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FURTHER OBSERVATIONS ON THE METABOLIC STIMULATING EFFECT OF SALICYLATE

BY

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It has been shown (Cochran, 1952) that salicylate causes a pronounced and progressive increase in oxygen consumption when given in full therapeutic dosage to normal and subacute rheumatic subjects. It was suggested that this effect of salicylate might be of fundamental importance in the therapeutic action of the drug. The present paper is a continuation of this work and concerns two further aspects. Firstly, is seemed possible that salicylate might behave in an anomalous fashion in the acutely ill febrile patient, and therefore the effect of the drug on oxygen consumption in the treatment of acute rheumatic fever has been studied. Secondly, it is well known that salicylate (*ortho*-hydroxybenzoate) is effective in the cure of acute rheumatic manifestations, while its isomers (*para*- and *meta*-hydroxybenzoate) are inactive. The effect of these isomers on oxygen consumption has been studied.

Method

Oxygen consumption was measured, using a closed-circuit type spirometer, and the values obtained were corrected

for temperature and barometric pressure. The rheumatic fever patients had three consecutive five-minute tracings taken each morning at a constant time and the results were averaged. This routine was continued throughout the course of treatment. When it was desired to test the effect of a single dose of a drug each subject acted as his own control and was in the fasting state. After two or three consecutive tracings a single dose of the test drug was given by mouth and serial estimations of oxygen consumption were made at roughly 20-minute intervals for two to three hours.

Results

Observations were made on three patients admitted with acute rheumatic fever who received aspirin in full therapeutic doses of approximately 2 g. four-hourly. In each case the expected clinical improvement with relief of arthritis and fall in temperature occurred within 24 to 48 hours of starting treatment. In Figs. 1 to 3 the daily levels of oxygen consumption are plotted with the oral temperature obtained just prior to the oxygen measurement. In Fig. 1 it is seen that although the temperature has fallen by 4.8° F. (2.7° C.) the level of oxygen consumption has actually increased. When aspirin is gradually withdrawn the metabolic rate slowly falls. In Fig. 2 the temperature has fallen by 4° F. (2.2° C.), but the metabolic rate remains at an elevated level until an abrupt fall occurs when aspirin is suddenly withdrawn. In Fig. 3 there is a similar pattern of changes. The abrupt fall in temperature is accompanied by a progressive rise in oxygen consumption, which again falls only when aspirin treatment is stopped.

A fourth patient was treated at first with sodium salicylate and sodium bicarbonate in equal doses of 20 gr. (1.3 g.) four-hourly. The initial clinical response was satisfactory, but on reducing the dosage a relapse occurred and treatment was changed to aspirin. A second relapse followed aspirin withdrawal, and a further course was given. The relationship of relapse to oxygen consumption is shown in Fig. 4. It is seen that recrudescence of symptoms occurred when the oxygen consumption had fallen to low levels, either in reduction of dosage or withdrawal of salicylate.

A comparison was made of the effects on oxygen consumption of single 3-g. doses of sodium salicylate and aspirin and single 5-g. dosage of the *para*- and *meta*-hydroxy isomers of salicylate. The tests were carried out on the same convalescent patient, and the results are shown in the Table. Sodium salicylate and aspirin caused respectively a 12% and 11% maximal increase in oxygen consumption, while the two isomers were without significant effect. Two convalescent patients were given the isomers over a four-day period in doses of approximately 2 g.

FIG. 1

FIG. 2

FIG. 3

FIG. 1.—Effect of aspirin on oxygen consumption and body temperature in a patient with acute rheumatic fever. Although the temperature has fallen by 4.8° F. (2.7° C.) the level of oxygen consumption has increased and slowly falls when aspirin is gradually withdrawn. FIG. 2.—Results obtained in a second patient with rheumatic fever. The temperature has fallen by 4° F. (2.2° C.), but the metabolic rate remains at an elevated level until an abrupt fall occurs when aspirin is suddenly withdrawn. FIG. 3.—Results obtained in a third patient with acute rheumatic fever. An abrupt fall in temperature is accompanied by a progressive rise in oxygen consumption, which falls only when aspirin treatment is stopped.

four-hourly. There was no significant increase in oxygen consumption with either *para*- or *meta*-hydroxybenzoate (Figs. 5 and 6).

Discussion

Barbour (1919) and Barbour and Devenis (1919) stated that salicylates increase the metabolism in afebrile subjects but lower it in febrile patients. These workers used a Benedict respiration chamber, and observations were made after the ingestion of single 1-g. doses of aspirin. It would

FIG. 4.—The relationship of relapse to oxygen consumption in a patient with acute rheumatic fever treated with salicylate. Recrudescence of symptoms occurs when oxygen consumption has fallen to low levels, either on reduction of dosage or withdrawal of salicylate.

Results Obtained when Single Doses of Sodium Salicylate, its Isomers, and Aspirin are Given on Different Days to a Convalescent Rheumatic Patient. Sodium Salicylate and Aspirin (3 g. Dose of Each) Cause Respectively a 12 and 11% Increase in Oxygen Consumption while the Isomers *Para*- and *Meta*-hydroxybenzoate (one 5-g. Dose of Each) are Without Significant Effect

Oxygen Consumption c.cm. min., at N.T.P.				
Average 3 Control Values	229	209	219	199
Drug Oral	Sod. Salicylate 3 g.	Aspirin 3 g.	Sod. <i>p</i> -OH-benzoate 5 g.	Sod. <i>m</i> -OH-benzoate 5 g.
20 min.	230	219	204	205
40 "	223	203	206	191
60 "	234	209	206	191
80 "	256	228	206	182
100 "	247	232	210	189
120 "	252	226	215	200
140 "	239	217	205	191
160 "	—	223	210	185
Maximal increase	12%	11%	Nil	3% (20 min. only)

seem that the pharmacology of salicylate, and in particular the effect of the drug on oxygen uptake, would be most profitably studied where full therapeutic doses are being given and are having the desired beneficial effect, as in the present study.

The metabolic rate rises in fever, and it has been estimated that it increases 7% for every degree F. of fever. In the patients studied the acute stage of rheumatic fever was associated with a raised metabolic rate. It is assumed that in an untreated case undergoing natural remission the fall in temperature and subsidence of symptoms would be accompanied by a parallel reduction in the level of oxygen consumption. In the treated rheumatic patients it has been shown that the level of oxygen uptake either increases or remains at an elevated level, while the temperature falls and symptoms are relieved. It is only on stopping salicylate therapy or on reducing dosage that the oxygen uptake falls to normal or near normal levels. There would seem to be

no doubt that salicylate has a metabolic stimulating effect in the febrile acute rheumatic patient; the increase in metabolism due to the drug is equal to or greater than the decrease in metabolism due to the lowering of temperature, and the net result is the maintenance of a high metabolic rate while full therapeutic doses are being given.

It is important to determine if the metabolic stimulating effect of salicylate is an essential part of the therapeutic action of the drug. It has been shown that the effect is not shared by the closely related salicylate isomers, *para*- and *meta*-hydroxybenzoate. There is no significant increase in oxygen consumption when these substances are given over a four-day period in amounts equivalent to full therapeutic dosage of salicylate. The salicylate isomers are known to be quite ineffective in the relief of acute rheumatic manifestations.

Further work is in progress to attempt to elucidate the therapeutic importance and the nature of the metabolic stimulating property of salicylate.

Summary

It has previously been shown that full doses of salicylate greatly stimulate the metabolic rate of normal and subacute rheumatic subjects. The present study concerns the metabolic effect of full therapeutic doses of salicylate in the treatment of acute rheumatic fever. Fall in temperature and relief of symptoms are associated with the maintenance of the original high level of oxygen consumption, and the level falls only when the drug is withdrawn or dosage reduced. It is concluded that salicylate has a metabolic stimulating effect in the acutely ill rheumatic patient.

The isomers of salicylate, *para*- and *meta*-hydroxybenzoate, which are without effect in the relief of the acute rheumatic state, do not significantly alter the metabolic rate of convalescent patients.

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FIG. 5.—Administration of sodium *para*-hydroxybenzoate in doses of 2 g. four-hourly for four days has no significant effect on oxygen consumption.

FIG. 6.—Administration of sodium *meta*-hydroxybenzoate in doses of 2 g. four-hourly for four days has no significant effect on oxygen consumption.

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