"THE TREATMENT OF JUVENILE RHEUMATISM WITH MASSIVE DOSES OF SALICYLATES."

A Thesis presented for the
Degree of Doctor of Medicine
of the University of Glasgow

by

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INTRODUCTION.

At the present time most of the salicylates used medicinally are synthesised but, as the name indicates, the natural source of the drug is the willow tree. Both the bark and the green willow shoots have been valued remedies from ancient times. The Papyrus Ebers (approximately 1500 B.C.) included "Rush from the Green Willow tree" as one of the ingredients of a cure for the Great Debility. A Greek Herbal, compiled during the first century A.D. by Dioscorides of Anazarba in Cilicia, was a source from which herbalists of all nations obtained much information. The English version, translated by John Goodyer in 1655, revealed an extensive knowledge of the properties of the willow and recorded its value in the treatment of corns and scurf, as an analgesic for "ye griefs of the eares", and as an excellent fomentation for gout. More recently, Hasselquist (1872) described how the small willow, known as Calaf, was the popular remedy for the continual fevers so common in Egypt during the Summer Season.

A decoction of willow bark was used as a febrifuge throughout Europe. Though Hanzlik (1926) stated that

the French, both before and during the Napoleonic Wars, had found that it was a successful substitute for quinine, it is surprisingly difficult to trace any writings about this use of the drug. One of the first was the letter from the Rev. Mr. Edmund Stone that was read before the Royal Society in 1763. The extraordinary bitterness of the willow bark had led him to believe that it might have similar properties to Peruvian bark. Since there was no mention of this possibility in books of botany and dispensaries, he decided to study this problem. The investigation lasted five years and proved that the powdered bark cured agues and intermittent disorders and had all the properties of quinine, though not always in the same degree. In his paper he advanced the argument that - "as this tree delights in a moist or wet soil, where agues chiefly abound, the general maxim, that many natural maladies carry their own cures along with them or that their remedies lie not far from their causes, was so very apposite to this particular case,....". It is a remarkable coincidence that, when Maclaglan in 1876 reported the successful use of salicin in the treatment of acute rheumatism, he gave almost the same reasons for his choice of the drug. "A low-lying, damp locality, with a cold rather than a warm climate, give the conditions under which rheumatic fever is most

readily produced. On reflection it seemed to me that the plants whose haunts best corresponded to such a description were those belonging to the natural order Salicinaceae; therefore I determined to search for a remedy for acute rheumatism among the salicinaceae, the various forms of willow". As a result of the interest aroused by this paper, Ensor (1876) drew attention to the fact that an infusion of willow tops had long been the traditional remedy for acute rheumatism amongst the Hottentots and the Dutch farmers in the interior of South Africa.

It is surprising, that the value of the salicylates in the treatment of acute rheumatism escaped notice for so long. A possible explanation is that the illness was uncommon until large numbers of countryfolk migrated to the squalor and poverty of the new industrial towns. But a more probable reason is that successful treatment was impossible in the absence of a correct diagnosis or an understanding of the natural course of the disease.

Sydenham (1848) described acute rheumatism accurately and graphically in the 17th century, but the morbid anatomists did not appreciate its relationship to disease of the heart until much later (Baillie, 1793 : Dundas, 1809).

The acuity of this observation is readily underestimated unless one remembers that Corvisart did not publicise Auenbrugger's neglected work on percussion until 1808, and that Laennec reported his discovery of the stethoscope eleven years later. Once these new methods of examination were adopted, physicians were able to diagnose the "metastases" of rheumatic fever to the heart at the bedside, instead of at autopsy. They soon realised how often rheumatism caused chronic ill health in adults but a long time elapsed before acute rheumatism and rheumatic carditis were recognized as one of the scourges of childhood.

Leonard Findlay (1931) remarked on this fact in his introduction to the "Rheumatic Infection in Childhood" and pointed out that the true incidence of the disease did not become apparent until the clinical examination of children was conducted in the same manner as the adult. This more careful examination also helped to establish the idea of the rheumatic origin of chorea. The first British paper on the relationship between chorea and rheumatism had been published by Copland in 1821 but it was not until the 1860's and 1870's that chorea, arthritis and carditis were generally recognised as being manifestations of the one disease.

The account of the action of salicin upon acute

rheumatism was published by Maclaglan (1876) at a most fortunate time. By then, the course of the disease was understood and its composite nature appreciated. The value of routine charting of the temperature as an aid to diagnosis had been accepted and the jibe that the procedure "could only amuse physicians in those little German hospitals where the number of the staff almost equalled that of the patients", had been discredited. This method showed quite clearly the striking effect of the drug upon the fever. The discovery was welcomed because the failure of 18 vaunted remedies during the preceding fifty years, had produced a sense of futility about the possibility of successful treatment (Garrod, 1890: Gull and Sutton, 1869).

Maclaglan recommended large doses and prescribed 20 - 30 grains of salicin every 2 hours for adults; and in very acute cases, the same quantity every hour until pain was relieved and the temperature normal. He expressed the opinion that if large and frequently repeated doses were accepted as the only form of treatment, valvular disease of the heart would, within the next generation, become very much less common than it had been.

At the same time as Maclaglan's empirical discovery, Kolbe announced an economical method of preparing salicylic

acid synthetically (Sollmann, 1948). Buss, in 1875, demonstrated its antipyretic action in typhoid, tuberculosis, diphtheria and in four patients suffering from acute rheumatism. A year later Stricker recognised the great therapeutic value of the drug in rheumatic fever. Both Maclaglan and Stricker believed that the salicylates were specific for the disease. Nevertheless some clinicians, who acknowledged the effect of the drug upon the joint pains and the temperature doubted whether it prevented cardiac damage. In 1881 and 1882 the Medical Society of London discussed the question whether "salicylic acid robs acute rheumatism of its main terror - the liability to heart disease"(Broadbent, 1882). Numerous papers and statistics were presented but at the end of it all the problem remained unsolved (Barlow, 1883; Coupland, 1882; Gilbart-Smith, 1882; Powell, 1882).

No such doubt troubled D.B. Lees (1908-09) who was convinced that the salicylates did more than relieve the rheumatic pain. He believed it would soon be generally accepted that salicylate was as specific against the rheumatic process, as quinine was against malaria or mercury against syphilis. He argued that the reason for unsuccessful treatment in acute and subacute rheumatism

or chorea was ineffective dosage. In a mild case, a sufficient dose was 150 grains of salicylate a day but it was often necessary to increase this to 200 grains or 250 grains and in severe cases to 400 grains per day. He had been able to raise the dose of a boy aged 15 years, with a tremendous crop of nodules to a maximum of 600 grains of salicylate with 1,200 grains of bicarbonate per day. There was no danger if certain essential precautions were observed. These were that twice as much sodium bicarbonate as sodium salicylate must be given, that the urine must be alkaline, and that the dose must not be increased unless the bowels had moved on the same day.

The inevitable reaction against such heroic treatment took place and in 1926 Hanzlik wrote in his monograph on the salicylates that the idea of the specificity of the drug had been abandoned by students and investigators of the subject. Master and Romanoff (1932) in a paper on the treatment of rheumatic fever with and without salicylates, came to the same conclusion and expressed the opinion that these drugs were not specific but "merely extremely efficient analgaesics and antipyretics for this disease."

In 1929 Swift expressed concern lest the widespread

use of salicylates had altered the clinical picture of the disease so much that few were aware of the natural course and duration of the infection. He recommended that the classification introduced by Friedlander, some fifty years earlier, should be adopted. This recognised monocyclic, polycyclic and continuous forms of the rheumatic infection. Monocylic rheumatism occurred in a third of all the victims and this group recovered without relapse in 3 weeks and escaped visceral damage. Most patients, however, fell into the polycyclic group and had recurring bouts of fever and joint pains. Cardiac damage was common. The continuous form occurred less frequently but usually affected children, who had no resistance to the disease and sustained severe injury to their hearts. Swift analysed his cases in this way and showed that salicylates were efficacious in monocyclic rheumatism, masked relapses and induced a false sense of security in the polycyclic form; and were of no benefit in the continuous type of rheumatism.

Opinion in this country has favoured the idea that salicylates are specific for the arthritis which is a manifestation of the rheumatic infection but that they do not have any beneficial effect on any other lesions. Rolleston (1928) in his Harveian Oration stated that

vigorous treatment with salicylates - "will cut short rheumatic fever and so prevent cardiac complications; but once these have begun the influence of salicylate is disappointing".

The reason for the beneficial action of the salicylates in rheumatism is not known. Stockman (1913) pointed out that salicylic acid or ortho-hydroxy-benzoic acid was formed by introducing the (OH) group into benzoic acid in the ortho position. If the (OH) was changed to the meta or para position the anti-rheumatic action was abolished and the toxicity greatly reduced.

The theories that have been advanced to explain the action of the drug all reflect the ideas about the aetiology of rheumatism prevailing at that particular time. Maclaglan (1876) thought that rheumatism and ague belonged to the same morbid group and that the specific action of the salicylates was comparable to that exerted by quinine upon malaria. The miasmatic theory was replaced by the infective theory of the disease. It received confirmation in 1900, when Poynton and Paine isolated the diplococcus rheumaticus. Lees (1908) thought that the specific action of the salicylates was due to their bactericidal properties. Hanzlik (1926) disapproved of the theory that the

bactericidal action was due to the liberation of free salicylic acid from sodium salicylate when the CO_2 tension in the blood was increased because this was only possible at a pH of the blood that was not compatible with life.

At the present time rheumatism is often regarded as a manifestation of an abnormal immune response. Great significance is attached to the similarity between the arthritis of serum sickness and acute rheumatism. Derick, Hitchcock and Swift (1928) showed that early, adequate and prolonged administration of aspirin to patients who had received injections of anti-pneumococcal horse serum, prevented the arthritis of serum sickness. They suggested that the drug reduced the amount of antibody in circulation either by diminishing its production or by altering the cell permeability so that none could diffuse into the blood. Thus passive sensitisation of the connective tissue of the joints was prevented and arthritis avoided.

Coburn and Kapp (1943) reported that sodium salicylate modified the precipitation of an antigen by inactivating the antibody. The extent of the inhibition depended on the concentration of the salicylate.

In a recent survey of the aetiology of rheumatism

Levinthal (1943) expressed the opinion that the presence of antibodies in the circulation was a valuable defense mechanism against harmful intra-cellular antigen-antibody clashes such as occur in rheumatism. Glazebrook and Cookson (1947) accepted this and pointed out that if rheumatism resulted because there was insufficient antibody to prevent an abnormal immune response, then the aim of medical treatment must either be to stimulate antibody formation or to mitigate the cellular damage. The work of Derick, Hitchcock and Swift (1928) demonstrated that the salicylate had no stimulant effect upon antibody formation but decreased the amount available. If the object was to increase antibody formation it was irrational to prescribe the salicylates. As an alternative Glazebrook and Cookson (1947) suggested that the drug prevented the damaged cell protoplasm from coagulating, its action resembling that of heparin which opposed the coagulation of the blood and of cell protoplasm and prevented the liberation of histamine. They claimed that the salicylates owed their beneficial action in rheumatism to their anti-coagulant properties.

The inhibitory effect of the salicylates upon the action of histamine has also been shown in an interesting

series of investigations on the enzyme hyaluronidase (Swyer, 1948). This enzyme is widely distributed and can be obtained from bulls' testes, umbilical cords, snake venom and from upwards of 200 strains of haemolytic streptococci. It hydrolyses the hyaluronic acid that forms the ground substance of connective tissues and favours the diffusion of bacteria and toxic substances. As rheumatism affects predominantly mesenchymal structures and usually follows streptococcal infections, it is possible that the enzyme is concerned in the production of the disease.

Guerra (1946) injected the enzyme plus an indicator such as India ink, intradermally into the shaved skin of a rabbit's abdomen, and noted the amount of spread that occurred. He found that the oral or intravenous administration of sodium salicylate decreased the spreading effect of hyaluronidase, and the degree of inhibition varied with the dose of salicylate prescribed. He also stated that the intradermal injection of hyaluronidase and Evans Blue gave "unique reactions with enormous diffusion of the dye and local oedema" in persons who either have or have had rheumatic fever. Salicylates reduced the spreading effect in these subjects.

Hechter (1946) found that the spread did not depend

upon the intradermal injection of hyaluronidase and suggested that the simple mechanical action of a local increase of interstitial pressure explained the phenomenon. The initial spread was proportional to the thickness of the bleb, and was not influenced by the salicylates. Swyer (1948) also failed to confirm Guerra's claim that sodium salicylate inhibited the skin diffusing activity. He discovered that Guerra's preparation of hyaluronidase contained histamine and that this substance by its action on the capillaries enhanced the spreading effect. The salicylates had no action upon the pure enzyme but markedly inhibited that of any preparation that contained histamine. He suggested that the salicylates antagonised the histamine.

Interest in the treatment of rheumatism with salicylates was re-awakened by the writings of Coburn (1943; 1945). This work is of importance because it introduced a simple method of determining the level of salicylate in the plasma and thereby afforded the means of discovering the optimum dosage. It also re-stated the old claim that there were good reasons for believing that salicylates suppressed the sterile inflammatory rheumatic reaction and so inhibited further cardiac damage.

In his paper Coburn described the results of an

investigation into the effect of salicylates on acute rheumatism. The work consisted of two parts. The preliminary portion was designed to show the greater efficacy of large over small doses of sodium salicylate. For this purpose 43 patients were treated with small or 'inadequate' daily doses of 3 - 6 grams whilst 18 other men received either orally or intravenously 10 grams or more of the drug per day. He found that sodium salicylate in small quantities relieved the symptoms and pyrexia, but 19 out of this group of 43 patients had polycyclic attacks of rheumatism and 16 of them developed cardiac valvular disease during the next two years. In contrast to this the 18 men treated with massive doses showed a rapid clinical recovery and all escaped valvular disease.

The second part of the paper was based on the presumption that the erythrocyte sedimentation rate expressed the degree of the rheumatic activity and that a fall in the rate indicated a suppression of the rheumatic reaction. He therefore decided to investigate the relationship between the level of salicylate in the blood plasma and the erythrocyte sedimentation rate. Two groups of 20 patients were selected. The first contained those, with proven polycyclic attacks, who had been receiving 6 grams or less of sodium salicylate per day. In these

cases the levels of salicylate in the plasma varied between 0 - 25 mgms. per cent. Whilst on this course of treatment the erythrocyte sedimentation rates had fluctuated and been raised on an average for 49 days and, at its conclusion, the rates were not only still elevated but showed no tendency to a progressive fall. From this it was deduced that doses of less than 6 grams per day were inadequate and that though plasma levels of less than 25 mgms. per 100 ml. sufficed to alleviate symptoms they had no effect on the suppression of the rheumatic reaction. The sodium salicylate was then increased to a minimum of 10 grams per day, either orally or intravenously, and as a result the erythrocyte sedimentation rate fell promptly to normal. Hence these massive doses, that achieved levels of salicylate in the plasma between 35 - 50 mgms. per cent., were believed to suppress the cardiac damage. The second group contained only those patients whose first attack was so severe that it was unlikely to be monocyclic. They received 10 grams of sodium salicylate, either orally or intravenously, from the time of starting treatment and attained plasma levels of at least 35 mgms. per cent. Within 6 days their erythrocyte sedimentation rate began to fall progressively and reached normal within 21 days. All these patients escaped valvular heart

disease.

From this Coburn concluded that levels of at least 35 mgms. per cent caused a rapid fall of the erythrocyte sedimentation rate to normal and were necessary to suppress the rheumatic reaction. Levels below 20.0 mgms. per cent relieved symptoms but masked the rheumatic process.

By combining these two series it will be seen that 38 patients, composed of 18 from the preliminary study and the group of 20 in his later study, received large doses from the onset of treatment. All these escaped valvular damage. The remaining 63 patients were 43 from the initial experiment and 20 from the second study, who had received either inadequate dosage throughout their course, or for several weeks before the sodium salicylate was increased to the required minimum of 10 grams per day. Physical signs of heart disease developed in 21 out of the 63 in this group.

Coburn estimated that the daily oral dosage necessary for the maintenance of an adequate blood level varied between 0.13 and 0.19 grams per kilogram of body weight, or approximately 1½ grains per pound of body weight. This gave very satisfactory results but intravenous infusions produced the desired level more rapidly. He therefore

recommended the following schedule of treatment :-

"Day 1 .... 10 grams of sodium salicylate in 1000 cc. of 0.9% NaCl by I.V. drip in 4 - 6 hours.

Day 2 .... If any rheumatic symptoms persisted or if the temperature has not reached normal, 20 grams of sodium salicylate are given in 2000 cc. of 0.9% NaCl in 8 hours.

Day 3 .... Repeat day 2 if necessary. If afebrile and symptom free 10 grams of sodium salicylate is adequate.

Day 4 - 6 Sodium salicylate infusions continued until the E.S.R. has made a 20% drop.

Day 7 - 30 Oral therapy replaces I.V. therapy. Doses of 1.6 gram of sodium salicylate and 0.6 gram of sodium bicarbonate are administered every four hours day and night. A total of 10 grams of sodium salicylate is given daily.

Day 30 ... After two weeks or more in which the E.S.R. is within normal limits the patient is allowed a trial week in bed without salicylates. If still symptom-free and the E.S.R. is still normal the patient is allowed up progressively. If frank symptoms develop then another 2 weeks therapy is indicated."

In a later paper Coburn (1945) stressed the point that salicylate was not the final answer to the problem of the treatment of rheumatism. It did not cure but reduced the liability to valvular damage of the heart by suppressing the inflammatory process. Massive salicylate therapy was only a part of the treatment of the disease. He believed that proper care should be modelled on the routine adopted

by the U.S. Navy. This consisted of admission to hospital at the onset of the rheumatic attack and adequate salicylate therapy to cause a rapid and progressive fall in the sedimentation rate. Once this had been achieved the patient was transferred by air to California where he was exposed to increasing amounts of sunlight and allowed a carefully controlled resumption of physical activity.

In considering Coburn's views it must be borne in mind that he treated young adults between 17 and 28 years of age. It is well known that this age group tends to have monocyclic attacks of rheumatic fever and that the fatality rate is low and the likelihood of valvular disease is small. An accurate, long term comparison of the frequency of cardiac damage in adults and children is complicated by the increased liability of the latter to recurrent attacks of the disease.

De Liee, Dodge and McEwan (1943) pointed out that this difficulty could be obviated by analysing first attacks only. In a survey of the literature they showed that the incidence was greatly increased in childhood; and this was borne out in their own series of cases in which persistent carditis was four times more common under the age of 12 years than in adults over 25 years of age. Leonard Findlay (1931) stated that:- " the smallest number of deaths and the

longest duration of the cardiac infection occurred when the rheumatism was contracted between 20 and 30 years of age." In an adult the arthritic manifestations are prominent and acute and the patient is forced to seek early medical attention. This fact was commented on by Manchester (1946) who found that the severity of the acute manifestations compelled soldiers and sailors to report sick before irreparable visceral damage occurred or the infection became chronic.

In childhood this is not the case and the transient pains are either not noticed or neglected and, all too frequently, the child is either brought to the doctor only when cardiac damage is far advanced. This aspect of the problem is illustrated by the analysis of 1,000 consecutive cases of juvenile rheumatism quoted by Thornton in the chapter on Supervisory Centres in the Practitioner Handbook on Child Health.

Acute polyarthritis	18.5%
Subacute rheumatism (includes insidious carditis) ..	52.0%
Chorea	19.0%
Chorea with concurrent subacute rheumatism	10.5%

It is thus seen that in many cases the damage has already been done and it is too late to suppress the inflammatory reaction. Therefore, it becomes a matter

of great urgency that the early stages of the rheumatic infection in childhood should be recognized and treatment begun at once.

Far more attention has been devoted to that part of Coburn's paper concerned with the effect of massive doses of salicylate upon the erythrocyte sedimentation rate than to his claim that cardiac valvular disease could be prevented or its extent limited. One reason for this is the long period of time that must elapse before clinical signs of the lesions develop. It is only now that the publication of such studies subsequent to massive salicylate therapy, can be expected. Another difficulty has been the existence of the different standards of assessing the activity or quiescence of the disease or the extent of the valvular scarring. This has always been a problem in rheumatism. It is a valid criticism of Coburn's results that no criteria of valvular disease or of the signs of heart disease are given. When he claims that in the group of twenty patients, with "attacks so severe that it seemed unlikely that they would be monocyclic", there were no residual cardiac valvular disorders at the end of a period of two years, one cannot help feeling that widely different standards are responsible for many of the divergent results and claims.

THE PRESENT INVESTIGATION.

It is obvious that despite all the investigations of the past seventy years, the problem of how the salicylates relieve the symptoms of acute arthritis remains unsolved. Many theories have been advanced but none is very convincing. Coburn's confident assertion that massive doses of salicylate would suppress the rheumatic reaction provided a fresh impetus for further studies. In some of these his claims have been criticised but even if only a proportion of cases escape valvular damage the use of large doses would be justified. Up to the present most investigations have been made on acute rheumatism in young adults. It is of even greater importance that massive salicylate treatment of rheumatism should be studied in children in whom, as has already been indicated, the disease is so much more dangerous and so often the precursor of the cardiac damage seen in adult life.

This study was planned to determine whether children would tolerate large doses such as Coburn advocates; the frequency of toxic symptoms; and the most suitable system of administration. Observations have also been made on the effect of "adequate" concentrations of salicylate in the plasma upon the erythrocyte sedimentation rate. In

the course of these investigations the opportunity arose to make some studies on rheumatic pneumonia and a short account of these is included. Unfortunately it has not been possible in the time available to follow up the cases for a long enough period and therefore the claim that cardiac damage can be limited by massive salicylate therapy has not been considered.

The subjects of these studies were thirty two children, eighteen boys and fourteen girls, between $4\frac{1}{2}$ and $12\frac{3}{4}$ years of age who were suffering from acute rheumatism. In addition six estimations of the concentration of salicylate in the plasma of five other children suffering from acute rheumatism who were treated with a mixture containing one part of sodium salicylate and two parts of sodium bicarbonate are included in Chart 6. The period of study was from November, 1947 to December, 1948. Facilities for this were kindly provided by Professor Stanley Graham in his wards in the Royal Hospital for Sick Children, Glasgow, and for the biochemical estimations by Dr. H.E. Wilson in the Biochemical Laboratory of the same hospital.

Salicylate estimations in the plasma were carried out according to the method described by A.F. Coburn (1943): the free salicylate in the urine by that of Smith, Gleason, Stoll and Ogorzelek (1946): the erythrocyte sedimentation

rates of the patients by the Westergren method. In those experiments on the erythrocyte sedimentation rate in which sodium salicylate was added to plasma according to the method described by Homburger (1946), the sedimentation rate was measured by the Wintrobe method and "corrected" from Whitby and Britton's chart (1942). All these estimations were made by the writer.

THE EFFECT OF SINGLE AND REPEATED DOSES OF SODIUM BICARBONATE UPON THE CONCENTRATION OF SALICYLATE IN THE BLOOD.

INVESTIGATION.

A knowledge of the concentrations of salicylate in the blood plasma after single doses of salicylate is important if the massive dosage suggested by Coburn (1943) is to be employed. Smith et al. (1946), Lester et al. (1946), Huntington et al. (1946), have all shown that the addition of sodium bicarbonate has little influence upon the levels of salicylate in the blood after single doses of the drugs. It was decided to check these findings. The levels of salicylate in the blood of two healthy subjects were investigated after single doses of sodium salicylate, a sodium salicylate-sodium bicarbonate mixture, and acetylsalicylic acid (Charts 1 & 2). Salicylate is usually administered at four hourly intervals and so, the total daily dose of the drug was calculated by means of the formula of 1½ grains per pound of body weight that was recommended by Coburn, and one sixth of this was given in each experiment. The levels of salicylate in the plasma were estimated every hour during the first four hours and at the end of nine hours.

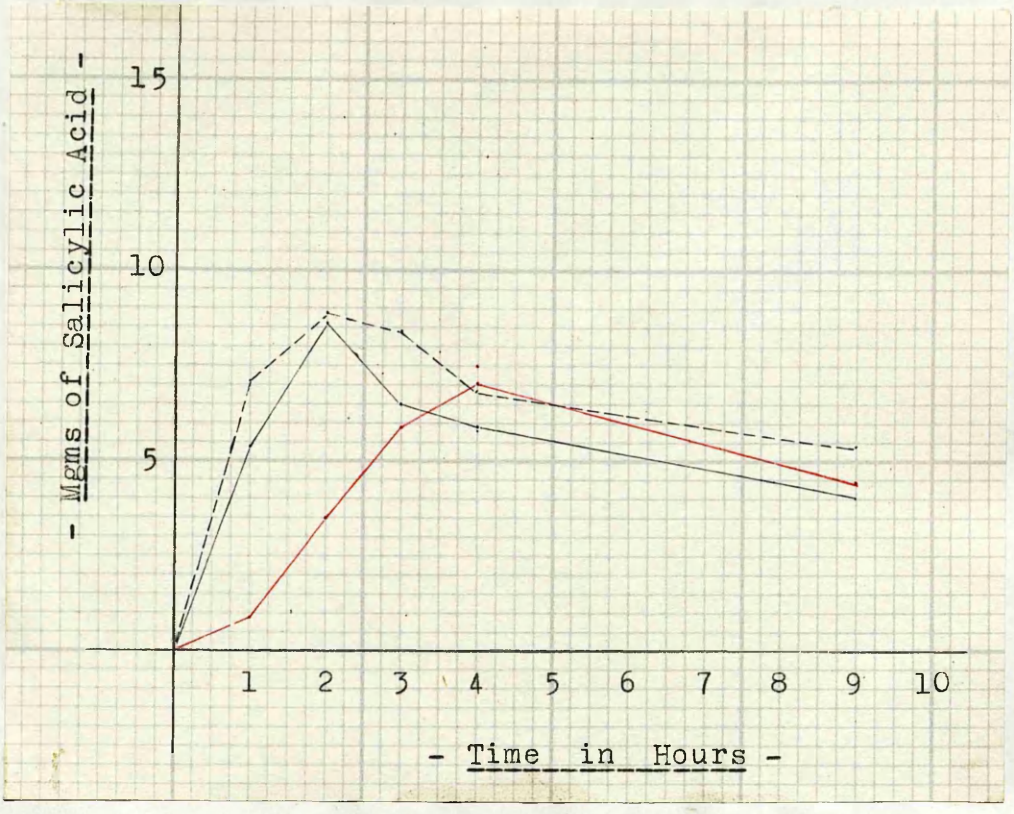


CHART 1.

The concentrations of salicylate in the plasma of a child after single doses of sodium salicylate, a sodium salicylate-sodium bicarbonate mixture, and acetylsalicylic acid, 1½ grains/pound/ day in each instance.

——— Sodium salicylate.

-------- Sodium salicylate-sodium bicarbonate mixture.

——— Acetylsalicylic acid (crushed).

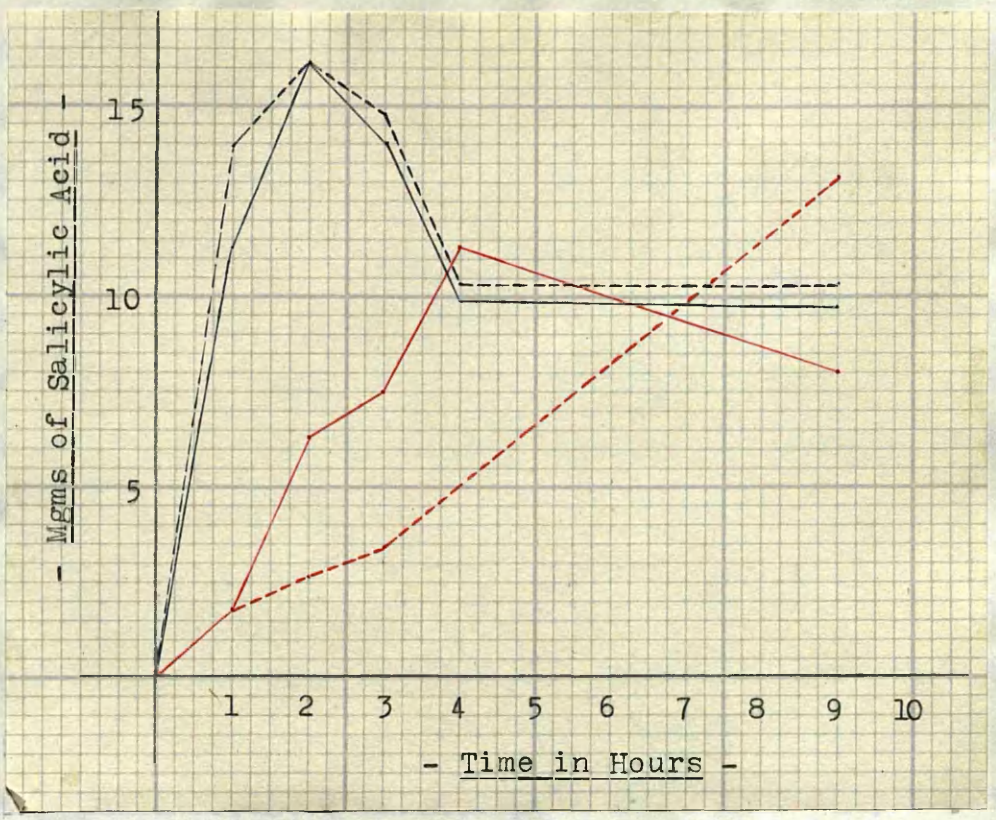


CHART 2.

The concentrations of salicylate in the plasma of an adult after single doses of sodium salicylate, a sodium salicylate-sodium bicarbonate mixture, and acetylsalicylic acid, 1½ grains/pound/ day in each instance.

——— Sodium salicylate.

-------- Sodium salicylate-sodium bicarbonate mixture.

——— Acetylsalicylic acid (crushed).

------- Acetylsalicylic acid (uncrushed).

The pattern of the absorption curves was similar in both subjects. In each, the sodium salicylate and the sodium salicylate-sodium bicarbonate mixture produced almost identical levels of salicylate in the plasma; they reached a peak within two hours and then fell slowly so that at the end of six hours a considerable concentration persisted in the blood. The acetylsalicylic acid was absorbed less rapidly and the maximum was reached after four hours when a gradual decline began.

The usual practice was to crush the aspirin tablets before their administration but on one occasion (Chart 2) they were swallowed whole. A prolonged delay in absorption resulted and the peak level of salicylate in the blood was not attained for nine hours.

On account of this delay further absorption curves were estimated after single doses of crushed acetylsalicylic acid tablets had been given to children (Chart 3). The individual doses were calculated in the same manner as before. The results confirmed that the peak level was usually reached four hours after the dose had been given though there was some variation in the rate of absorption. The presence of satisfactory levels after six hours was of considerable practical importance because this justified

the prescription of the drug at six hourly intervals.

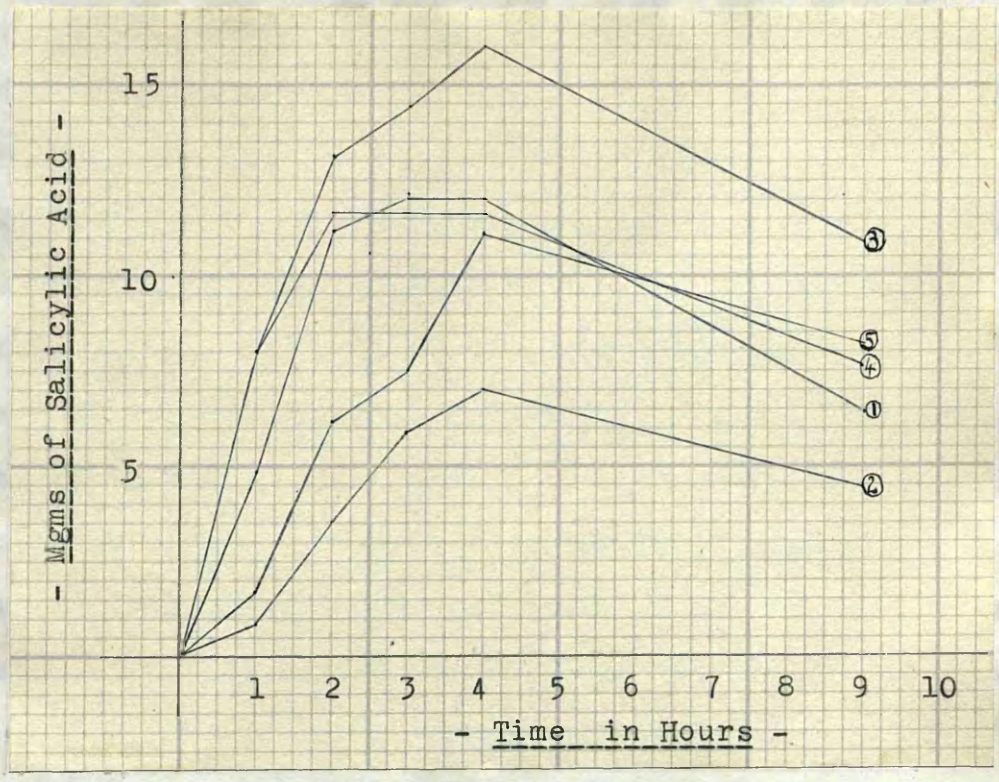


CHART 3.

The concentrations of salicylate in the plasma of 5 patients dosed with 1½ grains of crushed acetylsalicylic acid per pound of body weight per day.

Though the addition of a single dose of sodium bicarbonate has been shown to have little effect upon the level of salicylate in the blood, this does not necessarily apply during long continued administration. Smull, Wegria and Leland (1944) observed that the addition of sodium bicarbonate caused a considerable drop in the previously constant serum salicylate concentrations. Smith, Gleason et al. (1946) adapted Coburn's method of estimating the

level of salicylate in the plasma so that it was possible to determine the amount of free salicylate, salicylurates and total salicylates in the urine. They showed that the fall in the level of salicylate in the plasma after administration of alkali was accompanied by an increased excretion of salicylate in the urine, and particularly of free salicylate. It was therefore decided to study in two children suffering from acute rheumatism the effect on the level of salicylate in the plasma of repeated doses of alkali, and to make use of the above method for the estimation of the free salicylate in the urine. Attention was restricted to the excretion of the free salicylate fraction in the urine because of the difficulty in obtaining the reagent ethylene dichloride. In one of the children the effect of increasing the acidity of the blood was also investigated.

The first child (M.McD. Chart 4) had maintained, on a constant dose of salicylate, an average blood salicylate level of about 25 mgms. per cent without any wide fluctuations. Thirty grains (2 Gms.) of ammonium chloride were added and at the end of a week the level of salicylate in the blood had almost doubled. The ammonium chloride was then replaced by sodium bicarbonate with the result that the pH of the urine rose, the amount of free salicylate excreted in the urine increased and the level of salicylate in the plasma

fell. As soon as the sodium bicarbonate was discontinued, the pH of the urine was reduced, the amount of free salicylate in the urine diminished and the level of salicylate in the plasma rose to its former level.

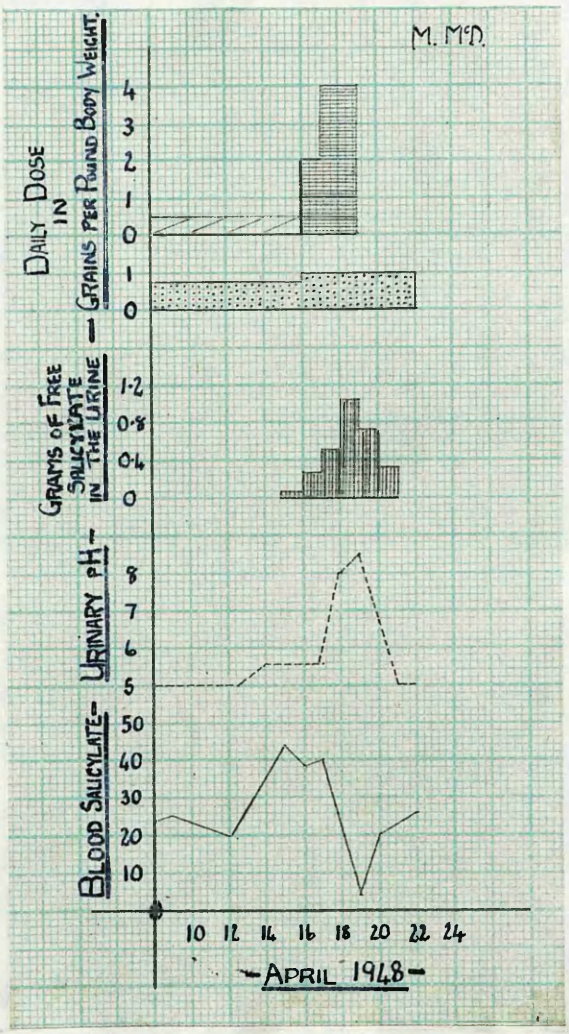


CHART 4.

The effect of oral doses of sodium bicarbonate upon the level of salicylate in the blood; upon the excretion of free salicylate in the urine; and upon the urinary pH.

... Sodium bicarbonate ... Ammonium chloride

... Acetylsalicylic acid.

The very close relationship that exists between the excretion of free salicylate and the pH of the urine was shown even more clearly in the case of W.G. (Chart 5).

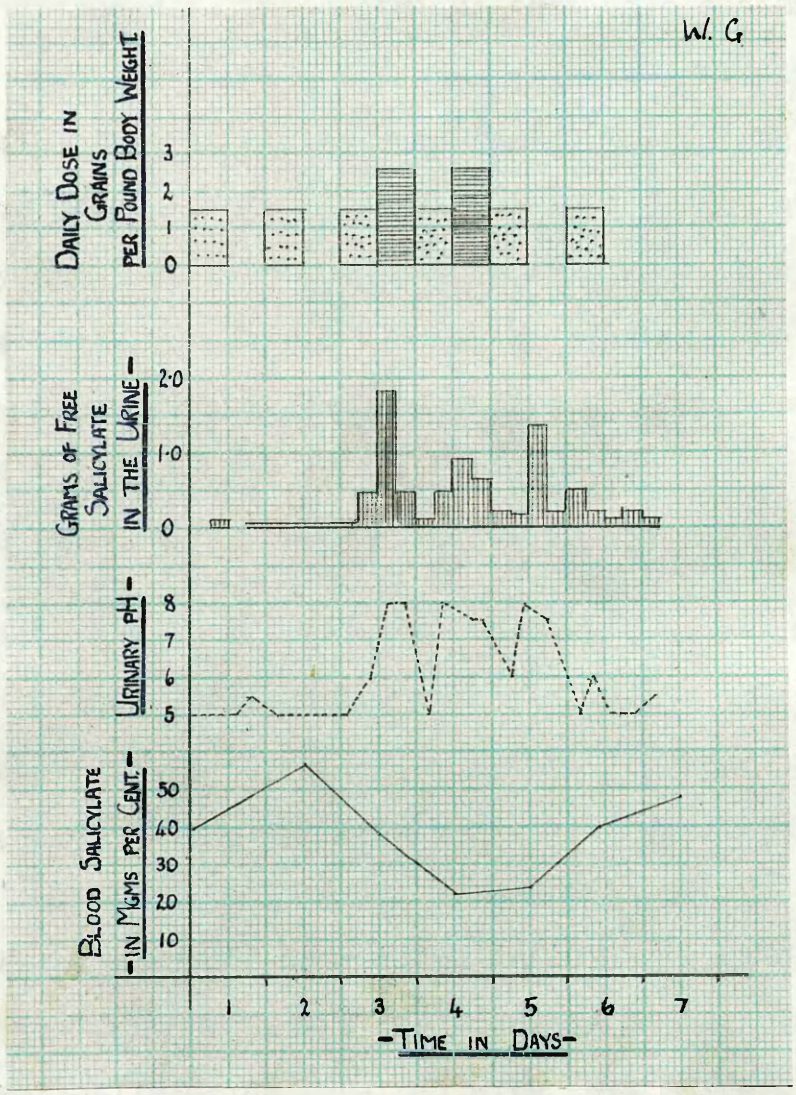


CHART 5.

The effect of oral doses of sodium bicarbonate upon the level of salicylate in the blood; upon the excretion of free salicylate in the urine; and upon the urinary pH.

... Sodium bicarbonate ... Acetylsalicylic acid.

All the urine passed during six days was collected in consecutive periods of six hours. In each specimen the quantity of free salicylate was estimated and the pH of the urine was measured. It is obvious that when sodium bicarbonate is given it has a rapid but transitory effect in reducing the level of plasma salicylate, and in increasing both the urinary pH and the output of free salicylate. Conversely, as soon as the alkali is withdrawn, the earlier levels are quickly restored. And the effect can be enhanced by giving the child ammonium chloride which, without alteration of the dose of salicylate, produces a rise in plasma salicylate and minimal urinary output.

For many years, it has been the custom at the Royal Hospital for Sick Children to prescribe sodium salicylate together with double the quantity of sodium bicarbonate. This has proved very satisfactory in that toxic symptoms have been infrequent and mild. The effect of doses of sodium bicarbonate upon the concentration of salicylate in the blood indicated the need to determine if satisfactory levels were really being obtained with this mixture. Therefore the levels of salicylate in the blood of a group of patients, who were being treated for rheumatic fever with a mixture containing one part of sodium salicylate to two parts of sodium bicarbonate, were estimated. The results were

disappointing because the concentration of salicylate in the plasma rarely exceeded 30 mgms. per 100 ml. and the curve often showed a tendency to fall rather than to rise. The distribution of the levels is shown in Chart 6. Obviously they are widely scattered. The average level does not rise much with increase of salicylate intake, being 15 mgms with a dosage of 1 gr. per lb. and only 22 mgms per 100 ml. with dosage of 1½ gr. per lb. per day.

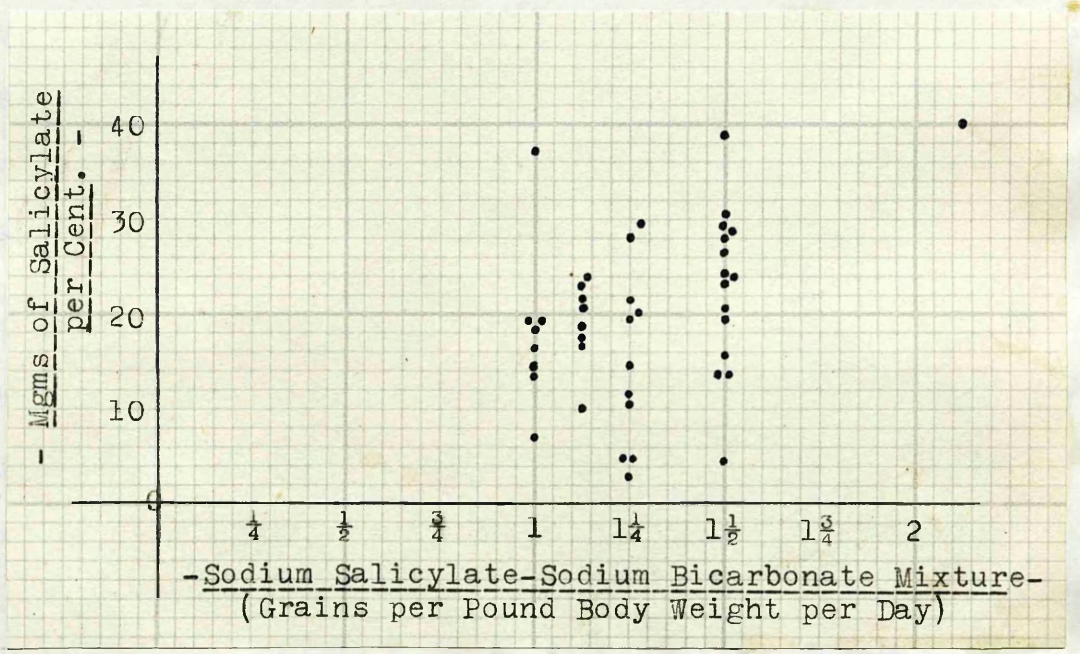


CHART 6.

The distribution of the levels of salicylate in the plasma of 17 rheumatic children treated with routine doses of a sodium salicylate-sodium bicarbonate mixture based upon their body weight.

There were two possible reasons for these results. One was that the dose of sodium salicylate was inadequate and the other that the amount of sodium bicarbonate in the mixture was excessive. The previous experiments had suggested that the latter was most probable and so the proportion of sodium bicarbonate was reduced either to equal the sodium salicylate or to half that amount. The alteration in a long established practice led to confusion and misunderstanding by the nursing staff and the attempt to obtain reliable information in this direction had to be abandoned. Instead the sodium salicylate-sodium bicarbonate mixtures were replaced by 5 grain tablets of acetylsalicylic acid. These were given without bicarbonate.

As soon as acetylsalicylic acid was substituted for the sodium salicylate-sodium bicarbonate mixture, without any increase in dosage, a marked improvement in the blood salicylate levels was noticed. Adequate levels were frequently attained. The concentrations in the blood after differing amounts of acetylsalicylic acid are shown in Chart 7. It is apparent that withdrawal of the alkali raised the plasma salicylate from the previous average figure of 15 mgms to 30 mgms, with an intake of 1 gr. per lb. per day; and from 22 mgms to 40 mgms per 100 ml., with an intake of 1½ gr. per lb. per day.

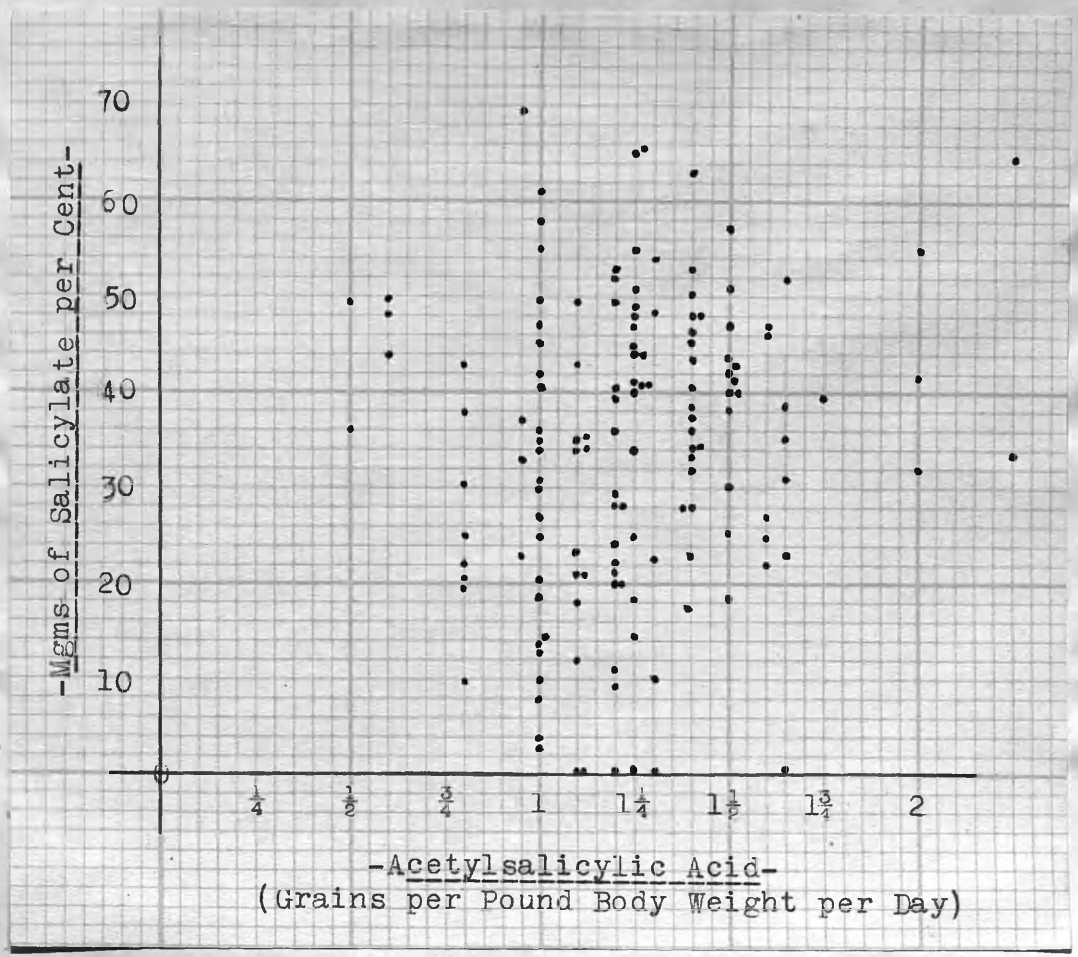


CHART 7.

The distribution of the levels of salicylate in the plasma of 25 rheumatic children treated with routine doses of acetylsalicylic acid based on their body weight.

DISCUSSION.

An important feature of Coburn's "rational treatment" of rheumatic fever is the necessity of building up rapidly a blood salicylate concentration of at least 35 mgms per cent. Various authors have suggested that the presence of

sodium bicarbonate in the traditional sodium salicylate mixture accelerated absorption. This affords a more acceptable explanation of the clinical custom of prescribing sodium bicarbonate in equal or double the quantity of sodium salicylate, than the original, but now rejected belief, that it protects the gastric mucosa. In an interesting paper Lolli and Smith (1946) claimed that carbon dioxide hastened gastric emptying and accelerated absorption. They stated that a moderate amount of sodium bicarbonate - "exerts an action substantially the same as that of an effervescent mixture" because carbon dioxide is liberated by the reaction of the hydrochloric acid of the gastric juice with the bicarbonate. As a result of the rapid emptying of the stomach, contact of the irritant with the sensitive gastric mucosa is reduced and the rate of absorption of salicylates from the intestine is increased.

This is a neat and attractive theory but it is not supported by the present investigation. Charts 1 and 2 show that sodium bicarbonate did not increase the rate of absorption of sodium salicylate. Indeed the curves that represent the concentration of salicylate in the plasma after a dose of sodium salicylate and the sodium salicylate-sodium bicarbonate mixture are practically identical.

It is evident that even without the help of sodium bicarbonate, the absorption of salicylate is rapid. In the case of sodium salicylate the concentration in the blood reaches a peak within two hours but acetylsalicylic acid is absorbed more slowly and the maximum concentration is only reached after four hours. The generally accepted conception is, that acetylsalicylic acid is decomposed almost entirely in the intestine, and its action is dependent on the liberation of salicylate. Smith, Gleason et al. (1946) stated - "the slower rise of the plasma salicylate curve after aspirin than after sodium salicylate suggests that acetylsalicylic acid may be hydrolyzed first before absorption". Another feature is that the concentration of salicylate in the plasma is slightly lower after a dose of acetylsalicylic acid than after sodium salicylate. This difference can be explained by the fact that acetylsalicylic acid contains only 4/5 ths as much salicyl as an equal quantity of sodium salicylate.

These findings correspond closely with those of Smith et al. (1946). They gave 2 grams of either sodium salicylate or acetylsalicylic acid to aviation students two hours after breakfast. In the case of sodium salicylate appreciable levels were found in the plasma within half an hour; the peak level averaged about 15 mgms per cent and

occurred after two hours and thereafter fell slowly. Acetylsalicylic acid produced a much slower rise and the average maximum level of about 10 mgms per cent was reached only after four hours and remained constant during the succeeding four hours. Lester et al. (1943) found that the maximum concentration reached after the ingestion of 0.65 grams was of the order of 4 mgms per cent and after 1.30 grams 8 mgms per cent. Huntington et al. (1946) showed that a single dose of 50 grains (3.3 grams) of aspirin or sodium salicylate with or without an equal quantity of sodium bicarbonate rapidly produced levels of 19 mgms per cent and in many instances there was considerable circulating salicylate at the end of fifteen minutes.

The salicylates are absorbed in varying degrees from the skin and mucous membranes, but the most effective site is the small intestine. When the drug is swallowed it is practically all absorbed in the small intestine and the amount excreted in the faeces is negligible. Hanzlik (1926) stated that the faeces, as a rule, were free from salicyl even after large doses and Coburn (1943) confirmed this opinion. The only exception occurs when the absorption from the small intestine is hindered by a protective coating. Huntington et al. (1946) refer to an "unfortunate experience" in which the use of keratin coated capsules of sodium salicylate led to an accumulation in the lower gut and the

sudden production of dangerous blood levels. Yet a delay in the absorption of the salicylates may be due to other factors. There is an interesting curve in Chart 2 which shows that after the administration of a single dose of uncrushed aspirin tablets, there was a prolonged delay in absorption. As a result of this experience, it is recommended that the tablets should be crushed before a large dose is administered.

Many years ago Morris and Graham (1931) drew attention to the fact that sodium bicarbonate increased the excretion of salicylate in the urine. They attributed this to the fact that the sodium bicarbonate prevented an impairment of the kidney function. The introduction of Coburn's method of estimating the level of salicylate in the blood was soon followed by the accidental observation of Smull, Wegria and Leland (1944) that sodium bicarbonate caused an abrupt fall in the concentration of salicylate in the blood. They investigated the matter more carefully and showed clearly that the concentration in the blood fell whilst sodium bicarbonate was being administered and rose again when it was stopped. Caravati and Cosgrove (1946) confirmed this and wrote - "the administration of sodium bicarbonate will increase the urinary excretion of salicylate promptly, and in general, the higher the pH of the urine,

the greater the excretion of salicylate." Smith et al. (1946) found that the administration of sodium bicarbonate along with salicylate produced lower levels than when salicylate was given alone. The increased excretion was confined to the free salicylate fraction and rose rapidly as the urinary pH rose above 7.

Similar results were obtained in this investigation and are recorded in Charts 4 and 5. They show that :-

1) Administration of sodium bicarbonate causes a fall in the level of salicylate in the plasma.

2) The fall in the level of salicylate in the plasma, is accompanied by an increased excretion of free salicylate in the urine.

3) The excretion of free salicylate in the urine varies according to the pH of the urine.

These observations explain why, though he was unaware of the implications, Lees (1908-09) insisted that twice as much sodium bicarbonate as sodium salicylate must be given, and that the urine must be rendered alkaline. It was only because of the alkalinisation that he was able to give with safety to a boy of 16 years the enormous dose of 600 grains (40 grams) of sodium salicylate per day. The blood levels attained with this heroic dosage could

have been reached more cheaply, safely, and quickly with the intake of a small fraction of the amount given.

A comparison of Charts 6 and 7 shows that the sodium bicarbonate-sodium salicylate mixture produced consistently lower levels than acetylsalicylic acid given alone and affords another demonstration of the effect of sodium bicarbonate upon the concentration of salicylate in the blood. The daily dose of 1½ grains of salicylate per pound of body weight, in the sodium bicarbonate-sodium salicylate mixture, rarely produced a level above 30 mgms per cent. This contrasts with Coburn's statement that levels of 35 - 50 mgms per cent could be attained with this amount of salicylate. However, there was the important difference that he prescribed one part of sodium bicarbonate and two parts of sodium salicylate whilst in this investigation the proportions were reversed. This suggests that the unsatisfactory levels in the blood recorded in Chart 6 are due to the large proportion of sodium bicarbonate in the mixture. Indeed Huntington, Ryan et al. (1946) saw no reason for giving more than 60 grains of sodium bicarbonate daily. It is significant that when a dose of 1 1/4 grains of acetylsalicylic acid was given without alkali, this often sufficed to maintain a level of 35 - 50 mgms per cent though this form of the drug only contains 4/5ths as much

salicyl as does sodium salicylate. Glazebrook and Cookson (1947) have stated that a daily dose of 8 grams (120 grains) of sodium salicylate will produce a plasma level of 36 mgms per cent in the average adult; but that if an equal dose of bicarbonate be given with the salicylate, then the daily dose of salicylate must be increased to 12 grams (180 grains) to obtain the same plasma concentrations.

SUMMARY.

1. The concentrations of salicylate in the blood produced by single doses of sodium salicylate, and a mixture containing equal parts of sodium salicylate and sodium bicarbonate were almost identical. Maximum levels were reached in two hours and a slow decline began after four hours.

2. The concentrations of salicylate in the blood produced by single doses of acetylsalicylic acid were lower than those obtained by the same dose of sodium salicylate or a sodium salicylate mixture. Maximum levels were reached after four hours: thereafter the fall was so slow that six hourly dosage of acetylsalicylic acid was possible. Acetylsalicylic acid tablets must be crushed to avoid delayed absorption.

3. The prolonged administration of sodium bicarbonate caused a fall in the level of salicylate in the blood. Continued intake of ammonium chloride has the opposite effect. When alkali was given there was an increased excretion of free salicylate in the urine and this varied according to the pH of the urine.

4. Doses up to 1½ grains per pound body weight per day of a mixture containing one part of sodium salicylate and two parts of sodium bicarbonate failed to produce adequate concentrations in the blood.

5. Six-hourly doses of 1 - 1½ grains per pound of body weight per day of acetylsalicylic acid frequently produced adequate concentrations in the blood, and the average blood levels obtained in a large series of observations was much higher than when comparable doses of salicylate-sodium bicarbonate mixtures were given. The increase in level was from an average of 15 to 22 mgms., with alkali, to 30 to 40 mgms., without alkali.

6. It would appear, from these findings, that children require similar doses of salicylates to adults to enable a concentration in the blood to be attained which would satisfy Coburn's stipulations for the successful treatment of rheumatism, and that the salicylate should be given without alkali.

THE MAINTENANCE OF MASSIVE SALICYLATE THERAPY AND OF A HIGH BLOOD SALICYLATE LEVEL OVER A PROLONGED PERIOD.

There is not much information, obtainable from the literature, on the course of events when continued massive doses of salicylate are given to children suffering from acute rheumatism. Much has been written about the treatment of young adults but the dosage suitable for them does not necessarily apply to children. There is general agreement that when adults are treated with massive doses of salicylate, adequate concentrations in the blood are both attained and maintained without much trouble or difficulty. But amongst those who have had experience with children, there is less uniformity of opinion. It has been shown in the previous section of this paper that the required levels can be attained. It is important to learn what happens when they are maintained for some time.

Taran and Jacobs (1945) found that when equal parts of sodium bicarbonate and sodium salicylate were prescribed for children in oral doses of 1½ grains per pound (0.22 Gm per Kilo) of body weight per day, there were no difficulties in keeping adequate blood levels. Fashena and Walker (1944) found that doses of 0.2 - 0.22 grams of sodium salicylate per kilogram were needed during the

initial 24 hours and that the amount could then be reduced to 0.15 - 0.17 gram per kilogram of body weight without a fall of the blood level. Acutely ill patients were more inclined to show signs of salicylate intoxication than convalescent children. Stevens and Kaplan (1945) decided that the dosages and blood levels recommended for young adults, i.e. 1½ grains per pound (0.22 Gms. per Kilo.) of body weight per day, cannot be prescribed for children with safety. Dubow and Solomon (1948) concluded that if either sodium salicylate or acetylsalicylic acid was prescribed, without sodium bicarbonate, for children between 4 - 11 years, then 0.15 gram per kilogram of body weight maintained a satisfactory therapeutic level for a long period; and 0.10 gram per kilogram of body weight was insufficient. Maggioni (1948) aimed at a level of 25 mgms. per 100 ml. or higher and obtained this with a total daily dosage of 0.12 - 0.18 grams per kilogram of body weight. Wegria and Smull (1945) treated children with enteric coated tablets containing 0.3 gram of sodium salicylate and found that by this means vomiting was almost entirely eliminated. High levels of salicylate in the plasma were obtained only by doubling the estimated maintenance dose (1½ grains per pound or 0.22 gram per kilogram of body weight per day) for the first four doses.

Coburn (1943) believed that it was important to achieve a level of at least 35 mgms. per cent quickly if the liability to cardiac damage was to be limited. Because of this the recommendation of Wegria and Smull (1945) that the first four doses should be doubled was adopted. The size of each dose was calculated from the daily requirement of 0.22 gram per kilogram of body weight.

Five children suffering from acute rheumatism were treated in this way with four-hourly doses of acetylsalicylic acid. A high concentration of salicylate in the blood was achieved rapidly, but it involved the use of such enormous doses of acetylsalicylic acid that the writer was unable to avoid a sense of anxiety. There was no means of judging what the response of each new patient would be. Blood levels varied widely; some bordered on Coburn's minimum adequate level of 35 mgms. per cent whilst others exceeded his maximum figure of 50 mgms. per cent. It was felt that this scheme of treatment was dangerous and invited the occurrence of the graver forms of salicylate poisoning. Chart 8 shows the marked variations in the early levels and the difficulty of avoiding large fluctuations.

Therefore, it was no longer considered essential to

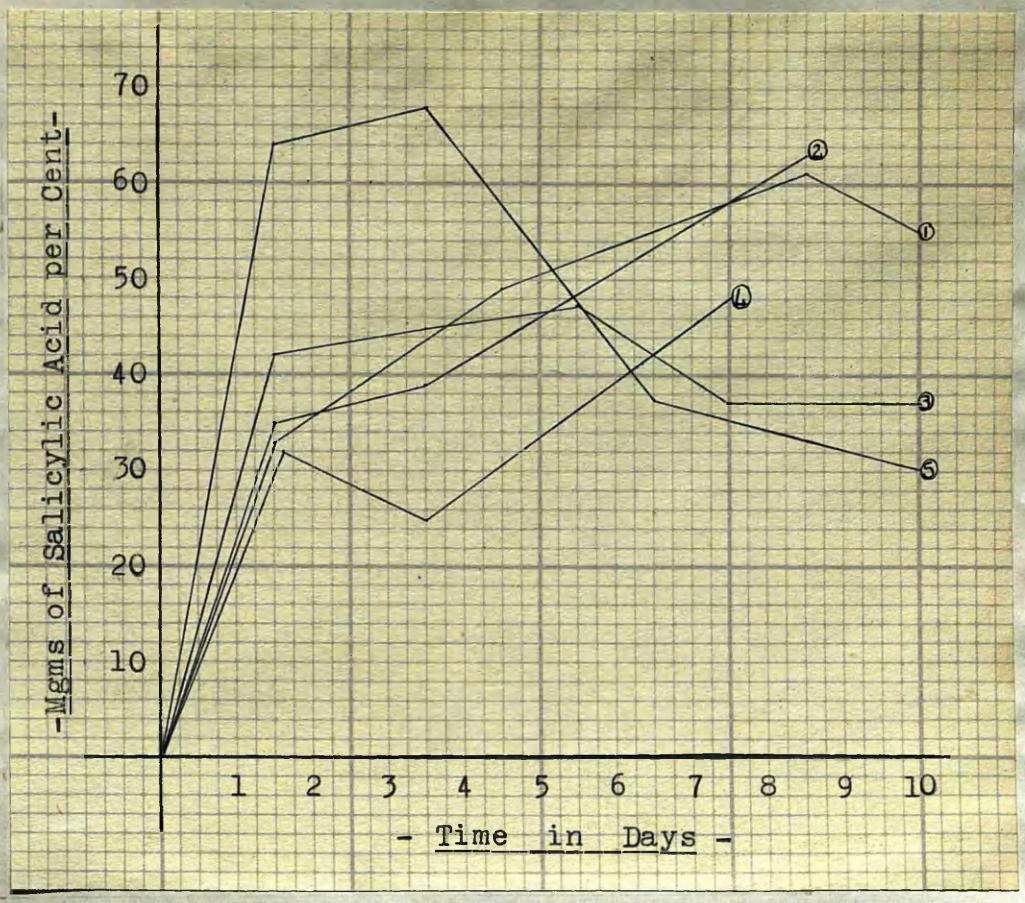


CHART 8.

The wide variation in the levels of blood salicylate produced by a scheme of dosage based on the recommendations of Wegria and Smull.

achieve a minimum level of salicylate in the blood of 35 mgms. per 100 ml. within the first 24 - 48 hours, but rather to delay this until the third day or even longer. The prescription of 1½ grains of acetylsalicylic acid per pound of body weight (0.22 gram per kilogram) for two or three days was a sufficient loading dose and it was then reduced to 1 1/4 grains or less per pound of body weight (0.18 gram per kilogram) per day. By this means satisfactory treatment was possible and the blood levels were usually stabilised between 40 and 50 mgms per 100 ml. (Chart 9). The concentrations of salicylate in the blood during the first ten days of the courses are shown. In the case of curve 6 sodium bicarbonate was added during the period shown by the broken line and the effect of this in lowering the level of salicylate in the blood is clearly demonstrated.

The success of any system of dosage depends largely upon the degree of supervision that is exercised. For this reason an effort was made to keep all the children who were being treated with massive doses of salicylate in the Royal Hospital for Sick Children itself, but it was sometimes necessary to transfer patients to the Country Branch before their course was completed. There the majority of the patients were convalescent and the nursing

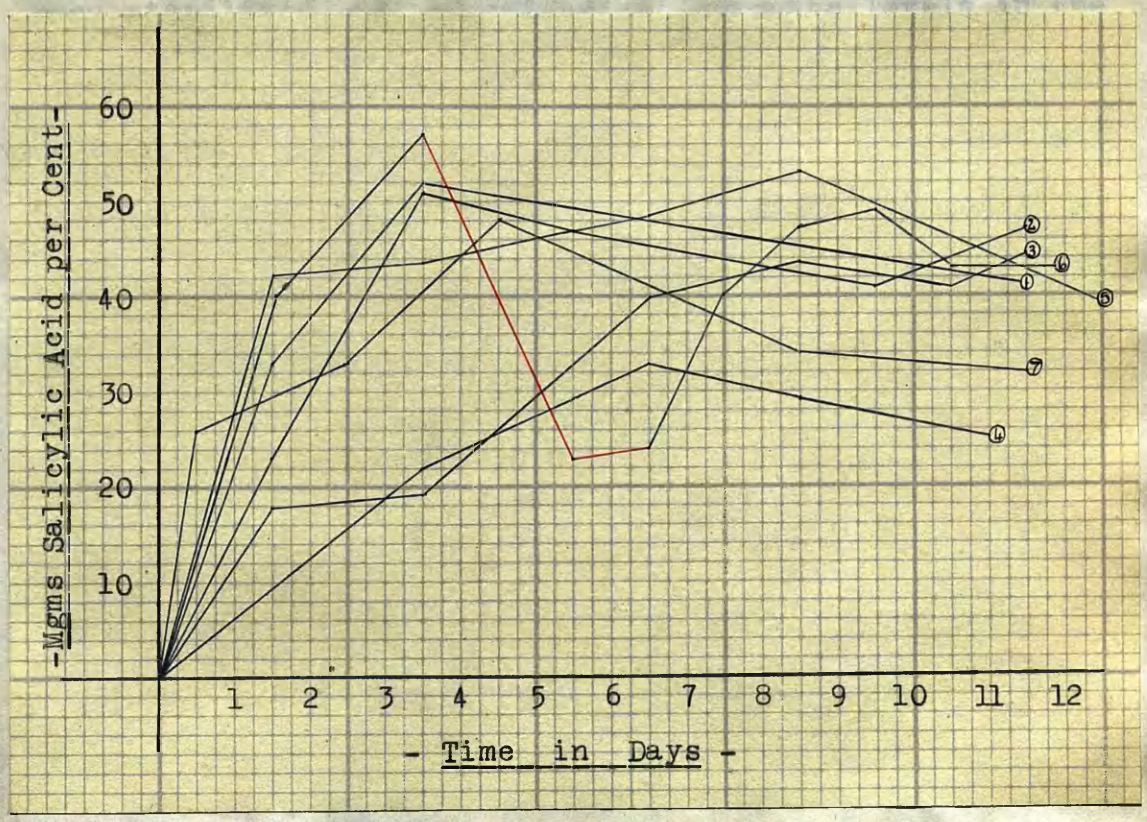


CHART 9.

The levels of salicylate in the plasma obtained by an initial dose of acetylsalicylic acid of 1½ grains (0.22 Gm. per Kilo.) per pound of body weight per day.

——— Period when Sodium Bicarbonate was given.

staff much smaller and for these reasons supervision was less meticulous. It was noticed that patients who had been stabilised and had maintained adequate levels in the parent hospital showed lower blood levels when they were transferred to the Country Branch. Chart 10 records the results of the last three estimations before discharge to the Country Branch and the first three after arrival there, wherever possible.

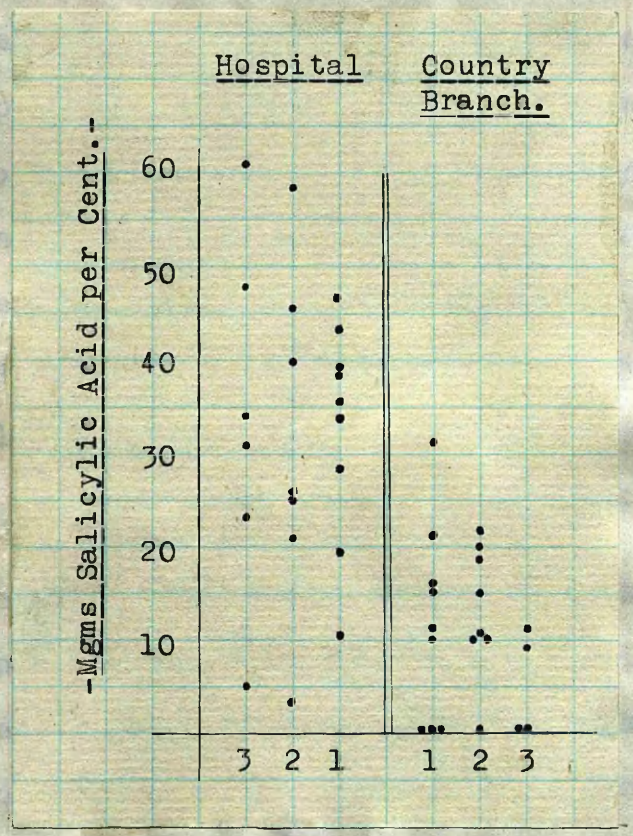


CHART 10.
The concentrations of salicylate in the blood of 9 patients who received the same dose of salicylate in Hospital as at the Country Branch.

The treatment of juvenile rheumatism with massive doses of salicylate soon revealed that the main problem was not one of attaining a concentration of 35 - 50 mgms. per cent in the blood but the frequent necessity of stopping the drug because severe toxic symptoms occurred between these levels. This subject will be discussed later. Hanzlik (1926) stated that the absence of toxicity meant the absence of therapeutic efficiency. If this statement was modified to read - "absence of toxicity means the absence of an adequate therapeutic blood level" it would certainly apply to the group of children whom we have attempted to treat with large doses of salicylates. These signs were sometimes insignificant but, nevertheless, were always present. A satisfactory blood level can be attained without difficulty but nice judgment is often required to strike a balance between the dose needed to maintain the blood level and that which will produce toxic symptoms.

The present investigation showed that this ideal was fulfilled only when the concentration of salicylate in the blood was built up to a minimum of 35 mgms. per cent over a period of 2 - 3 days instead of within 24 hours. The most convenient and reliable scheme was to prescribe 1½ grains of acetylsalicylic acid per pound of body weight (0.22 gram per kilogram) for the first two or three

days, and then to reduce it to 1 1/4 grains (0.18 gram per kilogram) or less. Some of the advantages of a gradual increase were that a smaller dose of salicylate was required, that the levels of salicylate in the blood did not fluctuate so wildly as they did with larger dosage, and the symptoms of salicylism were less frequent and mild. This modification of Coburn's recommendation that an adequate level of salicylate in the blood should be attained speedily, is open to the criticism that the heart may be seriously damaged during the delay. It is a lesser evil than the interruption or discontinuance of treatment because of toxic symptoms. Graham and Parker (1948) adopted a similar scheme with considerable success. They agreed with Manchester (1946) that sudden increases in the concentration of salicylate in the blood were potent causes of salicylism. Such an increase was produced in five children treated in accordance with the recommendations of Wegria and Smull (1945) but treatment had to be stopped in one and severe intoxication developed in three other cases. These results strengthened the adverse impression that had been formed about this scheme and did nothing to dispel the belief that it was dangerous. The extent of the risk becomes apparent when it is realised that a loading dose of 2½ grains of salicylate per pound of body

weight (0.36 gram per kilogram) was required during the first day i.e. a child who weighed 60 pounds (27 Kilos) received 150 grains (10 grams) within 24 hours.

It is possible, though unlikely, that some of these difficulties might have been overcome by the intravenous administration of salicylates. Despite the fact that Coburn had favoured this form of treatment, it was not used because of the technical difficulties of the procedure in children. A more serious objection was advanced by Taran and Jacobs (1945) who reported that the administration of the drug by this route had caused the death of a child suffering from rheumatic carditis. Even in adults the disadvantages outweight any possible benefits. The Committee on Salicylate Therapy (1944) and Irving Wright (1945) both reported that the only advantage of the intravenous therapy was when vomiting or any other symptoms prevented oral administration. Griffiths (1947) stated that the method was undesirable and unnecessary; and Rosenberg and Hench (1946) denied that it was a "superior, more scientific form of treatment". Manchester (1946) was an exception and recommended the intravenous therapy in severe and intractable cases of rheumatism.

Any system of oral dosage will prove unsatisfactory

unless the patient is given and takes his medicine at the prescribed times. This entails close and efficient supervision and its absence is a frequent cause of inadequate levels of salicylate in the blood. The importance of this factor became obvious during the present investigation and is clearly demonstrated in Chart 10. Huntington, Ryan et al. (1946) reported that the salicylates were often taken irregularly after a few weeks. They attributed this to the fact that the drug was apt to induce a sense of irresponsibility even in normal subjects. Butt, Leake et al. (1945) stated that the only explanation for unexpectedly low levels was that "these subjects in some manner did not take the salicylate which was ordered for them". If these lapses occur in hospital, there is little chance that massive doses of salicylate can be used in a private home.

SUMMARY.

1. Adequate levels of salicylate were obtained within 24 hours when a loading dose in excess of 1½ grains per pound (0.22 gram per kilogram) was prescribed. This scheme of dosage may produce dangerously high concentrations and wide fluctuations in the blood salicylate. It is considered dangerous and is not recommended.

2. Large doses of salicylate were better tolerated when

the concentration in the blood was raised to an adequate level over a period of 2 - 3 days. This was obtained by a dose of 1½ grains of acetylsalicylic acid per pound (0.22 gram per kilogram) of body weight during the first 2 - 3 days, and 1¼ grains per pound (0.18 gram per kilogram) or less for the remainder of the course. On this routine a plasma salicylate level of 25 to 47 mgms. per cent could be maintained in hospital.

3. Careful supervision was essential to maintain adequate concentrations in the blood. For this reason, the treatment of a patient at home with massive doses of salicylate is unlikely to be successful or safe.

SALICYLATE INTOXICATION.

When salicylate was first introduced for the treatment of rheumatism, it was the custom to prescribe large doses of the drug and it is not surprising that references to most of the signs and symptoms of salicylate intoxication appeared in the early papers. Amongst these was a description of those haemorrhagic episodes that are at present attracting attention (L.E. Shaw, 1886-87). For a long time there was a clinical impression that poisoning was more common with the synthetic salicylate than with the drug prepared from natural sources. Hanzlik (1926) states that this idea was finally discredited by the results obtained in different parts of the country by several clinicians who were unaware of the character of the salicylate that they used.

When smaller dosage became popular these occurrences either became less frequent or were no longer reported. Salicylate intoxication, however, continued to appear but most cases occurred amongst small children who had accidentally drunk a liniment that contained oil of wintergreen, or in infants whose parents had dosed them injudiciously on aspirin for some trivial febrile condition. Erganian, Forbes and Case (1947) described thirteen such cases amongst children between 3 weeks and 4½ years of age;

and Barnett, Powers, Benward and Hartmann (1942) five more between 8 months and 5 10/12 years. These authors reminded clinicians that salicylates were poisonous when given without proper supervision and that this fact was in danger of being forgotten.

The enthusiasm with which Coburn's methods were adopted inevitably led to a great increase of salicylate poisoning and many fatalities. These accidents were most common in patients who were being treated by the intravenous method and were not infrequently attributable to the failure of the medical and nursing staff to realise the significance of the early signs of toxicity.

VOMITING AND CONSTIPATION.

The common symptoms of salicylate poisoning encountered in this investigation were vomiting, hyperpnoea, and listlessness. These three were important because treatment had to be stopped when any one of them was severe. Such a step was not infrequent and the following table gives the reasons for discontinuing treatment:-

TABLE 1. THE REASONS FOR STOPPING TREATMENT.

Name	Reason for stopping treatment
J.C. ...	(1) Marked hyperpnoea Drowsy; vomited once. (2) Drowsy; looks ill Vomited twice. (3) Hyperpnoea Looks ill; vomited twice.
A.C. ...	Vomited three times Tinnitus Onset of congestive failure.
P.M. ...	Persistent vomiting Marked hyperpnoea Looked ill Blood salicylate 55.0 mgms. %
C.B. ...	(1) Marked hyperpnoea (2) Marked hyperpnoea Looks ill.
S.M. ...	Very listless and drowsy.
R.S. ...	Vomited twice.
J.W. ...	Marked hyperpnoea Looks very ill Blood salicylate 65.5 mgms. %
E.D. ...	Persistent vomiting.
T.M. ...	Hyperpnoea Looks ill Listless and drowsy Incontinent of urine and faeces.
J.B. ...	Vomited three times.
R.McC. ...	Vomited twice.
D.McC. ...	Marked hyperpnoea Pulmonary oedema.

Vomiting has been reported to be most frequent during the first week of treatment and particularly when there had been an abrupt rise in the level of salicylate in the blood (Keith and Ross, 1945). Graham and Parker (1948) noticed that after the first week of treatment higher plasma levels were well tolerated and so they made it their practice to maintain a level somewhat lower than 35 mgms. per 100 ml. for the first 5 - 7 days and to increase the dosage thereafter. The unexpected occurrence of sickness later in the course of treatment has much greater significance and should suggest the possibility of overdosage. A good example of this is the case of P.M. aged 7 years, who was admitted suffering from rheumatic carditis and treated with large doses of acetylsalicylic acid. She received 100 grains (6.6 grams) during the first 24 hours and then 60 grains (4 grams) daily. Vomiting occurred on the second day but there were no further symptoms until the sixth week when she complained of abdominal pain and began to vomit continuously. The blood salicylate was found to be 55.0 mgms. per cent. Hyperpnoea developed later. Treatment was stopped and she made a rapid recovery.

The belief that the vomiting caused by salicylate intolerance can be prevented by keeping the bowels freely opened has become firmly established in clinical medicine.

Langmead (1906) came to the conclusion that the "noteworthy point is that all the patients were constipated before the onset of symptoms, so that a greater accumulation than usual might have taken place. Clearly the indication, then, is to see that the bowels are kept well opened whilst salicylate is being given." Lees (1908-09) who was in the habit of giving enormous doses of salicylates - up to 600 grains (40 grams) per day - supported this view and suggested that in order to avoid toxic symptoms the dose should never be increased unless the bowels had moved on that day. Years later Morris and Graham (1931) wrote that if Langmead's advice was remembered it was seldom necessary to interrupt treatment.

The prevalence of vomiting in the present series of cases afforded an opportunity to determine whether Langmead's conclusions were correct. The results of this study are shown in Chart 11 which shows when vomiting occurred and the state of the bowels in each child during the first month of treatment. It will be seen that no relationship exists between vomiting and constipation, and that vomiting is most common during the earlier part of the course.

The concentrations of salicylate in the plasma were not shown in Chart 11 and so, Table 2 was devised to show both the level of salicylate and the condition of the

bowels on the days when the children vomited. Some instances of vomiting were excluded from the table because the plasma salicylate level had not been estimated on the same day.

TABLE 2. RELATIONSHIP BETWEEN VOMITING, PLASMA SALICYLATE, AND CONSTIPATION.

Name	Date	Blood level in mgms. %	Whether bowels moved	Number of days constipated.
D. McF.	6.3.48	33.3	no	1
E. D.	23.1.48	29.3	yes	-
	24.1.48	29.0	no	1
M. S.	2.3.48	33.7	yes	-
A. C.	9.1.48	48.6	yes	-
	11.1.48	54.7	no	1
	12.1.48	40.9	yes	-
P. M.	12.2.48	32.0	no	1
	19.3.48	55.0	yes	-
R. McC.	18.2.48	34.8	no	2
J. B.	7.11.48	16.4	no	1
A. Li.	7.1.48	14.0	no	2
W. G.	27.2.48	41.9	no	1
	29.2.48	44.9	no	1
	1.3.48	47.4	yes	-
	23.4.48	40.0	yes	-
	26.4.40	38.4	yes	-
J. C.	6.3.48	62.2	yes	-
	25.3.48	17.6	yes	-
A. W.	19.7.48	41.9	no	1
D.McC.	22.5.48	42.9	no	1
	25.5.48	48.3	no	1
	29.5.48	42.1	no	2
W. S.	10.7.48	45.5	no	1
D.C.	9.7.48	27.2	yes	-
	12.7.48	20.4	yes	-
	14.7.48	55.4	no	-
J.W.	6.1.48	38.3	yes	-
	13.1.48	65.5	no	1
	14.1.48	65.0	no	2
E.W.	7.5.48	22.1	yes	-
	27.5.48	47.6	yes	-

Name	Date	Blood level in mgms. %	Whether bowels moved	Number of days constipated.
S. M.	23.5.48	48.0	yes	-
H. McG.	30.8.48	34.4	yes	-
A. Le.	21.8.48	52.0	no	1
M. A.	29.8.48	41.6	no	3
	1.9.48	32.0	no	2
	3.9.48	34.0	yes	-
	9.9.48	24.8	yes	-
	20.9.48	40.0	yes	-

Average level of plasma salicylate when vomiting occurred in 40 cases - 37.1 mgms. per cent.

Incidence of vomiting :-

20 times when constipated
20 times when bowels had moved.

Once more the presence or absence of constipation has been shown to have little effect upon the frequency of vomiting. In contrast to this, most of the vomiting occurred when the concentration of salicylate in the plasma exceeded 30 mgms. per cent. The average level at which vomiting appeared was 37.1 mgms. per cent but this knowledge is of little practical value. On the other hand, the fact that children may vomit when a level of 30 mgms. per cent has been reached is important because it draws attention to the possibility that toxic symptoms may be experienced before Coburn's adequate level of 35 - 50 mgms. per cent has been attained.

CHART 11. The relationship between the state of the bowels and the incidence of vomiting.

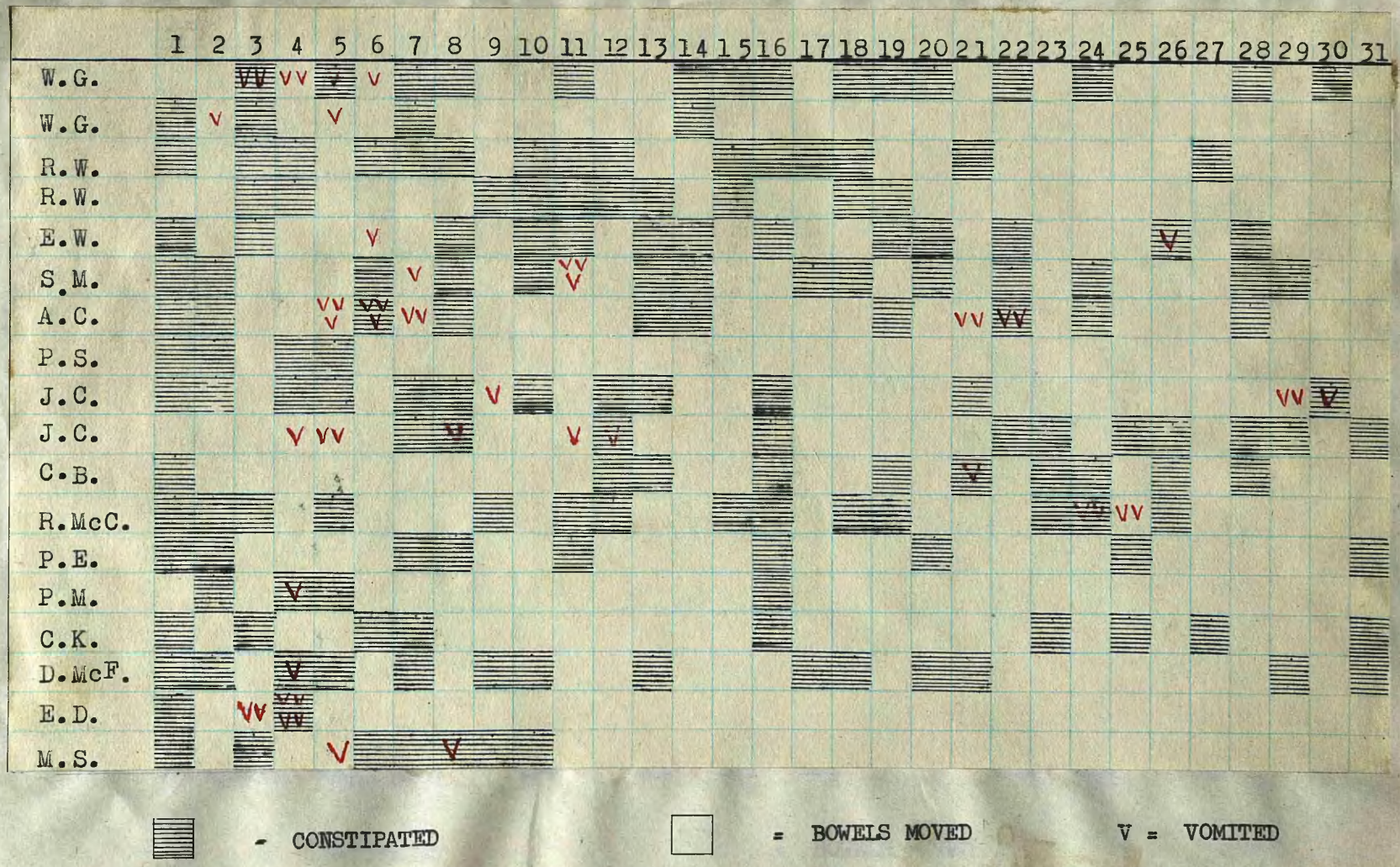
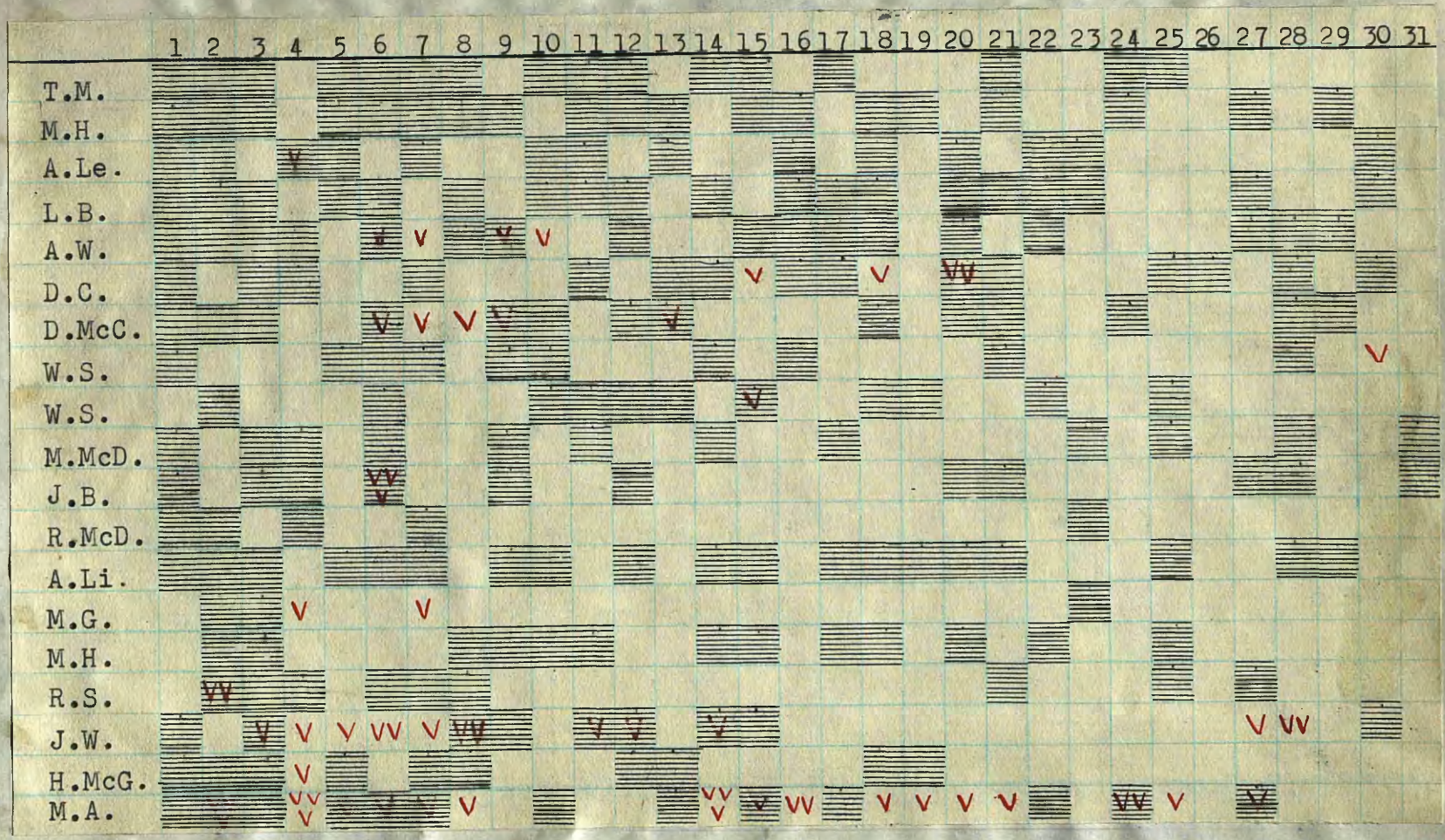


CHART 11 - (Continued)



= CONSTIPATED = BOWELS MOVED V = VOMITED

The influence of the concentration of salicylate in the plasma upon the occurrence of vomiting has been reported by others. Wegria and Smull (1945) found that levels over 50 mgms. per cent produced vomiting in some cases; Caravati and Cosgrove (1946) that in 38 per cent of their patients receiving oral salicylates, nausea and vomiting developed at a mean plasma salicylate level of 36.6 mgms. per cent; Graham and Parker (1948) that nausea occurred at a mean value of 26.7 mgms. per cent and vomiting at a mean value of 28.2 mgms. per cent.

FLUID INTAKE.

In this investigation no attempt was made to ensure a large fluid intake. Griffiths (1947) recommended that if salicylates were administered absolutely regularly with an adequate quantity of water (3,000 ml. per day for adult patients) the level in the blood remained at or near the optimum. It may be that the lethargy and the toxic appearance of the children in the present series was largely due to inadequate fluid intake and the adoption of Griffith's recommendation would have prevented them. Cahill (1946) gave 8 - 10 ounces of water with each dose and was in this way able to prevent nausea.

HYPERPNOEA.

Hyperpnoea first appears as a slight increase in the depth of breathing and may only become apparent when the patient moves in his bed or pulls up his shirt to allow an examination of the chest. As the blood level rises, the amplitude of the respirations increases and the erroneous impression may be produced that the rate has been slowed. A further rise of the concentration of salicylate in the blood causes a more rapid respiratory rate and the breathing becomes even deeper, noisy and hissing. By this time the patient is in danger of developing the more serious signs of salicylate intoxication and it is essential to omit one or two doses, or to stop the drug entirely.

The levels at which hyperpnoea occurred are shown in Table 3.

TABLE 3. HYPERPNOEA AND BLOOD SALICYLATE LEVEL.

Name	Date	Blood level in mgms. %
C.B.	28.2.48	24.8
P.M.	19.3.48	55.0
R.McC.	9.2.48	49.3
	11.2.48	37.3
M.McD.	14.3.48	64.8
	26.3.48	30.8
	15.4.48	43.5
W.G.	26.4.48	38.4
	30.4.48	47.6
	5.5.48	43.7

Name	Date	Blood level in mgms. %
W.S.	19.6.48	34.3
	28.6.48	39.8
D.McC.	21.5.48	42.9
	27.5.48	54.0
	30.5.48	42.1
E.W.	10.5.48	33.7
	20.5.48	36.4
	23.5.48	50.3
J.W.	14.1.48	65.0
S.M.	20.5.48	28.0
	23.5.48	48.0
	25.5.48	36.0
M.H.	17.8.48	41.0
	20.8.48	55.2
	23.8.48	40.8
	27.8.48	40.8
H.McG.	31.8.48	34.4
	7.9.48	28.0
	10.9.48	32.8
A.Le.	21.8.48	52.0
	27.8.48	40.8
T.M.	17.8.48	32.8
	19.8.48	48.8
	23.8.48	34.0
	30.8.48	51.2
D.C.	9.7.48	36.2
J.C.	6.3.48	62.2
M.McD.	6.10.48	35.6
	8.10.48	38.0
	18.10.48	40.0
	21.10.48	40.0
M.A.	29.8.48	41.6
	31.8.48	32.0
	3.9.48	34.0
	6.9.48	47.2
	9.9.48	24.8
	13.9.48	31.2
	20.9.48	40.0

Average level ... 41.3 mgms. per cent.

Despite many investigations, there is still a

considerable difference of opinion about the cause of the hyperpnoea of salicylate poisoning. Troll and Menten (1945) divided the possible explanations into four groups.

The first of these is that the condition may be due to an acidosis. This is no new idea for Langmead (1906) thought that the air-hunger was similar to that which occurred in diabetic coma and that it was one of the symptoms of acid poisoning. Morris and Graham (1931) found hyperpnoea of a greater or lesser degree in all of their cases and regarded it as a typical acyanotic dyspnoea due to an acidosis of an acid-poisoning type. They suggested that an impairment of renal function was an important factor in its production. Johnson (1930), as a result of administering salicylates in doses equivalent to 0.2 Gm. per Kilo. to rabbits and cats, concluded that there was a fixed-acid acidosis compensated for by loss of carbon dioxide. He dismissed the possibility that the salicylates might cause an alkalosis by stimulating respiration because the apnoea that is found after forced ventilation did not occur.

The second suggestion is that there is a stimulation of the respiratory centre by the salicylates. This was the view of Marten - Odin (1932) who believed that the deep breathing was brought about through irritation of the

respiratory centre. Barnett et al. (1942), and Hartmann (1945) were of the opinion that there was a primary hyperventilation due to a specific central stimulation which led to a carbon dioxide type of alkalosis. This was then replaced by a ketosis due either to depletion of the glycogen reserves or to dehydration, and both of these factors would be increased in the presence of vomiting. The combined effect of central stimulation and acidosis accounted for the characteristic intense hyperpnoea. Somewhat similar opinions are held by Fashena and Walker (1944) who stated "it would appear that this distortion of the acid-base equilibrium which occurs in acute salicyl poisoning is a complex phenomenon resulting from many factors viz., primary stimulation of the respiratory centre, fixed acid acidosis, ketosis, and possibly other changes." The importance of the ketosis is doubtful for Myers and Ferguson (1929) found no increase in ketones in men or rabbits receiving large doses of salicylates. Rapoport and Guest (1945), as a result of experiments on monkeys and dogs and then in man, found that the salicylates caused a primary hyperventilation and a significant elevation of the serum pH in most instances. An hypnotic drug such as pentobarbital sodium suppressed the hyperventilation, though it increased the toxicity, and they interpreted this as an indication of a direct action of the salicylates on the

respiratory centre. Ryder, Shaver and Ferris (1945) reported a fatal case of salicylate poisoning in which a respiratory alkalosis developed and tetany was observed. Graham and Parker (1948) injected salicylates intravenously into rabbits and adult male patients suffering from chronic rheumatoid arthritis and concluded that the drug had a "direct stimulant effect on the respiratory mechanism which is independent of alteration of the blood acid-base balance." They remarked that the general assumption, that the salicylates have a direct stimulant effect on the respiratory centre, ignored the observation of Danewski that vagotomy inhibits the hyperpnoea in experimental animals. This fact was confirmed by experiments on both cats and rabbits. From their work it seems that the site of stimulation is a peripheral one acting through the vagal nerve fibres.

The third concept is that the hyperpnoea is due to an increased metabolism. This is supported by Dodd, Minot and Arena (1937) who, as a result of experiments on dogs, wrote - "the sensation of heat and the increase in gaseous exchange induced by salicylates appear to us to be of much greater importance in producing an increase of the respiratory rate and depth than any direct central action of the drug." These authors made the interesting observation that by artificially cooling animals that were being given salicylate there was no significant change in

the respiratory rate while the uncooled animals had extreme dyspnoea.

The fourth suggestion is that the salicylates damage the endothelium of the capillaries and that an early increase in the permeability of the vessels occurs. Ashworth and McKemie (1944) examined two fatal cases of salicylate intoxication and concluded that the - "severe generalized hyperemia in our two cases suggests the possibility of some capillary damage by the salicylates". Troll and Menten (1945) also found that in the course of damage to the tissues an early increased permeability of the vessels occurred. This increased the rigidity of the lungs and produced the "reflex dyspnoea" described by Christie (1938).

These differences of opinion indicate how difficult it is to explain the underlying mechanism of the hyperpnoea. Of the four possible causes, the theory that attributes the dyspnoea to increased metabolism is an unlikely one, and it seems more reasonable that the opposite is true and the dyspnoea stimulates metabolism. The demonstration that an alkalosis exists in salicylate poisoning undermines the belief that an acidosis is the causative factor of the dyspnoea. On the whole present opinion favours the view that the salicylates have a direct stimulant effect upon the

respiratory centre or, as Graham and Parker (1948) prefer, upon the respiratory mechanism.

DROWSINESS.

The appearance of listlessness and drowsiness may easily be missed during the first few days after admission to hospital when the child is a stranger and little is known about him. But in many cases there is an obvious pallor and the patient looks ill and has dry lips and a parched tongue. These symptoms afford a warning that careful supervision is required, and if they persist the dose of salicylate must be reduced or treatment stopped. A rapid and striking improvement occurs when this is done and within 24 hours a dull, lethargic child becomes quite animated.

HAEMORRHAGE.

Four other symptoms of salicylate intoxication are often mentioned in the literature. These are tinnitus, delirium, haemorrhages and an acneiform eruption. There were epistaxes in five patients and four of them were being treated with salicylates at that time. Because the prothrombin time of the blood of these children was not estimated, no opinion could be formed whether the haemorrhages were a manifestation of the rheumatic infection or the effect of the salicylate.

SKIN RASHES.

The occurrence of an acneiform rash has been mentioned by several writers. It was one of the three toxic reactions recorded by Coombs, Warren and Higley (1945) who were impressed with the frequency of toxic effects when the plasma salicylate was maintained at levels over 30 mgms. per cent. Graham and Parker (1948) saw two instances of rash, in the third week of salicylate therapy, when the plasma levels had fallen from an initial high level. Keith and Ross (1945) recorded the appearance of a rash in one patient of their series.

During the present investigation a rash was found on only one child and it was not at first recognized as being a toxic manifestation of salicylate therapy. The following is a summary of the story:- M.McD., aged 11 years and weighing 29.6 kilograms, was admitted to hospital on 13.3.48 as a case of subacute rheumatism and at once received massive doses of acetylsalicylic acid - 150 grains (10 grams) within the first 24 hours and 50 - 60 grains (3.3 to 4 grams) daily for the rest of her stay in hospital. On the day after admission to hospital (14.3.48) she attained a plasma salicylate level of 64.8 mgms. per cent and this fell to 38.3 mgms. per cent by 19.3.48. She was then found to have a crop of purulent vesicles over her

right buttock. One of the lesions was opened and from the pus a few colonies of staphylococcus aureus were grown. The pustules persisted and on 23.3.48 this note was made - "the diagnosis of this skin condition causes some difficulty - a staphylococcal skin infection - not echthyma or Bockhart's impetigo." She was treated with 50,000 units of penicillin four times a day. The rash healed by 31.3.48 though an occasional pustule was noticed subsequently. She was dismissed home on 22.4.48. Apart from the initial high blood levels the serial estimations in this child averaged about 25 mgms. per 100 ml. It is now believed that the eruption was either the direct result of salicylate toxicity or a sequel to the sweating induced by the drug. The case resembled those described by Graham and Parker (1948) in that the rash appeared when the level of salicylate in the plasma had fallen from the initial high concentration.

DEAFNESS AND TINNITUS.

Adults often complain of deafness and tinnitus during treatment with salicylates. This is so common that some clinicians believe that patients are receiving inadequate treatment if this symptom is absent. But is is of little value in young children who seldom complain of either deafness or a buzzing in the ears. They do experience these symptoms but the younger ones do not have the

vocabulary or are unable to explain their odd sensation. However, if the child is questioned carefully, he will often reveal that he has tinnitus and may even be persuaded to reproduce the hissing sound that is troubling him. In the case of older children the deafness can be detected more easily but it is not often a prominent feature.

DISCUSSION.

During the first part of this investigation the signs and symptoms of salicylism were not always appreciated and information about the concentration of salicylate in the plasma was a valuable safeguard against overdosage. But with more experience the various stages of salicylate intoxication were recognized clinically and their severity was assessed with considerable accuracy. This improvement in detection was accompanied by an apparent increase in the incidence of salicylism because many cases that had been overlooked before were now noted. The condition was seldom observed when the concentration of salicylate in the plasma remained low but occurred with increasing frequency as the level of the drug rose above 30 mgms. per cent. Indeed signs of salicylate intoxication became common when the concentration of salicylate in the plasma lay between 35 - 50 mgms. per cent. This provided unexpected support for the old clinical belief that the drug should be

prescribed in doses sufficient to produce symptoms of poisoning. It also renewed interest in the possibility that the common signs and symptoms of salicylism might provide a useful guide to the lvel of salicylate in the plasma.

The value of an estimation of the concentration of salicylate in the plasma is not questioned but reliance on the blood level implies certain limitations and disadvantages. The most important is that massive salicylate therapy must be restricted to hospital practice because the determination of blood levels requires laboratory facilities. In addition, the repeated withdrawal of blood may become an ordeal to some children. It was found in the present investigation that some subjects came to dread the procedure of blood sampling. For these reasons any alternative means of gauging the level of salicylate in the plasma was welcomed, even if it was but an approximation.

Amongst the older clinicians buzzing ears or deafness was commonly regarded as a reliable indication that an effective dose of salicylate had been prescribed. These symptoms proved of little value in this investigation because the children were seldom troubled by them.

Vomiting and listlessness occurred more often but their unpleasantness was a barrier to their use during a prolonged course of treatment. On the other hand, hyperpnoea possessed many advantages as an indicator. The breathing could be observed at any time; did not depend upon the co-operation of the child; and caused no distress. As the investigation progressed the presence of hyperpnoea was accepted as an assurance that the salicylate in the blood either had attained or was approaching an adequate concentration. The most satisfactory results were obtained when mild rather than obvious hyperpnoea was present because other toxic symptoms were not common at this stage. Success depended upon an ability to detect the increase in the depth of respiration that preceded acceleration of the rate of breathing.

SUMMARY.

1. The incidence of salicylate intoxication has increased since the resumption of massive salicylate therapy.

2. Vomiting, hyperpnoea and listlessness were common and the usual reasons for stopping treatment.

3. Vomiting was not caused by constipation but tended to occur when the concentration of salicylate in the blood

exceeded 30 mgms. per cent. The average concentration of salicylate in the blood when vomiting began was 37.1 mgms. per cent.

4. Hyperpnoea was noticed when the average concentration of salicylate in the blood was 41.3 mgms. per cent. The cause of the hyperpnoea of salicylate intoxication is not known but the various theories have been described. The early stage of hyperpnoea, i.e. increase in depth of respiration without increase of rate, was the best clinical indication that the concentration of salicylate in the plasma was adequate.

5. An acneiform rash developed in one child and has been described.

6. Children are often unable to describe tinnitus or deafness and so these were not common complaints.

RHEUMATIC PNEUMONIA.

In this investigation three cases developed clinical signs of pulmonary involvement, and a fourth showed X-ray evidence of consolidation. The possibility at once suggests itself that these cases were examples of rheumatic pneumonia. This condition has been the subject of several recent papers. Seldin, Kaplan and Bunting (1948) stated that two fairly distinct clinical syndromes have been evolved. The first of these occurs in the more severe types of the rheumatic infection and was described by Rabinowitz (1926) as - "those cases developed without upper respiratory symptoms or chill; they presented only slight cough, little toxaemia, irregular elevation of temperature, areas of marked dulness, and loud bronchial breathing with but few rales. They were of fleeting character, and, as a rule did not influence the prognosis." The second type is more severe and may end fatally. Gouley (1937) described these cases as - "a small group of patients in whom the pulmonary invasion is extremely rapid and widespread, accompanied by quickly developing dyspnoea and cyanosis." Griffiths, Phillips and Asher (1946) sub-divided this group into primary and secondary forms and classified the rheumatic pneumonias into 3 types :-

1. Primary acute pneumonitis in which the pneumonia is the initial symptom of the rheumatic episode.

2. Secondary acute pneumonitis which developed during one of the phases of polycylic rheumatism.

3. Subclinical pneumonitis which is often found accidentally and should be suspected "when a rheumatic fever patient is more ill than clinical findings would indicate."

The case histories of the four children who developed signs of pulmonary involvement will be described in detail.

CASE 1.

D.McC., aged 9 years, was admitted to hospital on 17.5.48. From the age of 5 years he had been subject to sore throats every autumn. In October 1947, he developed a sore throat, swollen cervical glands and became very pale. His condition was attributed to poison from his teeth and so eight teeth were extracted. From then onwards he was never well. On 23.5.48 he became paler, listless and breathless on exertion, and had vague pains in his legs. He was treated at home as a case of rheumatism for the next three weeks and then, because of a severe epistaxis, was admitted to hospital. On examination his apex beat was found in the 5th space one

inch outside the nipple line, and a loud systolic apical murmur was present. The lungs were clear. He was treated with acetylsalicylic acid 105 grains (i.e. 1½ grains per pound of body weight per day) from 18.5.48 to 22.5.48; 90 grains per day from 23.5.48 to 28.5.48; and 75 grains per day from 29.5.48 to 30.5.48 when treatment was stopped. Blood levels between 42 - 54 mgms. per 100 ml. were maintained. During most of this period he was inclined to be drowsy, listless, and his respirations were increased in amplitude though not in rate. In the evening of 30.5.48 he became very restless, his breathing rapid and deep, and he appeared ill. The acetylsalicylic acid was discontinued and sodium bicarbonate grains 30 was given every four hours. Next morning (31.5.48) he still looked ill, was very dyspnoeic and had a cough. His face was slightly puffy. The percussion note was resonant; the respiratory murmur was vesicular and there was abundant rale at both bases. On 1.6.48 the following note was entered in his case record - "boy looks pale and ill with cough and increase in respiration rate but not in temperature and pulse rate. He has, however, had a low grade fever for some days. Heart now not as large as on admission: apex beat in the 5th space one third of an inch outside the nipple line. No dulness but abundant fine rale all over left lung back and

front and at right base." X-ray of his chest showed - " + mediastinal and heart shadows: suggests infiltration and ++ oedema. No fluid visible in pleural sacs." The boy made rapid improvement and though scanty rale was present for a few days, this cleared by 6.6.48.

CASE 2.

J.W. aged 6 years, had scarlatina in September 1947 and was dismissed home well from the Fever Hospital about the beginning of October. Three weeks later she developed fever, and a slight rash appeared on her arms and legs. In early November she had epistaxes and a heart murmur was discovered. Since then, in spite of rest in bed, she had had some joint pains and several epistaxes. Because of these she was admitted to hospital. On admission she was found to have an enlarged heart. The apex beat was palpable in the sixth space half an inch outside the nipple line and there was a forceful thrust and a thrill which could not be timed because of the rapid heart rate (circa 140 per minute). The rhythm was regular. Systolic and diastolic murmurs were heard at the apex. The lungs were clear. She was given a mixture containing sodium salicylate grains 10 and sodium bicarbonate grains 20 every four hours from 4.1.48. On 6.1.48 her blood salicylate was 38.3 mgms. per 100 ml. The child vomited at least once each day and

because of this acetylsalicylic acid grains 10 was substituted for the sodium salicylate mixture on 10.6.48. There was no vomiting for the next two days.

On 13.1.48 she refused her food and vomited once. The blood salicylate concentration was 65.5 mgms. per 100 ml. Next day (14.1.48) the child, though afebrile, was pale and looked ill. Her pulse and respirations were rapid, she had a short dry cough and the alae nasae were dilating. An examination of the lungs showed that the percussion note was slightly impaired at the right apex in front and in the right axilla where the respiratory murmur was distinctly tubular and many fine crepitations were heard. There was no oedema. Later in the day the child's breathing became markedly acidotic and, as the level of salicylate in the blood was 65.0 mgms. per cent, the drug was stopped. By the evening she was restless, pale and very ill. An intensely tubular respiratory murmur could be heard at the right base and right axilla. Soon after this an intravenous drip was set up.

During the night the general condition improved and on 15.1.48 she was breathing more easily and slowly. She had a frequent cough and occasional small epistaxes. The condition of the lungs was unchanged. An X-ray film of the

chest showed extensive areas of consolidation in both lungs, enlarged heart shadows and a large pulmonary conus. On 17.1.48 she was noticed to have a puffy face and some lumbar oedema. She had a cough and there was much rale at the right axilla and right base. The oedema became more widespread and on 20.1.48 she was given Digoxin. There after she improved steadily and on 17.2.48 the following note was made - "remarkably well having regard to previous condition ... I think much of the unexpected improvement can be attributed to Digoxin."

CASE 3.

J.C., aged 7 3/12 years had been treated in the hospital for pericarditis in April 1946. About 18.2.48 he complained of headache, sore throat and anorexia, followed a few days later by pains in his knees and down his shins. He was admitted to hospital on 27.2.48 and found to have an enlarged heart with the apex beat palpable in the 6th space one inch outside the nipple line. Systolic and diastolic murmurs were heard at the base and apex. During the next six weeks he received two courses of salicylate therapy both of which were stopped because he developed signs of salicylism. On 19.4.48 he became fevered, had pains in his legs, and his erythrocyte sedimentation rate which had previously been 12 mms. rose

to 50 mms. in one hour. Treatment with sodium salicylate grains 10 every four hours was begun on 20.4.48 but though the temperature settled after three days there was an increase in the pulse rate. On the 24th he vomited, his respirations became more rapid and he began to cough. Widespread rhonchi were heard over the right lung. In the evening of 25.4.48 he vomited twice, his respirations became rapid and deep and he did not look well. The salicylates were stopped. Unfortunately the concentration of salicylate in the plasma was not measured during this course of salicylate medication but some hours after treatment was discontinued the level was 17.6 mgms. per cent. There was little improvement next day and on 27.4.48 the following note was made in his case record:- "temperature remains elevated and the child is very ill. Respirations are pneumonic in type - dilatation of the alae nasae, expiratory grunt and inversion of the respiratory rhythm. Frequent cough. Lungs - percussion note decreased in the right axilla and respiratory murmur harsh vesicular. Numerous rhonchi and rales scattered throughout both lungs." For the next five days he was treated with sulphamezathine and his condition gradually improved.

CASE 4.

W.S., aged 4 years and 10 months, was admitted on 24.5.48 suffering from rheumatic carditis. He was treated

with calcium aspirin 40 grains daily. On 2.6.48 he suddenly developed fever, sweated profusely and shivered. He did not feel ill. No cause was found for the condition. On 3.6.48 his chest was X-rayed and a widespread consolidation of the right lung was found. The blood salicylate level on 4.6.48 was 35 mgms. per 100 ml. During the next week his fever subsided though he did complain of two bouts of sweating. On 19.6.48 he seemed so well that the course of calcium aspirin was stopped.

These four cases are regarded as examples of rheumatic pneumonia. Cases 1, 2 and 3 fall into the 'severe' type described by Seldin, Kaplan et al. (1948), or the secondary acute pneumonitis of Griffiths (1946). The X-ray picture of D.McC. (case 1) shows an appearance very similar to the plates reproduced in the paper by Seldin et al. (1948). Case 2 illustrates the view of Griffiths et al. (1946) that - "where there is a primary right sided heart failure in rheumatic fever, pneumonitis is one of initiating causes." Case 4 is an example of subclinical pneumonitis.

Rheumatic pneumonia has been attributed to a specific rheumatic manifestation, to congestive failure, to intercurrent infection and to a combination of rheumatic activity and cardiac failure. All these theories have

been disputed. It is felt, though no proof is offered, that these complications which arose during the course of salicylate medication in the present series, were not accidental infections but a direct result of a high level of salicylate in the blood. Cameron (1948) in his Sidney Ringer Memorial Lecture on pulmonary oedema referred to the wide variety of drugs - one of these was methyl salicylate - that can cause pulmonary oedema after absorption into the blood stream. He had also been impressed by the frequency of severe dyspnoea before the oedema reached its clinical crisis and was inclined to the view that such respiratory embarrassment played an important part in the causation of the oedema.

Confirmation of the importance of dyspnoea and the exudation of plasma from the damaged capillaries is contained in Hadfield's (1938) paper on the "Rheumatic Lung". He described how the consolidated lung had a red, rubber-like consistency, and the small amount of fluid that could be expressed from it. The aerated parts, however, invariably showed acute oedema and contained a large excess of watery, blood stained fluid.

In many of the accounts of rheumatic pneumonia it is difficult to decide whether or not salicylates were given,

and when they were, few details about dosage are recorded. It is suggestive that two of the severe cases in this investigation had adequate levels of salicylate in the plasma and the third, though the concentration of salicylate in the plasma during the course of treatment was not estimated, had been unable to tolerate salicylate on two earlier occasions. Murphy (1945) mentioned that he encountered a fatal case of rheumatic pneumonitis with a level above 30 mgms. per cent. The paper by Stevens and Kaplan (1945) on salicylate intoxication affords some confirmation of the suggestion that there is a relationship between high blood salicylate levels and pulmonary lesions. They described four cases, one of which proved fatal. This patient attained an extremely high blood salicylate level and developed pulmonary oedema with signs of circulatory failure. Microscopic examination of the lungs showed - "early acute bronchitis, severe pulmonary oedema, extreme congestion and a few small perivascular haemorrhages within the interlobular septa." X-ray plates of these patients showed that one had appearances "consistent with bilateral bronchopneumonia", and the other had "a focus of irregular consolidation that could not be confirmed by clinical examination" in the upper lobe of the right lung.

THE EFFECT OF SALICYLATE ON THE ERYTHROCYTE SEDIMENTATION RATE.

It is widely accepted that, in the absence of gross anaemia, the presence of a raised erythrocyte sedimentation rate in a case of rheumatism indicates that the disease is still active. But if this estimation is used as a means of assessing progress or gauging the effect of a drug it is well to remember the advice given by Massell (1938) at a Round Table Conference of the American Academy of Pediatrics:- "many investigators who have written about the erythrocyte sedimentation rate in these conditions have claimed a remarkable infallibility. They have implied or stated directly that an elevated erythrocyte sedimentation rate proves the presence of active infection and that a normal E.S.R. proves the absence of active infection. If the word 'suggests' were substituted for 'proves' this statement would be more nearly correct."

Coburn (1943) claimed that massive doses of salicylate hastened the fall of the erythrocyte sedimentation rate to normal in cases of monocyclic rheumatism, and cited this in support of his view that the rheumatic activity was suppressed by the drug. If he is correct, cases with a blood salicylate level above 35 mgms. per cent should require

less time for the erythrocyte sedimentation rate to reach normal than those with levels below this figure. The results of the present investigation were analyzed in this way, and the result showed a close similarity between the two groups (Chart 12).

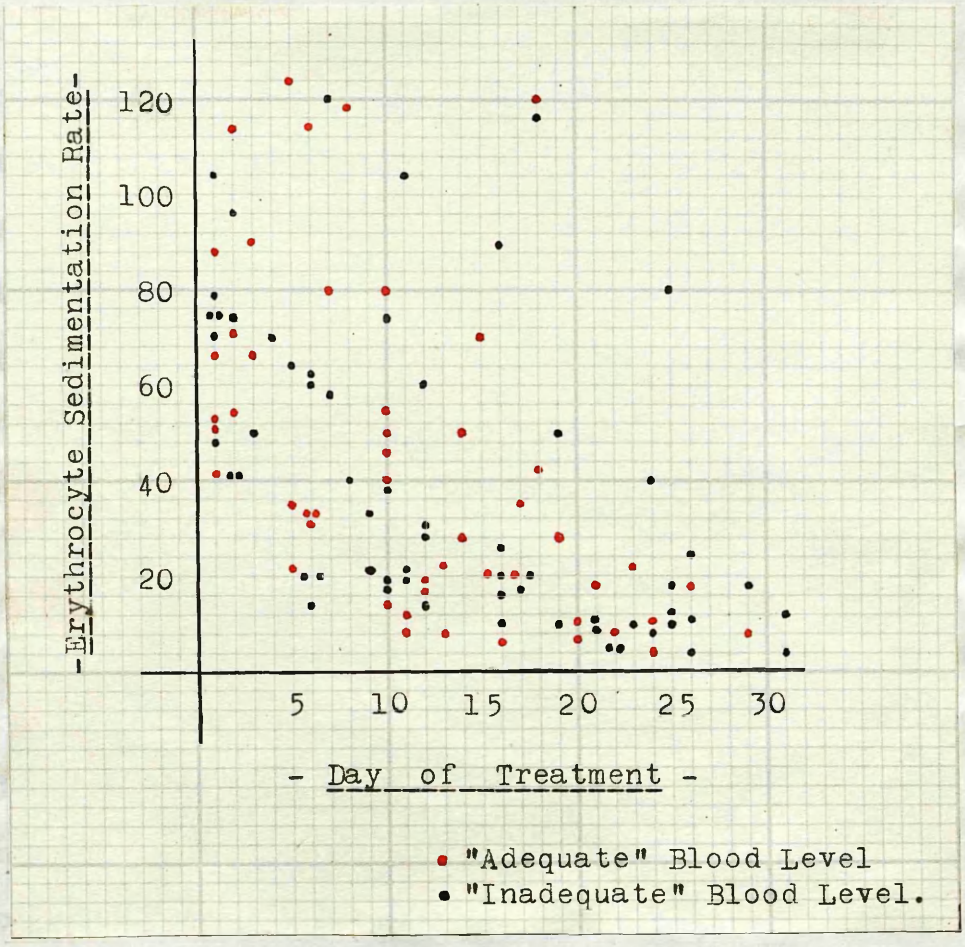


CHART 12.
A comparison of the effect of adequate and inadequate levels of salicylate in the blood upon the Erythrocyte Sedimentation Rate.

It therefore appears that massive doses of salicylate do not accelerate the fall of the erythrocyte sedimentation rate to normal. Similar conclusions have been reached by many others. Wegria and Smull (1945) found that the length of time needed for the sedimentation rate to reach normal differed only slightly in adequately treated and the control groups of cases. They thought, however, that early treatment might shorten the course of the disease. This was not the experience of Keith and Ross (1945) whose patients began salicylate therapy within one or two days of the onset of the illness. In spite of this advantage, the interval that elapsed before the erythrocyte sedimentation rate of these cases became normal ranged from 1½ - 12 weeks on the high dosage; and 2 - 12 weeks in those on the low dosage.

Warren et al. (1946) in a study of 186 cases of rheumatism found that large doses of salicylate were no more effective than small doses in reducing the raised sedimentation rate. They pointed out that in a certain number of cases the attacks were monocyclic and that in such cases the erythrocyte sedimentation rate showed a prompt return to normal. If salicylates were given to such individuals the erythrocyte sedimentation rate curve would suggest a markedly beneficial effect. In polycyclic

infections the erythrocyte sedimentation rate fluctuates. The administration of salicylates to these cases during a falling phase would lead to a false conclusion and the withdrawal of the drug, at the beginning of a rise, to the idea that the salicylate therapy had been discontinued prematurely. Wright (1945) found that the response of the sedimentation rate to both intravenous and massive oral dosage was disappointing and, in a large proportion of cases, failed to approach normal until the third to the sixth week of treatment.

On the other hand Manchester (1946) supported the claim that the erythrocyte sedimentation rate fell to normal much earlier in cases receiving massive dosage. Taran and Jacobs (1945), who worked with children, were of the same opinion. Reid (1948) also agreed with Coburn that a plasma salicylate level between 30 - 40 mgms. per cent caused a more rapid return of the sedimentation rate to normal (i.e. 10 mms. in 1 hour). He claimed that the average daily fall of the erythrocyte sedimentation rate to normal, or during the first 21 days if a normal reading had not been obtained in that time, varied according to the concentration of salicylate in the blood. The rate of fall was low when the blood salicylate level was reduced and high when the blood salicylate level was raised. The

average daily fall of adequately and inadequately treated cases of the present series was calculated in this way, but bore no relationship to the concentration of salicylate in the plasma. This is clearly seen in Table 4.

Name	Initial E.S.R.	Average blood salicylate level	Average fall/day.
J.B.	100	19.0	4.3
W.S. (1)	78	25.9	3.0
R.S.	77	19.8	3.7
M.H.	74	9.8	3.0
E.D.	70	21.3	3.0
T.C.	58	19.0	2.0
P.E.	56	19.0	2.0
A.Li.	42	16.5	1.2
M.McD.(1)	134	35.5	5.5
M.McD.(2)	114	36.8	4.4
M.A.	90	36.0	3.4
E.W.	88	32.3	3.5
C.K.	70	34.9	3.0
D.McF.	65	47.4	4.4
A.Le.	56	43.8	2.3
W.G.	55	42.4	4.3
D.C.	52	37.3	1.6
W.S. (2)	25	34.6	1.8

TABLE 4.

The relationship between the initial Erythrocyte Sedimentation Rate and the average daily fall of the Sedimentation Rate when the average concentration of salicylate in the blood was either above or below 30 mgms. %.

The cause of a high average daily fall was not the level of salicylate in the blood but the initial height

of the erythrocyte sedimentation rate. The exceptions were the cases of D.McF. and W.G. Both had been ill for some time before admission to hospital and it is probable that the sedimentation rate had begun to fall rapidly at the time when treatment was commenced. There was no support for Reid's conclusion that the fall of the erythrocyte sedimentation rate to normal is accelerated by adequate levels of salicylate in the blood.

The use of the erythrocyte sedimentation rate as an index of the efficacy of massive salicylate therapy, has not escaped criticism. Harris (1947) and Homburger (1946) have both stated that the action of the salicylates upon the sedimentation rate is not due to a suppression of the rheumatic process but to a non-specific action. They based their conclusions upon the fact that large doses of salicylate tended to lower the erythrocyte sedimentation rate nonspecifically in such widely different diseases as pulmonary tuberculosis, rheumatoid arthritis and generalised carcinomatosis. Rapaport and Guest (1946) found a significant reduction of the plasma fibrinogen during salicylate medication in both rheumatic and non-rheumatic subjects, and a lowering of the sedimentation rate. Homburger (1946) estimated that the reduction of the fibrinogen was comparable to that caused by liver toxins.

Lichty and Hooker (1941) suggested that the explanation of the non-specific action of the salicylates on the sedimentation rate was to be found in a paper by Bendien, Neuberg and Snapper. This work described in vitro experiments which showed that a minimum concentration of salicylate in the plasma of 90 - 120 mgms. per cent, reduced the erythrocyte sedimentation rate. The obvious criticism of these findings is that such levels are likely to cause death or grave signs of salicylate poisoning in a human patient. However, Homburger (1945) has since found that if sodium salicylate remained in contact with the plasma for 20 hours, at room temperature and under sterile conditions, then therapeutic levels of salicylate in the plasma produced marked slowing of the sedimentation rate.

Homburger's experiment was repeated in the present study but his findings were not confirmed. The addition of sodium salicylate up to concentrations of 100 mgms. per cent had little effect upon the erythrocyte sedimentation rate if the test was performed at once. When the estimation was made 20 hours after the addition of salicylate, the sedimentation rate was reduced in some but not in all cases. The variation in the findings is shown in Table 5. It is difficult, except in case 2, to find an explanation for

these differences. This patient suffered from nephrotic nephritis with low serum proteins and a raised serum cholesterol. A high cholesterol content in the blood is a recognized, though uncommon cause of an accelerated erythrocyte sedimentation rate (Ham and Curtis, 1938).

		ACTUAL E.S.R.						CORRECTED E.S.R.					
		Concentration of Salicylate in mgms. per cent.						Concentration of Salicylate in mgms. per cent.					
CASE		0	20	30	40	60	100	0	20	30	40	60	100
I	Immediate	65	62	-	62	-	64	30	30	-	30	-	30
	After 24 hrs.	63	64	-	56	-	10	30	22	-	14	-	10
II	Immediate	61	-	60	-	60	64	30	-	30	-	30	30
	After 24 hrs.	67	-	68	-	68	68	30	-	30	-	30	30
III	Immediate	64	67	-	66	65	65	30	30	-	30	30	30
	After 24 hrs.	60	54	-	31	16	2	22	15	-	5	4	2
IV	Immediate	63	-	-	64	63	64	30	-	-	30	30	30
	After 24 hrs.	64	-	-	66	66	53	30	-	-	30	30	10
V	Immediate	48	-	46	-	47	47	15	-	15	-	12	12
	After 24 hrs.	44	-	31	-	18	22	10	-	5	-	4	4
VI	Immediate	57	-	57	-	60	-	22	-	22	-	22	-
	After 24 hrs.	54	-	45	-	18	-	16	-	12	-	2	-
VII	Immediate	52	-	51	53	57	55	14	-	14	14	14	14
	After 24 hrs.	33	-	60	59	66	62	5	-	14	14	20	20
VIII	Immediate	59	-	57	-	57	57	22	-	20	-	20	20
	After 24 hrs.	45	-	35	-	22	18	10	-	5	-	5	5

TABLE 5. The Erythrocyte Sedimentation Rates obtained 30 minutes and 20 hours after the addition of increasing concentrations of salicylate to the plasma. "Corrected" readings were read from a chart (Whitby and Britton). This eliminated differences due to the variations in Packed Cell Volume in each experiment.

This whole experiment is subject to the criticism that, by allowing the plasma to stand for even so short a time as 5 - 6 hours significant slowing of the erythrocyte sedimentation rate will be produced (Ham and Curtis, 1938). This slowing was not usually seen in salicylate-free plasma that had stood at room temperature for 20 hours. A possible explanation of the effect of the salicylate is contained in the work of Ira Morrison (1946). She suggested that blood fibrinogen was composed of several fractions, and whilst one of these was very active in causing a rapid sedimentation rate, the others were relatively inert. The active fraction was called contractinogen. It was separated out by the lowest concentrations of the salting out solution, and "gradually clotted out of blood plasma upon standing in vitro, in spite of the presence of such anti-coagulants as oxalates and citrates." Morrison also remarked that - "this may help to explain why the blood sedimentation rate becomes slower after blood has been allowed to stand for several hours." This raises the possibility that the in-vitro addition of varying concentrations of salicylate causes contractinogen to clot and so slows the erythrocyte sedimentation rate. Whilst there is no doubt that such in-vitro experiments sometimes slow the erythrocyte sedimentation rate, the conditions are so artificial that one has little confidence that they reproduce the actions of the salicylates in the body.

The fact that the salicylates have not been shown to hasten the return of the erythrocyte sedimentation rate to normal does not necessarily mean that the drug has no anti-rheumatic action, and leaves untouched Coburn's claim that all the cases treated with adequate doses escaped heart damage. But a doubt about whether the drug can suppress the rheumatic reaction was raised by the case of W.G. (who, incidentally, showed a high average daily fall of his erythrocyte sedimentation rate). The boy was admitted to hospital on 24.2.48 and was found to have large nodules on his occiput and small ones on his knuckles and malleoli. His heart was enlarged and loud blowing systolic and diastolic murmurs were heard at his apex. Large doses of acetylsalicylic acid were prescribed and he soon achieved and maintained levels of salicylate in the blood between 35 and 58 mgms. per cent. The erythrocyte sedimentation rate fell rapidly from the initial reading of 55 mms. in one hour on 26.2.48 to 8 mms. in one hour on 7.3.48. In spite of this and his high level of salicylate in the blood, more than twenty small nodules developed on his left elbow and those on his knees and ankles became more numerous. Such an occurrence casts suspicion upon the claim that the rheumatic reaction has been suppressed, and emphasises the warning given by Massell (1938) that a normal sedimentation rate suggests but does not prove quiescence.

It is difficult to believe that the process has been combatted if it is accepted that the nodules afford visible evidence of an active rheumatic process. Murphy (1945) has also recorded the appearance of nodules when the level of salicylates was above 30 mgms. per cent. The case of L.B. provided an illustration that a low sedimentation rate does not necessarily indicate activity. She developed nodules at the end of her course of salicylate, and these persisted and became more obvious despite the fact that repeated estimations of the sedimentation rate never exceeded 11 mms. in one hour. She did not have congestive failure.

The view that nodules indicate activity is not universally accepted since some authorities believe that they appear during convalescence. Perry (1934) stated that - "as is usual the nodules developed at the end of or late in the attack and in nine of the cases they appeared when the erythrocyte sedimentation rate had fallen to between 10 and 20, in six the sedimentation rate was over 20 at the time the nodules first appeared, in the remaining case which was not seen until the nodules had appeared the erythrocyte sedimentation rate was 6."

SUMMARY.

1. Adequate concentrations of salicylate in the plasma do not accelerate the return of the erythrocyte sedimentation rate to normal.

2. Reid's claim that the average daily fall of the erythrocyte sedimentation rate to normal was increased by adequate concentrations of salicylate in the plasma, was not confirmed. A high average daily rate of fall in the erythrocyte sedimentation rate did not seem to depend upon the level of salicylate in the blood but on the initial height of the erythrocyte sedimentation rate.

3. The Erythrocyte Sedimentation Rates, obtained 30 minutes and 20 hours after the addition of increasing concentrations of salicylate to plasma, showed that prolonged standing reduced the erythrocyte sedimentation rate in some but not all cases. Homburger's findings were not confirmed.

4. The development of nodules, when the concentration of salicylate in the blood was maintained between 35 and 58 mgms. per cent, is described.

5. The conclusion drawn from this section of the work is that from investigations centred on the erythrocyte sedimentation rate, there is no advantage to the rheumatic child in administering massive doses of salicylate.

SUMMARY AND CONCLUSIONS.

The history of salicylate in the treatment of rheumatism is reviewed and particular attention given to the recent claim of Coburn that massive salicylate therapy will prevent the occurrence of cardiac damage.

A study of massive therapy in a group of rheumatic children is reported. The following paragraphs review the investigations which were made and the conclusions which have been drawn.

1. It has been shown that in children (i) a single dose of salicylate and (ii) a mixture of sodium salicylate and an equivalent amount of sodium bicarbonate produced almost identical concentrations of salicylate in the blood. Maximum levels were reached in two hours and a slow decline began after four hours.

2. A single dose of acetylsalicylic acid produced a lower concentration of salicylate in the plasma than the above, took four hours to reach a maximum, but the fall in the concentration thereafter was slow and justified the adoption of six hourly administration. It was shown that there was a gross retardation of absorption when the drug was given in tablet form.

3. Although with single doses of salicylate there was no material difference in the concentration of salicylate in the plasma if sodium bicarbonate was given at the same time yet with prolonged administration the addition of alkali produced a fall in the level of salicylate in the blood. Continued intake of ammonium chloride had the opposite effect. It was shown that these variations were associated directly with the pH of the urine and that the fall in blood level with alkali was due to increased excretion of free salicylate. This is important if a serious effort is being made to emulate Coburn and maintain a high blood salicylate level. Mixtures of one part of sodium salicylate and two parts of sodium bicarbonate failed to maintain adequate concentrations in the blood, the range being 15 to 22 mgms. per cent. Comparable six hourly doses of 1 to 1½ grains of acetylsalicylic acid per pound of body weight per day did produce continued high blood salicylate levels of between 30 and 40 mgms. per cent.

It must therefore be concluded that children require salicylate in doses comparable to those needed by adults to satisfy Coburn's stipulation for the successful treatment of rheumatism, and that the salicylate should be given without alkali.

4. Investigation of the effect of prolonged administration

of doses such as these showed that if a loading dose in excess of 1½ grains per pound body weight was given a very high concentration of salicylate in the blood was obtained, was unnecessary and in fact dangerous. Large does were tolerated better when the blood concentration was raised more slowly to an adequate level over a period of two to three days. This could be done by giving 1½ grains of acetylsalicylic acid per pound of body weight per day for two or three days and the level could then be maintained by 1 1/4 grains per pound of body weight per day. On this routine a plasma level between 25 to 47 mgms. per cent could be anticipated with confidence. The successful maintenance of such levels was shown to depend on the efficiency of the nursing staff and fell when the standard of nursing attention deteriorated.

For two reasons (i) because of the liability of the child to toxic upset in the initial stages of treatment, and (ii) because of the constant need for skilled nursing throughout the period of treatment it is apparent that massive salicylate therepy is suitable for use only in an efficient hospital and quite unsuitable for treatment at home.

5. The incidence of salicylate intoxication has increased since the resumption of massive salicylate therapy. Vomiting, hyperpnoea, and listlessness were common. Vomiting was not

caused by constipation but tended to show dependence on the blood salicylate level. The average blood salicylate concentration when vomiting began was 37 mgms. per cent. Hyperpnoea was noticed when the level of salicylate in the blood was 41 mgms. per cent and the early stage of hyperpnoea - increase in depth of respiration without increase in rate - was the best clinical indication that the concentration of salicylate in the plasma was adequate. Listlessness was common but difficult to assess, particularly in the first few days of treatment if the child has just been admitted to hospital and had therefore no "normal" behaviour to guide the observer's conclusions. Other signs of overdosage - an acneiform rash in one instance and epistaxis in three others - were too indefinite to be of clinical value in estimating an overdose of salicylate.

It was found that two commonly mentioned features of salicylate toxicity in adults - tinnitus and deafness - were not often noticeable in children.

6. The possible complications induced by massive salicylate treatment of rheumatism are further extended by the study of four instances of so-called rheumatic pneumonia. These developed when the blood salicylate was at a high level or a patient was unable to tolerate the drug. Though three made a spontaneous recovery on the discontinuation of

salicylate, the fourth was a source of considerable anxiety for some days andhad to be treated with intravenous fluid and oral digoxin before that anxiety was allayed. It is suggested that the occurrence of four rheumatic pneumonias in a small unselected series of 32 children with acute rheumatism is abnormal and indicates some association with the treatment they received - massive salicylate therapy. This again emphasises the unsuitability of such treatment for home use.

7. The sedimentation rate is generally accepted as an indicator, except in the presence of congestive failure, of the activity of a rheumatic infection. In this study it was found that adequate concentrations of salicylate in the plasma did not accelerate the return of the erythrocyte sedimentation rate to normal. A high average daily rate of fall did not seem to depend upon the level of salicylate in the blood but on the initial height of the erythrocyte sedimentation rate itself.

8. The erythrocyte sedimentation rate obtained thirty minutes and twenty hours after the addition of increasing concentrations of salicylate to the plasma in vitro, showed that prolonged standing reduced the rate in some but not all cases. This was taken as an indication that any fall

in the erythrocyte sedimentation rate in rheumatic children was associated with an improvement of their pathological condition and not with the blood level of salicylate; in fact that the erythrocyte sedimentation rate and the plasma salicylate levels were not related to one another. This conclusion was confirmed by the finding of freshly developed nodules in children whose blood salicylate had been maintained at values between 35 and 50 mgms. per cent. The present observations on the erythrocyte sedimentation rate, and some supporting evidence from the literature, are disappointing from a therapeutic point of view and do not give any support for continuing the use of massive doses of salicylates.

9. The overall impression is one of disappointment. In no single respect has it been possible to show any major benefits to the rheumatic child when large doses of salicylate were given. On the other hand such treatment may actually produce deterioration in the patient's condition by provoking signs of salicylate intoxication or precipitating an attack of rheumatic pneumonia. Further, the treatment is only feasible in hospital, with a high standard of nursing care, and unsuitable for use in the home. The greatest argument in favour of massive salicylate therapy, prevention of cardiac damage, was disproved by the development of cardiac

lesions in some of the children while under observation for this study.

The treatment of juvenile rheumatism with massive doses of salicylate cannot be recommended.

A P P E N D I X I.

METHOD OF DETERMINING THE PLASMA LEVEL OF SALICYLIC ACID.

Salicylate Therapy in Rheumatism.
A.F. Coburn) Bulletin Johns Hopkin's Hospital
73:435 (1943).

"1 cc of plasma is placed in a 30 cc stoppered flask. To this add 0.5 cc 5_N HCl and 20 cc of ethylene dichloride. The flask is agitated on a shaking machine for at least 5 minutes. An aliquot of 10 cc is removed in a syringe with a long needle, special care being taken not to contaminate the ethylene dichloride layer with the supernatant acid-water layer. The ethylene dichloride aliquot of 10 cc is placed in another stoppered flask to which is added 10 cc of distilled water and 0.5 cc of 1% ferric nitrate. The flask is again agitated in a shaking machine for 5 minutes. About 7 ccs of the supernatant purple water layer are removed. The colour is matched promptly in a colorimeter against a known standard concentration of sodium salicylate in plasma, which has been treated in parallel with the samples to be tested. The content of salicylate in plasma is calculated. It is convenient to use larger quantities of plasma if the salicyl radicle is below 100 gamma/cc. The content of the drug in the erythrocytes is negligible."

The method used in the determination of the free salicylate in the urine of M.McD. and W.G. (Charts 4 and 5).

Smith, Gleason, Stoll and Ogorzalek J.Pharmacology 87: 237

"STANDARD SOLUTIONS.

Sodium salicylate solution: 1.160 Gm of sodium salicylate dissolved in water and made up to 1 litre. 1 cc of plasma, 1 cc of water and 0.5 cc of 6 N HCl and 30 cc of ethylene dichloride in a 60 cc glass stoppered Pyrex bottle. Shake vigorously for 5 minutes in a shaking apparatus. Transfer the mixture to a 50 cc centrifuge tube and centrifuge for 5 minutes at a moderate speed. Remove the supernatant aqueous layer by aspiration. Transfer exactly 20 ccs of ethylene dichloride layer to a dry 60 cc glass stoppered bottle, add 10 cc of water and 0.25 cc of iron reagent. Shake for 5 minutes. Transfer at least 6 cc of supernatant aqueous layer to a colorimeter tube. Read in the Evelyn colorimeter using a filter with maximum transmission of 540 mu. Read from the ethylene dichloride curve for plasma.

SALICYL FRACTIONS IN URINE.

a. Urine diluted 1 to 10 or 1 to 20 and the extraction is carried through with ethylene dichloride as for plasma and the values are read in the ethylene dichloride curve of the graph.

b. Similar procedures used with carbon tetrachloride as the solvent and the results are read on the carbon tetrachloride curve of the graph.

c. A procedure similar to that with ethylene dichloride is employed but, instead of dilute acid and water, 0.5 cc dilute urine and 1 cc of concentrated HCl are added and the mixture hydrolysed for 3 hours by immersing the lower part of the bottles in the steam bath. After cooling 1.0 cc of water, 30 ccs of ethylene dichloride are added, and the procedure carried out at above. The readings are then made on the standard curve for ethylene dichloride and multiplied by the appropriate dilution factor. The results are calculated as below :-

$$SU = 2.00 \ (EDC - CCl_4)$$

$$SA = CCl_4 - 0.04SU$$

$$ST = EDC \text{ (hydrolysed)} + 0.33SU$$

where SA refers to free salicylate
SU refers to salicyluric acid
ST refers to total salicyl fractions as salicylate
EDC refers to reading on ethylene dichloride curve
CCl_4 refers to reading on carbon tetrachloride curve."

The method used in determining the Erythrocyte Sedimentation Rates 30 minutes and 20 hours after the addition of increasing concentrations of salicylates to the plasma. (Table 5.)

Homburger, F. Am. J. Med. Sci., 210: 168.

"The corrected sedimentation rate was determined by the method of Rourke and Ernstene, using as an anti-coagulant a dry mixture of 4 mgms of potassium oxalate and 6 mgms of ammonium oxalate in 5 ccs of blood.

For the study of the effects of salicylate, the plasma was separated from the cells by slow spinning and transferred to test tubes in amounts of 2 cc per tube; the sodium salicylate was then added in the form of a solution of 2 Gm in 100 ml of isotonic sodium chloride solution. One tube was left without salicylate as a control; to the others were added amounts to make concentrations of 20, 30, 60, 90, 120, 150, 180, 210 mgms per cent. The quantities of diluent were kept the same in all tubes by the additions of physiologic saline solution in amounts inversely proportional to the quantities of sodium salicylate used. Plasma thus prepared was kept sterile and was left standing for various lengths of time. In order to determine the erythrocyte sedimentation rate in such plasma, fresh cells were obtained from the same individual by slowly centrifuging oxalated blood and pipetting the cells into the prepared plasmas in

amounts resulting in the original haematocrit value and cells were left in contact for 30 - 120 minutes and the erythrocyte sedimentation rate was then determined as usual. All results are given in mms per minute and are corrected for a haematocrit of 45 per cent, according to the chart of Rourke and Ernstene. The use of this chart in the presence of salicylate is justified because this salt does not alter the mean corpuscular volume."

MODIFICATION.

In the present experiment the erythrocyte sedimentation rate was estimated by the Wintrobe method instead of by that of Rourke and Ernstene. The "corrected" readings for the Wintrobe method were obtained from a chart contained in "Disorders of the Blood", 4th Edition pg. 547, by Whitby and Britton.

APPENDIX II.

M.A., aged 5½ years, weight 15.4 Kilos. (34 pounds), was admitted to hospital on 27.8.48. Her illness began on 20.8.48 with frequent vomiting, but on 25.8.48 she developed pains in her right leg, right groin, and epigastrium. When she was admitted her ankle was slightly swollen; her apex beat was palpable in the fourth interspace in the nipple line and soft systolic and mid diastolic murmurs were heard at the apex. Treatment with acetylsalicylic acid was begun at once. Persistent vomiting throughout the course was ignored because the other signs of salicylate toxicity were mild and she had only slight hyperpnoea.

TREATMENT.

27.8.48 - 75 grains of acetylsalicylic acid
20.8.48 and 29.8.48 - 60 grains of acetylsalicylic acid/day
30.8.48 to 21.9.48 - dose varied between 30 - 50 grains of acetylsalicylic acid/day.

Blood salicylate in mgms. %	
29.8.48	41.6
31.8.48	32.0
3.9.48	34.0
6.9.48	47.2
9.9.48	24.8
13.9.48	31.2
16.9.48	32.8
20.9.48	40.0

Date and frequency of vomiting.			
28.8.48	3	11.9.48	2
29.8.48	1	13.9.48	1
30.8.48	3	14.9.48	1
31.8.48	1	15.9.48	1
1.9.48	1	16.9.48	1
2.9.48	1	17.9.48	1
3.9.48	1	19.9.48	2
9.9.48	2	20.9.48	1
10.9.48	1	22.9.48	1

E.S.R. in 1 hour		Dates when hyperpnoea occurred		Dates when drowsiness occurred
29.8.48	90	29.8.48	30.8.48	31.8.48
31.8.48	138	31.8.48	1.9.48	1.9.48
3.9.48	118	6.9.48	7.9.48	2.9.48
6.9.48	105	7.9.48	9.9.48	14.9.48
9.9.48	70	10.9.48	13.9.48	
13.9.48	42	20.9.48	22.9.48	
16.9.48	18			

C.B., aged 11½ years, weight 34 Kilos (75 pounds), was admitted to hospital on 19.2.48. During a previous admission in 1946, he had suffered from rheumatic carditis and pericarditis and was dismissed home with aortic valvular disease. He remained well, though he tired easily, until 14.2.48 when he complained of pains in his joints. During the next three days he became breathless, fevered and delirious. On admission he had no joint pains nor nodules. His pulse was collapsing in character, and his apex beat was palpable 1/2 inch outside the nipple line in the fifth interspace. The heart sounds were of poor quality and soft systolic and diastolic murmurs were heard at the apex. Two courses of salicylate therapy were stopped because he developed signs of salicylate toxicity. When he was dismissed home his cardiac condition was unchanged except that the quality of the sounds had improved.

TREATMENT.

1. Acetylsalicylic acid 90 grains/day from 21.2.48 to 28.2.48 when treatment was stopped.

2. Sodium salicylate grains 120
   Sodium bicarbonate grains 60 each day from 6.3.48 to 11.3.48 when treatment was stopped.

Blood salicylate in mgms. %		E.S.R. in 1 hour.		Date and frequency of vomiting.	
22.2.48	9.2	19.2.48	105	10.3.48	1
25.2.48	28.9	25.2.48	62		
29.2.48	24.8	2.3.48	61		
7.3.48	46.0	9.3.48	50		
9.3.48	53.9	16.3.48	25		
		23.3.48	24		
		20.4.48	40		
		18.5.48	9		

Dates when hyperpnoea developed	Dates when drowsiness occurred.
28.2.48	11.3.48
11.3.48	

J.B., aged 9½ years, weight 26.6 Kilos. (58½ pounds), was admitted to hospital on 2.11.47. Early in October he had complained of sore throat, sore ears, headache, fever and cervical adenitis for three days. On 31.10.47 his knees and ankles were painful and next day these joints, as well as his wrists, were swollen and sore. On admission his apex beat was palpable in the fourth interspace within the nipple line; a soft systolic murmur and a split second

sound were heard at the apex. The first of two courses of salicylates was stopped because of vomiting. On dismissal he had no enlargement of his heart but a loud systolic murmur was present at the apex.

TREATMENT.

1. Sodium salicylate grains 50
   Sodium bicarbonate grains 100 each day from 2.11.47 to 7.11.47 when treatment was stopped.

2. Sodium salicylate grains 50
   Sodium bicarbonate grains 25 each day from 10.11.47 to 2.12.47 when treatment was stopped.

Blood salicylate in mgms. %		E.S.R. in 1 hour.		Date and frequency of vomiting.
4.11.47	16.4	4.11.47	100	7.11.47 : 1
10.11.47	19.3	10.11.47	40	
13.11.47	22.6	19.11.47	20	
19.11.47	24.6	24.11.47	5	
24.11.47	22.5	2.12.47	3	
2.12.47	32.6	7.12.47	4.	

L.B., aged 6 4/12 years, weight 18.1 Kilos. (40 pounds), was admitted to hospital on 19.7.48. She had an attack of Scarlet Fever in February, 1948 and during March had pains in her legs and hands but no joint involvement. On 12.7.48 she became fevered and complained of pains in her legs and hands. Five days later the joints of her hands became swollen and red. When she was examined on admission her

metacarpal joints were swollen and red, her knees and ankles swollen and she resented any movement of her left elbow. A nodule was found on her right elbow. The apex beat was palpable in the fifth interspace one inch outside the nipple line. The heart sounds were rapid and of poor quality; a triple rhythm was heard at the apex. She had no pain after 21.7.48.

TREATMENT.

20.7.48 - Acetylsalicylic acid grains 70
21.7.48 to 4.9.48 - Acetylsalicylic acid grains 50 /day

Blood salicylate in mgms. %		E.S.R. in 1 hour		Dates when hyperpnoea occurred.
21.7.48	23.5	16.7.48	56	25.7.48
23.7.48	31.5	23.7.48	105	
29.7.48	15.2	4.8.48	22	
4.8.48	21.6	3.9.48	11	
9.8.48	34.0			
19.8.48	38.4			
3.9.48	32.0			

A.C., aged 12 years, weight 36.5 Kilos. (80 pounds), was admitted to hospital on 6.1.48. In September, 1947 she developed a sore throat and was absent from school for the next three weeks. During October she became listless and complained of stiff legs. She was kept in bed from then onwards but in spite of this, her left shoulder became painful on 20.12.47. On admission she was extremely ill;

there was a defective respiratory murmur at the base of the right lung and the liver was palpable four finger-breadths below the costal margin. She had no nodules. The apex beat was felt in the fourth interspace in the nipple line. The heart sounds were almost inaudible; systolic and diastolic murmurs were heard at the apex, and the presence of pericardial friction was queried. Treatment with salicylate was begun on 8.1.48 but was stopped on 11.1.48 because the patient developed congestive failure. The oedema became gross and failed to respond to treatment so the parents removed her from hospital against medical advice.

TREATMENT.

Sodium salicylate grains 120
Sodium bicarbonate grains 60 on 8.1.48

Sodium salicylate grains 75
Sodium bicarbonate grains 37½ on 9.1.48

Sodium salicylate grains 60
Sodium bicarbonate grains 30 on 10.1.48

Treatment stopped 11.1.48.

Blood salicylate in mgms. %		E.S.R. in 1 hour.		Date and frequency of vomiting.	
9.1.48	48.6	6.1.48	19	9.1.48	3
10.1.48	54.2	10.1.48	17	11.1.48	3
12.1.48	40.9	18.1.48	3	12.1.48	2
18.1.48	0.	23.1.48	5	26.1.48	2
		16.2.48	2	27.1.48	2
		29.2.48	3		
		3.3.48	2		

Dates when deaf.
11.1.48

Date when orthopnoeic
Date when orthopnoeic
19.1.48

D.C., aged 11 years and 10 months, weight 34.7 Kilos. (75 pounds), was admitted to hospital on 25.6.48 with swollen and tender wrists, ankles and toes. She had suffered from frequent mild sore throats, and her joints were liable to become swollen and painful after any slight strain.

TREATMENT.

Acetylsalicylic acid grains 90/ day from 26.6.48 to 29.6.48
Acetylsalicylic acid grains 75/ day from 30.6.48 to 14.6.48
Acetylsalicylic acid grains 40/ day from 15.6.48 to 19.6.48
Acetylsalicylic acid grains 50/ day from 19.6.48 to 10.8.48

Blood salicylate in mgms. %		E.S.R. in 1 hour.		Date and frequency of vomiting.	
28.6.48	28.0	26.6.48	52	9.7.48	1
30.6.48	52.0	5.7.48	40	12.7.48	1
8.7.48	40.5	12.7.48	20	14.7.48	2
10.7.48	27.2	18.7.48	15		
12.7.48	20.4	23.7.48	8		
15.7.48	55.4	3.8.48	6		
16.7.48	49.6	19.8.48	5		
18.7.48	36.2				
23.7.48	44.2				
4.8.48	50.4				
10.8.48	48.8				

Date when hyperpnoea occurred.	Dates when epistaxis occurred.	Dates when deafness occurred	Dates when tinnitus occurred
9.7.48	1.7.48	30.6.48	27.6.48
	3.7.48	2.7.48	28.6.48
	4.7.48		

J.C., aged 7 1/4 years, weight 20.2 Kilos. (45 pounds) a known case of rheumatic carditis, was admitted to RHSC on 27.2.48 because he had developed headache, sore throat, and anorexia on 18.2.48 and painful knees and shins on 20.2.48. On admission he had neither joint involvement nor nodules but had a collapsing pulse and his apex beat was in the sixth interspace one inch outside the nipple line. Systolic and diastolic murmurs were present at the base of the heart. Three courses of salicylate treatment were given but stopped because of toxic symptoms. Signs of pneumonia appeared during the last course on 25.4.48 and are described in the section on rheumatic pneumonia. He was discharged home on 23.6.48. His apex beat was in the sixth interspace 1½ inches outside the nipple line and systolic and diastolic murmurs were heard at the apex and base.

TREATMENT.

1. Sodium salicylate
   Sodium bicarbonate aa. grains 10 every 4 hours from 2.3.48 to 6.3.48.

2. Sodium salicylate grains 10
   Sodium bicarbonate grains 20 every four hours from 12.3.48 to 26.3.48.

3. Sodium salicylate grains 10 every four hours from 20.4.48 to 25.4.48.

Blood salicylate in mgms. %			E.S.R. in 1 hour.			Date and frequency of vomiting.		
4.3.48	:	29.5	2.3.48	:	70	6.3.48	:	1
6.3.48	:	62.2	8.3.48	:	76	26.3.48	:	2
8.3.48	:	0	14.3.48	:	90	27.3.48	:	1
14.3.48	:	30.3	23.3.48	:	82	24.4.48	:	1
16.3.48	:	29.5	30.3.48	:	70	25.4.48	:	2
19.3.48	:	15.0	7.4.48	:	16	28.4.48	:	1
25.3.48	:	23.5	13.4.48	:	12	1.5.48	:	1
25.4.48	:	17.6	20.4.48	:	50	2.5.48	:	1
			27.4.48	:	64			
			5.5.48	:	63			
			11.5.48	:	65			
			8.6.48	:	24			
			11.6.48	:	23			
			21.6.48	:	20			

Dates when hyperpnoea occurred.	Dates when drowsiness occurred.
6.3.48	6.3.48
25.4.48	13.3.48
26.4.48	26.3.48
27.4.48	25.4.48
	26.4.48
	27.4.48

T.C., aged 8 3/4 years, weight 25 Kilos. (55 pounds), was admitted to hospital on 10.9.48 suffering from rheumatic pericarditis. A well marked friction rub was heard. He was treated with a sodium salicylate-sodium bicarbonate mixture and showed no signs of salicylate toxicity. On discharge his heart was not enlarged but soft systolic and mid diastolic murmurs were present at the apex.

TREATMENT.

Sodium salicylate grains 60
Sodium bicarbonate grains 120 each day from 11.9.48 to 17.10.48 when treatment was stopped.

Blood salicylate in mgms. %		E.S.R. in 1 hour.	
13.9.48	21.6	11.9.48	58
16.9.48	18.4	16.9.48	60
20.9.48	17.2	20.9.48	38
23.9.48	23.2	23.9.48	28
27.9.48	23.6	27.9.48	18
1.10.48	10.0	1.10.48	20
6.10.48	19.6	6.10.48	6
12.10.48	20.4	12.10.48	5
		26.10.48	8.

E.D., aged 9 1/4 years, weight 20 Kilos. (44 pounds), was admitted to hospital on 21.1.48. She developed a painful right shoulder on 14.1.48 and since then complained of fleeting pains in both shoulders, wrist, fingers, knees and ankles. There was no swelling nor redness. Nodules were found when she was examined on admission. The apex beat was palpable in the fourth interspace in the nipple line; a systolic murmur conducted into the axilla was heard at the apex. The first of two courses of salicylate was stopped because she developed persistent vomiting on 24.1.48. She was transferred to the Country Branch on 23.2.48. When she was dismissed her heart was not enlarged and no murmurs were heard.

TREATMENT.

1. Sodium salicylate
   Sodium bicarbonate aa. grains 80/day on 22.1.48

   Sodium salicylate
   Sodium bicarbonate aa. grains 60/day on 23.1.48

2. Sodium salicylate
   Sodium bicarbonate aa. grains 60/day from 26.1.48 to 28.1.48

   Sodium salicylate
   Sodium bicarbonate aa. grains 90/day from 29.1.48 to 4.2.48

   Acetylsalicylic acid grains 80/day on 5.2.48

   Acetylsalicylic acid grains 40 - 50/day from 6.2.48 to 16.3.48.

Blood salicylate in mgms. %				E.S.R. in 1 hour.	
23.1.48	29.3	9.2.48	33.8	23.1.48	70
24.1.48	29.0	11.2.48	23.3	27.1.48	22
26.1.48	2.6	14.2.48	21.3	6.2.48	17
27.1.48	10.0	18.2.48	35.5	11.2.48	7
30.1.48	18.7	27.2.48	0	16.2.48	11
2.2.48	12.0	3.3.48	18.2	21.2.48	13
6.2.48	16.4	9.3.48	0	23.2.48	4
7.2.48	37.5				

Patient vomited twice on 23.1.48
six times on 24.1.48.

P.E., aged 12 3/4 years, weight 28.5 Kilos. (62½ pounds), was admitted to hospital on 13.12.47. He had had tonsillitis early in November, 1947 and had not been well since that time. On 1.12.47 he complained of pain in his right knee and a few days later in elbows and ankles. When he was examined

after admission he had no nodules. His apex beat was felt in the fifth interspace just outside the nipple line, and systolic murmurs were heard at the apex and base. He was treated with a sodium salicylate-sodium bicarbonate mixture and showed no signs of salicylate toxicity. On 12.1.48 he was transferred to the Country Branch. His heart was still slightly enlarged when he was dismissed home and a soft systolic murmur was present at the apex.

TREATMENT.

Sodium salicylate grains 75
Sodium bicarbonate grains 150 each day from 13.12.47 to 18.12.47.

Sodium salicylate grains 90
Sodium bicarbonate grains 180 each day from 19.12.47 to 3.2.48.

Blood salicylate in mgms. %		E.S.R. in 1 hour.	
15.12.47	14.5	13.12.47	75
22.12.47	21.6	22.12.47	35
29.12.47	34.3	29.12.47	27
6.1.48	25.5	6.1.48	40
9.1.48	19.0	11.1.48	15
13.1.48	15.0	27.1.48	16
27.1.48	15.0	3.2.48	13
3.2.48	9.1	24.2.48	8.

W.G., aged 12 years, weight 26.5 Kilos (58 pounds), was admitted to hospital on 25.2.48. He had suffered from frequent sore throats since he was eight years old. On 7.12.47 he complained of a painful right ankle but was

able to return to school within a week. His left ankle became swollen and sore on 29.12.47 and within a few days other joints were involved. Salicylates were prescribed by the family doctor on 2.1.48 but fleeting pains in the joints persisted. On 23.2.48 he complained of palpitations and admission to hospital was arranged. Nodules were found on his occiput, knuckles and knees on admission. The apex beat was palpable in the sixth interspace in the nipple line; a loud systolic and early diastolic murmurs were heard at the apex and a doubtful diastolic murmur along the left border of the sternum. He received two courses of salicylate therapy in hospital; the first was therapeutic, the second was given in order to measure the excretion of free salicylate in the urine. Whilst under treatment the nodules became very numerous on his elbows and knees.

TREATMENT.

1.	26.2.48	- 120 grains acetylsalicylic acid/day
	27.2.48	- 90 grains acetylsalicylic acid/day
	28.2.48	- 75 grains acetylsalicylic acid/day
	29.2.48 to 11.3.48	- 60 grains acetylsalicylic acid/day
	12.3.48 to 24.3.48	- 50 grains acetylsalicylic acid/day
	25.3.48	- 80 grains acetylsalicylic acid/day
	26.3.48 to 13.4.48	- 60 grains acetylsalicylic acid/day
2.	22.4.48 to 25.4.48	- 90 grains acetylsalicylic acid/day
	26.4.48 to 28.4.48	- 90 grains of acetylsalicylic acid and 160 grains of sodium bicarbonate per day.
	29.4.48 to 5.5.48	- 90 grains acetylsalicylic acid/day

Dates and frequency of vomiting.	Dates when hyperpnoea occurred.
27.2.48 : 2	26.4.48
28.2.48 : 2	27.4.48
29.2.48 : 1	30.4.48
1.3.48 : 1	2.5.48
23.4.48 : 1	3.5.48
26.4.48 : 1	4.5.48
26.4.48 : 1	5.5.48

Blood salicylate in mgms. %

27.2.48 : 41.9	24.4.48 : 40.0	
29.2.48 : 44.9	25.4.48 : 57.2	
2.3.48 : 47.4	26.4.48 : 38.4	
4.3.48 : 35.5	27.4.48 : 22.8	
8.3.48 : 36.3	28.4.48 : 24.8	
12.3.48 : 58.0	29.4.48 : 40.0	
14.3.48 : 43.4	30.4.48 : 47.6	
19.3.48 : 22.0	3.5.48 : 51.0	
23.3.48 : 10.0	4.5.48 : 42.0	
6.4.48 : 30.7	5.5.48 : 43.7	
13.4.48 : 13.9		

E.S.R. in 1 hour.

26.2.48 : 55
2.3.48 : 30
7.3.48 : 8
14.3.48 : 7
6.4.48 : 5
25.4.48 : 5
3.5.48 : 4
9.5.48 : 5

Tinnitus occurred on 29.2.48.

Details of the excretion of free salicylate in the urine and the pH of the urine in the experiment shown in Chart 5.

Date	Grams of free salicylate	pH of Urine
24.4.48	0.083	5
	0	5
	0.10	5.5
25.4.48	0.003	5
	0.006	5
	0.013	5
	0.007	5
26.4.48	0.444	6
	1.872	8
	0.457	8
	0.022	5

Date	Grams of free salicylate	pH of Urine
27.4.48	0.396	8
	0.959	7.5
	0.615	7.5
	0.269	6
28.4.48	0.188	8
	1.342	7.5
	0.226	6
	0.480	5
29.4.48	0.215	5.5
	0.103	5
	0.204	5
	0.055	5.5

M.He., aged about 9 years, weight 27.1 Kilos. (60 pounds), was admitted to hospital on 7.8.48. In January, 1948 she began to complain about joint pains and intermittent abdominal pain which lasted for six to eight weeks. On 4.8.48 her joints again became painful and her right knee and mid phalangeal joints became swollen. She had an epistaxis. No nodules were found on admission to hospital. Her heart was enlarged and the apex beat was palpable in the fifth interspace a quarter of an inch outside the nipple line. A harsh systolic murmur and a doubtful diastolic murmur were heard at the apex of the heart. She was treated with acetylsalicylic acid and adequate levels were maintained without difficulty. Sweating was a prominent symptom.

TREATMENT.

7.8.48 to 8.8.48 - acetylsalicylic acid 90 grains/day.
9.8.48 to 8.9.48 - acetylsalicylic acid 75 grains/day.

Blood salicylate in mgms. %		E.S.R. in 1 hour.		Dates when hyperpnoea occurred.
8.8.48	18.8	10.8.48	14	14.8.48
10.8.48	18.4	17.8.48	14	16.8.48
13.8.48	40.0	20.8.48	20	17.8.48
15.8.48	44.0	23.8.48	6	18.8.48
17.8.48	41.0	31.8.48	25	20.8.48
20.8.48	55.2	6.9.48	4	23.8.48
23.8.48	40.8			27.8.48
27.8.48	40.8			
31.8.48	44.0			
3.9.48	48.0			
6.9.48	47.2			

Date when deafness occurred.

12.8.48

M.H., aged 7 years, weight 20.1 Kilos. (48 pounds) was admitted to hospital on 26.12.47. She had growing pains in 1943. Towards the end of November, 1947 she developed tonsillitis and on 25.12.47 complained of pains in her feet and left knee. Next day the right knee was also sore and her wrists were red and swollen. On admission she had no nodules and her heart was not enlarged. A systolic murmur was heard at the apex. She had an epistaxis on 29.12.47. There was no vomiting nor hyperpnoea.

TREATMENT.

Sodium salicylate grains 60
Sodium bicarbonate grains 120 each day from 26.12.47 to 4.2.48.

Blood salicylate in mgms. %		E.S.R. in 1 hour.	
2.1.48	21.4	27.12.47	74
6.1.48	5.0	2.1.48	57
7.1.48	3.0	6.1.48	20
20.1.48	10.6	20.1.48	10
27.1.48	11.3	24.2.48	7

C.K., aged 4½ years, weight 15.8 Kilos. (35 pounds), was admitted to hospital on 13.3.48. In October, 1947 he fell down some stairs and after this complained of sore knees. He was examined at a clinic and the diagnosis of primary tuberculous infection was made. On 23.1.48 he was sent to a convalescent home but his health did not improve. On 23.2.48 he began to have repeated epistaxes and a systolic murmur was heard. When he was admitted to hospital he was very pale and his tonsils were greatly enlarged. His apex beat was palpable half an inch outside the nipple line and a loud systolic murmur was heard over this area. He had no nodules. On discharge from hospital the condition of his heart was unchanged.

TREATMENT.

Sodium salicylate grains 75 Sodium bicarbonate grains 37½	on 16.3.48	
Sodium salicylate grains 45 Sodium bicarbonate grains 22½	each day	from 17.3.48 to 25.3.48
Sodium salicylate grains 60 Sodium bicarbonate grains 30	each day	from 26.3.48 to 13.4.48.

Blood salicylate in mgms. %		E.S.R. in 1 hour.	Date when hyperpnoea occurred.
17.3.48 : 40.0		15.3.48 : 70	28.3.48
24.3.48 : 29.6		20.3.48 : 80	
26.3.48 : 38.5		26.3.48 : 18	
6.4.48 : 31.6		6.4.48 : 4	
13.4.48 : 0			

A. Le., aged 8 years and 10 months, weight 26.1 Kilos. (54 pounds), was admitted to hospital on 18.8.48. She suffered from a sore throat from 27.7.48 to 11.8.48. Abdominal pain began on 12.8.48 and on 15.8.48 the right great toe became painful. Two days later both her knees were swollen and sore. On admission she had no nodules; her knees and ankles were swollen. The apex beat was palpable in the fourth interspace one quarter of an inch outside the nipple line. A soft systolic murmur not conducted towards the axilla, was heard at the apex.

TREATMENT.

18.8.48 to 20.8.48 - acetylsalicylic acid 90 grains/day.
21.8.48 to 1.9.48 - acetylsalicylic acid 75 grains/day.
2.9.48 to 16.9.48 - acetylsalicylic acid 60 grains/day.

Blood salicylate in mgms. %		E.S.R. in 1 hour.	Dates when hyperpnoea occurred.
19.8.48 : 23.2		19.8.48 : 56	21.8.48
21.8.48 : 52.0		23.8.48 : 32	22.8.48
23.8.48 : 48.0		27.8.48 : 45	23.8.48
27.8.48 : 40.8		31.8.48 : 28	24.8.48
31.8.48 : 53.2		6.9.48 : 10	25.8.48
6.9.48 : 43.2			26.8.48
10.9.48 : 35.2			27.8.48
16.9.48 : 34.4			

Patient vomited on 21.8.48; was drowsy on 2.9.48.

A. Li., aged 10 years, weight 28.4 Kilos. (62½ pounds), was admitted to hospital on 2.1.48. His tonsils were removed early in December, 1947 and from then onwards he was not well. On 22.12.48 both his knees and ankles became swollen and painful. He was treated with salicylates but the joint pains kept on recurring. When he was examined on admission his right knee and ankle were swollen and red. His apex beat was felt in the fifth interspace in the nipple line. A soft systolic murmur was heard over this area. On discharge from hospital his heart was not enlarged and the sounds were pure.

TREATMENT.

2.1.48 to 8.1.48 -	Sodium salicylate	grains	60
	Sodium bicarbonate	grains	120/day.
9.1.48 to 15.1.48 -	Sodium salicylate	grains	90
	Sodium bicarbonate	grains	180/day.
16.1.48 to 2.2.48 -	Sodium salicylate	grains	90
	Sodium bicarbonate	grains	45/day.

Blood salicylate in mgms. %		E.S.R. in 1 hour.		Date and frequency of vomiting.	
3.1.48	13.9	3.1.48	42	7.1.48	1
5.1.48	7.1	8.1.48	22		
8.1.48	14.0	12.1.48	17		
12.1.48	19.1	27.1.48	18		
19.1.48	28.6	24.2.48	3		
27.1.48	15.6				
2.2.48	10.9				

R. McC., aged 9 8/12 years, weight 24.6 Kilos. (44 pounds), was admitted to hospital on 26.1.48. In July 1947 he contracted Scarlet Fever and in the middle of September developed chorea. The choreiform movements persisted and so he was kept in bed until the date of admission to hospital. Up till then all cases of rheumatism had been treated with a sodium salicylate-sodium bicarbonate mixture and the concentrations of salicylate in the plasma were disappointing. He was selected as a suitable subject for an experiment to determine whether adequate levels could be obtained with acetylsalicylic acid, and the effect of sodium bicarbonate upon these levels. Treatment was stopped on 19.2.48 because of vomiting.

TREATMENT.

30.1.48 to 8.2.48 - 60 grains acetylsalicylic acid/day.
9.2.48 to 16.2.48 - 60 grains acetylsalicylic acid and 60 grains sodium bicarbonate/day.
17.2.48 to 19.2.48 - 60 grains acetylsalicylic acid/day.

Blood salicylate in mgms. %		E.S.R. in 1 hour.		Dates and frequency of vomiting.	
31.1.48	12.0	26.1.48	7	18.2.48	2
5.2.48	34.1	3.2.48	5	19.2.48	2
9.2.48	49.3	10.2.48	5		
11.2.48	37.3	11.2.48	8		
16.2.48	24.2				
18.2.48	34.8				

Dates when hyperpnoea developed.

9.2.48
11.2.48.

D. McC., aged 9½ years, weight 32 Kilos. (70 pounds), was admitted to hospital on 17.5.48. A description of his case (D.McC.) is given in the section on Rheumatic Pneumonia. He had no cardiac enlargement but had an apical systolic murmur on dismissal.

Blood salicylate in mgms. %			E.S.R. in 1 hour.			Dates when hyperpnoea occurred.
18.5.48	:	8.5	17.5.48	:	42	21.5.48
20.5.48	:	41.6	23.5.48	:	32	23.5.48
22.5.48	:	42.9	30.5.48	:	22	24.5.48
25.5.48	:	48.3	4.6.48	:	30	25.5.48
27.5.48	:	54.0	13.6.48	:	25	27.5.48
30.5.48	:	42.1	20.6.48	:	20	28.5.48
			27.6.48	:	16	30.5.48
			20.7.48	:	6	31.5.48

Dates when drowsiness occurred	Dates when deafness occurred.
23.5.48	28.5.48
	30.5.48

M. McD. (1), aged 11 years, weight 29.6 Kilos. (65 pounds), was admitted to hospital on 13.3.48. She developed tonsillitis on 6.2.48 and a fortnight later complained of pain in her toes. This pain persisted until 6.3.48 when she complained of stiffness of her arms, back, neck and ankles. On admission to hospital she was obviously ill and unwilling to move her neck, shoulders or ankles. No nodules were present. Her apex beat was palpable in

the fourth interspace half an inch outside the nipple line. A systolic murmur was present at the apex and base. She received a very large loading dose of acetylsalicylic acid during the first day of treatment; later in the course the effect of ammonium chloride upon the concentration of salicylate in the plasma was studied; and finally sodium bicarbonate was shown to reduce the concentration of salicylate in the plasma and to increase the excretion of free salicylate in the urine. She developed a pustular rash and this has been fully described in the text.

TREATMENT.

13.3.48	-	150 grains of acetylsalicylic acid
14.3.48 - 5.4.48	-	50 to 60 grains acetylsalicylic acid/day
6.4.48 - 15.4.48	-	50 grains acetylsalicylic acid and 30 grains ammonium chloride/day.
16.4.48	-	60 grains acetylsalicylic acid and 120 grains sodium bicarbonate/day.
17.4.48 - 18.4.48	-	60 grains acetylsalicylic acid and 240 grains sodium bicarbonate/day.
19.4.48	-	60 grains acetylsalicylic acid/day.

Blood salicylate in mgms. %

14.3.48	64.8	9.4.48	25.3
16.3.48	69.5	12.4.48	21.3
19.3.48	38.3	15.4.48	43.5
24.3.48	20.8	16.4.48	37.3
26.3.48	30.8	17.4.48	37.0
2.4.48	19.6	19.4.48	4.8
5.4.48	25.3	20.4.48	20.0
7.4.48	24.9	22.4.48	26.9

Dates when hyperpnoea occurred

14.3.48
15.3.48
26.3.48
15.4.48

E.S.R. in 1 hour

14.3.48	134
20.3.48	120
26.3.48	30
5.4.48	12
12.4.48	5
19.4.48	5.

Details of the excretion of free salicylate in the urine and the pH of the urine in the experiment shown in Chart 4.

Date	Grams of free salicylate		pH of urine
15.4.48	0.020		5.5
	0.022		5.5
	0.002		5.5
	0.005		5
		Total 0.049	
16.4.48	0.034		5
	0.108		5.5
	0.142		5
	0.013		5
		Total 0.297	
17.4.48	0		-
	0.022		5.5
	0.32		5.5
	0.265		7
		Total 0.607	
18.4.48	0.429		5
	0		-
	0.446		8
	0.273		8
		Total 1.148	
19.4.48	0.093		8
	0.212		7.5
	0.299		7.5
	0.068		7
		Total 0.672	
20.4.48	0.098		5
	0.097		6
	0.061		5
	0.060		5
		Total 0.316	

M. McD. (2), aged 11 years, weight 36.1 Kilos. (80 pounds), was re-admitted to hospital on 3.10.48. She had been treated with a daily prophylactic dose of sulphadiazine for some months after discharge but had latterly neglected to take the drug. On admission she had acute rheumatic polyarthritis. Her apex beat was palpable in the fourth interspace in the nipple line and a soft systolic murmur was heard over this area. There were no nodules. On 4.1.49 her heart was not enlarged and a soft systolic murmur was heard.

TREATMENT.

4.10.48 - 105 grains acetylsalicylic acid.
5.10.48 - 9.11.48 - 90 grains of acetylsalicylic acid/day.

Blood salicylate in mgms. %		E.S.R. in 1 hour.		Dates when hyperpnoea occurred.
6.10.48	35.6	4.10.48	114	6.10.48
8.10.48	38.0	8.10.48	113	8.10.48
12.10.48	39.2	12.10.48	80	9.10.48
15.10.48	36.0	15.10.48	45	13.10.48
18.10.48	40.0	18.10.48	35	18.10.48
21.10.48	40.0	21.10.48	28	21.10.48
25.10.48	40.0	25.10.48	22	22.10.48
28.10.48	42.0	28.10.48	18	
2.11.48	21.0	2.11.48	12	

Date when deafness occurred.	Date when drowsiness occurred.
6.10.48	7.10.48.

D. McF., aged 8 7/12 years, weight 22.2 Kilos. (49 pounds), was admitted to hospital on 3.3.48. About 5.2.48 he was suspected of having appendicitis but this diagnosis was not confirmed. On 29.2.48 he became listless, his ankles were swollen and his knees were stiff. He complained of pain when he walked. When he was examined on admission his apex beat was palpable in the fourth interspace within the nipple line, a systolic murmur was heard at the base and there were no nodules. He was treated with acetylsalicylic acid and whilst he was taking the drug developed nodules on his elbow and over the tendo Achilles. During the night of 8.3.48 he developed hallucinations. He was transferred to the Country Branch on 22.3.48. On discharge his heart was not enlarged but he had a soft apical systolic murmur.

TREATMENT.

4.3.48	-	100 grains acetylsalicylic acid
5.3.48 - 7.3.48	-	60 grains acetylsalicylic acid/day
8.3.48 - 24.3.48	-	40-50 grains acetylsalicylic acid/day
25.3.48	-	80 grains acetylsalicylic acid
26.3.48 - 13.4.48	-	60 grains acetylsalicylic acid/day.

Blood salicylate in mgms. %		E.S.R. in 1 hour.		Date when drowsiness appeared.
5.3.48	33.3	3.3.48	65	7.3.48
8.3.48	49.7	8.3.48	21	
12.3.48	61.0	16.3.48	8	
16.3.48	45.7	6.4.48	6	
19.3.48	34.2			Date when tinnitus occurred.
23.3.48	10.0			
6.4.48	20.0			8.3.48.
13.4.48	11.4			

H. McG., aged 7 11/12 years, weight 22.9 Kilos. (50 pounds), was admitted to hospital on 27.8.48. Erythema marginatum was noticed on his abdomen, buttocks and legs on 25.8.48. Next days the rash was more marked and he complained of pains in his ankles, knees, wrists, groin and neck. His throat was sore. When he was examined on admission the rash was still present on the flexor surfaces of his arms. His ankles, knees, wrists and elbows were swollen and tender. The tonsils were enlarged. The apex beat was palpable in the fifth interspace half an inch outside the nipple line and systolic murmurs were heard at the apex and base. He was discharged home after ten days because the family were emigrating to Australia.

TREATMENT.

27.8.48	- 60 grains acetylsalicylic acid
28.8.48 - 29.8.48	- 90 grains acetylsalicylic acid/day
30.8.48	- 75 grains acetylsalicylic acid
31.8.48 - 2.9.48	- 60 grains acetylsalicylic acid/day
3.9.48	- 90 grains acetylsalicylic acid
4.9.48 - 13.9.48	- 75 grains acetylsalicylic acid/day.

Blood salicylate in mgms. %	E.S.R. in 1 hour.	Dates when hyperpnoea occurred.
29.8.48 : 24.8	29.8.48 : 120	30.8.48
31.8.48 : 34.4	31.8.48 : 119	31.8.48
3.9.48 : 23.6	3.9.48 : 118	4.9.48
7.9.48 : 28.0	7.9.48 : 97	7.9.48
10.9.48 : 32.8	10.9.48 : 38	

Dates when drowsiness occurred.	Dates and frequency of vomiting.
31.8.48 4.9.48 10.9.48	30.8.48 : 1 2.9.48 : 2
Date when deafness occurred.	**Date when sweating occurred.**
31.8.48	29.8.48.

T.M., aged 11 years, weight 27.6 Kilos. (61 pounds), was admitted to hospital on 13.8.48. He had been listless, pale and 'off his food' for several days before admission and then developed a red and swollen right ankle. This was at first regarded as a traumatic injury but later his left elbow became swollen, red and tender and he complained of abdominal pain. He was sent to hospital as a case of acute appendicitis but this diagnosis was altered to one of acute rheumatism. When he was examined on admission his apex beat was felt in the fourth interspace within the nipple line and a soft systolic murmur was heard at this area. He was treated with acetylsalicylic acid but treatment was stopped on 30.8.48 because of salicylate toxicity.

TREATMENT.

14.8.48 - 17.8.48 - 90 grains acetylsalicylic acid/day.
18.8.48 - 22.8.48 - 75 grains acetylsalicylic acid/day.
23.8.48 - 60 grains acetylsalicylic acid.
24.8.48 - 27.8.48 - 75 grains acetylsalicylic acid/day.
28.8.48 - 90 grains acetylsalicylic acid/day.
29.8.48 - 30.8.48 - 75 grains acetylsalicylic acid/day.

Blood salicylate in mgms. %		E.S.R. in 1 hour.		Dates when hyperpnoea occurred.
17.8.48	32.8	17.8.48	95	17.8.48
19.8.48	48.8	23.8.48	40	20.8.48
23.8.48	34.0	27.8.48	45	21.8.48
27.8.48	30.0	30.8.48	40	23.8.48
30.8.48	51.4	7.9.48	15	25.8.48
		10.9.48	11	26.8.48
				30.8.48

Date when tinnitus occurred	Date when deafness occurred
15.8.48	17.8.48

Patient was very drowsy and incontinent of faeces on 30.8.48.

P.M., aged 7 years, weight 20.4 Kilos. (45 pounds), was admitted to hospital on 9.2.48. Every morning for three weeks in January, 1947 she suffered from pain and stiffness of her neck and hands. At the beginning of January, 1948 she began to have flitting pains in her hands, arms, neck and knees but it was not until 2.2.48 that her right knee became swollen. When she was examined on admission, she had nodules on her elbows and hands. The heart was not enlarged and no murmurs were heard. She was transferred

to the Country Branch on 23.2.48. On dismissal her apex beat was palpable in the fourth interspace in the nipple line and no murmurs were present.

TREATMENT.

11.2.48	-	100 grains acetylsalicylic acid
12.2.48 - 13.2.48	-	60 grains acetylsalicylic acid/day.
14.2.48 - 17.2.48	-	75 grains acetylsalicylic acid/day.
18.2.48 - 11.3.48	-	60 grains acetylsalicylic acid/day.
12.3.48 - 19.3.48	-	90 grains acetylsalicylic acid/day. because of a misunderstanding.

Blood salicylate in mgms. %		
12.2.48	:	32.0
14.2.48	:	25.0
18.2.48	:	46.7
27.2.48	:	0
2.3.48	:	10.0
9.3.48	:	0
19.3.48	:	55.0

E.S.R. in 1 hour.		
11.2.48	:	41
14.2.48	:	15
21.2.48	:	16
30.3.48	:	6

Dates and frequency of vomiting.		
12.2.48	:	1
18.3.48	:	1
19.3.48	:	3
20.3.48	:	1

Dates when hyperpnoea occurred.

19.3.48.

S.M., aged 5 years, weight 15.4 Kilos. (34 pounds), was admitted to hospital on 17.5.48. In January, 1948 she developed a 'chill' and had vague pains in her legs and side. Front that time onwards, she never felt really well. On 30.4.48 her right knee and ankle became swollen and red. During the next week she sweated a great deal and on 12.5.48 she complained of vomiting, a heaving chest and nausea.

When she was admitted to hospital the apex beat was palpable half an inch outside the nipple line in the fifth interspace. Systolic and diastolic murmurs were heard at the apex. She was treated with acetylsalicylic acid but treatment had to be stopped because she became so listless and drowsy. On dismissal her apex beat was just outside the nipple line and a systolic murmur was heard at this area.

TREATMENT.

18.5.48 - 22.5.48 - 50 grains acetylsalicylic acid/day.
23.5.48 - 29.5.48 - 40 grains acetylsalicylic acid/day.

Blood salicylate in mgms. %			E.S.R. in 1 hour.			Dates and frequency of vomiting.		
20.5.48	:	28.0	18.5.48	:	66	23.5.48	:	1
23.5.48	:	48.0	25.5.48	:	50	27.5.48	:	3
25.5.48	:	36.0	31.5.48	:	20			
			29.6.48	:	3			

Dates when hyperpnoea occurred.	Dates when drowsiness occurred.
20.5.48	23.5.48
23.5.48	24.5.48
24.5.48	25.5.48
25.5.48	26.5.48
	27.5.48
	28.5.48
	29.5.48

M.S., aged 5 11/12 years, weight 19.5 Kilos. (43 pounds), was admitted to hospital on 27.2.48. He had complained about stiff, sore joints in the morning for the previous fortnight. At night his ankles ached. When he was admitted he was found to have nodules on his occiput, scapulae, elbow, hands and the tendons of the peroneii. The apex beat was palpable in the fourth interspace in the nipple line. A soft systolic murmur was heard over this area. He was discharged home on 7.3.48 and the condition of his heart was unchanged.

TREATMENT.

1.3.48 - Acetylsalicylic acid grains 100
2.3.48 - 7.3.48 - Acetylsalicylic acid grains 60/day.

Blood salicylate in mgms. %	E.S.R. in 1 hour.	Dates and frequency of vomiting.
2.3.48 : 33.7	2.3.48 : 35	2.3.48 : 1
4.3.48 : 38.6		5.3.48 : 1
7.3.48 : 63.3		

W.S., aged 4 10/12 years, weight 15.8 Kilos. (35 pounds), was admitted to hospital on 24.5.48. On 14.3.48 he had had tonsillitis and a pain in his right leg. From then onwards he had not been well, had lost weight and lacked energy. On admission his apex beat was palpable in the sixth interspace one inch outside the nipple line. Systolic and diastolic murmurs were heard at the apex and

a doubtful diastolic at the base. Towards the end of his first course of salicylate therapy acetylsalicylic acid was substituted for calcium aspirin. A week after this course of treatment was stopped he developed pain, tenderness and slight swelling of his elbows. When he was finally discharged home his apex beat was palpable in the sixth interspace half an inch outside the nipple line. A systolic and mid diastolic murmur was heard at the apex. No diastolic murmur was present at the base.

TREATMENT.

1. 25.5.48 to 31.5.48 - Calcium aspirin - 48 grains/day
   1.6.48 to 16.6.48 - Calcium aspirin - 60 grains/day
   17.6.48 to 19.6.48 - Acetylsalicylic acid 50 grains/day.

2. 26.6.48 to 27.6.48 - Acetylsalicylic acid 60 grains/day
   28.6.48 to 20.7.48 - Acetylsalicylic acid 50 grains/day
   21.7.48 to 27.7.48 - Acetylsalicylic acid 40 grains/day.

Blood salicylate in mgms. %		E.S.R. in 1 hour.		Dates and frequency of vomiting.	
27.5.48	19.2.	24.5.48	78	22.6.48	1
30.5.48	23.6	29.5.48	65	10.7.48	1
4.6.48	35.0	4.6.48	22		
7.6.48	29.8	14.6.48	10		
10.6.48	25.0	25.6.48	25	Dates when hyperpnoea occurred.	
14.6.48	22.3	5.7.48	7		
19.6.48	34.3	12.7.48	4		
28.6.48	39.8	19.7.48	5	5.6.48	
30.6.48	37.6			19.6.48	
8.7.48	45.5			20.6.48	
12.7.48	17.6			28.6.48	
15.7.48	23.3			29.6.48	
19.7.48	46.6			20.7.48	

P. S., aged 8½ years, weight 28.8 Kilos. (63 pounds), was admitted to hospital on 27.10.47. During September, 1947 she had tonsillitis and was treated with sulphonamides. In the middle of October she complained of pains in the groins and left knee. These persisted and she was admitted to a surgical ward because of an effusion in both knees and her ankle. On 7.11.47 she was transferred to a medical ward as a case of acute rheumatism. On examination the apex beat was felt in the fourth interspace in the nipple line. A soft systolic murmur was heard over this area. She was removed from hospital before the completion of treatment because the family were planning to emigrate to South Africa.

TREATMENT.

2.11.47 - 7.11.47 - Sodium salicylate grains 60
Sodium bicarbonate grains 120 each day.

8.11.47 - 12.11.47- Sodium salicylate grains 90
Sodium bicarbonate grains 180 each day.

13.11.47 - 14.11.47- Sodium salicylate grains 90
Sodium bicarbonate grains 45 each day.

Blood salicylate in mgms. %		E.S.R. in 1 hour.	
8.11.47	19.2	8.11.47	40
10.11.47	23.6	10.11.47	36
12.11.47	14.7		
15.11.47	24.3		

R. S., aged 9 years, weight 21.3 Kilos. (47 pounds), was admitted to hospital on 19.10.47. He had rheumatic fever at the age of 6 years. Between 13.10.47 and 18.10.47 he was listless and vague abdominal pains and an ache in the legs. On 19.10.47 he had an epistaxis and haematemesis. On admission the apex beat was palpable in the sixth interspace one inch outside the nipple line. He had a collapsing pulse and a loud systolic murmur at the apex. He was transferred to the Country Branch on 14.11.47. One course was stopped because of vomiting.

TREATMENT.

1. 20.10.47 - 21.10.47 - Sodium salicylate grains 60
   Sodium bicarbonate grains 120/day
2. 24.10.47 - 11.11.47 - Sodium salicylate grains 60
   Sodium bicarbonate grains 120/day.

Blood salicylate in mgms. %		E.S.R. in 1 hour.		Date and frequency of vomiting.	
31.10.47	19.6	21.10.47	77	21.10.47	2
4.11.47	20.0	28.10.47	22		
7.11.47	19.8	4.11.47	11		
10.11.47	27.0	7.11.47	10		
12.11.47	26.5	12.11.47	8		
		18.11.47	6		

A.W., aged 7 4/12 years, weight 22 Kilos. (48 pounds), was admitted to hospital on 14.7.48. He had felt easily tired for the previous three months. On 6.5.48 he complained of abdominal pain and vomiting and a provisional diagnosis of

rheumatism was made though this was later revised and his appendix was removed on 8.5.48. In spite of the operation he remained a sickly child and was confined to his bed. He complained of occasional pains in his calves and right wrist. On admission he was described as a small, pale, listless boy who looked ill. He had no nodules nor joint involvement. The apex beat was felt in the fifth interspace 1/4 inch outside the nipple line; and systolic and diastolic murmurs were heard at the apex. An X ray plate of his lungs taken at this time showed an increased heart shadow, lung congestion and a small amount of fluid in both pleurae. He developed a cough on 19.7.48; an impaired note at the right base as well as rales and rhonchi on 21.7.48; and congestive cardiac failure on 27.7.48.

TREATMENT.

16.7.48 - 19.7.48 - 75 grains acetylsalicylic acid/day.
20.7.48 - 19.8.48 - 40-50 grains acetylsalicylic acid/day.

Blood salicylate in mgms. %			E.S.R. in 1 hour.			Dates when hyperpnoea occurred.	
16.7.48	:	31.2	14.7.48	:	47	17.7.48	
17.7.48	:	34.8	23.7.48	:	28	18.7.48	
19.7.48	:	41.9	8.8.48	:	15	19.7.48	
21.7.48	:	14.8	25.8.48	:	10	20.7.48	
23.7.48	:	17.2				22.7.48	orthopnoea
29.7.48	:	16.4				26.7.48	"
8.8.48	:	15.6				28.7.48	"
18.8.48	:	47.2				4.8.48	"

Date when vomiting occurred.

19.7.48

E. W., aged 7 years, weight 22.0 Kilos. (49 pounds), was admitted to hospital on 2.5.48. She developed scarlet fever on 28.3.48 and when she arrived home on 17.4.48 she was noticed to be pale and listless. On 30.4.48 she complained of pain in the right hand and hip. Next day her right hip and right knee were swollen and she was unable to stand. On admission her heart was not enlarged but a soft systolic murmur was heard at the apex.

TREATMENT.

3.5.48 - 9.5.48 - 80 grains acetylsalicylic acid/day.
10.5.48 - 17.5.48 - 60 grains acetylsalicylic acid/day.
18.5.48 - 23.5.48 - 70 grains acetylsalicylic acid/day.
24.5.48 - 15.6.48 - 60 grains acetylsalicylic acid/day.

Blood salicylate in mgms. %		E.S.R. in 1 hour.		Date and frequency of vomiting.	
7.5.48	22.1	2.5.48	88	7.5.48	1
10.5.48	33.7	12.5.48	55	27.5.48	1
12.5.48	29.5	18.5.48	20		
17.5.48	21.5	26.5.48	10		
20.5.48	36.4	31.5.48	7		
23.5.48	50.3	22.6.48	12		
26.5.48	47.6	9.7.48	8		
3.6.48	39.6				
15.6.48	22.3				

Dates when hyperpnoea occured	Date when tinnitus occurred.
10.5.48	10.5.48
11.5.48	
20.5.48	
23.5.48	
24.5.48	
25.5.48	

J. W., aged 6 years, weight 18.0 Kilos. (40 pounds), was admitted to hospital on 3.1.48. A description of her case (J.W.) is given in the section on Rheumatic Pneumonia. She developed severe salicylate poisoning and so treatment was stopped on 14.1.48. Oedema was present between 17.1.48 and 26.1.48.

TREATMENT.

4.1.48 - 9.1.48 - Sodium salicylate grains 60
Sodium bicarbonate grains 120 on each day.
10.1.48 - 14.1.48 - Acetylsalicylic acid grains 50 on each day.

Blood salicylate in mgms. %		E.S.R. in 1 hour.		Dates and frequency of vomiting.	
6.1.48	38.3	6.1.48	35	5.1.48	1
13.1.48	65.5	13.1.48	10	6.1.48	1
14.1.48	65.0	27.1.48	13	7.1.48	1
15.1.48	22.9	11.2.48	8	8.1.48	1
		24.2.48	5	9.1.48	1
		23.3.48	9	10.1.48	2
		13.4.48	5	13.1.48	1
				14.1.48	1
				28.1.48	1
				29.1.48	1

Date when hyperpnoea occurred.	Date when drowsiness occurred.
14.1.48	14.1.48

R. W., aged 6 years, weight 22.6 Kilos. (50 pounds), was admitted to hospital on 15.11.47. He had been subject to sore throats for several years. In September, 1947 he complained of pains in his ankles and was treated with rest in bed and 30 grains of sodium salicylate a day. He developed a sore throat on 15.11.47 and next day had pains in his knees and left wrist. On admission his apex beat was palpable in the fifth interspace a quarter of an inch outside the nipple line. A systolic murmur was audible at the apex. When he was discharged home on 18.2.48 the size of his heart remained unchanged but he had developed a systolic and diastolic murmur at the base in addition to the systolic murmur at the apex.

TREATMENT.

1. 17.11.47 - 19.11.47 - Sodium salicylate grains 60
   Sodium bicarbonate grains 120/day
   20.11.47 - 23.1.48 - Sodium salicylate grains 60
   Sodium bicarbonate grains 30/day.

2. 30.1.48 - 18.2.48 - 60 grains acetylsalicylic acid/day.

Blood salicylate in mgms. %		E.S.R. in 1 hour.		Date when epistaxis occurred.
18.11.47	18.3	18.11.47	50	27.11.48
22.11.47	17.4	25.11.47	20	
26.11.47	28.6	6.1.48	6	
		20.1.48	10	
31.1.48	8.0	27.1.48	9	
2.2.48	4.0	5.2.48	7	
5.2.48	13.2	9.2.48	5	
9.2.48	25.0	16.2.48	6	
11.2.48	8.0			
16.2.48	14.7			

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A P P E N D I X III.

CHART 1.

The concentrations of salicylate in the plasma of a child after 12½ grains of sodium salicylate, a sodium salicylate-sodium bicarbonate mixture, and acetylsalicylic acid.

NAME	Hours after Dose	CONCENTRATIONS OF BLOOD SALICYLATE IN MGMS. %			
		Sodium Salicylate	Sod.Salicyl. & Sod.Bicarb.	Aspirin (Crushed)	Aspirin (Uncrushed)
O'D.	1	5.4	7.1	0.8	-
	2	8.6	8.8	3.5	-
	3	6.5	8.4	5.9	-
	4	5.9	6.8	7.0	-
	9	4.0	5.4	4.4	-

CHART 2.

The concentrations of salicylate in the plasma of an adult after 40 grains of sodium salicylate, a sodium salicylate-sodium bicarbonate mixture, and crushed and uncrushed acetylsalicylic acid.

NAME	Hours after Dose	CONCENTRATIONS OF BLOOD SALICYLATE IN MGMS. %			
		Sodium Salicylate	Sod.Salicyl. & Sod.Bicarb.	Aspirin (Crushed)	Aspirin (Uncrushed)
J.C.S.	1	11.3	13.9	1.7	1.7
	2	16.2	16.2	6.3	2.6
	3	14.0	14.7	7.5	3.4
	4	9.8	10.3	11.3	-
	9	9.6	10.3	8.0	13.2

CHART 3.

The concentrations of salicylate in the plasma of 5 patients dosed with 1½ grains of crushed acetylsalicylic acid per pound of body weight per day.

NAME	CONCENTRATIONS OF BLOOD SALICYLATE IN MGMS. %				
	1 hour after dose	2 hours after dose	3 hours after dose	4 hours after dose	9 hours after dose
I. D.	4.8	11.2	12.0	12.0	6.4
II. O'D.	0.8	3.5	5.9	7.0	4.4
III. H.	8.0	13.2	14.4	16.0	10.8
IV. D.	8.0	11.6	11.6	11.6	7.6
V. J.C.S.	1.7	6.3	7.5	11.3	8.0

CHART 4.

The effect of oral doses of sodium bicarbonate upon the level of salicylate in the blood; upon the excretion of free salicylate in the urine; and upon the urinary pH.

This diagram is based upon figures that are recorded in Appendix 2, patient M. McD.

CHART 5.

The effect of oral doses of sodium bicarbonate upon the level of salicylate in the blood; upon the excretion of free salicylate in the urine; and upon the urinary pH.

This diagram is based upon figures that are recorded in Appendix 2, patient W.G.

CHART 6.

The distribution of the levels of salicylate in the plasma of 17 rheumatic children treated with routine doses of a sodium salicylate-sodium bicarbonate mixture based upon their body weight.

The details of the levels of salicylate in the blood, the body weight and the doses of salicylate that were administered to 12 of the above children are recorded in Appendix 2 under the initials J.B.; T.C.; J.C.; P.E.; W.G.; M.H.; A.Li.; M.McD.; P.S.; R.S.; J.W. and R.W.

The five other children were studied for very short periods and no information about them has yet been recorded. The levels of salicylate in the plasma and the dose of sodium salicylate per pound of body weight used in treating these patients were:-

Patient	Sodium Salicylate per pounds of body weight	Plasma salicylate in mgms. %
T.B.	1½	28.3
M.G.	1½	4.2
J.L.	1½	26.5
		20.8
R.McD.	1½	14.4
H.McN.	1	22.6

CHART 7.

The distribution of the levels of salicylate in the plasma of 25 rheumatic children treated with routine doses of acetylsalicylic acid based on their body weight.

The details of the levels of salicylate in the blood, the body weight and the doses of acetylsalicylic are all recorded in the case histories in Appendix 2.

CHART 8.

The wide variation in the levels of blood salicylate produced by a sceme of dosage based on the recommendations of Wegria and Smull.

Curve	1	..... D.McF.
"	2	..... M.S.
"	3	..... M.McD.
"	4	..... P.M.
"	5	..... W.G.

The case histories of the above patients are recorded in Appendix 2.

CHART 9.

The levels of salicylate in the plasma obtained by an initial dose of acetylsalicylic acid of 1½ grains per pound (0.22 Gm. per Kilo.) of body weight per day.

Curve	1	..... D.C.
"	2	..... A.Le.
"	3	..... M.H.
"	4	..... E.W.
"	5	..... D.McC.
"	6	..... W.G.
"	7	..... T.M.

The case histories of the above patients are recorded in Appendix 2.

CHART 10.

The concentrations of salicylate in the blood of 9 patients who received the same dose of salicylate in Hospital as at the Country Branch.

These patients were E.D.; P.E.; W.G.; M.H.; C.K.; A.Li.; D.McF.; P.M.; and E.W. Their case histories are recorded in Appendix 2.

A P P E N D I X IV.

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