SODIUM SALICYLATE AND PROBENECID IN THE TREATMENT OF CHRONIC GOUT*

ASSESSMENT OF THEIR RELATIVE EFFECTS IN LOWERING SERUM URIC ACID LEVELS

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Very little is known about the aetiology of acute attacks of gout or the mode of action of colchicine in relieving them. Their relationship to high serum uric acid levels and urate deposition is obscure, for maintaining serum levels at normal together with a negative urate balance does not prevent their occurrence. Fortunately the vast majority of acute attacks readily respond to colchicine in proper dosage, and the few exceptions may be treated with phenylbutazone ("Butazolidin").

Unlike the acute variety, chronic gout appears to be closely related to high serum and tissue fluid uric acid levels with supersaturation and deposition of urates in various tissues, especially joint structures and bursae. Uric acid deposition induces a chronic inflammatory reaction, and increasing size of the deposits leads to progressive and even total destruction of the affected joints. Urate deposition is often confirmed by the presence of tophi, but even in their absence it may be inferred by isotopic uric acid dilution studies. Such studies have shown that the miscible pool of uric acid in normal adults ranges from 731 to 1,341 mg. (Benedict, Forsham, and Stetten, 1949; Geren, Bendich, Bodansky, and Brown, 1950; Bishop, Garner, and Talbott, 1951). In gouty persons the miscible pool is greatly increased and may be as high as 30,000 mg. (Benedict and others, 1950). This enormous increase cannot be accounted for by uric acid in solution and must indicate the presence of solid phase urate which has taken part in dilution of the isotope.

The patient with chronic gout complains of increasing stiffness, pain, and deformity of one or more joints, symptoms which are unaffected by colchicine and which ultimately give rise to severe crippling and invalidism. Until 1950, it had not been found possible to maintain the serum uric acid at normal levels, and the progress of chronic gouty changes had never been arrested. Since 1950,

however, the continuous administration of sodium salicylate or probenecid ("Benemid") has been shown to maintain a prolonged lowering in the serum uric acid levels, and this has proved of great value in the treatment of chronic gout.

The effect of sodium salicylate in increasing urinary uric acid excretion in gouty persons has been known since 1877, and its ability to reduce the serum uric acid since 1914. When given continually it is a most useful drug in maintaining the serum uric acid of chronic gouty persons at a normal or near normal level, an effect which persists for upwards of 3 years and is accompanied by complete or very marked improvement in the symptoms and signs of the disorder (Marson, 1952, 1953a). The lowering of serum uric acid levels is accompanied by mobilization of deposited urate, as shown by shrinkage or total disappearance of tophi, recalcification of areas of bone absorption, and a prolonged increase in the urinary uric acid levels (Marson, 1952, 1953a). Isotopic studies have shown a marked diminution in the metabolic pool of uric acid during salicylate therapy (Benedict and others, 1950). The delayed recognition of the beneficial effects of sodium salicylate may have been due to the following reasons:

(1) Gutman (1950) and Talbott (1953a) rejected continuous administration of salicylate because the early development of toxic symptoms prevents adequate dosage. It has been shown, however, that, although most patients suffer salicylism initially, a majority develop a tolerance within 1-6 weeks, and thereafter are able to take the required dosage with no more than occasional and minor symptoms (Marson, 1953a).

(2) Bauer and Klemperer (1944) reported that the effect of salicylate on depressing the serum uric acid is short-lived. This assertion has since been disproved and patients have maintained marked lowering of serum uric acid for periods of upwards of 3 years.

(3) Jennings (1937) reported that normal levels of blood uric acid could be maintained by administering sodium salicylate in a daily dosage of 80 gr. 3 or 4 days

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a week. Bauer and Klemperer (1944) and Marson (1953a) were unable to confirm this finding. Such intermittent therapy has never been shown to arrest chronic gouty changes.

Wolfson and others (1948) reported that caronamide (4'-carboxyphenyl-methanesulphonanilide) increased uric acid excretion in normal subjects, and Gutman (1950) reported the use of this drug in thirteen gouty subjects. With a daily dosage of 12 to 13.5 g. a marked lowering in the serum uric acid levels resulted. However, the large number of tablets consumed daily was objectionable, and various toxic reactions occurred, including gastrointestinal symptoms, drug fever, and drug rash. This drug is no longer used.

A new benzoic acid derivative, probenecid ('Benemid': p-(di-n-propylsulfamyl)-benzoic acid), structurally related to caronamide, introduced into clinical medicine by Boger and others (1950), was found to have a marked effect on blocking the tubular secretion of penicillin, para-aminosalicylic acid, para-aminohippuric acid, and phenolsulphonphthalein. It was later shown to block tubular reabsorption of certain glomerular constituents (Schneider and Corcoran, 1950) including uric acid (Gutman, 1950). These effects were similar to those obtained with caronamide but could be obtained with a much smaller dosage, 2 g. probenecid being equivalent to 24 g. caronamide. Since that time various reports have been published on the value of probenecid in the treatment of chronic gout, and there can be no doubt that, in a daily dosage of 2 g., it causes a marked lowering in serum uric acid levels, a marked initial increase in urinary uric acid excretion, and great general improvement in chronic gouty patients. It also causes a shrinkage in the metabolic pool of uric acid (Bishop, Rand, and Talbott, 1951).

Gutman (1950, 1951a) reported a series of fourteen patients in whom probenecid in a daily dosage of 2 g. caused a mean increase in urinary uric acid excretion of 58.5 per cent., and a sustained fall in serum uric acid to approximately half the initial level. In a series of fifteen patients a dose of 1 g. daily produced a mean decrease of 24 per cent. in serum level (Gutman, 1951b). Pascale and others (1952) reported that in seventeen gouty subjects 2 g. probenecid daily induced a fall in the serum uric acid level at the end of 72 hrs to 42-70 per cent. of previous levels with an average fall to 55 per cent. Impaired renal function was demonstrated in three further subjects in whom probenecid failed to lower the serum uric acid. Two illustrations (Talbott, 1953b) demonstrate the effect of probenecid on serum uric acid levels in two of a large series of

patients, but it is not stated whether these are representative of the whole series, nor is the dosage of probenecid recorded. The first case was treated for 26 months and the average serum levels were approximately 8.65 mg. during a control and 4.66 mg. during probenecid treatment (a fall to 54 per cent. of initial levels). Talbott stated that the lowest uric acid figure (3.0 mg.) was noted within the first month of treatment. The second patient received probenecid for 14 months, and the serum level fell from an initial average of 9.5 mg. to an average on probenecid of 6.5 mg. (a reduction to 68.4 per cent. of the control level).

It has been reported that when salicylates are given concomitantly with probenecid the uricosuric effect is nullified (Gutman and Yü, 1952). Pascale and others (1952) found that, whereas 2 g. probenecid daily effected a marked lowering in the serum uric acid level in gouty patients, the addition of 1.3 g. acetylsalicylic acid 6-hrly nullified this effect.

It would appear likely that the beneficial effects of both probenecid and salicylates are dependent upon the lowering of serum (and tissue fluid) uric acid levels, with arrest of further deposition of urate and partial reabsorption of deposits. If this hypothesis is correct it becomes important to assess the relative merits of salicylate and probenecid in lowering the serum uric acid level, and an attempt to do this is recorded below.

Patients Investigated and Methods

A series of 21 chronic gouty patients has been studied closely over the past 45 months, and an attempt has been made to maintain a continuous lowering in the serum uric acid levels with either salicylates or probenecid therapy.

The diagnosis of gout was based upon a history of attacks of acute arthritis, the witnessing of one or more such attacks together with response to colchicine therapy (0.5 mg. 2-hrly until pain disappears or diarrhoea occurs), and a raised serum uric acid level. Approximately half the patients had demonstrable tophi and a further half had a family history of gout. The patient was judged to be suffering from chronic gout if the joint pain had persisted for longer than 3 months and was unaffected by a course of colchicine therapy.

All patients had a minimum of three estimations of the uric acid before therapy and were advised to take a normal diet and an increased fluid intake. They were all supplied with crystalline colchicine tablets (0.5 mg.) with instructions to treat all acute episodes with one tablet 2-hrly until the pain has disappeared or diarrhoea occurred. They then commenced salicylate or probenecid therapy and were usually admitted to hospital for close study at this time. After discharge they attended a gout clinic at intervals of not longer than a month, and at each visit progress was recorded, uric acid estimated, and the appropriate therapy prescribed.

Some patients received salicylate continuously (Cases 1-17) and others probenecid (Cases 18-21). Four (Cases 8, 15, 19, 11) received both drugs at different times. Sodium salicylate was administered in a daily dosage of 60-120 gr. (usually 90 gr.), normally equally spaced in three doses. At first it was combined with an equal dose of sodium bicarbonate, but more recently it was usually dispensed alone as a fluid with a flavouring agent and sodium sulphite as a preservative. The patient received a freshly dispensed mixture at each visit and it was never administered for longer than one month. Probenecid was administered in a daily dosage of 2 g. equally spaced over four doses.

Uric acid determinations were performed by the colorimetric method of Brown (1945). Estimations in one hundred non-gouty persons (Marson, 1953a) had shown a mean serum uric acid of 4.54 ± 0.15 mg. per 100 ml. in males, and 3.82 ± 0.14 mg. per 100 ml. in females.

In addition to the long-term investigations, it was felt advisable to assess results after single doses of sodium salicylate and probenecid. The patients selected for this trial were a female aged 60 yrs, suffering from rheumatoid arthritis, and three males, aged 59, 47, and 42 yrs, two with gout and one with rheumatoid arthritis (Cases I-IV).

All these subjects were in hospital receiving normal mixed diets with the exclusion of any high purine foods. No drugs were administered except on the test days; on these days the subjects remained in bed, and their diet and fluid intake was limited to 10 oz. milk at 7 a.m., 11 a.m., 1 p.m., and 3 p.m. The bladder was emptied at 7 a.m. and thereafter 2-hrly until 3 p.m. The test days were as follows:

- (a) *Control*.—10 oz. water at 9 a.m.
- (b) *Sodium Salicylate*.—100 gr. freshly prepared, administered orally in 10 oz. water at 9 a.m.

- (c) *Probenecid*.—2 g. with 10 oz. water at 9 a.m.
- (d) *Sodium Salicylate*.—100 gr. with 2 g. probenecid and 10 oz. water at 9 a.m.
- (e) *Probenecid*.—4 g. with 10 oz. water at 9 a.m. (two subjects only).

All test days were separated by at least 3 clear days. The 2-hr urine samples were tested for uric acid (Bidmead, 1951), and creatinine (Folin, 1914); Fig. 7 shows mean results expressed as uric acid : creatinine ratios. It was assumed that neither drug has any significant effect upon creatinine excretion. A similar technique has been used in assessing the relative uricosuric effects of ACTH and sodium salicylate (Marson, 1953b).

Estimations of serum salicylate were done in six subjects (Cases A-F) in similar circumstances to the patients on test day (b). The serum salicylate was estimated by the method of Smith and Talbott (1950).

In another individual (Case X), not one of the series of 21, a further investigation was carried out to assess the results of combining probenecid administration with salicylate. The subject was male, aged 42 years, and suffered from chronic gout. He was in hospital and received a normal mixed diet with the exclusion of high purine foods. The serum and total urinary uric acid were estimated daily and, after an initial control period, sodium salicylate was administered in a dosage of 30 gr. 8-hrly. This was continued, and after 8 days, probenecid was also administered in a dosage of 0.5 g. 6-hrly and the tests continued for a further 8 days (Fig. 8).

Results

Seventeen chronic gouty patients received continuous salicylate therapy for periods of 9-45 months. During this time the serum uric acid was estimated at least once every 4 weeks. Table I shows the

TABLE I
SERUM URIC ACID LEVELS IN SEVENTEEN PATIENTS WITH CHRONIC GOUT
BEFORE AND DURING SODIUM SALICYLATE THERAPY

Case No.	Duration of Therapy (months)	Mean Serum Uric Acid (mg./100 ml.)						Maintained Serum Uric Acid (per cent. of initial level)	
		Initial			During Therapy				
		Mean	Number of Observations	Standard Deviations of Observations	Mean	Number of Observations	Standard Deviations of Observations		
(Fig. 3)	1	45	7.8	5	2.43	4.1	46	1.63	52.6
	2	42	7.5	8	3.85	2.6	64	0.59	34.7
	3	41	5.0	22	0.33	3.4	78	1.29	68.0
(Fig. 2)	4	41	4.8	17	0.67	2.2	47	0.74	46.2
	5	34	8.5	3	0.51	4.2	47	1.68	49.4
	6	32	8.2	17	0.73	3.4	27	1.09	41.5
(Fig. 6)	7	30	6.8	7	0.62	5.3	72	1.53	77.9
	8	27	8.6	14	1.41	3.3	34	0.81	38.4
	9	24	9.1	3	2.72	3.6	35	1.09	39.6
	10	19	7.5	3	0.53	5.1	31	1.10	68.0
	11	18	10.6	35	2.12	6.1	77	1.72	57.5
	12	15	9.3	4	1.43	2.9	14	0.79	31.2
	13	14	7.4	11	1.50	5.0	40	1.29	67.6
	14	13	6.8	10	0.34	4.2	11	1.02	61.8
	15	12	5.0	9	0.50	1.8	15	0.31	36.1
(Fig. 5)	16	11	9.0	13	1.02	4.1	11	0.19	45.6
	17	9	6.3	6	0.91	2.3	12	0.86	36.7
Average	25								50.2

* In Case 2, sodium salicylate was replaced by aspirin during 27 months.

mean uric acid levels before and during therapy; the figures in the last column indicate the extent of therapeutic lowering of the uric acid concentration. Uric acid estimations during the first 3 weeks of therapy have not been included. The Table includes all patients treated at the clinic with continuous salicylate administration for a minimum period of 9 months, with the exception of two in whom a raised blood urea was present and therapeutic depression of serum uric acid levels was found impossible, and a further two whose co-operation was insufficient to justify inclusion in this study. It is seen that in six of the seventeen patients the uric acid was maintained at an average of less than 40 per cent. of the pre-treatment figures, and in a further four patients at a level below 50 per cent. of the initial level. The percentage fall with salicylate bears no relationship to the initial level (Fig. 1). In

only four of the seventeen patients was it found impossible to maintain the level below the mean for normal persons. The four exceptions comprised the three patients in whom salicylism was troublesome and the fourth patient was the most jovial but probably least reliable of the series.

Table II illustrates similar figures for six chronic gouty patients (Cases 11, 15, 18-21) to whom probenecid was administered continuously for periods of 12-19 months. In no patient was it found possible to maintain the serum uric acid at a mean level below 50 per cent. of initial figure. In only one case was the uric acid reduced to a level below the mean for normal persons. It should be noted that the initial uric acid levels of patients in Table II was somewhat higher than that of those in Table I (mean 8.35 and 7.5 mg./100 ml. respectively).

During both salicylate and probenecid therapy, the serum uric acid was maintained at an average of 50.2 and 67.9 per cent. of the initial levels respectively (observed difference = $2.64 \times$ standard error).

Four patients (Cases 8, 11, 15, 19) received continuous salicylate and probenecid therapy at different times. Table III shows the changes in serum uric acid levels during each of the two forms of treatment. In each case, salicylate (sodium salicylate in Cases 8, 11, 15, and aspirin in Case 19) effected an appreciably greater lowering of the serum uric acid level than did probenecid.

The effects of prolonged salicylate therapy are illustrated in Figs 2 and 3 (Cases 2 and 4). It is obvious that any defect in co-operation of

Fig. 1.—Serum uric acid levels in seventeen patients during prolonged salicylate therapy (percentage of control levels).

TABLE II
SERUM URIC ACID LEVELS IN SIX PATIENTS WITH CHRONIC GOUT
BEFORE AND DURING PROBENECID THERAPY

Case No.	Duration of Therapy (months)	Mean Serum Uric Acid (mg./100 ml.)						Maintained Serum Uric Acid (per cent. of initial level)
		Initial			During Therapy			
		Mean	Number of Observations	Standard Deviations of Observations	Mean	Number of Observations	Standard Deviations of Observations	
11	19	10.6	35	2.12	7.1	28	1.32	66.0
(Fig. 4) 18	19	11.5		1.41	5.8	23	0.61	50.4
19	18	7.2	8	1.06	4.7	20	0.70	65.3
(Fig. 5) 15	15	5.0	9	0.50	3.1	17	0.41	62.8
20	13	9.1	27	1.68	6.7	11	1.81	73.6
21	12	6.7	10	1.38	6.0	14	1.11	89.2
Average	16							67.9

the patient will give rise to increased variability of the uric acid levels. The steady deterioration of salicylate in fluid form, together with the relative inaccuracy of measurement of fluid doses may explain the decreased variability of levels in Case 2 (Fig. 3) when the sodium salicylate was replaced by aspirin.

If frequent estimations of serum uric acid are performed at the start of salicylate therapy it is usually found that a maximal depression occurs within the first 3 weeks and that the uric acid is not maintained at this very low level. The lowest levels recorded in Case 4 (Fig. 2) were 0.8 and 0.9 mg./100 ml. on the third and sixth days respectively,

Fig. 2.—Serum uric acid levels in a gouty patient (male, aged 56, Case 4) before and during 41 months of sodium salicylate therapy (120 gr. daily).

TABLE III
SERUM URIC ACID LEVELS IN FOUR PATIENTS WITH CHRONIC GOUT
BEFORE AND DURING SALICYLATE AND PROBENECID THERAPY

Case No.	Duration of Therapy (months)	Drug	Mean Serum Uric Acid (mg./100 ml.)						Maintained Serum Uric Acid (per cent. of initial level)
			Initial			During Therapy			
			Mean	Number of Observations	Standard Deviations of Observations	Mean	Number of Observations	Standard Deviations of Observations	
(Fig. 6) 8	27	Sod. Sal.	8.6	14	1.41	3.3	34	0.81	38.4
	3	Probenecid	—	—	—	4.8	3	0.30	55.9
(Fig. 5) 15	12	Sod. Sal.	5.0	9	0.50	1.8	15	0.31	36.1
	15	Probenecid	—	—	—	3.1	17	0.41	62.8
19	3	Aspirin	7.2	8	1.06	2.0	6	0.64	27.8
	18	Probenecid	—	—	—	4.7	20	0.70	65.3
11	18	Sod. Sal.	10.6	35	2.12	6.1	77	1.72	57.5
	19	Probenecid	—	—	—	7.1	28	1.32	66.0

The observed differences in uric acid levels during the two forms of therapy were 6.8 (Case 8), 10.2 (Case 15), 8.9 (Case 19), and 3.2 (Case 11) times the standard errors.

whereas the mean level during 41 months of treatment was 2.2 mg./100 ml. In Case 15 (Fig. 5), a level of 1.5 mg./100 ml. obtained on the seventh day, was, with one exception, the lowest figure obtained during one year's treatment.

Probenecid, like salicylate, causes an early maximal depression of serum uric acid which is not maintained (Fig. 4, Case 18). The lowest level (3.9 mg./100 ml.) occurred on the seventh day, and the level then rose gradually during the next 3 months. The mean level during 19 months of treatment was 5.8 mg./100 ml.

Figs 5 and 6 illustrate graphically the relative effects of sodium salicylate and probenecid in lowering the serum uric acid level. In Fig. 5 (Case 15) every estimation of uric acid during salicylate therapy is seen to be lower than the lowest reading during probenecid administration. In Fig. 6 (Case 8) only two of the many uric acid estimations during sodium salicylate therapy were higher than the three estimations made during probenecid therapy.

Table IV shows the results of experiments on Cases I-IV, four additional subjects, not included in the series of 21, designed to compare the uricosuric effects of single doses of sodium salicylate and

TABLE IV

URINARY URIC ACID : CREATININE RATIOS
in four patients during the 6 hours following the control period (C), 100 gr. sodium salicylate (S), 2 g. probenecid (P₂), 100 gr. sodium salicylate with 2 g. probenecid (S+P₂), and 4 g. probenecid (P₄).

Case	Drug	Urinary Uric Acid : Creatinine Ratio (percentage of initial level)			
		Initial	During Therapy		
		— 2-0 hrs	0-2 hrs	2-4 hrs	4-6 hrs
(e)	C	100	103	94·5	79
(a)	S	—	330	485	446
I (b)	P ₂	—	263	251	264
(d)	S + P ₂	—	339	392	411
(c)	P ₄	—	246	324	280
II	C	100	99	95	93
	S	—	282	353	270
	P ₂	—	237	248	164
	S + P ₂	—	137	258	272
	P ₄	—	140	263	284
III	C	100	71	78	57
	S	—	400	375	332
	P ₂	—	258	273	231
	S + P ₂	—	214	243	242
IV	C	100	92·5	102	69
	S	—	237	336	302
	P ₂	—	248	202	164
	S + P ₂	—	230	220	212

probenecid, given either separately or together, during the 6 hours after administration. 100 gr. sodium salicylate induced an appreciably greater uricosuric effect than 2 or 4 g. probenecid in all phases of the test (Fig. 7). This was such that after the first 2 hours the uricosuric effect of salicylate was

double that induced by 2 g. probenecid. When the two drugs were given together the uricosuric effect was roughly comparable with that obtained by 2 g. probenecid alone.

Table V shows serum salicylate levels in Cases A-F, six additional subjects (four with rheumatoid arthritis and two with gout) after the oral administration of 100 gr. sodium salicylate.

Fig. 8 shows serum and urinary uric acid levels in Case X, a gouty subject (not one of the series), before treatment, during administration of 90 gr. sodium salicylate daily, and later during additional administration of 2 g. probenecid daily. The addition of probenecid had no significant effect upon the uric acid levels and the combination of the two drugs continued to effect a marked reduction in the serum level and an increase in the urinary excretion.

Toxic Effects of Probenecid.—In view of conflicting reports concerning the toxic effects of probenecid, great care was taken to record their occurrence. Toxic symptoms occurred in nine of the fifteen patients treated with probenecid. With two exceptions, the drug was administered in a daily dose of 2 g. spaced over four doses.

Two severe reactions occurred:

(1) Case 5, a male aged 46 years, received the drug in a dose of 0.5 g. four times daily; 45 minutes after

TABLE V
SERUM SALICYLATE LEVELS IN SIX PATIENTS DURING THE NINE HOURS
AFTER ORAL ADMINISTRATION OF 100 gr. SODIUM SALICYLATE IN 10 oz. WATER.
Patients received 10 oz. milk 2 hrs before start of test, and at 2nd, 4th, 6th, and 8th hours of test.

Diagnosis	Patient	Weight (lb.)	Serum Salicylate (mg./100 ml.)								
			0 hrs	$\frac{1}{2}$ hr	$\frac{1}{2}$ hr	1 hr	2 hrs	4 hrs	6 hrs	8 hrs	9 hrs
Rheumatoid Arthritis	A	116	—	23.8	32.7	43.7	37.0	28.2	21.3	18.1	17.9
	B	147	—	28.4	31.9	44.1	39.6	30.5	25.8	22.9	21.0
	C	105	—	24.5	27.3	35.3	34.9	30.9	28.5	25.3	24.3
	D	221	—	14.7	17.8	23.9	26.7	24.3	23.0	20.8	19.8
Gout	E	202	—	14.5	16.6	28.1	28.1	23.5	18.2	17.4	14.6
	F	168	—	24.0	34.2	35.3	37.0	33.9	30.8	27.0	26.7
Mean		159.8	—	21.65	26.75	36.07	33.88	28.81	24.6	21.91	20.71

taking the fourth tablet, he felt hot, perspired profusely, and had a slight headache, but felt fit again after 2 hrs. He took a further tablet some 6 hrs later and had a return of symptoms which were more severe but again disappeared after 2 hrs. A further tablet was taken after another 6 hrs and once more he perspired and felt hot 45 minutes later, but his headache became intense and he lost consciousness for 10 minutes. Further therapy was stopped and the untoward symptoms disappeared within 18 hrs.

(2) Case Y, a male aged 50 years, received 0.5 g. probenecid three times daily. On the tenth day of treatment he developed a generalized maculo-papular rash with intense irritation, sore throat, and malaise. The temperature was 102° F. and the pulse rate 140. Further probenecid was stopped and the symptoms disappeared within 3 days. Six days later 0.5 g. probenecid was administered together with phenegan. Within 6 hrs the patient developed very severe malaise, with a return of the rash and sore throat. His temperature reached 104° F. and the pulse rate was 160 and irregular. For the next 24 hrs the patient's condition caused considerable anxiety to his general practitioner. Further probenecid was stopped; the rash disappeared after 2 days but the malaise persisted for a further 3 days.

Six patients suffered gastro-intestinal symptoms:

(1) Case P. Female, aged 49 years, anorexia, nausea, and vomiting developed on the second day of treatment. The symptoms persisted for a week and disappeared within 36 hrs of stopping further therapy.

(2) Case Q. Male, aged 45 years, epigastric discomfort and flatulence occurred from the second to fourteenth day, after which he became symptom-free. He was normally singularly free from alimentary symptoms and firm persuasion was necessary to get him to continue taking the drug.

(3) Case 8. Male, aged 51 years, anorexia and nausea occurred on the second day and vomiting on the third. Probenecid was stopped and no further symptoms occurred on recommencing the drug 2 months later.

(4) Case R. Male, aged 51 years, heartburn and a cramp-like pain across the upper abdomen occurred on the fourteenth day. The symptoms were fairly severe for a few days but gradually disappeared during the next 3 weeks.

(5) Case S. Male, aged 44 years, anorexia and nausea occurred from the third to seventh day of therapy.

(6) Case T. Male, aged 60 years, received probenecid for several months. Although he could tolerate 1.5 g. daily, raising the dose to 2 g. constantly induced heartburn.

One further patient, a male aged 29 years (Case 20), complained of pain in the left loin on the second day of treatment. The pain became severe and after 4 days the probenecid was stopped. The pain disappeared on the following day and did not recur when probenecid was restarted a week later. No other cause for the pain being found, it was assumed to be a result of probenecid administration.

Discussion

Chronic gout results from progressive deposition of urate in joint structures with ensuing tissue destruction, together with chronic inflammatory changes. Since 1950 it has been found possible to effect an appreciable and continued reduction in serum uric acid concentration to levels at which further precipitation of urate does not occur.

This measure might be expected to prevent further deterioration in the patient's condition and there is now ample evidence to confirm this. Furthermore, considerable solution and disappearance of urate deposits can be obtained, and this is usually accompanied by progressive improvement and later complete alleviation of the symptoms of chronic gout. It is likely that the rate and extent of urate reabsorption are related to the level of uric acid in the tissue fluid, and that so long as chronic symptoms persist the serum uric acid should be maintained at the lowest possible level. Once all chronic symptoms have resolved, it is no longer so essential to reduce the uric acid to the minimum, provided the level does not exceed that at which further deposition of urate could occur. This desired effect is obtained by the continued administration of drugs which have an effect on tubular cells whereby the reabsorption of uric acid is decreased, renal clearance increased, and the serum level reduced. Caronamide was the first such drug to be administered, but is no longer used,

and the present choice lies between probenecid and salicylate, the latter in the form of sodium salicylate or aspirin.

Probenecid is administered in tablet form, the normal dose being 0.5 g. four times daily. A larger dose usually produces gastro-intestinal symptoms, and a smaller dose is less effective. Various reports have indicated that the serum uric acid is reduced to approximately 50-70 per cent. of initial levels, but no attempt has been made to compare these changes with those obtained by salicylates, and little account has been taken of the fact that a maximum fall in serum uric acid usually occurs within the first few days of therapy and thus gives an exaggerated impression of the action of the drug (see Figs 2,

4, and 5). The latter fact applies equally to salicylate medication, and in presenting the results with the two drugs (Tables I-III) no account has been taken of the uric acid estimations during the first 3 weeks of treatment. Furthermore, critical assessment of published results on uric acid depression with either drug is impossible unless clear mention has been made of the period of therapy during which the uric acid was estimated. The present work has shown that in a series of seventeen patients receiving salicylate for periods of 9-45 months, the uric acid was maintained at a mean of 50 per cent. of the initial level (Table I), and that in a series of six patients receiving probenecid for periods of 12-19 months, the uric acid was maintained at a mean of

68 per cent. of the initial level (Table II). These changes were such that the uric acid was maintained at a mean level below that for normal persons in thirteen of the seventeen patients receiving salicylate, and in one of the six patients receiving probenecid. The results suggest that salicylate has an appreciably greater effect in lowering the serum uric acid than probenecid. In view of the drugs having been administered to two different series of patients, it was decided to give both drugs at different times to four other patients (Table III, and Figs 5 and 6). In each case salicylate had a significantly greater effect than did probenecid.

Further assessment of the relative effects of the two drugs was obtained by comparing the changes in the urinary uric acid : creatinine ratio during the 6 hours following the administration of 100 gr. sodium salicylate and 2 g. probenecid. The uricosuric effect of the salicylate was found to be approximately double that of the probenecid.

Both drugs are absorbed rapidly and give peak

Fig. 7.—Mean urinary uric acid : creatinine ratios in four patients after oral administration of:
 (a) 100 gr. sodium salicylate
 (b) 2 g. probenecid
 (c) 4 g. probenecid (two patients only)
 (d) 100 gr. sodium salicylate + 2 g. probenecid
 (e) control period.
 (Results charted at middle of 2-hr periods.)

concentrations within 2 hours of ingestion. The salicylate dosage provides a level of serum salicylate throughout the test which approximates to that obtained by the continuous administration of 30 gr. thrice daily. A single dose of 2 g. probenecid produces a level approaching 20 mg./100 ml. after 2 hours not falling below 5 mg./100 ml. within 8 hours, whereas the continued administration of 0.5 g. every 6 hours maintains a plasma concen-

tration of between 2-6 mg./100 ml. (Boger and others, 1950).

Previous reports have stated that the coincident administration of probenecid and salicylates nullifies the uricosuric effect (Pascale and others, 1952; Gutman and Yü, 1952). The present work conflicts with this finding, for when single doses of the two drugs were combined an appreciable uricosuric effect occurred which was comparable with that obtained

Fig. 8.—Effect of sodium salicylate alone and combined with probenecid on serum and urinary uric acid levels and urinary uric acid : creatinine ratio in a gouty patient (male, aged 42, Case X).

by probenecid alone. Furthermore, in a patient in whom the serum uric acid was maintained at a low level with continued salicylate therapy, the addition of probenecid failed to alter the uric acid concentration.

It appears, therefore, that with the exception of the few cases who cannot tolerate it in sufficient dosage, salicylate is likely to be more effective than probenecid in obtaining rapid relief of chronic symptoms. Chronic gout is a hopeless condition unless properly treated and patients should have every opportunity of obtaining full therapeutic relief. If facilities for close study are not available, it is probably more satisfactory to commence treatment with probenecid. In this event, however, if full relief is not obtained within a few months, the patient should not be regarded as incurable until salicylate therapy has been given a proper trial.

Allergic reactions to probenecid occurred in two of forty cases treated by Gutman and Yü (1952). Two of the present series of fifteen patients suffered severe sensitivity reactions to probenecid. Six patients suffered gastro-intestinal symptoms at the onset of treatment, but these disappeared with continued therapy.

The toxic effects of continuous salicylate therapy have been discussed previously (Marson, 1953a); further experience has amplified the earlier finding that, after the first few weeks, the large majority of patients tolerate the required dosage of salicylate (usually 90 gr. daily) with either complete freedom from salicylism or occasional and mild tinnitus and deafness. At the start of treatment it is useful to have the patients in hospital so that the salicylate dosage can be regulated to minimize the early toxic symptoms. In only five of forty patients have toxic symptoms been sufficiently severe to prevent continuous therapy in a dosage sufficient to maintain an appreciable lowering of the serum uric acid levels.

One difficulty with sodium salicylate therapy is the unpleasant taste of this drug in liquid form, but this can be avoided by dispensing it in capsules. Another disadvantage is the development of increased deafness in those already partially deaf; in such cases probenecid is to be preferred.

It is important to stress that, with the exception of those patients with impaired renal function, continued administration of salicylate or probenecid will effect a cure in most cases of chronic gout.

Summary

(1) An attempt has been made to compare the effects of salicylate and probenecid in lowering the serum uric acid of gouty patients.

(2) A maximum fall in serum uric acid levels occurs within a few days of commencing salicylate or probenecid. This is not maintained and gives an exaggerated impression of the effects of either drug during prolonged therapy.

(3) Seventeen chronic gouty patients received continuous salicylate therapy for 9-45 months. The mean level of serum uric acid was 50 per cent. of the initial level, and in thirteen of the seventeen patients the uric acid was maintained below the normal mean level in healthy subjects.

(4) Six chronic gouty patients received probenecid for 12-19 months. The mean level of serum uric acid was 68 per cent. of initial level, and in one of the six patients the uric acid was maintained at lower than the normal mean level.

(5) Four patients received salicylate and probenecid at different periods. In each case salicylate had a greater depressant effect on the serum uric acid level.

(6) Single doses of 100 gr. (6.5 g.) sodium salicylate had approximately double the uricosuric effect of single doses of 2 g. probenecid during the 6 hours following administration of the drugs.

(7) The coincident administration of probenecid and salicylates did not nullify the uricosuric effect.

(8) Toxic symptoms occurred in nine of the fifteen patients receiving probenecid. A rapid tolerance usually developed, but two severe reactions were encountered which necessitated withdrawal of the drug.

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Salicylate de soude et *probenecid* (Benemid) dans le traitement de la goutte chronique—l'évaluation de leurs effets relatifs sur la baisse du taux sérique d'acide

RÉSUMÉ

(1) On a tenté de comparer l'effet réducteur du salicylate de soude et du *probenecid* sur l'acide urique sanguin des gouteux.

(2) La plus grande chute du taux d'acide urique sanguin se produisit au bout de quelques jours de traitement par le salicylate ou le *probenecid*. Cette chute, capable de créer une opinion exagérée sur les effets de ces substances, ne se maintient pas au cours du traitement prolongé.

(3) Dix-sept gouteux chroniques furent soumis au traitement salicylique continu pendant 9 à 54 mois. Le chiffre moyen d'acide urique sanguin fut 50 pour-cent du chiffre initial et chez 13 malades sur 17 il fut en dessous de la moyenne pour des sujets normaux.

(4) Six gouteux chroniques furent soumis au *probenecid* pendant 12 à 19 mois. Le chiffre moyen d'acide urique sanguin fut 68 pour-cent du chiffre initial et chez un malade sur six il fut en dessous de la moyenne normale.

(5) Quatre malades furent traités par le salicylate et par le *probenecid* pendant de différentes périodes. Dans tous les cas l'effet réducteur du salicylate sur le taux sérique de l'acide urique fut plus prononcé.

(6) L'effet uricosurique d'une dose de 6,5 grammes de salicylate de soude fut deux fois plus grand que celui d'une dose de 2 grammes de *probenecid*, pendant six heures après l'administration de chaque médicament.

(7) L'administration simultanée de *probenecid* et de salicylates n'annulait pas l'effet uricosurique.

(8) Des symptômes toxiques se sont présentés chez neuf sur quinze malades au *probenecid*. Généralement une tolérance apparaissait vite mais on s'est heurté à deux réactions graves demandant la suppression du médicament.

Salicilato de sodio y *probenecid* (Benemid) en el tratamiento de la gota crónica—valoración de sus efectos relativos sobre la baja de la cifra sérica de ácido

SUMARIO

(1) Se ha tratado de comparar la acción reductiva del salicilato de sodio y del *probenecid* sobre el ácido úrico sanguíneo de los gotosos.

(2) La mayor caída de la cifra de ácido úrico sanguíneo ocurrió pocos días después de empezar el tratamiento con el salicilato o el *probenecid*. Esta caída, susceptible de crear una opinión exagerada respecto a los efectos de estos medicamentos, no se mantuvo con prolongar el tratamiento.

(3) Diecisiete gotosos crónicos fueron tratados sin interrupción con salicilatos durante 9 a 54 meses. La cifra media de ácido úrico sanguíneo fué el 50 por ciento de la cifra inicial y en 13 de los 17 enfermos no alcanzó la media para sujetos normales.

(4) Seis gotosos crónicos fueron tratados con *probenecid* durante 12 a 19 meses. La cifra media de ácido úrico sanguíneo fué el 68 por ciento de la cifra inicial y en uno de ellos no alcanzó la media normal.

(5) Cuatro enfermos recibieron el salicilato y el *probenecid* durante varios períodos. En todos los casos el efecto reductivo del salicilato sobre la tasa sérica del ácido úrico fué más pronunciado.

(6) Durante las seis horas después de su administración, el efecto uricosúrico de una dosis de 6,5 gramos de salicilato de sodio fué dos veces mayor que el de una dosis de 2 gramos de *probenecid*.

(7) La administración simultánea de *probenecid* y de salicilato no anulaba el efecto uricosúrico.

(8) Síntomas tóxicos presentaron en nueve de los quince enfermos tratados con *probenecid*. Por lo general, una tolerancia solía establecerse rápidamente pero en dos casos hubo una reacción grave necesitando la cesación del medicamento.