29.4	22.4	14.7	19.6	15.6	4.2
30	62.4	49.8	20.4	27.2	28.1	14.6

(5)

TABLE 8.

Total Salicylate in Plasma mgms.%	Total Salicylate in Sweat (6)
22.6	Nil.
18.0	Nil.

TABLE 9.

Plasma Salicylate mgms.%	Free Salicylate mgms.% (3)	Salicylate in Pleural Fluid mgms.%
19.8	7.1	8.6

(1) The concentration of salicylate in the red cells was calculated from the haematocrit volume, and the concentration of salicylate in the plasma and whole blood.
(2) Obtained by dividing the concentration of salicylate in the red cells by the percentage of water in the red cells. This water was taken to be 66.6% from the figures given by McLeod (1941).
(3) Obtained from the curve shown in Figure 24.
(4) By the same method used for the estimation of total salicylate in the plasma.
(5) Both patients had been receiving rectal salicylate for 4 days prior to this time.

(6) The sweat was obtained following the subcutaneous injection of Pilocarpine nitrate grs.1/10th. with a clean dry sponge. One cc. of sweat was used.

Discussion of results.

The discussion of permeability obviously does not apply to those body fluids which are products of active secretion. It is seen that no measurable salicylate was found in the sweat of the two patients studied although both were receiving moderate doses of sodium salicylate (8 gms.daily). It seems it is correct to assume that permeability does apply to the distribution of a drug between plasma, red cells, fluid accumulation in body cavities, and the C.S.F. (Davies (1943)). The individual variation of these distributions in the cases shown here from the free salicylate in the plasma was in some cases marked, probably because the plasma level taken at the time of removal of the specimens did not necessarily represent the average plasma level during the time of equilibration, as it was found that during dialysis it took 24 hours to reach equilibrium of free salicylate.

But sufficient figures have been shown in the case of the red cells to indicate that the concentration in the water of the red cell can approach that of the free salicylate in the plasma. Although the protein content of the various fluids has

not been recorded here, pleural fluids generally have a higher protein content than the C.S.F. There would be an equilibrium between bound and unbound salicylate in each fluid provided the fluid contained protein, and as only the free salicylate is dialyseable it is to be expected, and has been shown, that the concentration in the pleural fluid is higher than that of the free salicylate of the plasma.

In Table 5, the C.S.F. in the first case shown is much below the free salicylate of the corresponding plasma. The total salicylate in the plasma had been maintained for three days above 25.0 mgms.% with a minimum calculated free salicylate level (from Figure 24) of 10 mgms.%. Thus even after three days the concentration of salicylate in the C.S.F. had not reached equilibrium with the free salicylate in the plasma. In the second case for three days the plasma level had been above 25.0 mgms.% with a minimum calculated free salicylate of 10 mgms.% but for the preceding two days plasma levels had been high (as shown in the corresponding plasma free salicylate level). Here the C.S.F. concentration is higher than the minimum free salicylate level but not so high as the final plasma free salicylate. This is interpreted to indicate that although equilibrium may be reached, the process is slow, lagging behind any rise in the free salicylate of the plasma.

General Conclusions.

It has been shown that the free salicylate increase in the plasma is proportionately greater, and the increase in the bound salicylate proportionately smaller, as the total salicylate in the plasma rises. For example, at a total concentration in the plasma of 15.0 mgms.% the free salicylate is 33% of the total salicylate, while at a total of 30.0 mgms.%, it is 42%, and at a total salicylate of 50 mgms.% the free salicylate is 54%. It has also been shown that the free salicylate with certain reservations approaches the concentration in body fluids and red cells.

From these two findings it may be said that as the total plasma salicylate rises, the concentration in body fluids rises relatively to a greater extent.

While massive salicylate therapy has yet to be finally assessed, it would seem that higher plasma levels lead to a disproportionately higher concentration in the body fluids which may have a therapeutic bearing.

CHAPTER V.

THE EXCRETION OF SALICYLATE

It was considered that the routes by which salicylate could be excreted were the sweat, the faeces and the urine. An examination was made of these possible routes by which salicylate might be excreted.

1. Excretion in the Sweat.

It has been shown that after administration of large oral doses of sodium salicylate, negligible quantities of salicylate were detected in the sweat even after stimulation of sweat production by pilocarpine (Chapter IV.)

2. Excretion in the Faeces.

Hanzlik (1926) stated about salicylates that on account of their rapid absorption, the faeces as a rule contained exceedingly small amounts, if any, at all. There appears to be no other authoritative statement on this subject.

In this investigation some ten samples of faeces were examined from patients receiving salicylate in varying doses, and during the periods when the concurrent administration of acid and alkaline salts were producing marked effects on the plasma levels. Four samples were examined from cases receiving 12 gms. of sodium salicylate daily and four consecutive stools

were examined from a patient receiving 24 gms. of sodium salicylate daily. This latter patient had been given salicylate over a long period and was showing only moderate plasma concentrations in spite of such a large dose, a feature of long continued salicylate administration.

Method.

5 gms. of the stool under examination were emulsified in 10 ccs. of distilled water and placed in a conical flask in which 10 ccs. of concentrated HCl had been placed. The contents were then hydrolysed by boiling for four hours, the flask being attached to a reflux condenser to prevent any carry over of salicylate. The contents were allowed to cool and were then filtered. 2 ccs. of the filtrate were extracted with ethylene dichloride as in the method for estimation of total salicylate in the urine described below. This method was checked with normal stools containing no salicylate, and with stools to which known quantities of sodium salicylate had been added. The method appeared to be accurate to within 8%.

Results and Conclusions.

Only four of the eighteen stools examined yielded a trace of the salicylate which when related to the total weight of faeces passed in the 24 hour period varied from 0.2 to 0.5 gm. The remainder showed no measurable salicylate. It may be said

then that no matter in what dose or with what substance sodium salicylate is administered only negligible quantities, if any, are passed in the faeces. This is further evidence that the acid and alkaline substances which if given concurrently with sodium salicylate vary the plasma levels do not produce this action by preventing absorption of the salicylate.

3. Excretion in the Urine.

Feser and Friedberger (1875) were the first to study the quantitative excretion of salicyl in the urine, recovering some 63% of the quantities administered. Mosso (1889) pointed out that they had not considered salicyluric acid in their estimations, and when this was included, he was able to recover up to 100% of the dose administered. Wiley (1906) could only recover 46% in the urine but Holmes (1925) was able in the majority of cases to find 90%, but in a few cases which he did not explain, only 80%. Fleischer (1875) was the first to state that the addition of sodium bicarbonate to sodium salicylate shortened the period of excretion of a fixed dose of salicylate. Ehrmann (1907) was able to confirm this work but Hanzlik et al. (1917) were on two occasions unable to find increased excretion of salicylate in patients receiving large doses of sodium salicylate and sodium bicarbonate.

The most comprehensive study on the metabolism of salicylate is the work of Kapp and Coburn (1942) who showed that salicylates were excreted in the urine partly as free salicylate, partly as salicyluric acid, and partly as the glycuronides of salicylic acid. In addition to these substances containing the salicyl radicle two other substances were isolated. However they stated that normal individuals excrete 80% of the administered salicylate as compounds containing the salicyl radicle. They found that after some days the free salicylate fraction in the urine increased markedly.

Smith et al. (1946) using four hourly doses for 12 hour periods in convalescent patients found that the amount of free salicylate excreted when sodium bicarbonate was given along with sodium salicylate was appreciably greater than when sodium salicylate was given alone. Secondly, the amount of salicyluric acid excreted was greatest after the administration of ammonium salicylate, and least when bicarbonate was given concurrently with sodium salicylate. The average total glycuronides excreted with all forms of therapy were remarkably similar. However, they state that the total amount of salicylate excreted was not appreciably greater when sodium salicylate was administered with sodium bicarbonate. They also found a relationship between the renal clearance of salicylate and the pH of the urine.

This Investigation.

The scope of this investigation was to determine with continued doses of sodium salicylate, the effect on excretion, of substances that when administered concurrently with sodium salicylate affect the plasma levels of the drug.

Method.

The method developed by Smith et al. (1946) from the work of Kapp and Coburn (1942) whereby the salicyl fractions and the total salicylate in urine may be estimated was used throughout the following investigations. This method makes use of the different amounts of salicyluric acid extracted by ethylene dichloride and carbon tetrachloride respectively from the urine and the fact that both extract all free salicylate. The total salicylate is estimated after hydrolysis in the presence of strong acid. The authors assume that the salicyl glycuronate fraction is equal to the total salicylate minus the sum of the free salicylate plus the salicyluric acid. For free salicylate and salicyluric acid this method was found on checking with known quantities to be accurate to within 5%.

A. The Excretion of Total Salicylate in the Urine.

Two patients under treatment with sodium salicylate receiving 6 gms. daily in divided four hourly doses were investigated. During each day of the period studied plasma levels were

obtained, 24 hour specimens of urine measured, and the total salicylate excreted in 24 hour periods determined. For 5 days control observations were made while the patients were receiving sodium salicylate alone. During the next 5 days, an equal quantity of sodium bicarbonate was administered with the sodium salicylate, and for the last 5 day period, 1 gm. of Ammonium chloride was given with the sodium salicylate. The results are shown in Table 10, and in Table 11.

B. The Excretion of the Salicyl Fractions in the Urine:

(1) With Moderate Oral Doses of Sodium Salicylate.

(a) A young adult male who was convalescent was given sodium salicylate 12 gms. daily with an equal quantity of sodium bicarbonate in divided four hourly doses, for several days until plasma levels were steady. For the next 12 days plasma levels of salicylate were obtained, 24 hour specimens of urine measured and collected, and all salicyl fractions in the urine determined. During the first three days of this period an equal quantity of bicarbonate was administered with the salicylate, during the next five days the bicarbonate was withdrawn, and during the last four days Ammonium chloride 1 gm. was administered concurrently with the salicylate every four hours. The results are shown in Table 12.

TABLE 10.

A.B. Male, 42 yrs.

Date	Plasma Level mgms.%	Amount of Urine in 24 hrs. ccs.	Total Salicylate Excreted gms.
Sodium Salicylate 6 gms. daily alone.			
27/1/47	21.2	1120	2.85
28/1/47	24.2	1010	3.25
29/1/47	28.1	1025	2.88
30/1/47	24.2	1225	2.75
31/1/47	20.1	1025	2.92
Average for period,		1081	2.93
Sodium Salicylate 6 gms.daily plus equal quantity sodium bicarbonate.			
1/2/47	19.4	1083	3.35
2/2/47	23.6	1140	3.42
3/2/47	23.8	1254	3.64
4/2/47	20.2	1250	3.33
5/2/47	19.2	855	3.21
Average for period,		1116	3.39
Sodium Salicylate 6 gms. daily plus Ammonium Chloride 6 gms. daily.			
6/2/47	26.6	1425	3.08
7/2/47	29.2	1140	2.57
8/2/47	29.2	1083	2.50
9/2/47	27.6	1197	2.75
10/2/47	23.5	1140	2.92
Average for period,		1197	2.76

TABLE 11.

D.M. Male, 68 yrs.

Date	Plasma Level mgms.%	Amount of Urine in 24 hrs. ccs.	Total Salicylate Excreted gms.
Sodium Salicylate alone 6 gms. daily.			
27/1/47	24.2	2020	3.42
28/1/47	26.8	1255	3.62
29/1/47	22.8	1200	3.00
30/1/47	28.5	1865	2.92
31/1/47	26.7	1925	2.52
Average for period,		1653	3.09
Sodium Salicylate 6 gms. daily plus equal quantity Sodium Bicarbonate.			
1/2/47	23.4	1500	3.66
2/2/47	23.4	1250	3.92
3/2/47	23.0	1710	3.49
4/2/47	19.2	2337	4.04
5/2/47	18.2	2560	3.02
Average for period,		1871	3.62
Sodium Salicylate 6 gms. daily plus Ammonium Chloride 6 gms. daily.			
6/2/47	18.6	2565	3.40
7/2/47	19.3	1482	2.71
8/2/47	24.4	2622	2.39
9/2/47	26.3	2183	1.98
10/2/47	27.3	2109	3.07
Average for period,		2192	2.71

TABLE 12.

J.M. Male, 32 yrs.

Day	Plasma Level mgms.%	Amount of Urine in 24 hrs. ccs.	24 Hour Excretion of			
			Salicyluric Acid gms.	Free Salicylate gms.	Salicyl Glycuronates gms.	Total Salicylate gms.
Sodium Salicylate 12 gms. daily with equal quantity of Sodium Bicarbonate.						
1	20.2	1860	2.78	3.86	1.49	8.13
2	18.2	1900	2.96	4.89	1.53	9.38
3	16.4	1770	2.67	3.31	1.37	7.35
Average for period,		1843	2.80	4.02	1.48	8.28
Sodium Salicylate 12 gms. daily alone.						
4	17.5	1150	1.29	1.06	1.44	3.79
5	22.9	1105	2.42	3.65	.99	6.96
6	23.6	1250	1.87	2.03	1.12	5.02
7	24.1	1360	1.98	1.50	1.82	5.30
8	22.8	2260	2.30	1.51	1.39	5.20
Average for period,		1425	1.99	1.95	1.35	5.25
Sodium Salicylate 12 gms. daily plus Ammonium Chloride 6 gms. daily.						
9	21.6	1900	1.02	0.96	1.70	3.69
10	33.0	1740	1.46	1.65	1.35	4.46
11	33.2	2280	1.45	1.66	2.16	5.27
12	31.8	1870	1.68	1.54	2.34	5.56
Average for period,		1558	1.40	1.45	1.89	4.72

(b) The same observations were repeated with another convalescent adult. In this case, however, the investigation was started with sodium salicylate alone, 10 gms. daily in divided four hourly doses, which dosage of salicylate was continued throughout the period studied. When the plasma levels had become steady, the investigation was commenced with salicylate alone for four days, followed by four days with concurrent administration of Potassium citrate 1 gm. every four hours. Finally, for the last four days the patient was given the same dose of salicylate plus 1 gm. of ammonium chloride every four hours. The observations obtained are shown in Table 13.

(2) With Massive Doses of Sodium Salicylate.

A patient with rheumatic fever who had been on prolonged dosage with sodium salicylate was receiving 24 gms. of the drug in divided four hourly doses with an equal quantity of bicarbonate. Observations on plasma and urine were made as before for four days, and repeated for another 3 days while bicarbonate was withdrawn. These results are shown in Table 14.

Conclusions.

1. Excretion of Total Salicylate. It will be seen from Tables 10 to 14 that the concurrent administration of sodium bicarbonate

TABLE 13.

W.H. Male, 19 yrs.

Day	Plasma Level mgms.%	Amount of Urine in 24 hrs. ccs.	24 Hour Excretion of Salicyluric Acid gms.	Free Salicylate gms.	Salicyl Glycuronates gms.	Total Salicylate gms.
Sodium Salicylate 10 gms. daily alone.						
1	18.2	1860	1.26	0.65	1.82	3.73
2	23.7	1360	1.93	2.44	1.98	6.35
3	25.6	1160	1.11	1.49	1.84	4.44
4	24.2	820	.89	2.06	2.01	4.96
Average for period,		1300	1.29	1.66	1.91	4.87
Sodium Salicylate 10 gms. daily, plus 6 gms. Potassium Citrate daily.						
5	22.6	1780	2.49	6.23	1.20	9.92
6	18.4	1985	2.05	3.08	1.52	6.65
7	16.6	1990	1.46	3.63	2.28	7.37
8	15.2	1560	2.24	3.84	1.63	7.71
Average for period,		1829	2.06	4.19	1.65	7.91
Sodium Salicylate 10 gms. daily, plus 6 gms. Ammonium Chloride daily.						
9	17.8	1780	1.37	1.74	2.11	5.22
10	28.4	2300	1.38	0.22	2.56	4.161
11	28.4	1840	1.30	0.33	2.47	4.13
12	29.6	1160	1.22	0.57	2.39	4.18
Average for period,		1770	1.31	0.71	2.38	4.42

TABLE 14.

W.S. Male, 21 yrs.

Day	Plasma Level mgms.%	Amount of Urine in 24 hrs. ccs.	24 Hour Excretion of Salicyl-uric Acid gms.	Free Salicylate gms.	Salicyl Glycur-onates gms.	Total Sali-cylate gms.
Sodium Salicylate 24 gms. daily with equal quantity of bicarbonate.						
1	39.0	2220	3.95	9.34	2.18	15.47
2	35.6	1755	3.29	7.94	1.58	12.81
3	42.1	2660	1.67	7.72	2.18	11.57
4	38.6	2010	3.57	9.70	2.63	15.90
Average for period,		2161	3.12	8.67	2.14	13.94
Sodium Salicylate 24 gms. daily alone.						
5	48.2	2350	3.66	4.27	3.49	11.42
6	53.5	1760	2.75	2.02	4.35	9.12
7	56.2	1850	2.81	2.38	3.16	8.35
8	55.2	2430	2.86	2.85	3.20	8.91
Average for period,		2097	3.02	2.88	3.55	9.45

produced a marked rise in the total salicylate excreted in the urine. This excretion of total salicylate was lowest when an acid salt was administered concurrently but not markedly lower than the excretion of total salicylate when sodium salicylate was administered alone. It will be seen from the 24 hour volumes of urine passed in the period studied, that neither increased diuresis nor diminished output of urine played a part in the amount of salicylate excreted.

The average percentages of the total dose administered which were excreted in the urine in all these cases was:

I.	With the addition of an alkaline salt,	65%
II.	With sodium salicylate alone,	44%
III.	With the addition of ammonium chloride,	42%

These figures are lower than the 80% assumed by Smith et al. (1946) using this method. They indicate a marked increase in excretion of total salicylate with the addition of an alkaline salt. They are lower than those obtained by earlier workers but the methods of estimation of excretion used by these workers was faulty according to Hanzlik (1926).

2. Excretion of Salicyluric Acid. The excretion of salicyluric acid is greatest with the concurrent administration of an alkaline salt, Tables 12 to 14. This finding is not in agreement with that of Smith et al. (1946), who found that the greatest

amount excreted was when an acid salt was given concurrently with sodium salicylate. There is little difference in the amounts of salicyluric acid excreted when sodium salicylate is given either alone or with an acid salt.

3. Excretion of Salicyl Glycuronates. The quantities of salicyl glycuronates which are excreted in the urine vary little but do appear to be significantly greater with the concurrent administration of an acid salt. They appear to increase in the urine proportionately to increase in total dosage of sodium salicylate.

4. Excretion of Free Salicylate. The fraction in the urine which shows greatest variation in excretion is the free salicylate fraction. Here the greatest excretion is with the addition of an alkaline salt, while the smallest excretion is with the concurrent administration of an acid salt. This is the fraction which produces the significant difference in total excretion of salicylate with the addition of the different acid and alkaline salts. The varying excretion of this fraction is of an order which might explain the effect of these salts on the plasma concentrations of salicylate, as shown.

C. The Effect of Para-aminobenzoic Acid on Excretion of Salicylate in the Urine:

As para-aminobenzoic acid had been shown to cause an increase in the plasma salicylate concentration when administered

concurrently with sodium salicylate, excretion studies were carried out on two patients under treatment for rheumatic fever, to ascertain if this effect was produced by altered excretion. Dry et al. (1946) had found that the concurrent administration of para-aminobenzoic acid decreased the total salicylate excreted in the urine.

The patients studied were receiving sodium salicylate grs.30 with an equal quantity of bicarbonate every four hours. Plasma levels were obtained, the 24 hours specimens of urine collected and measured, and all salicyl fractions determined in the urine for several days. Then para-aminobenzoic acid was added for a further period and all observations repeated. Details and results are shown in Tables 15 and 16.

It will be seen that the administration of para-aminobenzoic acid produces an effect similar to the administration of an acid salt. The total excretion of salicylate is decreased, a finding in agreement with the findings of Dry et al. (1946). The most marked effect was produced on the free salicylate fraction which is much diminished. The decrease in excretion of the free salicylate coincides with the rise in plasma levels of salicylate.

TABLE 15.

M.H. Female, 16 yrs.

Day	Plasma Level mgms.%	Amount of Urine in 24 hrs. ccs.	24 Hour Excretion of Salicyluric Acid gms.	Free Salicylate gms.	Salicyl Glycuronates gms.	Total Salicylate gms.
Sodium Salicylate 12 gms. daily with Sodium Bicarbonate 12 gms. daily throughout.						
1	28.2	495	1.81	1.93	0.19	3.93
2	27.6	630	1.49	2.07	0.32	3.88
3	29.1	620	1.57	2.02	0.45	4.04
Average for period,		581	1.62	2.01	0.32	3.95
Plus Para-aminobenzoic Acid 12 gms. daily.						
4	35.1	1810	1.48	2.48	0.43	4.39
5	46.8	890	0.71	1.04	0.10	1.85
6	41.8	360	0.54	0.60	0.08	1.22
Average for period,		1020	0.91	1.39	0.20	2.55
Para-aminobenzoic Acid withdrawn						
7	30.2	420	1.36	2.29	0.39	4.04
8	26.2	565	1.25	1.97	0.28	3.50
Average for period,		492	1.30	2.13	0.33	3.77

TABLE 16.

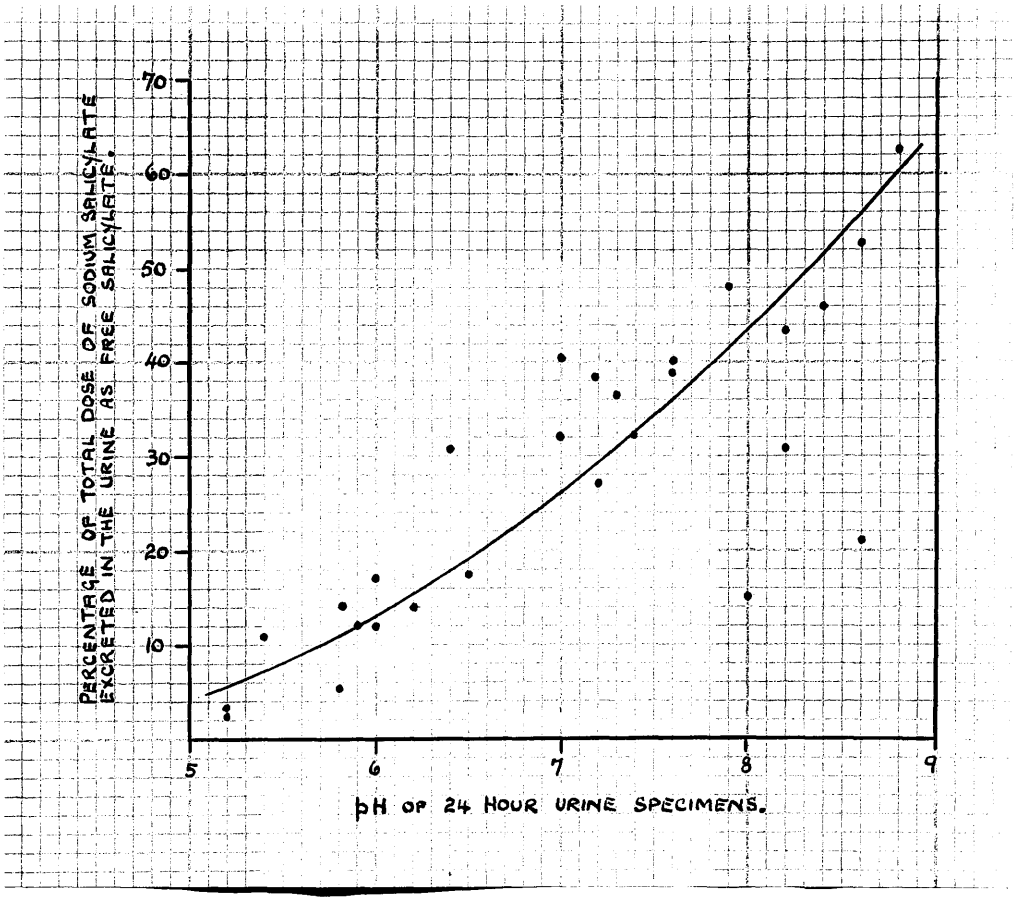
W.S. Male, 21 yrs.

Day	Plasma Level mgms.%	Amount of Urine in 24 hrs. ccs.	24 Hour Excretion of Salicyluric Acid gms.	Free Salicylate gms.	Salicyl Glycuronates gms.	Total Salicylate gms.
Sodium Salicylate 12 gms. daily with equal quantity of Sodium Bicarbonate daily.						
1	19.2	2100	3.58	2.60	0.90	7.08
2	22.2	2470	3.42	2.30	1.12	6.84
3	19.0	2610	3.59	1.82	1.20	6.61
Average for Period,		2393	3.53	2.24	1.07	6.84
Plus Para-aminobenzoic Acid 24 gms. daily.						
4	31.6	2610	4.01	0.54	1.30	6.26
5	43.2	1790	2.86	0.17	1.32	4.45
6	41.4	1510	3.02	1.19	1.33	5.54
Average for Period,		1970	3.29	0.63	1.31	5.41

D. The Relationship of Excretion of Salicylate to pH of the Urine.

It had been noted at the start of the previous investigations that the lowest excretions of the free salicylate fraction coincided with the lowest pH of the specimens of urine obtained. Consequently the pH values were determined of all specimens of urine by the use of indicators. In order to relate the excretion of the free salicylate fraction to pH of the urine in all cases a common factor was determined, being that percentage of the total daily dose which was excreted in the urine as free salicylate. This percentage is shown against the pH of the urine specimens in Figure 27.

FIGURE 27.



It will be seen that as the pH of the urine rises so does the percentage of the total dose excreted in the urine as free salicylate. This supports the evidence of Smith et al. (1946) that renal clearance of salicylate rises with the pH of the urine, and the statement of Caravati and Cosgrove (1946) that plasma levels depend on the pH of the urine.

It will have been noted from Table 13 that potassium citrate increased the excretion of salicylate in the urine therefore increased excretion can be promoted by drugs other than sodium bicarbonate. As both drugs increase the pH of the urine this tends to show that pH of the urine is the factor controlling excretion rather than the concurrent administration of a particular drug. The same effects were noted with both Ammonium Chloride and Para-aminobenzoic Acid, both of which reduced the pH of the urine thereby decreasing excretion of salicylate. It would appear then that an alkaline urine with sufficient fluid intake are essentials to the treatment of salicylate poisoning, and that knowledge of the pH of the urine will go far to explain wide differences in plasma concentrations in individuals on the same dosage of sodium salicylate.

SUMMARY.

It has been shown in this Chapter that alkaline and acid salts with para-aminobenzoic acids vary the excretion of salicylate mainly by affecting the excretion of the free salicylate. By co-ordination of plasma levels it has been shown that this variation in excretion of free salicylate is the probable mechanism by which plasma concentration of salicylate is varied by these drugs when administered concurrently with sodium salicylate. The excretion of the free salicylate fraction has been shown to be closely correlated with the pH of the urine.

CHAPTER VI.

THE TOXIC MANIFESTATIONS OF SODIUM SALICYLATE

Signs and symptoms of toxicity with sodium salicylate are not infrequently observed and are well known. They were first observed by Stricker (1876), Tuckwell (1876) and Hall (1904). Mental upset was described by Daly (1878) and later by Caussade and Charpy (1921). Langmead (1906) first reported acetone in the urine following salicylate administration. Hamilton (1875), Rosenbloom and Johnston (1919) and Myers (1920) were among the first to emphasise that hyperventilation occurred with salicylate. Since 1920 many workers have given accounts of the toxic effects of sodium salicylate but there has been no account in the literature which has correlated the individual toxic manifestations with the plasma levels at which they occurred. The reason for this is that methods of estimation of plasma salicylate were developed only in 1943.

Recently Jager and Alway (1946) found that toxic symptoms were generally greater with rise in plasma levels but no serious toxic effects occurred below 40.0 mgms.%, and plasma levels of 50.0 mgms.% were maintained in some cases for long

periods without untoward effect. Nausea and vomiting appeared early but tended to disappear with continued dosage as did acneiform eruptions. They found that hyperventilation occurred in many patients above a level of 40.0 mgms.%. One case developed pulmonary oedema at a level of 80.0 mgms.%. Manchester (1946)[1] thought that nausea, transient vomiting, tinnitus, deafness, vertigo and sweating were of no significance and could be ignored. More serious toxic manifestations were severe dyspnoea, delirium, excessive vomiting and skin eruptions. Warren et al (1946) thought that the earliest warning of severe toxicity was hyperventilation which if ignored was followed by maniacal delirium, tetany, and loss of consciousness.

If large doses of sodium salicylate are to be used, more accurate information about the occurrence and order of appearance of toxic manifestations seems desirable. It appeared logical to relate the toxicity to plasma levels of salicylate, a more direct method than relation to dosage which introduces many factors such as age, weight, fluid intake, route of administration, and concurrent administration of other drugs.

A. The Relationship to Plasma Levels.

In this investigation the plasma salicylate concentration of venous blood was determined in patients when they

initially experienced a toxic effect of sodium salicylate. These patients were receiving salicylate for various reasons and include normal convalescents, cases of rheumatic fever, and cases of rheumatoid arthritis. In this way some 88 observations were made in 58 patients, and the toxic manifestations found can be considered a representative collection in a group of adults. The toxic manifestations have been shown in Table 17, in the order of ascending mean plasma levels at which they initially occurred. There is a variation in the levels of individual toxic symptoms, but that the mean plasma levels shown are representative is indicated by the ordered rise of both minimum and maximum plasma levels at which these toxic symptoms occurred.

Not included in Table 17 are observations on a number of patients who exhibited toxic manifestations at very low plasma levels after a comparatively small dose of sodium salicylate. Three cases developed erythematous rashes of the chest, neck, face, and flexor aspects of the arms within the first 24 hours of administration, plasma levels showing an average of 19.2 mgms.%. A further two cases developed an acneiform rash on the face, arms, and abdomen after having received salicylate for several weeks. These patients previously had higher plasma concentrations than at the time the rash was detected. Three

patients on small dosage experienced sudden onset of tinnitus, deafness, nausea and vomiting with an average plasma level of 7.2 mgms.%. With the exception of acneiform eruptions all these cases are considered to be personal idiosyncrasy to the drug.

TABLE 17

TOXIC MANIFESTATION	No. of Observations	Plasma Levels in mgms.% Lowest	Highest	Average
Tinnitus,	9	10.0	39.4	24.3
Deafness,	9	10.0	48.0	25.5
Nausea,	9	12.6	39.6	26.7
Vomiting,	10	16.3	38.6	28.2
Transient Albuminuria,	4	25.2	41.6	32.1
Hyperventilation,	10	21.0	44.2	32.8
Marked Sweating in Afebrile Patient,	8	22.6	48.0	36.6
Headache,	5	20.3	58.1	39.8
Vertigo,	1	40.0	-	40.0
Severe Drowsiness,	4	36.6	42.5	40.4
R.B.Cells in Urine,	2	43.6	50.0	46.8
Acetone in Urine,	2	41.5	56.0	43.7
Mental Confusion,	4	41.0	53.6	46.9
Excitement and Euphoria,	2	42.5	53.6	48.1
Pulmonary Oedema,	1	49.4	-	49.4
Severe Dyspnoea,	3	46.0	53.6	50.9
Haemorrhagic Signs,	1	51.8	-	51.8

Discussion.

In general toxic symptoms became more severe and more frequent as the plasma concentration of salicylate increased.

Tinnitus, Deafness, Nausea and Transient Vomiting.

These toxic effects were not regarded as being of serious consequence and rapidly stopped on ceasing salicylate administration, rarely being present 48 hours after stopping the drug. It was usual in the presence of these symptoms to continue administration without modification of dosage. Often with continued therapy the severity of these symptoms would regress, and after several days would disappear, later much higher plasma levels being attained without their reappearance. Thus, with continued dosage, an increasing tolerance to sodium salicylate develops.

Persistent Vomiting.

This was an indication to stop the salicylate for at least a temporary period, and if the patient vomited more than four times in the 24 hours this was always done. The vomiting usually ceased within 24 hours of stopping the drug and in four of the cases shown in Table 17 when vomiting ceased, recommencement of the same dosage the next morning gave good results. Two cases did not again experience vomiting, in one it was transient

and disappeared within a day and only in one case did it re-appear and persist. This also indicates that initial toxic effects often disappear with continued therapy.

Transient Albuminuria.

Four patients showed albuminuria up to 1 gm.per litre of urine, but in each case this cleared within three days without modification of dosage; however, in all cases the fluid intake was increased. During the period in which albuminuria was present there were no casts or R.B.C. in the urine.

Sweating in the Afebrile Patient.

Sweating in a fevered patient may be part of the antipyretic action of sodium salicylate and was not considered in this investigation. In cases where there was no temperature severe sweating, wetting both the pyjamas and the bed linen, was not of infrequent occurrence. In patients receiving the sodium salicylate by the intravenous route there was delay in the appearance of this sign of toxicity, the severe sweating appearing two to three hours after the completion of the injection, when plasma levels had fallen from the peak concentration obtained immediately after the injection. This delay was also frequent with the onset of hyperventilation after intravenous administration of the drug.

Hyperventilation.

The significance of hyperventilation following salicylate administration was investigated in animals and is fully discussed in Chapter VII. Hyperventilation was not seen below a level of 21.0 mgms.% in any patient, the average figure being 32.8 mgms.%. It will be noted from Chapter I., page 39 that this average figure is not significantly different from the average plasma level at which a fall in the CO_2 Combining Power became apparent. Hyperventilation tended to become less and eventually disappear if plasma levels were maintained at the same level but became more marked if the plasma level was raised. Morris and Graham (1931) have shown that the amount of salicylate present in the blood during a low CO_2 period could at the most account for only a negligible diminution of the CO_2 and made it clear that the fall in CO_2 was not the result of its replacement by salicylic acid. The other possibilities are discussed in Chapter VII.

Acetone in the Urine.

Table 17 shows that acetonuria only occasionally appears in adults during salicylate therapy. In the 58 cases observed acetone was detected in only two patients. The plasma concentrations rose much higher in numerous patients some of

whom had severe toxic manifestations without the appearance of acetone. This does not bear out in adults what Anderson (1945) found in children, that ketosis follows sooner or later if salicylate intoxication is present, as most of the patients in this series received sodium salicylate for long periods. The work of Myers and Ferguson (1929) indicates clearly that both in man and in animals the administration of sodium salicylate leads to little change in the acetone content of the blood, even in the case of animals when fatal doses of salicylate were used. That acetone and ketosis played no part in the so called 'acidosis' of salicylate intoxication was shown by Morris and Graham (1931) who found that the administration of large doses of glucose had no effect in preventing this phenomenon. It appears then that ketosis plays no part in the production of hyperventilation and fall in the CO_2 combining power in patients receiving sodium salicylate.

Among the toxic symptoms of salicylate poisoning are a lowered fluid intake with severe sweating, which may cause dehydration, and if these are associated with anorexia and vomiting, they may cause a tendency to ketosis. This may explain the very occasional occurrence of acetone in the urine in adults and is considered the probable reason for its more frequent

occurrence in children by Erganian et al (1947). Its more frequent appearance in children receiving salicylate can be better understood when one considers how readily dehydration and ketosis are induced in the child.

R.B.C. in the Urine.

Only two patients under observation produced scanty red cells in the urine which disappeared within a few days on continued therapy. One tends to regard the appearance of red cells in the urine in these cases as of no significance as no other signs of haemorrhage were discovered. There was no reappearance although salicylate was continued for some time.

Headache and Vertigo.

Headache occurred in five patients and was occipitofrontal in site. It was severe for a short period only and then tended to diminish. One patient complained of persistent headache from the start to the end of therapy but in no case did it interfere with sleep or warrant the cessation of the drug.

Vertigo was found in one patient only who was able, nevertheless, to stand unaided although he experienced the sensation that objects were revolving round him and staggered when walking.

Mental Symptoms.

Severe drowsiness, mental confusion, excitement and euphoria were noted in that order as the plasma concentrations rose. In the group of patients which exhibited mental confusion one patient was completely disorientated, another was delirious, while yet another showed confabulation. All these signs improved rapidly and disappeared when the salicylate was discontinued. No patient observed in this series lost consciousness.

Severe Dyspnoea and Pulmonary Oedema.

The patients who exhibited these signs had been hyperventilating for some time on continued therapy. The respiration became more marked and the patients were considered to have severe dyspnoea when they were unable to carry on a normal conversation because of shortness of breath. There was no evidence of cardiac failure or of a pulmonary lesion at this time. The pumonary oedema ensued suddenly in a patient who had been hyperventilating for 24 hours but cleared rapidly on the cessation of the drug and the administration of sodium bicarbonate orally with morphine and atropine parenterally.

Haemorrhagic Signs.

A careful search was made for haemorrhagic signs in all patients. Two patients had epistaxis during salicylate

therapy but unfortunately plasma levels were not obtained. No other evidence of haemorrhage was obtained except in one case on intravenous therapy and this is of enough interest to warrant a more detailed report and discussion.

B. A Description of Haemorrhage during Salicylate Therapy which caused Death.

M.P. Female aged forty-one years. Housewife. This patient was admitted to Eastern District Hospital on 1.10.46 complaining of pain, stiffness in the knees, ankles, wrists and hands for the past eighteen months. During the latter period she had received penicillin treatment, physiotherapy, and small doses of oral salicylates without effect. When seen she presented the following picture:-

General Examination.

The patient was an emaciated woman with marked muscular wasting, who lay motionless in bed and could do nothing for herself.

Locomotor System.

Elbows.	Fixed in 90° of flexion.
Wrists.	No deformity present but marked limitation of movement with tenderness and pain on attempting active movement.
Hands.	Small muscle wasting with spindle shaped joints, and tenderness with limited movement.
Hips.	Limitation of movement with fixation and semi-flexion.
Knees.	Fixed in full flexion. Painfully tender, excruciatingly so on attempted active or passive movement.
Ankles.	Swollen, tender and painful with oedema.
Spine.	Marked rigidity.

Cardiovascular System.

There was no enlargement or evidence of cardiac failure. There was a propagated mitral systolic murmur.

Other Systems.

There was no evidence of splenic enlargement or of glandular involvement, and no other abnormalities were detected.

Investigations.

W.B.C.	8.000/cu.mm.
R.B.C.	3.5 million/cu.mm.
Hb.	12 gms.%
E.S.R.	80mms./1st.hr. 110 mms/2nd.hr. (Westegren)

In view of the pain and tenderness of the joints it was decided to give sodium salicylate by the intravenous route, followed by high oral dosage to maintain a high level of salicylate in the circulation. It had been our experience with other cases of rheumatoid arthritis that massive salicylate dosage had given marked relief of pain at least for a temporary period enabling active movements to be started and physiotherapy to be instituted, and it appeared to be indicated in this case as smaller oral doses had failed to give relief. It was decided to give 10 grams of sodium salicylate in 1,000 ccs. of normal saline daily for four days, to be followed by oral sodium salicylate 10 grams daily with an equal quantity of sodium bicarbonate.

Progress.

4.10.46. Intravenous administration over 8 hour period.

5.10.46. Intravenous administration over 8 hour period. Plasma salicylate level before commencement being 33.6 mgms.%.

6.10.46. Plasma level before injection 32.0 mgms.%. Intravenous administration over 8 hour period.

The patient complained of tinnitus and some deafness after the first day with some sweating in the evenings. This did not worry her unduly especially as the pains in her joints had become much easier during the 5.10.46. On the evening of 5.10.46 she experienced some nausea and vomited once during the evening but she felt well afterwards and was well on the following morning.

7.10.46. Plasma level before injection 55.0 mgms.%.
Intravenous administration over 8 hour period.

After the administration the patient complained only of tinnitus and felt well. There were only slight pains in the joints and all movements were much easier, her knees being less stiff. She fed herself for the first time since admission and was happier and brighter than at any time before. The respiratory rate was slightly increased.

8.10.46. Oral administration was commenced at 10 a.m. 60 grs. of sodium salicylate with an equal quantity of sodium bicarbonate was given every 4 hours.

In the evening the patient was well, having no pain in the joints and all movements were easier than before. Hyperventilation was present but not marked.

9.10.46. 8.30 a.m. Patient became semi-comatose and perspired freely. She became ashen grey in colour with cyanosis of the extremities and marked hyperventilation. The pulse was rapid and thready.

The hyperventilation led the house physician to think that severe acidosis was the cause of the distress so potassium citrate and sodium bicarbonate gr.60 of each were administered hourly. Two hours later she was unable to swallow, so intravenous glucose 25% was commenced but within a few minutes the pulse became irregular, severe cyanosis developed and the patient died. Immediately after death haemorrhage was found from the rectum and voided urine was blood-stained.

Post-Mortem Report.

General: Copious haemorrhage had taken place into the pleural cavities. Huge blood clots were lying in them, and the parietal pleura showed an oozing surface with recently formed fibrin attached. Smaller haemorrhages were also present in the pericardium and in the perirenal tissues.

Lungs: Both lungs were oedematous and contained much blood.

Heart: The pericardium was adherent to the apex anteriorly and posteriorly with evidence of an old rheumatic endocarditis on the mitral cusps. Dilatation of the right ventricle was present with the wall showing a poor colour. There were numerous pericardial petechiae.

Liver: The liver was nutmeg in colour with flame shaped haemorrhages present under its capsule. Sections showed advanced fatty degeneration with marked hyperaemia.

Kidneys: Large, firm and hyperaemic.

Gastro-intestinal tract: Some punctate bleeding points were present in the mucosa of the large intestine and petechiae was seen throughout the mesentery and peritoneum.

Joints: No haemorrhage was seen but evidence of the rheumatoid process was present.

Brain: There were numerous petechiae with congestion of the brain surface and marked oedema.

Commentary:

This case was one of chronic rheumatoid arthritis with an old rheumatic endocarditis and adherent pericardium. Subserous haemorrhage and oedema cerebri were the terminating stages before death.

Discussion:

Whereas the patient was well more than 24 hours after the last intravenous injection and showed no signs of severe salicylate poisoning during earlier therapy, it is not considered that salicylate caused death other than by producing haemorrhage. Hyperventilation associated with cyanosis was evident at 8.30 a.m. on the morning of death, but had not been manifest previously. Moreover, at the time of appearance of these symptoms sodium bicarbonate was being given every four hours with the salicylate. The level of 55 mgms.% had been obtained two days before death, and a level of 59 mgms.% the day preceding death without upset.

It is interesting to note that Quincke (1888) described a case which ended fatally after receiving sodium salicylate and which showed much the same post-mortem features as this case. Link et al (1943) were the first to show the production of hypocoagulability of the blood and hypoprothrombinaemia by salicylate in the rat after Stahmann et al (1944) and Heubner and Link (1941) had shown by chemical study that

salicylic acid was an important degradation product of the haemorrhagic agent 3,3' methene bis (4 hydroxycoumarin). This has been confirmed in man by Meyer and Howard (1943) who found that it was counteracted by vitamin K therapy, and also by Rappoport et al (1943) during salicylate therapy of rheumatic children. Owen and Bradford (1946) in the treatment of 25 rheumatic children with massive therapy comparable to the doses being used in this case found hypoprothrombinaemia which occurred during the first week. This lasted several days, with near normal levels being found in the second week, and normal levels in the third week on continued therapy. Although two cases fell below the critical level of prothrombin (20%) and twelve cases fell below 30%, only five of these cases showed mild haemorrhage such as epistaxis or nail bed haemorrhages.

Clausen and Jager (1946) observed that spontaneous haemorrhage due to the prothrombinopoenic effect of salicylates is rare and when present is apparently not a factor in causing death from salicylate intoxication. Manchester (1946)[1] using the same dosage in rheumatic fever cases as was used in this case found that the prothrombin fell during the first week thereafter rising but did not reach a critical level and no haemorrhagic tendencies were noted in over 160 patients with

intensive therapy. Stress, however, has been laid upon haemorrhage as one of the most striking complications of salicylate therapy and in recent years case reports have been published of deaths from haemorrhage by Troll et al (1945) and Ashworth and McKemie (1944), but as in this case, prothrombin levels were not determined.

In dosage and in time of haemorrhage this case parallels those of Owen and Bradford (1946) with the exception that the haemorrhages were severe and death the result. This haemorrhage occurred at the time in therapy at which Manchester (1946)[1] found maximum hypoprothrombinaemia using the same dosage. A reason must be sought for the severe haemorrhage. Link et al (1943) suggested a parallelism between the effects of dicoumarol and that of salicylates which Owen and Bradford (1946) discount as in their cases the hypoprothrombinaemia was transient and disappeared with continued therapy, moreover no liver damage was detected by the cephalin-cholesterol and hippuric acid tests. The fact that vitamin K therapy can prevent this hypoprothrombinaemia (Meyer and Howard 1943) suggests that it is not caused by liver damage. However, Lutwak-Mann (1942) showed that liver glycogen disappeared following salicylate therapy. It is of interest that this case showed

advanced fatty degeneration of the liver with hyperaemia and that severe haemorrhage caused death, facts which tend to support a suggestion of Link et al (1943) that the action of salicylate is parallel to that of dicoumarol. It appears that with massive intravenous therapy using sodium salicylate, vitamin K might be of protective value if given concurrently, even although such cases of severe haemorrhage are rare.

C. The Incidence of Toxic Symptoms with Plasma Levels over 35.0 mgms.%.

Since Coburn (1943) stated that massive therapy with salicylate gave improved therapeutic results in rheumatic fever, there has been a tendency on the part of workers to use larger doses. From patients that were given high doses of sodium salicylate the toxic symptoms have been reviewed in all those whose plasma levels rose above 35.0 mgms.%. This was the level which Coburn (1943) claimed should be minimal in the treatment of rheumatic fever. Altogether some 33 patients whose plasma level rose above 35 mgms.% are shown in Table 18, together with the incidence of toxic manifestations.

It will be seen from Table 18 that the incidence of deafness, tinnitus and nausea is high. In all cases these less severe toxic symptoms were ignored. Vomiting occurred in just

over one quarter, and hyperventilation in just under one third respectively of these patients. The incidence of the other toxic symptoms is reasonably high. It would seem that if plasma levels of over 35 mgms.% are to be maintained the patients should be kept under close observation and if possible frequent estimations made of the plasma concentrations of salicylate.

TABLE 18

The incidence of toxic manifestations in 33 patients whose plasma level rose above 35 mgms.%.

Toxic Manifestations	Percentage Incidence
Tinnitus, ...	96%
Deafness, ...	100%
Nausea, ...	48%
Hyperventilation, ...	30%
Vomiting, ...	27%
Marked sweating in afebrile patient,	12%
Headache, ...	12%
Severe drowsiness, ...	12%
Mental confusion, ...	6%
Severe Dyspnoea, ...	6%
Transient Albuminuria, ...	6%
R.B.C. in Urine, ...	6%
Acetone in the Urine, ...	6%
Excitement and euphoria, ...	6%
Epistaxis, ...	6%
Vertigo, ...	3%
Pulmonary Oedema, ...	3%
Severe Haemorrhage, ...	3%

D. The Influence of Coincident Administration of Alkali on Toxic Manifestations.

1. Sodium Bicarbonate.

It has been shown that in patients who develop toxic manifestations to salicylate, these toxic effects tend to develop at certain levels, and become more frequent as the level rises. It would appear therefore logical to assume that as sodium bicarbonate produces lower plasma levels, the addition of alkali would reduce or prevent some of the toxic effects of a given dose of salicylate by directly depressing the plasma level. This, in fact, was exactly what took place, the following cases being presented in illustration.

W.S.Male, 19 years. Recurrent rheumatic polyarthritis. At the time of these observations the patient was receiving 24 gms.of sodium salicylate daily in four hourly divided doses with an equal quantity of sodium bicarbonate.

Date	Plasma Level mgms.%	Toxic Manifestations
26.3.47	39.0	
27.3.47	35.6	Patient up. Slight tinnitus and deafness but no other manifestations of salicysm during this period.
28.3.47	32.4	
29.3.47	42.1	
30.3.47	38.6	

The sodium bicarbonate was withdrawn on the 1.4.47 and the following observations made.

Date	Plasma level mgms.%	Toxic Manifestations
4.4.47	59.5	Confined to bed with marked tinnitus, deafness, perspiration, headache and nausea.
5.4.47	56.2	
6.4.47	50.1	Hyperventilation noted all day with vomiting in the evening and much malaise and perspiration.

Sodium salicylate was discontinued temporarily on the evening of 6.4.47.

This patient had been receiving sodium salicylate over a period of three months, this accounting for the large doses used with the production of only moderate plasma levels. This shows again that continued salicylate therapy with the same dose gradually leads to lower plasma levels.

J.M. Male, 48 years. Hemiplegia with Fibrositis. This patient received 10 gms. of sodium salicylate daily in four hourly divided doses, equal quantities of sodium bicarbonate being given where shown.

Date	Plasma level mgms.%	Toxic Manifestations
With Sodium Bicarbonate		
9.10.46	20.4	
10.10.46	23.2	The only symptoms in this period were slight tinnitus and some deafness.
11.10.46	21.3	
12.10.46	21.2	
13.10.46	18.5	
Sodium bicarbonate was withdrawn on the 16.10.46.		
18.10.46	35.7	Tinnitus and deafness marked.
19.10.46	41.0	Mental excitement, confusion,
20.10.46	31.4	hyperventilation and nausea.
21.10.46	33.2	Confusion and mental symptoms have disappeared but nausea, hyperventilation and nausea still apparent.

Thus it would seem that sodium bicarbonate when administered together with sodium salicylate reduces toxic

symptoms by the production of lower plasma salicylate levels.

2. The Influence of Sodium Lactate when given intravenously.

Two groups of four patients in each group were given 10 gms. of sodium salicylate in 1000 ccs. of normal saline for three days. To the sodium salicylate in normal saline of one group was added sodium lactate to make a concentration of M/6 in 1000 ccs. The toxic symptoms were recorded for each group, and these are represented in Table 19.

TABLE 19

Toxic Manifestation	Nos.of Patients showing the Toxic Manifestation	
	Without Sodium Lactate	With Sodium Lactate
Tinnitus,	4	4
Deafness,	4	4
Nausea,	4	1
Vomiting,	1	-
Severe Sweating,	4	3
Hyperventilation,	4	2
Mental Confusion,	1	-
Severe Dyspnoea,	1	-

There appears to be a reduction in the incidence of toxic symptoms when sodium lactate is administered concurrently with sodium salicylate. But as each group consists of different individuals, the significance of the figures presented is not so great, the series being small.

E. The Mechanism in the Production of Vomiting.

Vomiting is one of the most disturbing early features of salicylate intoxication and if persistent, interrupts therapy. It occurs when salicylate is administered orally, rectally or intravenously. Using all three routes plasma concentrations were obtained when vomiting occurred for the first time. These levels are shown in Table 20.

TABLE 20

Route of Administration	No.of Cases	Plasma level mgms.%		
		Low	High	Average
Oral,	8	16.0	38.6	28.2
Rectal,	4	30.0	46.1	38.2
Intravenous,	3	32.6	48.8	40.5

The opportunity was taken to examine the vomitus from two rectal and all intravenous cases. The total salicylate content of the vomitus was estimated by the same method used for total salicylate in the urine, as has been previously described. No salicylate was detected in the vomited material, a finding which is paralleled by that of Caravati and Cosgrove (1946) who found no salicylate in the gastric aspirates of patients experiencing nausea while on intravenous salicylate therapy. From this it is concluded that the emetic action of sodium salicylate in rectal

and in intravenous cases is of central origin. It will be seen that with the group shown the plasma levels at which vomiting occurred on rectal and intravenous therapy are comparable, being some 10 mgms.% higher than with oral therapy. It would appear then that there is some local effect in the upper gastro-intestinal tract which plays a part in inducing vomiting with oral therapy, as this occurs at lower levels of plasma salicylate. This might be an indication to use the rectal route in those patients who vomit persistently while on oral therapy.

General Conclusions.

(1) The toxic manifestations of sodium salicylate in the 58 patients studied tend to appear in a definite order and can be related to plasma levels initially, although tolerance to salicylate develops with continued therapy. (2) The incidence of toxic manifestations with plasma levels over 35.0 mgms.% is high. (3) Haemorrhage is a rare complication of salicylate therapy but can occur with fatal results. (4) Concurrent administration of alkali tends to reduce toxic manifestations by reducing plasma levels of salicylate. (5) Vomiting during salicylate administration is of central origin but a local action in the stomach with oral dosage is probable.

CHAPTER VII.

AN INVESTIGATION OF SALICYLATE HYPERVENTILATION

The hyperventilation produced by Sodium Salicylate has been noted both with oral and intravenous therapy in man, and has been related elsewhere to plasma levels. In view of a widely held opinion that high plasma levels are of better therapeutic value in the treatment of rheumatic fever, and in view of the occurrence of hyperventilation at these high levels, it was decided that a detailed investigation of the mechanism of production of the hyperventilation should be undertaken. To overcome the many difficulties in studying this phenomenon in patients, experiments were carried out on cats and rabbits.

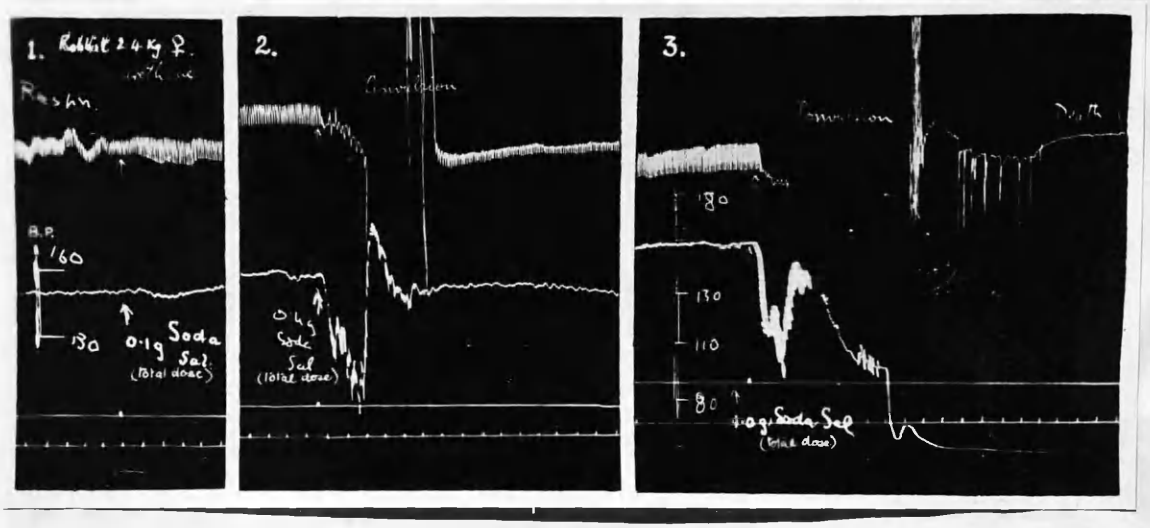
A. The Action of Intravenous Sodium Salicylate in Cats and Rabbits.

In rabbits, intravenous sodium salicylate in small doses (0.04 gm./kg.) caused an increase in amplitude and acceleration of respiration, with a slight fall in B.P., followed by a rise in B.P. Larger doses of sodium salicylate (0.17 gm./kg.) caused inhibition of respiration, a fall in B.P., and convulsions. The onset of these convulsions, which were

clonic then tonic in nature, took place before asphyxia could act and must have been of central origin. After recovery respiration may continue inhibited for some time. A dose of 0.45 gm./kg. caused death. The B.P. fell rapidly, the heart became irregular, respiration was inhibited, convulsions ensued, and asphyxia complicated the picture. These actions are shown in Fig.28.

In the cat similar results were obtained whether the animals were anaesthetised with ether, chloralose, or nembutal. Sodium salicylate 0.1 gm./kg. caused a rise in B.P. and a sharp hyperventilation which came on within a few seconds of the injection into the jugular vein, this hyperventilation lasting some time after the disturbance of B.P. had ceased. Some of these effects with salicylates in animals have been noted by Blanchier (1879), Chirone and Petucci (1878), and Hurtley and Trevan (1916).

FIGURE 28



Rabbit, female, 2.4 Kg., Urethane 10%, 4.0 mls./Kg., intravenously. Upper record respiration with inspiration on the downstroke, second line carotid B.P., third line injections, fourth line time in 30 sec.intervals.

1. Shows the effect of sodium salicylate 0.04 gm./Kg. intravenously, in stimulating respiration.

2. Shows the convulsant effect of sodium salicylate 0.17 gm./Kg. intravenously.

3. Shows the fatal action of sodium salicylate 0.45 gm./Kg. intravenously. Cardiovascular failure precedes respiratory failure.

It can be estimated from these experiments that intravenous sodium salicylate is toxic to the heart and dilates blood vessels. It stimulates the respiratory and cardiovascular mechanisms and in larger doses inhibits these mechanisms, stimulating the motor centres of the cerebrum. In larger doses still it depresses the upper centres and paralyses central nervous system function.

B. Direct Stimulation or Upset in Acid Base Balance as an Explanation of Salicylate Hyperventilation.

Investigating salicylate toxicity Johnson (1930) decided that the hyperventilation was due to a fixed acid acidosis, and Morris and Graham (1931) believed that salicylate led to the production of a non gaseous acidosis, but Odin (1932) found that there was an associated respiratory alkalosis. Goodman and Gilman (1941) stated that the increase in respiration was due to a direct action on the respiratory centre; and in children Barnett et al (1942) noted a CO_2 deficit alkalosis associated with the hyperventilation. Working with salicylate on monkeys and dogs, Rappoport et al (1943) found primary hyperventilation with decrease in CO_2 tension. Fashena and Walker (1944) noted a small reduction in CO_2 combining power without respiratory change and decided that this could only be accounted

for by accumulation of fixed acids. A shift of acid base balance to respiratory alkalosis was described in the case of a 16 years old Negro by Ryder et al (1945). In children Erganian et al (1947) were of the opinion that hyperventilation was caused primarily by the salicylate giving an incomplete respiratory alkalosis, which was followed by compensatory excretion of excess bicarbonate by the kidney.

Thus in more recent years, there has been a consensus of opinion that salicylate produces hyperventilation by direct stimulation of the respiratory centre, and that this hyperventilation is followed by a respiratory alkalosis.

In an attempt to determine whether the hyperventilation was caused by acid-base change in the blood, or whether it was caused by an intrinsic stimulant action of salicylate on the respiratory centre, the following experiments were undertaken on cats and rabbits:

(a) Observations were made on the CO_2 combining power of arterial blood, plasma salicylate levels, respiration, and B.P., before, immediately after, and at intervals after an intravenous injection of sodium salicylate sufficient to produce respiratory stimulation.

(b) The effect on the hyperventilation of simultaneous massive doses of sodium bicarbonate with the salicylate, were observed.

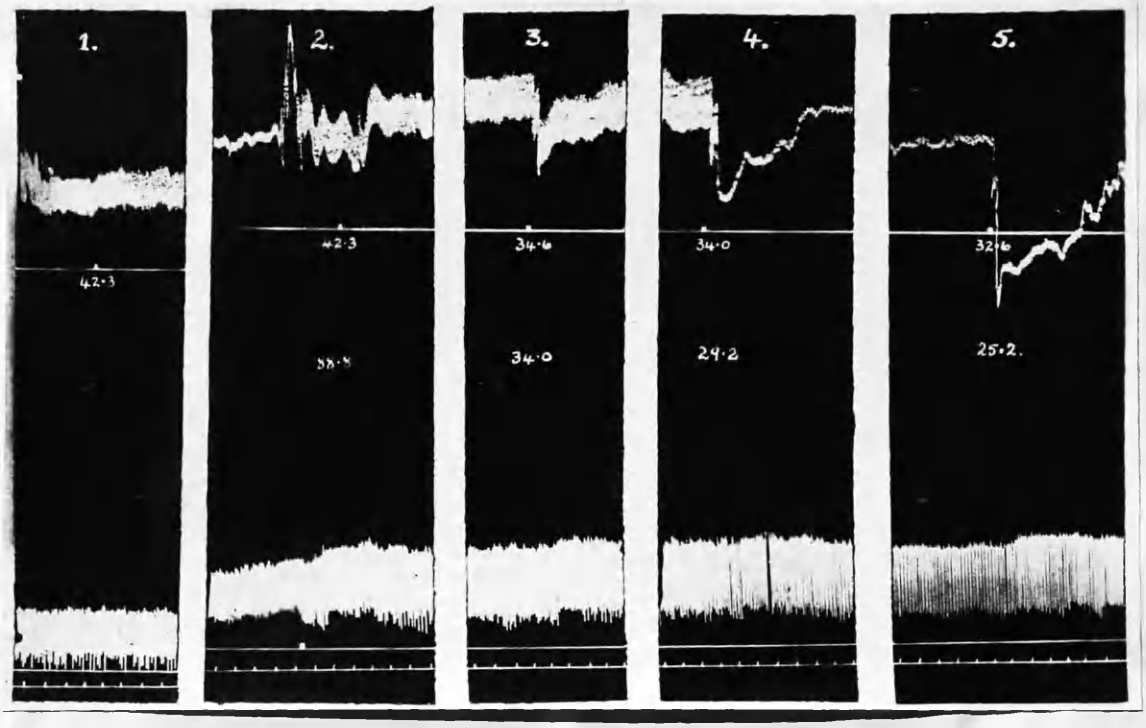
(c) The effect of the previous administration of massive

doses of sodium lactate on the hyperventilation produced by salicylate were observed.

(d) The effect on the hyperventilation of the simultaneous administration with the sodium salicylate of massive doses of the sedative drugs,
(i) Morphine sulphate,
(ii) Hexobarbitone soluble,
and the sedative ions,
(iii) Ca ions as calcium gluconate,
(iv) K ions as Potassium chloride,
were observed.

These observations with all relevant details are illustrated in Figures 29 to 33 with the conclusions drawn therefrom. No illustration of the effect of potassium chloride is appended as there was no modification whatever of the hyperventilation produced by the intravenous injection of salicylate, when this salt was given with the salicylate.

FIGURE 29

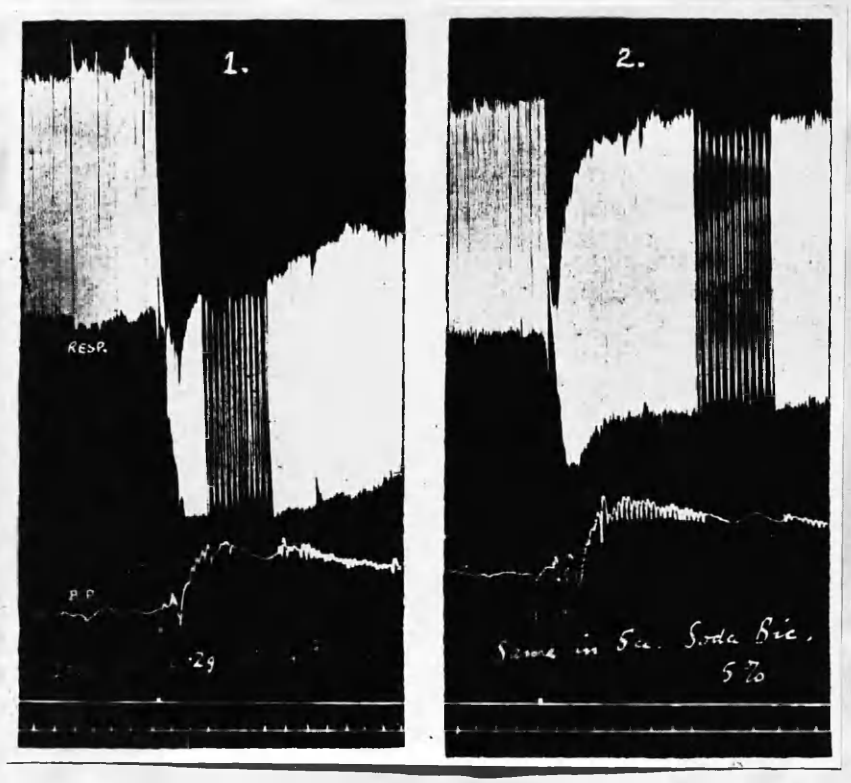


Cat, male, 3.4 Kg. Ether and chloralose 80 mg./Kg. Upper line shows carotid B.P., second line shows points where blood samples were taken, with immediately below the CO_2 combining power in volumes per cent, third line shows the plasma salicylate levels in mgms.%, fourth line shows the respiration with inspiration on the downstroke, fifth line shows injection point of sodium salicylate 0.1 gm./Kg., the lowest line shows time in 30 sec.intervals.

1. Shows normal control.
2. Shows the effect of sodium salicylate 0.1 gm./Kg. It has produced a rise in B.P. and hyperventilation.
3. Shows sample taken at 6 mins. after the injection.
4. Shows sample at 12 mins.
5. Shows sample at 24 mins., the effects of haemorrhage are manifest.

It will be seen that there was no deviation from the normal CO_2 combining power immediately after the injection of the salicylate and yet the stimulation of respiration was immediate. As hyperventilation continued there was a gradual fall in CO_2 combining power. The plasma salicylate was high after the injection but fell markedly in the next 6 mins., more gradually thereafter. The rapid fall was probably caused by diffusion into the tissues.

FIGURE 30



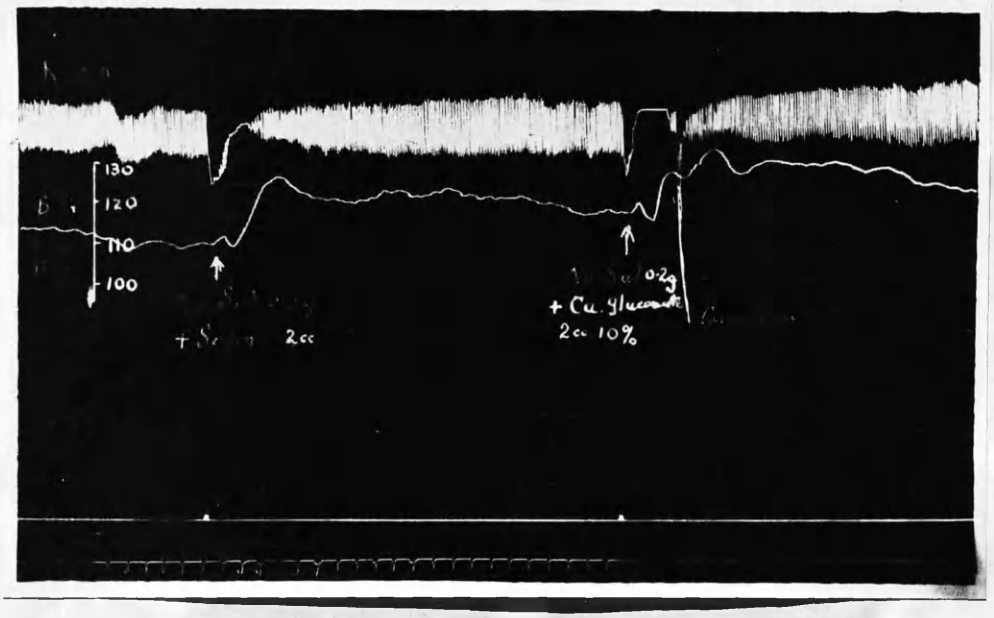
Rabbit, male, 2.4 Kg., Urethane 10%, 4.0 mls./Kg., intravenously. Upper line shows respirations with inspirations on the downstroke, the second line shows carotid B.P., the third line shows point of injection, and the fourth line shows time in 30 sec.intervals. Increase in drum speed is shown at intervals.

1. Shows hyperventilation and rise in B.P. after the intravenous injection of sodium salicylate 0.2 gm./Kg.

2. Shows the same effect when Sodium salicylate 0.2 gm./Kg. is given in sodium bicarbonate 5 mls. of a 5% solution.

It is shown that sodium salicylate retained its stimulant effect on respiration in the presence of sodium bicarbonate.

FIGURE 31



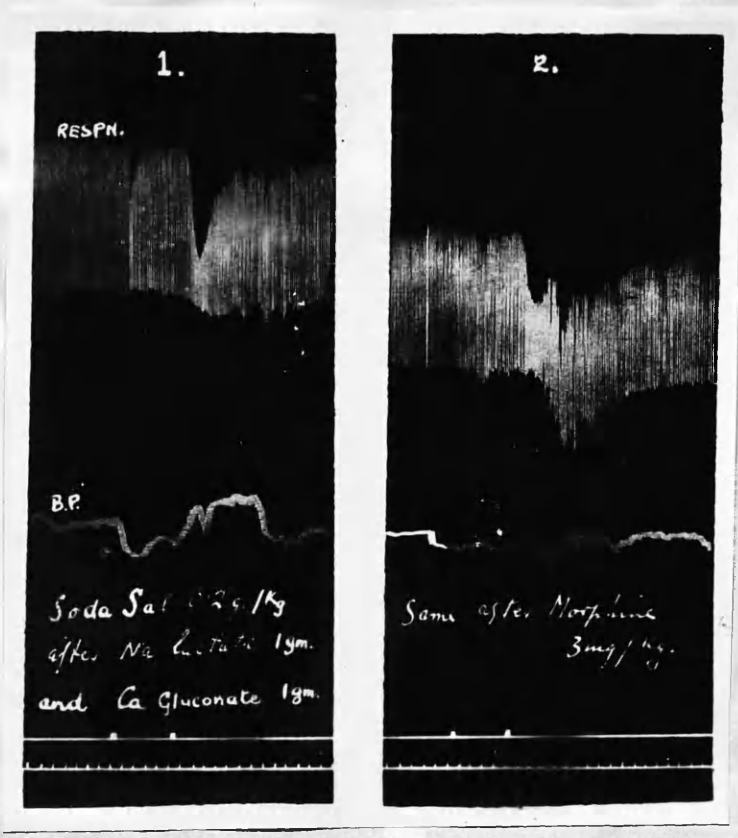
Rabbit, male, 2.0 Kg, Urethane 10% 4.0 mls./Kg., intravenously. Upper line shows respiration with inspiration on the downstroke, second line shows carotid B.P., third line shows injections, fourth line time in 30 sec.intervals.

The first injection demonstrates the effect of sodium salicate 0.1 gm./Kg. in raising B.P. and stimulating the respiration. In this example the stimulation takes the form of spasmodic increase of inspiratory tone rather than hyperventilation.

The second injection shows the same effect from the same dose of salicylate given in Calcium gluconate 2 mls. of a 10% soln. Here the spasmodic increase in inspiratory tone is followed by a short convulsion.

It is found that increased calcium concentration in the blood does not prevent the action of sodium salicylate on respiration and B.P., nor the convulsant action on the C.N.S.

FIGURE 32



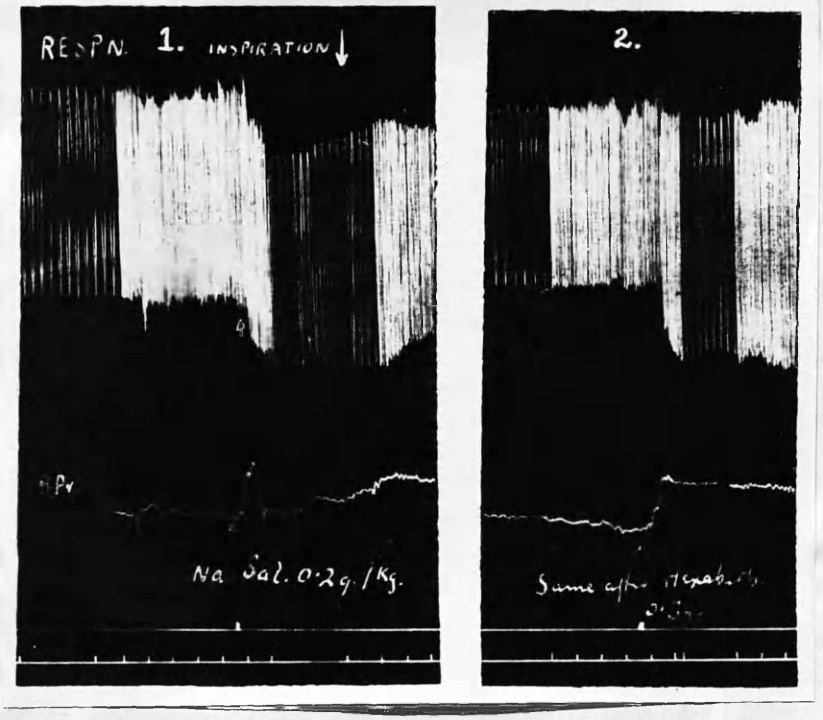
Rabbit, female, 2.2 Kg.Urethane 10%, 4.0 Mls./Kg., intravenously. Upper record is respiration with inspiration on the downstroke; the second line shows carotid B.P., the third line shows injections, and the lower line time in 20 second intervals.

1. Demonstrates the effect of sodium salicylate 0.2 gm./Kg., intravenously, when given immediately after sodium lactate 0.46 gm./Kg. and Calcium gluconate 0.46 gm./Kg., intravenously.

2. Shows the effect of sodium salicylate 0.2 gm./Kg. i.v. when given immediately after morphine sulphate 3 mgm./Kg. I.V.

It is seen that the previous administration of sodium lactate and calcium gluconate together, or of morphine sulphate, does not modify the effect of sodium salicylate on the respiration.

FIGURE 33



Rabbit, male, 2.4 Kg. Urethane 10%, 4.0 mls./Kg., intravenously. Upper record respiration with inspiration on the downstroke. The second line shows carotid B.P.; the third line shows injections and the fourth line shows time in 30 secs. Increased drum speeds are shown at intervals.

1. Shows the action of Sodium Salicylate 0.2 gm./Kg. in stimulating respiration.

2. Shows the same action when Sodium Salicylate is given one minute after Hexobarbitone soluble 0.2 gm./Kg., intravenously.

There is no modification in the effect of Sodium salicylate on respiration when administered after Hexobarbitone soluble in large doses.

Discussion.

The illustration (Fig.29) shows that the CO_2 combining power of the plasma is not immediately upset following the intravenous injection of sodium salicylate, although hyperventilation follows immediately on the injection. This observation was confirmed in other animals. This could be evidence in favour of an immediate upset in the pH of the blood by the salicylate followed by a compensatory hyperventilation, or evidence of direct effect on the respiratory centre producing hyperventilation. Both conditions would be followed by a reduction in the CO_2 combining power, in the first instance indicating an acidosis, and in the second instance indicating a gaseous alkalosis from the hyperventilation. It has been shown by Morris and Graham (1931) that salicylic acid in the blood can not account for the reduction of CO_2 combining power by replacement of CO_2; Myers and Ferguson (1929) have shown that there is little change in the acetone content of the blood with salicylate administration, and as the pH of sodium salicylate in solution is to the alkaline side of neutrality, it seems highly unlikely that sodium salicylate injected intravenously produced the hyperventilation and reduction in CO_2 combining power by interfering with the pH of the blood. This is supported by Rappoport and Guest (1945) who could find

no pH change in the blood of animals after the administration of big doses of sodium salicylate.

It has been shown in Chapter VI. that ketosis plays little part in the picture of salicylate hyperventilation and moreover there was no time during which ketosis could develop, as stimulation of respiration followed the injection of salicylate immediately.

That the hyperventilation was not caused by an acidosis was further shown by the fact that coincident administration of a large quantity of alkali (Fig.30) did not prevent the hyperventilation from appearing or modify it in any way.

It appears then that there is direct stimulation of the respiratory centre causing hyperventilation which in turn leads to a gaseous alkalosis with reduction in CO_2 combining power. During the animal experiments it was also noted that when the dose of sodium salicylate was not large enough to produce any hyperventilation there was no fall in the CO_2 combining power.

Now, it has been shown in Chapter I., that in patients on continuous dosage with sodium salicylate the concurrent administration of bicarbonate produces lower plasma salicylate concentrations. It has also been shown that hyperventilation

occurs at a certain concentration of salicylate in the plasma (Chapter VI.). Thus the concurrent administration of bicarbonate with continued salicylate administration tends to reduce the concentration of salicylate in the plasma below the level at which hyperventilation is manifested. It follows that if hyperventilation is prevented or reduced, the reduction in CO_2 combining power will be prevented or returned to normal, as has been discussed above.

These observations explain why the addition of bicarbonate to sodium salicylate when administered to patients tends to prevent the reduction in CO_2 combining power and hyperventilation, a fact which has led earlier workers to assume the presence of an acidosis.

It is also interesting to note that in this series of animal experiments massive doses of sedatives were unable to prevent the salicyl hyperventilation (Figs.32 & 33) and that the administration of sodium lactate and calcium gluconate were also without effect (Figs.31 & 32).

C. Site of Action of Sodium Salicylate in Producing Hyperventilation.

It has been generally assumed by those authors who favoured the view of direct stimulation that the site of action

of salicylate was the respiratory centre. However, Gesell (1940) wrote: "If ever there was a conviction firmly entrenched in physiology it was the monopoly of the chemical control of breathing by the respiratory centre. It was a shaky foundation upon which all of us worked". Pi-Suner as far back as 1918 considered that in addition to central chemical influences there must be a peripheral regulatory factor acting through receptors which are also sensitive to chemical factors. Bagoury and Samaan (1941) have studied respiratory reflexes by injecting ketone bodies into the pulmonary circulation. They prevented any possible central action of the drug. The vagal excitation arose from sensory nerve endings in the lung, these pulmonary nerve endings being sensitive to both mechanical and chemical stimuli. Winder and Winder (1933) examining the action of sulphides found that strong respiratory reflexes were evoked from the chemoreceptors of the carotid body. Haggard and Henderson (1922) studying the respiratory reflexes after sodium sulphide injected intravenously considered the respiratory effects in these cases were due to the action on the vagal endings in the lung, in view of the difference in responses depending on whether one is dealing with intact or vagotomised animals.

It was considered in the light of the above reports

that the direct stimulation of salicylate might be caused by (a) action on the respiratory centre, (b) action on the carotid bodies, (c) action through the peripheral vagus, or (d) some combination of these factors. A search of the literature yielded no work investigating this point except the work of Danewski (1876) who stated that if the vagi were cut before the injection of sodium salicylate the respiration was only slightly accelerated by the injection. This respiratory rate then returned to the same rate as in the control untreated animals with sectioned vagi. From this interesting observation he drew the remarkable conclusion that the drug acted independently of the vagus mechanism.

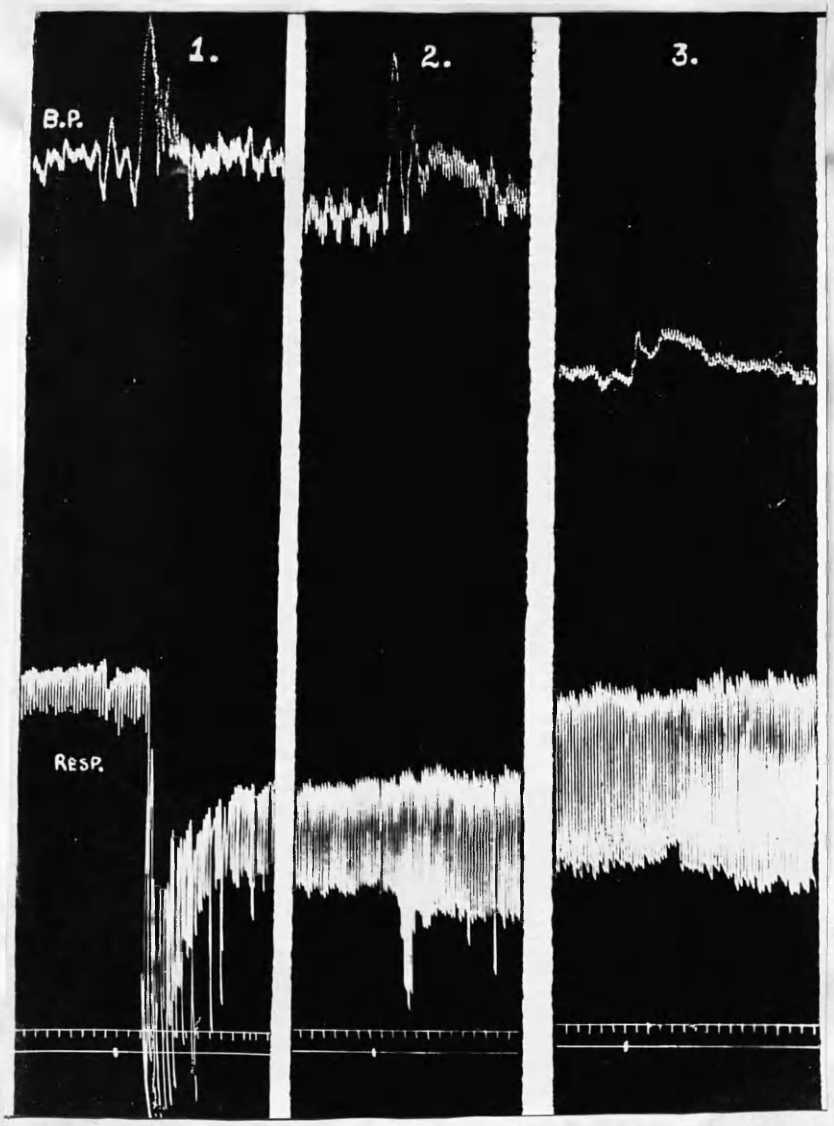
This Investigation.

To determine the site of action of salicylate in producing hyperventilation, experiments were performed on rabbits and cats anaesthetised and prepared as described.

1. The Carotid Bodies. The effect of sodium salicylate before and after extirpation of both carotid bodies was tried in rabbits and cats. Extirpation of the carotid bodies raised the B.P. in rabbits but had less effect in cats. The respiratory stimulant action of sodium salicylate was not altered. This is shown in a cat in Fig.34.

2. The Peripheral Vagus. Bilateral section of the vagi in the lower neck slows the rate and increases the amplitude of respiration to a characteristic rhythm and may raise the B.P. in rabbits but lowers it in cats. After bilateral section of the vagi the effect of sodium salicylate in appropriate doses was modified greatly. If the dosage given was sufficient in any one animal to cause hyperventilation but not convulsions, then cutting the vagi abolished the greater part of the hyperventilation. This is shown in Fig.34 where a chloralosed cat was given 0.1 gm.Kg. after bilateral vagotomy with extirpated carotids. A similar result is shown in a rabbit in Fig.35.

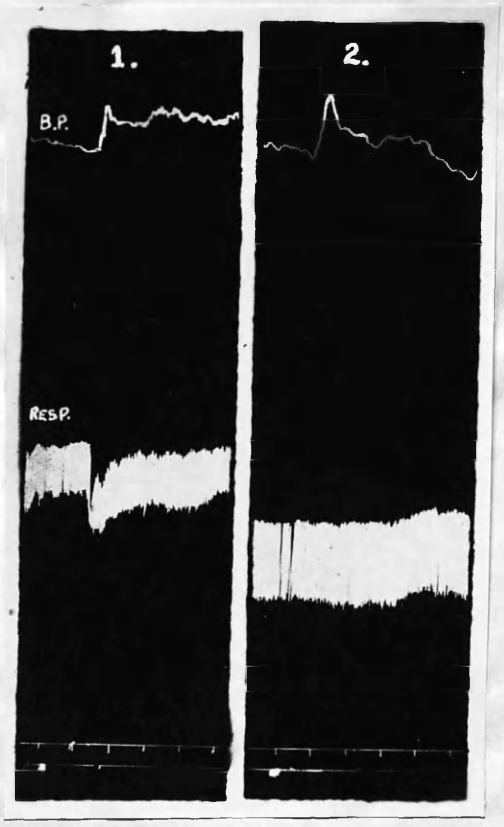
FIGURE 34



Cat, male, 3.2 Kg. Ether and Chloralose 80 mg./Kg. Upper record carotid B.P.; second line respiration with inspiration on the downstroke; third line time in 30 second intervals; fourth line injections.

1. Shows the rise in B.P. and hyperventilation from sodium salicylate 0.1 gm.Kg. intravenously.
2. Shows the similar effect with the same dose of sodium salicylate after extirpation of both carotid bodies.
3. Shows greatly diminished effect with the same dose of sodium salicylate after bilateral vagotomy.

FIGURE 35



Rabbit, 2.6 Kg. Urethane 10% 4.0 mls./Kg. intravenously. Upper record shows carotid B.P.; second line shows respiration with inspiration on the downstroke; third line shows time in 30 sec. intervals; fourth line shows injections.

1. Shows rise in B.P. and Hyperventilation after Sodium Salicylate 0.1 gm./Kg. intravenously.

2. Shows the action of the same dose of sodium salicylate after bilateral extirpation of the carotid bodies and bilateral vagotomy. The B.P. effects are unchanged but the effect on respiration is greatly diminished.

Thus sodium salicylate apparently acts through the peripheral vagus and to some extent centrally as there is very slight stimulation of respiration after section of the vagi.

Further investigations of these findings were carried out as follows on an anaesthetised cat, and subsequently repeated on cats and rabbits:

1. The intravenous injection of sodium salicylate 0.1 gm./Kg. produced characteristic hyperventilation.

2. Acetyl choline 2 /Kg. was given intravenously and produced a temporary fall in B.P.

3. Atropine sulphate 2 mg./Kg. was given intravenously and followed immediately with the same dose of Acetyl choline as given in 2. There was no effect on B.P., therefore the Atropine sulphate had been sufficient to paralyse the parasympathetic outflow.

4. Immediately after 3, Sodium salicylate was again injected as in 1 above. The effect was precisely the same as was obtained in 1. producing hyperventilation. Thus paralysis of efferent parasympathetic action does not prevent sodium salicylate from producing hyperventilation.

5. Vagotomy was performed and when respiration had settled to its characteristic rhythm sodium salicylate was injected as in 1. The effect on respiration was greatly modified, being reduced to one tenth or less of its effect in 1.

Thus, if enough Atropine is given to paralyse the motor nerve endings of the parasympathetic the effect of sodium salicylate on the respiration is unaltered, but the greater part of this effect is abolished by vagotomy. It would appear then that

the action of sodium salicylate is by means of the afferent vagi, through which it presumably initiates reflex respiratory movements. About 10% appears to remain as a direct stimulation of the respiratory centre in the medulla after vagotomy. These effects are illustrated in Fig.36. All the effects described and illustrated were repeated and confirmed in each case. In all some twelve cats and eighteen rabbits were used in these experiments.

The exact site of action of sodium salicylate in producing hyperventilation through the peripheral vagus could be

(a) the vagal nerve endings in the lung as indicated by the work of Haggard and Henderson (1922) with sodium sulphide, or,

(b) the aortic chemoreceptors as indicated by the work on these chemoreceptors by Schweitzer and Wright (1938), and Schmidt and Comroe (1940).

The technique of isolating these aortic chemoreceptors is exceedingly complicated and required special apparatus which was not available.

It is interesting to note that Churchill and Cope (1929) considered the dyspnoea observed in pulmonary oedema to be attributable to excitation of the sensory nerve endings in the lung, for pulmonary oedema following a high concentration of salicylate in the plasma was observed in a patient as a toxic manifestation of sodium salicylate and followed the hyperventilation.

FIGURE 36

Cat, male, 3.0 Kg. Ether. Upper record shows carotid B.P.; second line shows respiration with inspiration on the downstroke; third line shows injections; fourth line shows time in 30 second intervals.

1. Shows hyperventilation after sodium salicylate 0.1 gm./Kg. intravenously.

2. Shows the same effect from the same dose of sodium salicylate after atropine sulphate 2.5 mg./Kg.

3. Shows very slight stimulation of respiration with the same dose of sodium salicylate following bilateral vagotomy.

Summary of Findings and Conclusions.

Evidence has been presented which indicates that the hyperventilation produced by sodium salicylate is caused mainly by peripheral stimulation of the vagus and only slightly by direct effect on the respiratory centre. This mechanism is independent of upset in acid base balance of the blood but the hyperventilation may be followed by a respiratory alkalosis.

GENERAL SUMMARY OF CONCLUSIONS

To complete this thesis, the following brief summary is presented of the conclusions reached in the preceding investigations:

CHAPTER I. Although maximum plasma concentrations occur two hours after oral administration of sodium salicylate, four hourly dosage maintains plasma concentrations satisfactorily. The dose can be related to body weight but increases in dosage above 14 grs.per stone body weight give marked increases in plasma concentrations. Sodium bicarbonate administered concurrently reduces plasma levels while Ammonium chloride raises them. Long continued administration of sodium salicylate leads to gradually decreasing plasma concentration of salicylate. The concurrent administration of para-aminobenzoic acid has much the same effect as ammonium chloride in that it raises the plasma salicylate concentration. A low fluid intake will give a marked rise in plasma concentration of salicylate on continued dosage, a factor of considerable interest in children where diminished fluid intake is an early feature of salicylate poisoning, but exercise on the other hand has no effect on the

plasma levels of salicylate. Inadequate shaking of bottles containing sodium salicylate - sodium bicarbonate mixtures or long standing of these mixtures, leads to inaccurate dosage with consequent effect on plasma concentrations. In adults the administration of 150 grs. or more of sodium salicylate per day leads to a fall in the alkali reserve which can be readily counteracted by the administration of sodium bicarbonate. At the end of chapter I. the method of estimation of plasma salicylate was briefly described, together with a modification found necessary for the estimation of very small amounts of salicylate in the plasma.

CHAPTER II. Rectal absorption of sodium salicylate is slower than with oral administration but adequate plasma levels may be maintained by eight hourly rectal enemata of sodium salicylate alone. The technique of administration is simple and this form of administration is well tolerated with little upset in bowel rhythm. The addition of sodium bicarbonate rectally decreases the absorption of sodium salicylate markedly while if given concurrently by the mouth facilitates elimination of the salicylate. Rheumatic fever cases can be treated throughout by rectal enemata of sodium salicylate as effectively as by oral administration of the drug.

CHAPTER III. The plasma concentrations obtained by daily intravenous administration compare unfavourably with those obtained by the administration of the same amount of the drug daily by the mouth. The reduction in alkali reserve is more marked with intravenous injection of the drug and toxic effects more severe. These observations led to the abandonment of the intravenous route as a method of administration of sodium salicylate.

CHAPTER IV. The concentration of salicylate in the body fluids is governed by the free salicylate fraction in the plasma which increases relatively but to a greater extent as the total salicylate in the plasma rises. Thus as the total salicylate in the plasma increases there is a proportionately greater increase in the concentration in the body fluids. The concentration in the C.S.F., however, lags behind the free salicylate of the plasma and requires many days to reach an equilibrium with it, but concentration of salicylate in other fluids is more comparable to the free salicylate in the plasma.

CHAPTER V. There is negligible excretion of salicylate in the sweat and faeces at any time. The concurrent administration of an alkaline salt increases the excretion of salicylate in the urine, especially the free salicylate fraction, while

the concurrent administration of an acid salt or para-aminobenzoic acid has the opposite effect. This variation in excretion is of an order which would explain the differences in plasma concentrations when these substances are administered concurrently with sodium salicylate. As the excretion of free salicylate can be directly correlated to the pH of the urine, and all these substances produce changes in the pH of the urine, it is suggested that the pH of the urine governs the excretion of the urine rather than the actual substance administered with the salicylate. From this it is assumed that in treating cases of salicylate poisoning the urine should be rendered alkaline and adequate fluid intake (as was shown in Chapter I.) maintained.

CHAPTER VI. The toxic effects of sodium salicylate can be directly related to the plasma concentrations except in a few cases of idiosyncrasy. Tolerance develops if a plasma concentration is maintained, while concurrent administration of alkali diminishes the toxicity of a fixed dose of sodium salicylate by reducing plasma levels of salicylate. (The individual toxic manifestations were discussed in this chapter and the relationship of salicylate administration considered. A case which ended fatally through haemorrhage while receiving sodium salicylate was discussed in detail.) Toxic manifestations

above 35.0 mgms.% are of reasonably high incidence. Vomiting is of central origin except for the probability of a local action in the stomach with oral administration.

CHAPTER VII. Evidence was presented indicating that the hyperventilation produced by sodium salicylate was caused mainly by peripheral stimulation of the vagus and only slightly by direct effect on the respiratory centre. The mechanism whereby the respiration was stimulated was found to be independent of upset in the acid base balance of the blood although hyperventilation may be followed by a respiratory alkalosis. This explains the reduction in alkali reserve as judged by the CO_2 combining power of the plasma found with salicylate therapy.

B I B L I O G R A P H Y

1. ANDERSON, J.A., (1945), in Textbook of Pediatrics, Mitchell-Nelson. W.B.Saunders & Co., Philadelphia.

2. ANSBACHER, S., (1944), Vitamins and Hormones, N.Y.Acad.Press.

3. ASHWORTH, C.T., and McKEMIE, J.F., (1944), J.A.M.A., 126, 806.

4. BALL, F.E., (1945), News Letter, 2, 10.

5. BAGOURY, M.M., and SAMAAN, A., (1941), J.Egypt.Med.Assoc., 24, 211.

6. BARNETT, H.L., POWERS, J.R., BENWARD, J.H., and HARTMANN, A.F., (1942), J.Pediat., 21, 214.

7. BENDA, R., and POIROT, G., (1946), Bull.mém.Soc.de Hôp.de Paris, Nos.3-7, 127.

8. BLANCHIER, (1879), quoted from Hanzlik, P.J., (1926).

9. BLUME, W., and NOHARA, F.S., (1933), Arch.Exp.Path. & Pharmak., 173, 413.

10. BROADBENT, W.H., (1876), Lancet, I., 254.

11. BRODIE, B.B., UDENFRIEND, S., and COBURN, A.F., (1944), J.Pharm. & Exp.Therap., 80, 114.

12. BUSS, (1875), quoted from Hanzlik, P.J., (1926).

13. CAHOURS, (1844), Ann. de Chim. et de Phys., 10, 337.

14. CARAVATI, C.M., and COSGROVE, E.F., (1946), Ann.Int.Med., 24, 638.

15. CARNOT, P., and BLAMOUTIER, P., (1925), Paris Méd., 2, 477.

16. CAUSSADE, G., and CHARPY, P., (1921), Rev.de Méd., 38, 127.

17. CHABANIER, H., LEBERT, M., and LOBO-ONELL, C.,(1923), Compt.rend.soc.biol., 88, 178 and 608.

18. CHIRONE, and PETRUCCI, (1878), quoted from Hanzlik, P.J., (1926).

19. CHURCHILL, E.D., and COPE, O., (1929), J.Exp.Med., 49, 531.

20. CLARKE, T.W., (1906), Amer.J.Med.Sci., 132, 429.

21. CLAUSEN, F.W., and JAGER, B.V., (1946), J.Lab.& Clin.Med., 21, 428.

22. COBURN, A.F., (1943), Bull.Johns Hopkins Hosp., 73, 435.

23. COQUONIN, (1922), quoted from Hanzlik, P.J., (1926).

24. DALY, F.H., (1878), Brit.Med.J., I., 87.

25. DANEWSKI, (1876), quoted from Hanzlik, P.J., (1926).

26. DAVIS, B.D., (1943), J.Clin.Invest., 22, 753.

27. DELORE, (1925), quoted from Hanzlik, P.J., (1926).

28. DODD, K., MINOT, A.S., and ARENA, J.M., (1937), Amer.J.Dis.Child., 53, 1435.

29. DRY, T.J., BUTT, H.R., and SCHEIFLEY, C.H., (1946), Proc.Staff Meetings Mayo Clin., 21, 497.

30. EHRMANN, R., (1907), Münch.Med.Woch., 54, 2595.

31. ERGANIAN, J.A., FORBES, G.E., and CASE, D.M., (1947), J.Pediat., 30, 129.

32. FASHENA, G.J., and WALKER, J.N., (1944), Amer.J.Dis.Child, 68, 369.

33. FESER and FRIEDBERGER, (1875), quoted from Hanzlik, P.J., (1926).

34. FINDLAY, L., (1931), The Rheumatic Infection in Childhood, Arnold.

35. FLEISCHER, R., (1875), Berl.Klin.Woch., 12, 529 and 547.

36. GESELL, R., (1940), quoted from Pî-Suner, A., (1947).

37. GILBERT, A., COURY, A., and BENARD, H., (1921), Compt.rend.soc.biol., 85, 421.

38. GOODMAN, L., and GILMAN, A., (1941), The Pharmacological Basis of Therapeutics. The MacMillan Co., New York.

39. HAGGARD, H.W., and HENDERSON, H., (1922), Amer.J.Physiol., 61, 289.

40. HALL, W., (1904), quoted from Hanzlik, P.J., (1926).

41. HAMILTON, (1875), quoted from Hanzlik, P.J., (1926).

42. HANZLIK, P.J., (1926), Medicine, 5, 197.

43. HANZLIK, P.J., SCOTT, R.W., and REYCRAFT, J.L., (1917), Arch.Int.Med., 20, 329.

44. HANZLIK, P.J., SCOTT, R.W., and THOBURN, T.W., (1917), J.Pharm.& Exp.Therap., 9, 247.

45. HEUBNER, C.F., and LINK, K.P., (1941), J.Biol.Chem., 138, 529.

46. HEYN, L.G., (1912), J.A.M.A., 58, 1013.

47. HOLMES, E.G., (1925), J.Pharm. & Exp.Therap., 26, 297.

48. HUNTINGDON, R.W., RYAN, R.D., BUTT, H.R., GRIFFITH, G.C., MONTGOMERY, H., SOLLY, R.F., and LEAKE, W.H., (1946), Ann.Int.Med., 24, 1029.

49. HURTLEY, W.H., and TREVAN, J.W., (1916), J.Physiol., 50, Proc.XLIX.

50. IRVING, G.R., (1923), Arch.Pediat., 40, 832.

51. JACOBY, M., (1908), Biochem.Zeit., 9, 522.

52. JAGER, B.V., and ALWAY, R., (1946), Amer.J.Med.Sci., 211, 273.

53. JOHNSON, C.C., (1930), J.A.M.A., 94, 784.

54. KAPP, E.M., and COBURN, A.F., (1942), J.Biol.Chem., 145, 549.

55. KOLBE, and LAUTEMANN, (1860), Ann.di Chem.u Pharm., 115, 157.

56. LANGMEAD, F., (1906), Lancet, I., 1822.

57. LEES, D.B., (1908), Proc.Roy.Soc.Med., (Pharm.Sect.) 1908-1909, 34.

58. LEROUX, (1827), quoted from Hanzlik, P.J., (1926).

59. LESNÉ, (1922), quoted from Hanzlik, P.J., (1926).

60. LESTER, D., LOLLI, G., and GREENBERG, L.A., (1946), J.Pharm. & Exp.Therap., 87, 329.

61. LINK, K., OVERMAN, R.S., SULLIVAN, W.R., HEUBNER, C.F., and SCHEEL, L.D., (1943), J.Biol.Chem., 147, 463.

62. LUTEMBACHER, R., (1921), Presse Méd., 29, 895.

63. LUTWAK-MANN, C., (1942), Biochem.J., 36, 706.

64. MACKENZIE, J.W.A., (1943), Arch.Dis.Child., 18, 28.

65. MACLAGAN, T., (1876), Lancet, I., 349.

66. MANCHESTER, R.C., (1946)(1), J.A.M.A., 131, 209.

67. MANCHESTER, R.C., (1946)(2), Arch.Int.Med., 78, 170.

68. da MATTA, A.A., (1916), J.A.M.A., 67, 1979.

69. McEACHERN, G.C., (1945), News Letter, 2, 1-8.

70. McLEOD, (1941), Bard, P., in McLeod's Physiology in Modern Medicine, H.Kimpton, London.

71. MEARA, F.S., (1910), Amer.J.Med.Sci., 139, 328.

72. MENDEL, F., (1905), Münch.Med.Woch., 52, 165.

73. MEYER, O.O., and HOWARD, B., (1943), Proc.Soc.Exp.Biol. & Med., 53, 234.

74. MORRIS, N., and GRAHAM, S., (1931), Arch.Dis.Child., 6, 273.

75. MOSSO, U., (1889), Arch.Exp.Path. & Pharmak., 26, 267.

76. MYERS, H.B., (1920), J.A.M.A., 75, 1783.

77. MYERS, H.B., and FERGUSON, C., (1929), J.Pharm.& Exp. Therap., 35, 313.

78. ODIN, M., (1932), Acta Med.Scand., Supp.50, 177.

79. OWEN, G.C., and BRADFORD, H.A., (1946), Ann.Int.Med., 25, 97.

80. PETERS, J.P., (1935), Body Water, Baillière, Tindal & Cox, Lond.

81. PIRIA, (1838), Ann.de Chim.et de Phys., 69, 298.

82. PÎ-SUNER, A., (1918), Treb.Soc.Biol.de Barcelona, 3, 54.

83. PÎ-SUNER, A., (1947), Physiol.Review, 27, I.

84. QUINCKE, (1888), quoted from Sollman, T., (1936).

85. RAPPOPORT, S., and GUEST, G.M., (1945), J.Clin.Invest., 24, 759.

86. RAPPOPORT, S., WING, M., and GUEST, G.M., (1943), Pro.Soc. Exp.Biol.& Med., 53, 40.

87. REINHOLD, J.G., FLIPPIN, H.F., DOMM, A.H., and POLLACK, L., (1944), Amer.J.Med.Sci., 207, 413.

88. ROBERTSON, H.F., SCHMIDT, R.E., and FEIRING, W., (1946), Amer.J.Med.Sci., 211, 67.

89. ROSENBLOOM, J., and JOHNSTON, J.R., (1919), J.A.M.A., 72, 22.

90. RYDER, H.W., SHAVER, M., and FERRIS, E.B., Jnr., (1945), New Eng.Med.J., 232, 617.

91. SCHMIDT, C.F., and COMROE, J.H., (1940), Physiol.Review, 20, 115.

92. SCHWEITZER, A., and WRIGHT, S., (1938), Quart.J.Exp.Physiol., 28, 33.

93. SMITH, P.K., GLEASON, H.L., STOLL, C.G., and OGORZALEK, S., (1946), J.Pharm.& Exp.Therap., 87, 237.

94. SMULL, K., WÉGRIA, R., and LELAND, J., (1944), J.A.M.A., 125, 1173.

95. SOLLMAN, T., (1936), Pharmacology. W.B.Saunders & Co., Lond.

96. STAHMANN, M.A., HEUBNER, C.F., and LINK, K.P., (1944), J.Biol.Chem., 138, 513.

97. STRICKER, DR., (1876), Berl.Klin.Woch., I., 15 and 99.

98. TARAN, L.M., and JACOBS, M.H., (1945), J.Pediat., 27, 59.

99. TIERNEY, N.A., (1946), J.A.M.A., 131, 280.

100. TROLL, M. and MENTIN, M.L., (1945), Amer.Dis.Child., 69, 37.

101. TUCKWELL, (1876), quoted from Hanzlik, P.J., (1926).

102. Van LEEUWEN, W.S., and DRZIMAL, H., (1924), Arch.Exp.Path. & Pharmak., 102, 218.

103. Van SLYKE, D.D., and CULLEN, G.E., (1917), J.Biol.Chem., 30, 289.

104. VELASQUEZ, B., (1939), Prensa Med.Argent., 26, 958.

105. WARREN, H.A., HIGLEY, C.S., and COOMBS, F.S., (1945), Proc.Cent.Soc.Clin.Research, 18, 30-31.

106. WARREN, H.A., HIGLEY, C.S., and COOMBS, F.S., (1946), Amer.Heart J., 32, 311.

107. WÉGRIA, R., and SMULL, K., (1945), J.Pediat., 26, 211.

108. WÉGRIA, R., and SMULL, K., (1945), J.A.M.A., 129, 485.

109. WILEY, W.H., (1906), U.S.Dept.Agric.Bur.Chem.Bull, 84, Pt. II.

110. WINDER, C.V., and WINDER, H.O., (1933), Amer.J.Physiol., 105, 311.