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CLINICAL EFFECTS OF "NATURAL" AND "SYNTHETIC" SODIUM SALICYLATE

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A COOPERATIVE INVESTIGATION

It has been claimed that the sodium salicylate prepared from natural oils is superior as a therapeutic agent to the sodium salicylate prepared by synthetic methods. If this claim be justified, then the natural form of the drug should be prescribed by physicians; but if the claim be unsubstantiated, then the additional expense of the natural product is unnecessary and the synthetic drug is to be preferred. The Council on Pharmacy and Chemistry of the American Medical Association has undertaken to investigate various aspects of this question, and papers dealing with the literature,[1] the effect of the drug on animals[2] and the chemical purity of commercial sodium salicylate[3] have already appeared. In determining the relative therapeutic value of the two forms of sodium salicylate, however, clinical evidence of the proper sort is of paramount importance. The efficacy of the drug in relieving pain, and especially its value in acute rheumatic fever, can be determined only by studies on patients; while the toxic effects of the drug on animals cannot be transferred unreservedly to man, especially when we are dealing with patients already subjected to the pathologic changes of acute rheumatic fever.

It is not easy, however, to obtain reliable clinical evidence on such a subject. The personal equations of different observers, the tendency to bias, differences in the modes of administration, in the doses employed, and in the cases selected for treatment, all tend to obscure the significance of reported results. In order to obtain trustworthy data, it is necessary that a considerable number of observations on patients should be made under conditions which eliminate personal bias and reduce to a minimum the errors inherent in statistics.

METHOD OF INVESTIGATION

In order to obtain data as free as possible from error, the Council requested the cooperation of a number of clinicians of recognized standing. They were asked to use and to note the effects of test-powders of sodium salicylate without knowing the sources, natural or synthetic, of the individual powders. Should there be a marked difference in the two forms of the drug, it might be expected that an expert clinician could detect which form he was using. If differences were present, but less marked, a study of the collected reports should show these differences. The following letter was therefore addressed to the clinical consultants of the Council on Pharmacy and Chemistry, to all members of the Association of American Physicians, and to all members of the American Therapeutic Society:

July 20, 1911.

Dear Doctor:—The Council on Pharmacy and Chemistry has undertaken to investigate the question whether there are any differences in the actions of "artificial" and "natural" sodium salicylates and would appreciate your cooperation. In order to place the evidence above any possibility of prejudice or bias, it is planned to issue to a number of clinicians boxes of ten powders, each powder of 10 or 15 or 20 grains (as preferred) of sodium salicylate. Half of these boxes will be filled with a good quality of synthetic sodium salicylate (Merck's), the other half with sodium salicylate which is being specially prepared by Professor Lloyd from oil of birch. These boxes will bear only a serial number and the clinician will be asked to treat each patient from one box only, and to report whether his observations permit him to arrange the results under two groups, as also the criteria and data which he used in making the classification. A comparison of his grouping with the list actually supplied to him should then show whether there is a real difference between the two products.

The following outline used by a collaborator in a somewhat similar investigation may serve as an illustration but it is not intended to restrict the observers in any way:

"The hospital was supplied with boxes containing ten powders each of 20 grains of sodium salicylate (200 grains) in each box. The residents were directed to administer to the rheumatic patients one powder, in water, every hour, until toxic; using only the contents of *one* package on each patient. The unused powders were to be returned for control. The record was to state:

"1. The number of the sample.

"2. The age and sex of the patient—record number.

"3. The total dose taken.

"4. The effects noted: (*a*) relief of pain; (*b*) antipyresis; (*c*) diaphoresis; (*d*) ear-effects; (*e*) gastric effects; (*f*) delirium; (*g*) albuminuria; (*h*) acetonuria; (*i*) other data."

Please note on the enclosed card whether we can count on your cooperation and if so when you will be ready to start and whether you wish the powders to be of 10, 15 or 20 grains. The Council would also be grateful for any suggestions.

Of the physicians addressed, eighty-two expressed a willingness to cooperate in the investigation. To each of these were sent ten boxes each containing ten powders of the size which the physician wished to administer. Each box bore a number whereby the source of the salicylate could be recognized when the report was received. In group A, Boxes 1, 2, 4, 7 and 10 contained the syn-

1. Eggleston, C.: The Relative Value of the "Natural" and the Synthetic Salicylate: A Study of the Literature, THE JOURNAL A. M. A., Dec. 7, 1912, p. 2057.

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

3. Hilpert, W. S.: The Purity of Commercial Sodium Salicylate, THE JOURNAL A. M. A. April 12, 1913, p. 1137.

thetic salt, and Boxes 3, 5, 6, 8 and 9 the natural salt. In group B, Boxes 2, 3, 5, 6 and 8 contained the synthetic and 1, 4, 7, 9 and 10 the natural salt. The following letter accompanied the powders:

August, 1911.

Dear Doctor:—As you have consented to cooperate with us in the sodium salicylate investigation, we are sending you ten boxes of sodium salicylate powders as requested for clinical tests, to determine whether there is any difference in the effects (desired or undesired) of the "natural" and "synthetic" substances. Each box bears a serial number and contains either "natural" sodium salicylate or "synthetic" sodium salicylate, the origin of which is recorded in this office. Please treat each patient from one box only and preserve a record of the phenomena. Preserve any unused powders for return to the laboratory, for control. The administration should be restricted to patients with typical acute articular rheumatism; or at least, other cases should be listed separately.

At the end of the investigation, please report your results and state whether you can attempt to identify the origin of the powders by your results, and what criteria and data you have used in this classification.

The following outline used by a collaborator in a somewhat similar investigation may serve as an illustration but it is not intended to restrict the observers in any way:

(For outline, see previous letter.)

CLINICAL REPORTS

I was asked by Dr. Torald Sollmann, chairman of the Council's Committee on Therapeutic Research, to review and analyze the clinical reports that had been received. For various reasons a considerable number of those to whom powders had been sent were unable to furnish data. The following review is based on reports received from twenty-seven clinical investigators, embodying approximately 230 separate observations on the effect of the salicylate powders used. As might be expected, the reports varied widely in the completeness of the data furnished, in the modes of administration, and in the diseases treated. A few observations had to be discarded because the investigators had not noted the numbers on the boxes from which the powders had been taken. It was necessary to summarize each report before attempting a comprehensive analysis. These summaries will be published as an appendix in the reprints of this paper.

On attempting to review these reports, one is immediately confronted by the diverse modes of administration and by the different diseases treated. It is manifestly impossible to compare the results of those who gave 200 grains of sodium salicylate in ten hours with the results of those who gave 45 grains a day; or to compare the effects when only frank cases of rheumatic fever were treated with the effects when various other joints, or muscular or nerve pains were attacked. For this reason the reports are not readily comparable, one with the other. Nevertheless, since each observer received an equal number of natural and synthetic powders and used these indiscriminately, the results form a reliable basis of comparison between the two sets of powders, for the variations in administration, type of case, etc., tend to distribute themselves equally between the two classes of salts. Indeed, these variations are in a certain sense advantageous, for they permit some comparison of the effect of the two sets of salts under different conditions.

In Table 1 I have summarized the principal results of the fifteen more complete reports. The relief of pain and fall of temperature were tabulated only for what seemed to be cases of true rheumatic fever, while the diaphoresis, gastric disturbances and ear-symptoms were tabulated for each set of powders administered. Occasionally a single patient received two or more sets of powders so that the total number of observations exceeded the total number of patients. Under the

TABLE 1.—PRINCIPAL RESULTS OF FIFTEEN REPORTS

Observer	No. of Patients	Administration			Relief of Pain						Fall of Temperature						Diaphoresis						Gastric Disturbance						Ear Symptoms					
		Usual Dose Grains	Usual Interval	Usual Total Amount	Relief		No Relief		Not Noted		Fall		No Fall		Not Noted		Present		Absent		Not Noted		Present		Absent		Not Noted		Present		Absent		Not Noted	
					N*	S*	N	S	N	S	N	S	N	S	N	S	N	S	N	S	N	S	N	S	N	S	N	S	N	S	N	S	N	S
Barnes, N. P.	7	10-20	3 a day...	...	..	1	..	..	..	..	..	..	..	..	..	1	..	..	..	..	8	12	..	..	1	2	7	10	..	1	..	..	8	11
Coleman, W.	24	20	2 hours...	200	10	11	1	2	1	..	6	9	4	1	2	3	4	4	6	8	2	1	2	1	9	11	1	1	..	3	10	9	2	1
Hall, A. J.	7	20	3 hours...	200	1	3	..	..	..	..	1	3	..	..	..	..	..	..	..	..	5	5	1	..	4	5	..	..	1	..	4	5	..	..
Hall, J. N.	5	15	1 hour....	120	1	3	..	1	..	..	1	2	..	..	..	2	1	2	..	..	..	2	..	..	..	..	1	4	1	4	..	..	..	..
Heyn, L. G.	10	20	1 hour....	200	4	3	1	..	..	1	5	3	..	1	..	..	5	5	..	..	..	..	2	1	2	2	1	2	3	4	1	1	1	..
Kolipinski, L.	5	15	3 a day...	...	1	2	..	..	..	..	..	..	..	..	1	2	..	..	3	3	..	..	..	..	3	3	..	..	..	..	3	3	..	..
Lucas, W. P.	4	10	4 a day...	...	2	4	..	..	1	..	2	..	..	1	1	3	1	1	..	..	3	3	..	..	..	..	4	4	..	..	..	..	4	4
Martin, C. F.	8	15	....	150	4	5	1	..	..	..	5	5	..	..	..	..	4	3	1	2	..	..	..	..	5	5	..	..	1	1	4	4	..	..
Roper, J. C.	10	15	2 hours...	150	5	5	..	..	..	..	5	5	..	..	..	..	5	5	..	..	..	..	1	3	4	2	..	..	4	4	1	1	..	..
Rudolf, R. D.	15	20	2 hours...	200	3	1	1	..	..	..	..	1	4	..	..	..	7	4	1	3	..	..	6	3	2	4	..	..	6	5	2	2	..	..
Skebelsky, J. W.	2	10	....	100	1	2	1	..	..	..	2	2	..	..	..	..	2	2	..	..	..	..	2	2	..	..	..	..	2	2	..	..	..	..
Taylor, D.	16	20	1 hour....	200	9	7	1	..	..	..	6	6	1	..	3	1	5	3	2	2	3	2	2	6	7	..	1	1	6	3	4	2	..	2
Williams, F. H.	6	10	1 hour....	100	3	3	..	1	..	..	1	3	2	1	..	..	2	4	1	..	..	..	1	1	2	3	..	..	..	2	3	2	..	..
Withington, C. F.	10	15	....	150	5	4	..	1	..	..	3	2	2	3	..	..	3	1	2	4	..	..	1	2	4	3	..	..	1	0	4	5	..	..
Wilson, J. C.	10	15	....	120	3	3	..	1	2	1	..	..	..	..	5	5	4	5	1	..	..	..	2	1	3	4	..	..	5	4	..	1	..	..
Totals	139	..	....	....	52	57	6	6	4	2	37	41	13	7	12	17	43	39	17	22	21	25	20	20	46	44	15	22	30	33	36	35	15	18
N's* used	..	..	....	....	62	..	..	..	..	..	62	..	..	..	..	..	81	..	..	..	..	..	81	..	..	..	..	..	81	..	..	..	..	..
S's* used	..	..	....	....	..	65	..	..	..	..	..	65	..	..	..	..	..	86	..	..	..	..	..	86	..	..	..	..	..	86	..	..	..	..
Percent.	..	..	....	....	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Positive	..	..	....	....	85	88	..	..	..	..	60	63	..	..	..	..	52	46	..	..	..	..	25	23	..	..	..	..	37	38	..	..	..	..

* N, Natural salicylate: S, Synthetic salicylate. Relief of Pain and Fall of Temperature were tabulated only in what seemed to be cases of acute articular rheumatism. Other symptoms were charted for all powders given.

columns "not noted" were included not only those cases in which the results were not noted, but also those in which the results were indecisive. Of 62 cases of rheumatic fever in which the natural sodium salicylate had been used, the pain was relieved in 52, or 85 per cent., and the fever fell in 37, or 60 per cent. Of 65 cases in which the synthetic sodium salicylate had been used, the pain was relieved in 57, or 88 per cent., and the temperature fell in 41, or 63 per cent. Diaphoresis occurred in 43 of 81 instances when the natural salt was used, or 52 per cent., and in 39 of 86 instances when the synthetic salt had been used, or 46 per cent. Similarly gastric disturbances occurred in 20 of 81 (25 per cent.) observations with the natural salt and in 20 of 86 observations (23 per cent.) with the synthetic salt. Ear symptoms occurred in 37 per cent. of the tests with the natural and in 38 per cent. of the tests with the synthetic salt. These slight differences, which, if anything, favor the use of the synthetic salt, are probably due to the ordinary statistical variations and, with a much larger series of cases, they would probably tend to disappear.

Various cerebral disturbances were occasionally noted. Drowsiness or stupidity was noted in one case in which the natural salt had been given, and in three cases in which the synthetic salt had been given. Slight delirium or confusion was noted in five patients receiving the natural salt and in three patients receiving the synthetic salt. More severe delirium was noted in four patients, two of whom received the natural salt and two the synthetic salt. Of the former, one was attributed to delirium tremens, and the other to cerebral rheumatism. One patient who received the natural salt developed melancholia.

Suppuration of the ear occurred in one patient who had received the natural salt. A rash appeared in one patient who had received the synthetic salt. Albuminuria developed in eight patients after administration of the natural salt and in seven patients after administration of the synthetic salt. Acetone developed or was increased in six patients after taking the natural salt and in four patients after taking the synthetic salt. The total number of urinary examinations reported was relatively small.

Two patients having acute articular rheumatism died during the administration of sodium salicylate. One of these patients received 70 grains of the synthetic salt and the other 60 grains of the synthetic salt. These amounts were small, being less than one-half of the total dosage administered to the majority of patients tabulated. The first of these patients died with manifestations of circulatory insufficiency and dilated heart. The second showed profuse sweating, epistaxis and wild delirium, dying with cerebral symptoms. In each case the death is to be attributed in the main to the rheumatic infection, which may on the one hand produce a definite form of acute myocarditis with myocardial insufficiency, and on the other hand severe cerebral symptoms, the so-called cerebral rheumatism. The administration of salicylates to such patients does not seem in general to be associated with unusual danger and among the cases reported by Dr. Taylor was a patient with cerebral rheumatism who received on one occasion 1,000 grains of the synthetic salicylate within 60 hours and on a second occasion he became delirious after taking 320 grains of the natural salt, the delirium being attributed to the rheumatism. Even though for the sake of argument, one attributes these deaths in part to the salicylates administered, there is no reason for assuming that the natural salt would have acted differently from the synthetic salt, for all the other data of this report show that the action and the toxicity of the two are identical.

CONCLUSIONS

The result of the cooperative investigation as to the relative therapeutic value of sodium salicylate derived from natural sources and of sodium salicylate prepared by synthetic methods shows no essential differences between the two. This was demonstrated not only by the opinions of those investigators who attempted to classify the effects of their powders but also by a study of all the reports submitted. The slight variations in one direction or the other as shown by our figures are such as one expects in any set of statistics. Indeed, the statistical variations in these figures are surprisingly small. Allowing, therefore, for statistical error, one must conclude that natural and synthetic sodium salicylate are indistinguishable so far as their therapeutic and toxic effects on patients are concerned.

THE TECHNIC OF ROENTGEN-RAY EXAMINATION OF THE GASTRO-INTESTINAL TRACT, AND THE INTERPRETATION OF SCREEN AND PLATE FINDINGS *

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The fundamental principle of Roentgen-ray examinations of the stomach and intestine is the visualization of their outline by filling them with substances opaque to the ray, a principle which we owe to Rieder, of Munich, who, in 1904, first used bismuth subnitrate for the purpose. From this has evolved the present-day technic of radiography of the digestive tract, the evolution being contributed to in minor particulars by numerous roentgenologists, and in major particulars by a few men of whom Holzknecht and Haudek stand out with signal prominence.

The occasional toxicity of bismuth subnitrate soon led to its supersession by bismuth subcarbonate and later the oxychlorid. Zirconium oxid has also been employed to some extent abroad. Chemically pure barium sulphate, because of its cheapness, has come into very general use both for enemas and for the opaque meal.

Bismuth subcarbonate is in common use. By its alkalinity peristaltic activity is depressed somewhat. The oxychlorid being lighter, is consequently better held in suspension. It does not interfere with peristalsis.

The finding of a suitable medium for the administration of the opaque salts by ingestion at the time of examination has given some difficulty. It is desirable that the mixture be more or less palatable, that it be thick enough to hold the opaque salt in good suspension, yet not too thick to fill all recesses, that it be not too stimulative of gastric secretion, and that it do not suppress peristalsis or produce early pyloric closure. When a large number of cases are examined the cost becomes a matter of importance.

The vehicles commonly used include water, milk (plain, condensed or fermented), mucilage of acacia,

* Read in the Section on Surgery of the American Medical Association, at the Sixty-Fourth Annual Session, held at Minneapolis, June, 1913.
* From the Mayo Clinic.