THE RELATIVE VALUE OF THE "NATURAL"
AND THE SYNTHETIC SALICYLATES

A STUDY OF THE LITERATURE*

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There is at present a fairly wide-spread belief that the salicylic acid which is derived from the natural oil of wintergreen or sweet birch, and the sodium salt of this acid are to be preferred to the corresponding synthetic preparations. This preference seems to be founded mainly on two claims. The first is that the "natural" or "true" salicylates are less toxic than the artificial; the second, that they are more active as antirheumatic agents. The adherents of these views are very firm in their convictions, and, what is more, certain manufacturers make very positive statements regarding the relative superiority of the former compounds. On the other side of the question there are many who are equally certain that no such difference exists. A third class of physicians, those who are either neutral or who do not take a positive stand with either side, is probably greater than the two partisan groups combined.

If there is no difference in the toxicity or in the activity of the two classes of salicylates it is of considerable importance to know it, for the "natural" variety is about sixteen times as costly as the artificial. On the other hand, if the artificial is really more toxic or less active, or both, as is strongly urged, we would be unjustified in depriving our patients of the advantages of the superior drug or in subjecting them to unnecessary risk of unfavorable effects from the more toxic, merely on the ground of economic difference. It therefore becomes an important matter to determine the validity of the several conflicting claims, if such be possible. The Committee on Therapeutic Research of the Council on Pharmacy and Chemistry of the American Medical Association has undertaken the solution of this question and will approach it from several points of view. The results of biologic investigation have already been published.¹ The results of chemical examinations and of therapeutic tests are forthcoming, and in this paper I shall attempt to review all of the evidence bearing on the question which can be found in the literature.

In the presentation of the results of my searches I shall endeavor to follow, as nearly as possible, a chronological order, and for the most part I shall make use of literal quotations from the several papers, thus letting their authors speak for themselves and avoiding the danger of misconstruing their statements.

In 1874 Kolbe first described a means of manufacturing salicylic acid artificially from phenol. In 1876 MacLagan² suggested the use of salicin in the treatment of rheumatism, based on the conception that rheumatism was, as malaria was then supposed to be, miasmatic in origin, and that salicin, like cinchona, was a natural remedy, found growing in the regions in which rheumatism was most prevalent. From about 1875 on, the literature on the beneficial action of one or another of the salicyl preparations in rheumatism grew apace, and along with the favorable reports came the records of untoward symptoms resulting from the new therapy;

but it is not until 1877 that one finds any definite comparison of the artificial acid with the acid derived from the oil of wintergreen or from salicin.

In that year Williams³ read a paper on the impurities of the artificial acid, which he ascribed to the presence of impurities in the parent phenol. He described a method by which he was able to purify the artificial acid so completely as to obtain an acid identical in every way with the natural product. He thought that the impurity was probably a derivative of cresol (cresylic acid) and of this he remarked:

Respecting the medicinal properties of this acid I can say nothing as yet; it may be, like paroxybenzoic acid, inert, and would then be simply a diluent of the salicylic acid, or it may be active as an antiseptic, or it may be mischievous; whatever it be there can, I think, be no doubt that the artificial salicylic acid at present used for medical purposes is not so pure or so uniform as is desirable, and that it should be more highly purified and freed from this second acid I have described before it or its salts are used in medicine.

In the discussion⁴ of Williams' paper Professor Redwood is cited as saying:

Mr. Williams has done a great deal toward affording the explanation of a fact which many had been aware of, namely, that the artificial salicylic acid sometimes failed in producing the effects anticipated, such as would be produced by the natural acid.

Mr. Plowman confirmed fully the statement that artificial salicylic acid frequently caused considerable derangement to the system. It had been given in St. Thomas' Hospital in doses of 20 grains every two hours and the results had frequently been to cause delirium. He was uncertain, however, whether the acid used was artificial or not, but from the price paid for it he thought that it was probably artificial.

In 1879, 1880, 1882 and 1888, the *Lancet* contained papers by MacLagan defending his stand with regard to the superior antirheumatic action of the natural salicylates as exemplified by salicin. His contentions were strengthened by occasional reports of the unfavorable effects of the impure artificial acid and its salts and it would seem that his views which referred the action of salicin to its presumed "natural relation" to rheumatism gained wide support and are, perhaps, to-day at the bottom of a similar idea regarding the difference between the actions of the "natural" salicylates and those of the artificial.

Following Williams, the next paper to appear bearing on the question was one by Fowler⁵ in 1881 from which I will quote:

In thirty-nine cases treated with pure salicylic acid [natural] toxic symptoms were present in ten only. In five there was deafness, in two deafness and tinnitus, in three deafness, tinnitus and vomiting. . . . As regards the relief from pain, subsidence of fever, and liability to relapse, the pure acid does not appear to act with greater benefit than the ordinary [artificial] acid. . . . The advantages claimed for the pure acid are that it rarely produces vomiting and never delirium. . . .

He also remarks that investigations which are going on show an impurity in the artificial acid, not, as yet, identified.

Fowler's observations are too few to permit of very definite deductions but it is to be noticed that his short series showed vomiting in 7.5 per cent. of the cases.

* This investigation was undertaken at the suggestion of the Committee on Therapeutic Research of the Council on Pharmacy and Chemistry of the American Medical Association.

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1. Waddell: Comparative Investigation of the Effects and Toxicity of Sodium Salicylates of Natural and Synthetic Origin, *Arch. Int. Med.*, December, 1911, p. 784.

2. MacLagan: *Brit. Med. Jour.*, 1876, I, 627.

3. Williams: *Pharm. Jour. and Tr.*, 1877-78, Series 3, viii, 735.

4. *Pharm. Jour. and Tr.*, 1877-78, viii, 796.

5. Fowler: *Lancet*, London, 1881, II, 1118.

This does not agree altogether with his further statement that one of the advantages claimed is that the "true" acid, "rarely produces vomiting." This percentage may have been a "rare occurrence" of the symptom as compared with what was seen after the use of the artificial acid which was then on the market. His evidence in favor of the "true" acid is, then, not very strong, for he finds no difference in the antirheumatic powers of the "true" and the artificial acids, and his incidence of vomiting from the "natural" is by no means low.

Broadbent⁶ expresses the belief that when toxic symptoms arise they are due to an impurity in the artificial drug. He says:

A question which we have not been able to resolve—indeed, I do not know that the material exists for its determination—is the relative advantages of the different salicyl compounds. It seems to me that the "natural" salicylic acid, as being less liable to contamination than the samples made from coal-tar compounds, is preferable to the latter; and it is a matter for inquiry which no doubt will be submitted to the test of experience, and which certainly I, for one, shall endeavor to elucidate.

Broadbent was a man of very wide experience as an internist and therapist, and yet he was able to offer no evidence regarding the relative merits of these two acids. But his suggestion that it would be better in all probability to employ the "natural" must have had some weight in influencing many of those who looked up to him for guidance. So far as I have been able to discover he did not publish anything further on the subject.

Latham,⁷ who was probably looked on as the greatest English authority on rheumatism in his day, laid down the following rules to ensure success in the treatment of that disease:

First, the true salicylic acid obtained from the vegetable kingdom must alone be employed. If you have to give large doses avoid giving the artificial product obtained from carbolic acid, however much it may have been dialyzed and purified. An impure acid will very quickly produce symptoms closely resembling delirium tremens. . . . Secondly, give the acid without any alkali or base. . . . Thirdly, place the patient fully under the influence of the drug—that is, let him have sufficient to produce cerebral disturbance—that is, buzzing in the ears or headache, or slight deafness. . . .

These statements are dogmatic and made without reservation, and are presumably based on the results of his clinical observations. Unfortunately, however, he cites no single case in substantiation of his statements. The reference to dialyzation and purification of the acid relates to the attempts by Dr. E. R. Squibb and others to remove the impurities from the artificial acid by dialysis. They claimed thus to produce a perfectly pure product, but it was subsequently shown that the impurities were not colloidal and that they dialyzed readily, so that the resulting product still contained much of the original impurity. Latham mentions no disadvantage of the artificial acid other than the production of delirium, and his subsequent remarks calling for the use of enough of the "true" acid to cause cerebral symptoms such as tinnitus, deafness and headache strongly suggest that if the "true" acid were carried farther in its use, it, too, might have given rise to delirium. He does not compare the efficacy of the two acids nor does he speak of the effects of the two on man in similar doses. His views must have been of great weight at the time, but his failure to

present the evidence on which he based his remarks detracts materially from the scientific value which can now be attached to them. We do not know from him that the "true" acid did not also produce unfavorable symptoms at times. We do not know that he ever used the artificial acid as a control. All that we do know from him is that he strongly advocated the choice of the "natural" acid; why, he does not tell us, save for the mention of the delirium. The first experimental work done on the determination of the relative advantages of the "natural" and artificial salicylates was that by Charteris and Maclellan.⁸

It is not within the scope of the present communication to discuss the details of these experiments or to challenge their conduct; I shall deal only with the conclusions that have been drawn from the results they obtained and will refer the reader to an article by J. A. Waddell¹ for detailed consideration of the individual experiments.

From their experiments they make the following deductions:

These experiments prove . . . that salicylic acid obtained naturally by oxidation of salicin, or from the oil of wintergreen, in 10-grain doses, has . . . no deleterious effect; that salicylate of soda obtained from the natural salicylic acid, in 32 grains, is not lethal, but that it causes prostration and lowers the temperature.

On the other hand, it is conclusively demonstrated that salicylic acid, artificial, in a 10-grain dose, causes first, paralysis of flexors; secondly, death by violent convulsions. Sodium salicylate, artificial, in 18-grain doses, is lethal. . . .

The deductions from these experiments indicate that artificial salicylic acid and its salt of sodium are dangerous and in large doses fatal to animals, while . . . natural salicylic acid and its salts of sodium are not.

They believe that this difference depends doubtless on some impurity in the artificial acid. This conclusion is strengthened by a letter which they received from G. G. Henderson of the chemical laboratory of the University of Glasgow, giving the results of his examination of samples of the two acids used by the authors. He found that the artificial was impure, containing "a small quantity of another acid which I have no doubt is the cause of the appearances observed after the use of artificial salicylic acid." Further, he says, "I should add that no trace of this substance is to be found in natural salicylic acid."

Subsequently Henderson isolated this impurity and Charteris and Maclellan tested it, finding that "the action of this impurity seems to be of the nature of a slow but certain poison, and the lethal dose is relatively much less than that of salicylic acid."

They close their paper with the following:

The obvious conclusions from these experiments are that artificial salicylic acid contains an impurity or impurities, and until this or these can be extracted by the aid of chemistry the internal administration of it or its salt of sodium should be discontinued. Large and repeated doses of the sodium salt are necessary in the treatment of acute rheumatism, and hence we may account for the restlessness, the confusion, and the delirium sometimes attendant on its use, which have been testified by clinical experience. It is more than probable, too, that the retarded convalescence occurring in some cases of acute rheumatism after the salicylate treatment is due to the great and protracted prostration which the impurity or impurities give rise to. It is to be remembered in connection with these symptoms that prescriptions of the salicylate of sodium are invariably made up, unless

6. Broadbent: *Lancet*, London, 1882, 1, 138.

7. Latham: *Brit. Med. Jour.*, 1886, 1, 735 (Croonian Lectures).

8. Charteris and Maclellan: *Brit. Med. Jour.*, 1889, II, 1208.

otherwise indicated, from the artificial and not the natural salt.⁹

The first criticism of the work of Charteris and Maclellan is that they have drawn far-reaching conclusions from decidedly insufficient evidence. They made only three experiments with sodium salicylate, one with the artificial and two with the "natural"; and only two tests of the salicylic acid, one with each variety. Further, as remarked by Waddell,¹ all of these tests seem to have been made on but two animals, one for the "natural," the other for the artificial. In addition, it is obvious that they tested the action of only one specimen of each of the preparations. They therefore made no controls of the reactions of the animals they used, and established a lethal dose as the result of a single test. The specimens of the preparations which they employed may or may not have been representative of what was to be found on the market at that time. And yet from these experiments on but two animals they offer without hesitation the explanation of many of the untoward symptoms seen at times during the therapeutic administration of the drug to man.

If their statement is correct regarding the dispensing of the artificial preparations, then how many of those who have reported favorably on the beneficial effects of the salicylates, without any specification as to which class of preparation they were using, have been, in fact, reporting the salutary action of the condemned artificial products? On the other hand, if Martindale and Squire are correct, how many of the unfavorable impressions relating to the action of the salicylates have been founded on the action of the "natural" preparations? The numbers were legion of these two groups of reports which appeared at about this time and in which there is no mention made of the source of the preparation.

Thus far Charteris and Maclellan's case in favor of the "true" salicylates is none too strong; we shall hear more of their work later.

The discussion¹⁰ of the paper by Charteris and Maclellan contains some points worthy of our attention. Dr. Shaw remarked that "all the evil effects generally attributed to the action of salicylate of soda were not due to extraneous causes. It was not only on account of price that it was preferred to salicin, as it was a more efficacious drug. He had seen delirium and hemorrhages following the use of salicin as well as after salicylate of sodium."

Haig said that he thought that the toxic effects of sodium salicylate had been exaggerated, but that there was a great difference in the different specimens. Taylor said that he gave 20 grains of sodium salicylate [artificial] every two hours and found delirium by no means uncommon. Myers "could not agree with the great danger of producing toxic effects with that drug" [i. e., artificial sodium salicylate]. Bruce said that he could not agree with Taylor, for he had rarely seen delirium, though he gave 15 grains or more every three hours. He thought the drug then in use finer than formerly, for toxic effects were rarely seen.

Shaw's remarks indicate that he considered many of the unfavorable effects of salicylate administration as due to the action of the salicylate itself and not to the presence of impurities derived from the phenol in the process of synthesis. He certainly implies this construc-

tion when he further adds that he has "seen delirium and hemorrhages following the use of salicin as well as after salicylate of sodium."

Haig's statement to the effect that there was a great difference between different specimens of the artificial salicylate of soda serves to strengthen the similar suggestion, which I made in discussing Charteris and Maclellan's results, that the specimens which they used may or may not have been representative of what was to be found on the market at that time.

Taylor's dose of the drug is rather high and it is not impossible that a similar amount of the "natural" salt would have produced a like result, for in the paper by Latham,⁷ he advises that sufficient of the "true" acid be given, "to produce cerebral disturbance," and subsequently says, "In the majority of cases 80 to 100 grains are enough." It takes approximately 115 grains of sodium salicylate to yield 100 grains of salicylic acid so that, given in doses of 20 grains every two hours, only six doses would more than correspond to 100 grains of the acid. In addition Haig, Myers and Bruce could not agree with the experiences of Taylor.

The experiences, then, of those who discussed the paper of Charteris and Maclellan tend, if anything, to oppose the idea of greater toxicity of the artificial salicylate of sodium, and to refer such unfavorable effects as are seen to the action of an excessive amount of salicylate, regardless of its source.

We now return to Charteris¹¹ and quote from a second paper of his in which he says that "there has been a steadily growing conviction that artificial salicylate of soda . . . is depressing, and further that in certain cases there is cerebral excitement culminating in delirium. . . ." He cites the experiments which he had described in the preceding communications. He then relates having tested two samples of supposedly "pure" artificial acid on rabbits, and 15 grains per 2½ pounds were found to be fatal.

Next, he cites Williams, whom I have already quoted.⁸ He followed Williams' directions for the purification of the artificial acid, preparing a pure salicylic acid which had the appearance of the "natural" and a similar melting-point. He made three tests on rabbits with this purified acid and found that "the result was most satisfactory"; "that there was no paralysis and no depression, but that, on the contrary, the animals were neither up nor down, but were able to run about with ease after the last injection."

As a result of these experiments he remarks that "these facts show that the process of purification, even on a small scale, is not tedious or difficult, and in all probability it could be done easily and thoroughly on a large scale with less loss of time, and at only a slightly increased cost, as compared with the present method [1890]."

Up to 1890, he says:

So far we had found none [i. e.: no specimens of artificial salicylic acid] able to stand the physiologic test. . . . But on Jan. 1, 1890, unsolicited, a Berlin firm communicated with me through their agents in London. This firm sent specimens supposed to be chemically pure, but when tested they were found to be not quite so, though relatively so. Since then specimens of acid have come from the same firm which give the same physiologic action as that from the natural salicylates.

He concludes by saying, "For internal use in medicine they [pharmaceutical chemists] should demand the

9. In the same volume (Brit. Med. Jour., 1889, II, 1315) Mr. Martindale writes in regard to this statement regarding the filling of prescriptions: "The reverse is the rule with all good dispensing establishments in London." Messrs. Squire & Sons confirm Martindale's statement.

10. Brit. Med. Jour., 1890, I, 350.

11. Charteris; Med. Chir. Tr., 1890, lxxiii, 141.

large crystalline form of the artificial acid, and from this alone should the salicylate of soda be prepared." Charteris had previously described the chemical and physical characters of the "natural" acid and of the completely purified artificial product. The two were the same.

The results of this second set of observations by Charteris tend to show that the deleterious actions of the artificial acid were not inherent in the acid but were wholly dependent on the presence of an impurity, a view suggested by most of the preceding authors, but, until now, not definitely established. They further show that it is quite possible so to purify this acid as to obtain a product having the physical, chemical and pharmacologic characteristics of the "natural" product. That this process of purification is neither complicated nor unduly costly seems to have been demonstrated by his work. Lastly the commercial purification of the artificial salicylate seems to have been accomplished to the extent of yielding a product in no way different from the "true" acid. These results, coming from one who formerly was so powerful an advocate of the use of none but the pure "natural" product, are the more convincing, for there can be no contention of blind adherence to a preconceived notion.

Charteris must certainly have convinced himself most firmly of the similarity between the completely purified artificial acid and the "natural"; of the equal efficacy of this purified product and the "natural"; and of the purity and efficacy of the sample of the commercially purified product, before expressing conclusions so diametrically opposed to those which he had previously expressed.

The objection may be raised here that his methods were not checked up by control experiments in this latter work any more than they were in the former. This objection has lost much of its validity, for at the time of this report he had made tests similar to the earlier ones on a much larger number of animals and with a considerable number of specimens of salicylic acid. Each test thus made served, in a measure, as a control for the succeeding. Nevertheless, it is regrettable that he still contented himself with a few tests when he might have made his evidence vastly more valuable had he but doubled or trebled their number.

In the same year that this last communication of Charteris' appeared, Dunstan and Bloch¹² published a paper in which they entered into a consideration of the chemical side of the relative purity of the two acids and discussed means of purification. They say:

Therapeutic observation has, however, disclosed the fact that both the commercial salicylic acid and that purified by dialysis produce effects when administered to the human subject which are not observed to result from the administration of the pure salicylic acid, prepared from the methyl salicylate contained in the natural oil of wintergreen.

They cite several observers who found from 6.5 per cent. to 30 or 40 per cent. of impurity in the commercial acid of that time.

They further remark, "It will be seen . . . that the toxic action of the artificial salicylic acid of commerce has been definitely traced to an impurity. . . ."

They found ortho-, meta- and paracresotic acids in the specimens which they examined.

In the same volume¹³ there is a report from Charteris on the results of biologic tests of these cresotic acids on rabbits. He found the ortho- and para-acids highly toxic to these animals [two animals, one for each of the

acids]. Metacresotic acid was non-toxic. He further made two tests on rabbits of purified artificial salicylic acid and found it to give satisfactory results; i. e. that it was not toxic.

To quote:

The ortho- and paracresotic acids by their physiologic action show that they are slow but certain poisons, causing prostration and paralysis affecting first the hind limbs and gradually extending over the body.

The well-defined crystalline form of the acid [artificial salicylic] with a melting-point of almost 157 C., should be the official form of the artificial salicylic acid, and from this alone should the salicylate of sodium be prepared.

I may add that if salicylic acid be prepared from synthetic carbolic acid, having a melting-point of 42 C., it then contains no impurity. Its melting-point is 157 C., and, its physiologic action is in every way satisfactory.

There is a fuller presentation of the same paper by Charteris in the *British Medical Journal*¹⁴ from which I quote his closing remarks:

. . . sufficient evidence has been adduced to show that in cases where poisonous symptoms have been evoked by the administration of large and repeated doses of the artificial salicylate of soda in rheumatism, they are dependent on its containing the impurities mentioned [that is, o- and p-cresotic acids]. Further experiments may be necessary to determine whether the amount of paracresotic acid contained in some samples of commercial salicylic acid is sufficient to produce poisonous effects on a human subject. My experiments show that when injected into small animals it is poisonous, though in a less degree than the ortho- acid, and that its poisonous effects are intensified when combined with the ortho- acid, and still more so when incorporated with this acid and salicylic acid.

Regarding the sodium salt of paracresotic acid he says that ". . . judiciously given, [it] may be of benefit in certain diseases."

These three communications, the one by Dunstan and Bloch, and the two by Charteris, serve further to establish the fact that the unfavorable actions of salicylic acid and its sodium salt, derived synthetically, are not inherent in these preparations but are due solely to the presence of impurities which it is quite possible to remove completely. They further confirm the previous work which showed that the artificial salicylates when efficiently purified are physiologically identical with the corresponding "natural" salicylates.

In spite of the work done by Charteris it is difficult to accept his contention that paracresotic acid is so much to blame for the production of the toxic effects as he says it is, for he himself admits that its sodium salt has been used in therapeutics. In Germany at about this time sodium paracresotate [paracresotinate] was in use in medicine and did not cause any severe toxic symptoms when given in doses of 5 grains each. Further, in the light of the work of Waddell,¹⁵ we are almost forced to reject this idea. Waddell has also shown that "mixtures of paracresotinate of sodium with natural sodium salicylate do not exhibit greater toxicity than the components. . . ." This contradicts the previous statement made by Charteris regarding their combined action. Further, in a letter to the *British Medical Journal*¹⁵ Professor Stockman takes exception to the contention that the toxic impurity of artificial salicylic acid is cresotic [cresotinic] acid. In this letter he says:

12. Dunstan and Bloch: *Pharm. Jour. and Tr.*, 1890-91, Series 3, xxi, 429.

13. Charteris: *Pharm. Jour. and Tr.*, 1890-91, Series 3, xxi, 430.

14. Charteris: *Brit. Med. Jour.*, 1891, I, 695.

15. Stockman: *Brit. Med. Jour.*, 1890, II, 1271.

That this substance is not creosotic acid seems to me to be proved by the following considerations:

1. The results of clinical experience with creosotate of sodium; it was used by Buss (1876) in doses up to 4.0 gm., by Gatti (1879) in 5.0 to 8.0 gm. doses, and by Demme (1889) in children up to 1.5 gm. None of these authors observed that it had any particular poisonous effects, and they agree in concluding that its action is practically identical with the action of salicylate of soda. It will be observed that Demme used paracreosotic acid, which is stated by Professor Charteris to be so poisonous that 2 grains of it killed a rabbit weighing $1\frac{1}{2}$ pounds.

2. The chemical constitution of creosotic acid. . . . Chemically it is very closely allied to salicylic acid, and from what we already know of the relationship in physiologic action among the members of this series, one could predicate with certainty that in action it would closely resemble salicylic acid.

Stockman is of the opinion that the specimens of creosotic acid which Charteris tested also contained the same unknown impurity as did the salicylic acid he had previously tested.

May¹⁴ cites the same observers as have just been mentioned in the quotation from Stockman. He notes that Demme gave 90 to 120 grains of paracreosotinic acid to men without the production of toxic symptoms. May conducted some experiments on man and animals with the several creosotinic acids [creosotic] and concludes by saying:

The creosotinic acids resemble salicylic acid in their action as antifermentatives, as bactericides, as antipyretics, and as specifics in acute rheumatism. Their toxic effect in animals is about the same, but orthocreosotinic acid is more depressing to the circulation.

These remarks by May and Stockman merely throw doubt on the accuracy of the determination of the precise chemical nature of the body which was the cause of the deleterious action of the salicylic acid which Charteris used, and the truth of the remarks of Stockman were, in turn, challenged by Dunstan. It would carry us too far afield to consider this phase of the problem. All that concerns us at the present moment is the question of the purification of salicylic acid and the action of the purified product.

Taking cognizance of these differences of opinion and the objections to Charteris' conclusions, we have not impaired the validity of his work with regard to the lack of toxicity of the purified artificial salicylates. And the number of experiments which he had by this time done with the purified products is sufficient to remove the objections on the ground of possible idiosyncrasies on the part of his animals.

I might here make brief mention of Henderson's¹⁷ observations on the question of the purification of salicylic acid. He tried many methods and found that the very simple one devised by Williams¹⁸ was the most satisfactory. He found as impurities creosotic acid, parahydroxybenzoic acid, and hydroxyisophthalic acid. He remarks, "It is therefore a comparatively simple matter to manufacture a pure salicylic acid—indeed, I understand that this is now being done." (1890.)

Stockvis¹⁸ seems to have been about the only man outside of Great Britain to make any studies on the relative advantages of the artificial and the "natural" salicylates. He cites the paper of, "Chartens and Machyon," which is obviously intended as a reference to that of Charteris

and Maclellan. Stockvis used the sodium salt of each of these acids.

His findings were, in brief: that the "natural" was much milder in its actions than the artificial; that the "natural" acid was excreted the more rapidly in the rabbit and man; that with the more rapid excretion of the "natural" there was a marked diuresis in addition (this was not true of the artificial), and that, in the same doses, the actions of the "natural" were less marked on the rabbit than those of the artificial, but that the lethal doses were quite the same. On frogs' hearts the salicylates caused depression, smaller doses of the artificial being required than of the "natural." He cites the experience of Moerel, who took the drug daily for fourteen days in doses of 0.2 gm. every four hours [about 3 grains four times a day]. On the first day he observed headache, which soon passed off; there was no effect on sleep, appetite or other function. The temperature was little altered. These symptoms were less marked in the case of the "natural" product. The pulse-rate was somewhat increased by the artificial and less by the "natural." Respiration was raised in rate by the artificial, and practically not at all by the "natural."

Taking all of the results together, Stockvis remarks that there is hardly to be noted any qualitative difference in action between the artificial and natural. He says that one must agree unconditionally with "Chartens and Machyon" that the difference is merely quantitative, and that the natural is the less toxic. That in the explanation of this difference the more rapid elimination of the natural plays a great part; this he attributes to "osmotic peculiarities" of this acid. He found that the electrical conductivities of the two acids were not identical, and that the "natural" was impure chemically, being mixed with an extremely small amount of oil of wintergreen. He said that our next task would be to free the natural acid completely from the methyl-salicyl-ester, and make comparisons of this with the pure artificial acid.

He concludes with the remark that "so much is evident; that the chemically impure 'natural' acid is less therapeutically than the chemically pure artificial."

In view of all of the previous work, one cannot be but struck by Stockvis' conclusion that the *milder* actions of the "natural" salicylates are due to their *impurity*, while the artificial compounds are pure. Such a view must be taken with considerable reserve, for it is opposed to all of the chemical and pharmacologic studies which we have thus far reported. In his work there is a further rather anomalous statement to the effect that, though the "natural" salicylates were found to be "less marked" in their actions than the artificial, the fatal dose was the same for the two forms. When we recall that he also said that "there is hardly to be noted any qualitative difference" between the two, and that "the difference is merely quantitative" we are at a loss to know how to reconcile two contentions so completely antagonistic.

It may be true that the "natural" gives a greater diuresis than the artificial, but just how this explains the "milder actions" of this product is by no means clear, particularly in the experiments in which the drugs were applied to the frogs' hearts. Why this diuretic effect of the "true" reduces its actions to a less marked grade, and does not similarly effect its lethal action is also difficult of comprehension.

The evidence brought forth by the self-made observations of Moerel is not convincing, for the differences he experienced in the effects of the two salicylates are so

14. May: Brit. Med. Jour., 1909, II, 791.

17. Henderson: Jour. Soc. Chem. Indust., 1890, IX, 591.

18. Stockvis: Wien. med. Presse, 1894, XXXV, 1209.

slight as to be accounted for as being the results of the psychic influences of a preconceived idea. Finally Stockvis' failure to look further into the literature of the subject than the earliest work by Charteris accords with the general superficial character of his observations.

Lewin¹⁹ adds nothing to what has already been discussed, but he repeats that the impurities of the artificial salicylic preparations are responsible for their side actions, such as delirium and cerebral excitement. While this is true regarding the difference between the actions of the two classes of salicylates, he remarks that it must be borne in mind that pure preparations are not devoid of side actions. These impurities are probably the ortho- or paracresotic acids. His work is not original. It is merely his summary of the literature, with the stamp of his interpretation of the value of the several ideas suggested. I introduce this merely on account of the fact that what appeared in Lewin's book must have had some influence in molding medical opinion on account of the reputation of the author.

Along with the preceding it may be well to cite the monograph by Pribram,²⁰ in which he reviews at length the greater part of the literature relating to the salicylate therapy of rheumatism. He details a very formidable array of unfavorable effects of the salicylates, without mentioning whether they resulted from the "natural" or the artificial, and then remarks that it is obvious that many of these phenomena, including death, were probably in no way attributable to the action of the salicylate, on which the blame was thrown.

The first of the American papers to deal with the question of the relative merits of the two forms of salicylate seems to be that by a pharmacist, Cone.²¹ His evidence is composed of citations from some of the authors whose work I have already discussed, and from some whose papers I have been unable to find, as Cone gives no references. Among the latter is one from Dr. H. M. Lyman, who said, in an address, that he had had the following early experiences with the use of salicylic acid and sodium salicylate: he "found that the results were not so good from preparations made in this country as from the original German article, due to impurities in the former." He reports a case of delirium tremens-like symptoms from its use.

Dr. Simon Baruch is cited as saying that to get the effect from the salicylates without their inconveniences, pure salicylic acid should be used; only that derived from the oil of gaultheria should be employed.

Dr. Abraham Meyer is reported as saying that only the salicylic acid from genuine oil of wintergreen should be used; that the others [i. e., the synthetic and the salicylic acid derived from the synthetic oil] cause disturbance of the stomach, and delirium.

After citing the work of Charteris and MacLennan, of Dunstan, and Charteris' second paper, Cone goes on to discuss the tests for purity and their ability to detect adulteration. He concludes as follows:

At present a very large percentage of the oil of wintergreen on the market is adulterated, mostly with the synthetic methyl salicylate, and this adulteration has been the most difficult to detect, possessing, as it does, about the same chemical composition and with physical characteristics nearly identical.

Pancoast and Pearson²² also have entered into the study of the purity of the salicylic acid sold as "natural,"

and, though it breaks the chronologic order, I shall bring in their findings at this point and discuss the two papers together.

They say:

Since the so-called natural salicylates have met with such wide-spread favor as therapeutic agents, there has been a tendency on the part of a few unscrupulous distillers, dealers and drug merchants, to substitute the low-priced synthetic products. This tendency has more rapidly grown as there has been no accurate means of detecting the sophistication.

For some years chemists have endeavored to detect the presence of synthetic methyl salicylate when added to oil of birch or gaultheria, but, owing to the great similarity of these products, the task has been very laborious. All three of these products contain at least 99 per cent. of absolute methyl salicylate.

While these two papers from pharmacists add very little of value from the clinical or experimental aspects of the question, they are of interest because they serve to show how slight the chemical differences between the "natural" and artificial salicylates are—not over 1 per cent. according to one—and how difficult it is to be certain that one really has the "natural" product, and not, in fact, a combination of the two. This suggests a little doubt as to whether all of those who have praised the "natural" salicylates so highly have in reality been using the drugs they lauded, or only mixtures of "natural" with the artificial. This applies particularly to the clinical reports, for in most of these the question of purity of the product was not investigated. The vast difference in the price of the two classes of salicylates makes adulteration far more probable than not in many instances. It is not improbable, then, that many have unwittingly sung the praises of the artificial in the belief that it was the pure "natural" salicylate.

The last three papers which I shall present are from American authors and are purely clinical in character; hence they are subject to the criticisms which I have just made regarding the possible impurity of the products used. It is certain that the authors were sincere in their beliefs that what they used was only the "natural" salicylate; but who is to check the purity of the salicylate that the local pharmacist uses in preparing the prescription? Even if he be acting in good faith, it is not probable that he can be any more certain of the purity of the preparation that is sold to him than is the physician of that he receives from the druggist.

The first of these papers is by Dr. Winters;²³ in it he speaks of the salicylates only in the course of the discussion of the treatment of rheumatism. He says that there is a positive chemical antidote to rheumatism and that "this antidote is an *organic* chemical compound. Synthetic salicylic acid has no effect." He gives no data on which he bases these statements. This is the strongest support of the "natural" salicylic acid and the most severe condemnation of the synthetic that I have found.

The second is based on the observations of Rosenzweig and Ronginsky.²⁴ As the result of some clinical observations on the artificial and "natural" salicylic acids they reported, "The 'natural' product does not depress the heart as much as the artificial product; it does not upset the stomach so much; it acts more rapidly." Like the preceding author, they do not give the data on which they base their statements; the statement quoted above was, in fact, reported as coming from them by a third person, Dr. Kahn, who had asked them to make the

19. Lewin: Nebenwirkungen der Arzneimittel, 1899, Bd. 3, p. 436.

20. Pribram: Nothnagel's Specielle Pathologie und Therapie, v. Part 2, 449.

21. Cone: Am. Jour. Pharm., 1903, lxxv, 401.

22. Pancoast and Pearson: Am. Jour. Pharm., 1908, lxxx, 407.

23. Winters, J. E.: Etiology of Rheumatism, etc., pamphlet published by author.

24. Rosenzweig and Ronginsky: Quoted by Kahn in Druggists Circular, 1908, III, 345.

observations. This kind of evidence is certainly far from convincing and has no scientific value.

The third of these papers is by Dr. Lambert,²⁵ in which he strongly advocates the use of the oil of sweet birch in preference to the synthetic salicylates, and in fact in preference to any other of the salicylates. He bases this on clinical experience and while he thus advocates the use of the "natural" salicylates, he does not by any means exclude the usefulness of the artificial, for he specifically says that if one of the common forms of salicylate does not agree with the patient we should try others until we find one that does: ". . . if the patient is resistant to that [true oil of birch], it should be changed to . . . some other form of salicylate."

It does not seem necessary to enter into a separate discussion of the last three papers, for such of the previous criticisms as apply would only have to be repeated.

Before summarizing it may be of interest to cite from two personal communications from Professor Stockman of the University of Glasgow to one of the members of the Committee on Therapeutic Research of the Council on Pharmacy and Chemistry. From the first, written in October, 1911, I shall quote:

Some years ago I examined five samples of artificial sodium salicylate from different manufacturers. I found that four of them were *practically chemically pure, and differed in no way as regards clinical action, and chemical tests from the "natural" sodium salicylate.*²⁶ So far therefore as my own experience goes I regard the matter as settled.

He further says that "gross differences certainly do not exist between the actions of pure artificial sodium salicylate and the so-called 'natural' product." In a second communication he says that he has gone into the question of the "natural" and synthetic salicylates and he has "found that the pure synthetic acid is not more poisonous than the other ('natural')." He also finds, as a result of therapeutic examinations, that creosotic (creosotinic) acids "can be given in doses similar to those of the salicylates."

Before drawing any conclusions from the material which I have been able to collect as bearing in any way on the question of the relative value of the artificial and "natural" salicylates, I shall briefly summarize the evidence brought forth in the papers and discussions which are here presented.

There is first the clinical evidence. I have been able to find only fourteen expressions of opinion from the clinical point of view favoring the "natural" salicylates over the artificial. One of this group (MacLagan)² speaks only in favor of salicin, and his reasons for his views go far to invalidate his contentions. A second (Charteris) favored the "natural" in his first paper only, and subsequently specifically advocated the use of the pure artificial salicylates. A third (Lambert) favors the "natural" but does not condemn the artificial, using it when the "natural" is ineffective. The rest of those who favor the "natural" salicylates in general give no evidence in support of their contentions, merely stating their views more or less firmly. Two do give clinical evidence for their contentions (Fowler and Stockvis), but in neither case is the evidence at all convincing. Only two (MacLagan, Winters) have challenged the therapeutic value of the artificial salicylates.

Second, there is the chemical evidence. This is of a positive nature and the findings are, in all probability, quite correct. It is to be remarked, however, that such

findings apply only to preparations on the market prior to 1900, and there is no evidence to show that the synthetic preparations of the present day are not chemically pure. There is, in fact, evidence to support the view that they are pure (Waddell¹). On this point we must remember that there is reason to believe that sodium paracresotinate in small amounts is not toxic to man,^{1, 15, 16} and this is the chief impurity blamed for the alleged inferior worth of the artificial salicylate.

There is experimental evidence from three sources only. First is that from Charteris, and Charteris and MacLennan. This ultimately showed that it is commercially possible to purify the artificial salicylic acid so completely as to yield a product, physically, chemically and pharmacologically identical with the "natural." And the author of this work advises the use of the artificial salicylic acid thus purified. The second experimental work is that of Stockvis. This, we have seen, means, if it means anything, that the artificial and "natural" salicylates have the same qualitative actions, but that the "natural" is *milder*, though no less fatal. The last experimental work, that of Waddell, gives very strong evidence that the *cheapest procurable artificial salicylates* of the present day are in no way different pharmacologically from the costly "natural."

In the period of thirty-eight years during which time the artificial salicylates have been in use in medicine, there are to be found, in the entire realm of accessible literature, less than twenty-five communications dealing, even casually, with the relative advantages of the artificial and the "natural" salicylates. In all these years many thousands of patients have been treated with large doses of the artificial salicylates and many of the ablest clinicians and the most acute observers in England, America and on the Continent have watched the results of such treatment. Yet there are a scant fifteen who have been led to report these preparations as being more harmful than any other form of salicylate administered under similar conditions, and in similar amounts. The rest have probably rightly attributed such ill effects as mental excitement, delirium, nausea, vomiting, tinnitus and the like to an excessive amount of the drug or to an idiosyncrasy on the part of the patient, or perhaps to both.

We have to remember, also, that nearly all of the reports of the deleterious actions of the synthetic salicylates were made well over ten years ago, and that it is possible that at that time certain samples of these products were badly contaminated.

At the present time the idea of the superiority of the "natural" salicylates is sedulously fostered by certain manufacturers, rather than by the experiences of the medical profession. In the "literature" and advertisements of one of these, Charteris is quoted as one of the powerful advocates of the "natural" salicylates. I would suggest that, in the future, mention should be made of his second and third papers, rather than of the first only.

In conclusion, let me say that I have presented all of the evidence from the literature which I can unearth. I have tried to make the excerpts and quotations in such a way as to present the opinions of the several authors with neither omissions nor alterations, such as might in the least alter the meaning that each wished to convey. Lastly, I have brought out such objections to the evidence on either side of the question as have occurred to me in the reading of these papers and in the writing of this one.

25. Lambert: The Use of Salicylates in Rheumatism, *THE JOURNAL A. M. A.*, Sept. 9, 1911, p. 898.
26. Italics mine.

From the material at hand there seem to be but two logical conclusions:

1. The evidence in favor of the "natural" salicylates rather than the artificial is extremely slight, or what amounts to the same thing, the evidence against the artificial salicylates is even less.

2. In nearly forty years of use by physicians all over the world, the artificial salicylates have been found quite as effective as the "natural" and no more liable to produce unfavorable actions under similar conditions than are these vastly more expensive "natural" products.

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A METHOD OF CONTINUOUS DILATATION OF EXTENSIVE URETHRAL STRICTURE

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Three decades ago the followers of Otis, who were very numerous, cut every stricture of the anterior urethra. To-day strictures of the pars anterior are rarely cut. This is owing to the teachings of Oberlaender, Wossidlo, Valentine and Kohlmann, and to the consequent increase of knowledge and more careful study of the dilatation treatment. It took years to establish the principle that sounds and dilators are not used to stretch strictures. Such an instrument in the urethra exerts a dynamic

Fig. 1.—Curves at membranous portion of urethra and penoscrotal junction (after Gray). In erection only one decided curve is present.

influence. According to Oberlaender, it induces retrograde metamorphosis, a reversion of the fibrillary tissues into the original small-celled deposit, permitting absorption. It has been intimated that the cells of the infiltrate are rendered soluble or diffusible or absorbable by peptonization; and again that absorption is favored by a teasing apart of cells, as in the Bier method of inducing artificial hyperemia. Whatever theory may finally explain the phenomenon, it may be fairly stated that pressure absorption of urethral inflammatory infiltrations, soft and hard, is an accredited and authentic observation.

After perineal section for strictures that narrow both the anterior and posterior divisions of the urethral

canal, it has been my practice to drain the bladder by the natural route, leaving a large soft rubber catheter in the urethra. This plan has some advantages. The period of convalescence is shortened, since the perineal wound closes more promptly if the urine be drained through the catheter. The urinary salts which irritate the mucosa and favor stricture formation (Keyes) are not permitted to touch the urethra. The caliber of the urethra is maintained or even increased, and the subsequent passage of instruments is rendered easy. Much of the tedious work of after-treatment, such as sounding, becomes unnecessary or is decidedly lessened. Soft and hard infiltrations of the pars anterior are removed by the pressure absorption induced by the presence of the catheter.

Fig. 2.—Sharp penoscrotal angle. The normal angle is shown as it is exaggerated by depression of the outer end of the catheter into urinary.

If a perineal drain alone be used, there is, of course, no continuous dilatation of the anterior urethra.

There is, however, one defensible objection to the use of the dilating catheter if employed as described above. Lying in the urethra and extending from the bladder to the external meatus it usually becomes sharply curved or angulated in the pars membranacea and at the penoscrotal juncture. The pressure induced by the sharply flexed catheter at the penoscrotal angle has led to abscess formation or extensive inflammatory reaction often enough to suggest the need of a departure from the plan of using the same catheter for drainage and dilatation, and of employing instead two large elastic soft rubber catheters, one as a perineal drain, the other for dilatation of the pars anterior.

It has been observed by those who are accustomed to drain the bladder through the urethra for certain conditions that a small soft thin-walled rubber catheter has less tendency to cause abscess than a large rubber tube with thicker walls. The former, however, is of much less value as a dilator, and is more difficult to retain in position. If the outer end of the catheter be drawn up over the abdomen and connected with a urinal at the side of the bed, one curve is made of the urethral canal, and the danger of abscess lessened. It is not easy, however, thus to hold a catheter in place because of unavoidable traction.

From Figure 1, it will be seen that if the external meatus be not depressed as it usually is in catheter drainage through the urethra, there need be no sharp angulation at the penoscrotal juncture. If the penile portion of the urethra be elevated the entire pars anterior becomes quite straight.