Phenolic Compounds in the Treatment of Rheumatic Fever

I. A Study of Gentisic Acid Derivatives

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The chemical compounds known to suppress the manifestations of rheumatic fever are reviewed and the antirheumatic nature of certain phenolic compounds discussed. We report on 75 patients with acute rheumatic fever who have been treated with gentisate compounds and discuss the records of 44 of these patients who have been followed for 3 to 20 months after discontinuing drug therapy. These patients were treated with sodium gentisate, "Gen," methyl cellulose-sodium gentisate and gentisic acid ethanamide. The urinary excretion records of these drugs are given with selected blood level studies. The antihyaluronidase effect of salicylic acid metabolites and the relationship of these phenolic compounds to the pituitary-adrenal axis are discussed.

The chemical compounds known to suppress the manifestations of rheumatic fever are phenolic acid derivatives and the hormones cortisone and adrenocorticotropic hormone (ACTH). These hormones have shed light on the pathogenesis of this disease but added little to our hope for better rheumatic fever therapy. Cortisone and adrenocorticotropic hormone are most effective in the severe form of acute rheumatic fever,1-15 but in general, their therapeutic results have been less satisfactory than those of salicylates1, 2, 5, 6, 8, 11, 12; the disease's manifestations recur when the hormones are stopped4, 5, 9, 10, 11 and the effect on carditis and valvular damage is of doubtful value.5-12 The monophenolic salicylates continue to be regarded as the most generally effective and practically useful form of rheumatic fever therapy and can be used to differentiate rheumatic fever from other diseases which have similar symptomatology.

It is significant that since the salicylates were introduced 75 years ago,13 they have not been replaced in the treatment of rheumatic fever. The salicylates are but one of several phenolic acid compounds that have antirheumatic properties. It has been demonstrated14 that the monophenolic o-cresotinic acid is effective in rheumatic conditions, but others15-16 have found this drug inferior to the salicylates. The m-cresotinic acid has an effect similar to that of sodium salicylate.16 A decoction of bilberry leaves, a constituent of which is the diphenolic hydroquinone, has been used in the treatment of rheumatism17 and also the acetyl derivative of m-cresotinic acid or amatin,18 which is tolerated by man up to 3 Gm. daily with good analgetic and antipyretic action and without it causing gastric irritation or marked perspiration. The drug salicyl resorcinol19 has been used for the treatment of rheumatism, and acute rheumatic fever manifestations are suppressed by gamma resorcylic acid, but the meta and parahydroxybenzoic acids are inactive.20 The phenolic compounds known to suppress some or all of the manifestations of rheumatic fever in the human have the following structures.

Monophenols

Salicylic acid

\[ \text{Salicylic acid} \]

Amatin

\[ \text{Amatin} \]

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Diphenols

Gentisic acid

\[
\begin{align*}
\text{OH} & & \text{COOH} \\
\text{O-H} & & \\
\text{CH}_3 & & \\
\end{align*}
\]

Gamma resorcylic acid

\[
\begin{align*}
\text{OH} & & \text{COOH} \\
\text{O-H} & & \\
\text{CH}_3 & & \\
\end{align*}
\]

Salicyl resorcinol

\[
\begin{align*}
\text{OH} & & \text{C} \\
\text{O-H} & & \\
\end{align*}
\]

The structures of these compounds show certain common features which may account for their antirheumatic action. They all contain an aromatic ring (and aromatic acids as a group are antiseptic without being toxic in man, a property practically unique), they are unstable in the body and have antipyretic and analgesic properties. All of these compounds have one carboxyl group and, with the exception of amatin, have one or more hydroxyl groups, with a hydroxyl group adjacent to the carboxyl group, a relationship which is probably of biochemical and therapeutic importance.21-29 No conclusion, as yet, can be drawn concerning the position that the second hydroxyl group must occupy or whether this second group must necessarily be of a phenolic nature. The introduction of a carboxylic group into the phenolic ring attenuates the toxic action of a phenol, especially when it occupies the meta or para position, and it increases the antiseptic action when it occupies the ortho position.21

There is little known about the mechanism of the action of these drugs or compounds, but it probably is due to one or more of the following properties. Many phenolic acid derivatives have (1) antihyaluronidase or limiting capillary diffusion action, (2) a blocking action on systems, due to their oxidation-reduction properties, (3) some bactericidal or bacteriostatic action, (4) an antimitotic influence, (5) perhaps an action of an adrenocortical nature mediated through pituitary stimulation or the provision of building blocks for the adrenal cortex and (6) probably some effect on allergic processes due to their ability to precipitate or combine with certain proteins. The orthohydroxy benzoic acids form highly colored complexes with a number of heavy metals and this property may cause stronger bindings to proteins. The first, second, fifth and sixth characteristics of phenols seem of greatest importance in rheumatic fever therapy in the light of our present knowledge.

The demonstration by Guerra22 that salicylate inhibits the activity of hyaluronidase in vivo but not in vitro suggested that this action might be due to a metabolite formed by the organism and it was found23 that gentisic acid is a metabolite of salicylic acid.

Since the successful use of sodium gentisate in five patients with acute rheumatic fever by Meyer and Ragan24 in 1948, Ory25 and his co-workers in Brussels and Camelin26 and his group in France have found sodium gentisate to be as therapeutically effective in rheumatic fever as the salicylates and to produce few if any toxic effects. Gorschuk27 believes that the therapeutic efficiency of sodium gentisate is greater than that of the salicylates, particularly its analgesic and antipyretic action. Testoni and Strano28 compared sodium gentisate with salicylates and found that sodium gentisate was equal, if not superior, to salicylates in the treatment of rheumatic fever, while Schaefer and Rashkoff,29 after comparing sodium gentisate and salicylates, concluded that sodium gentisate controlled the clinical manifestations of rheumatic fever as promptly and effectively as salicylates and did not produce any toxic symptoms, prolongation of prothrombin time, changes in the blood count nor changes in liver or kidney function. Boyd30 has treated 80 patients with various arthritic diseases with a combination of sodium gentisate and salicylates and with salicylates alone and found that the gentisate was remarkably free of toxic effects. After comparing sodium salicylate with sodium gentisate, Capretta31 concluded that the salicyl-
ate was more effective than sodium gentisate in acute articular rheumatism.

We have treated 75 patients having acute rheumatic fever with gentisic acid compounds and have followed 44 of these patients for from 3 to 20 months since discontinuing the drug. These 44 patients are equally divided into 22 patients who had a primary attack and 22 patients who had a recurrent attack of rheumatic fever.

Observations

Results of Treatment with Sodium Gentisate

A tablet or the powdered form of sodium gentisate, put up in capsules or in a liquid vehicle, was administered to 13 patients who had a primary attack of rheumatic fever. The drug was given for from 60 days to 6 months, with a starting schedule of 1.0 or 1.2 Gm. of sodium gentisate every three or four hours day and night. As improvement occurred, the amount of drug was gradually reduced to a minimum of 1.2 Gm. every four hours four times daily. Some of these patients obtained symptomatic relief within 24 hours after the sodium gentisate therapy was started, a few in four weeks, but most of these patients were symptom free within the first two weeks of treatment. Symptomatic relief occurred earlier in those patients who had the more severe form of rheumatic fever and who had the highest sedimentation rates. The temperature and heart rate became normal within two to three weeks and the sedimentation rate was normal in one to six weeks or in an average of four weeks. The only toxic reaction observed was nausea in two children, but when the sodium gentisate was given in a liquid vehicle the nausea promptly disappeared.

We have attempted to evaluate the degree of cardiac damage in these patients in whom gentisate treatment has been discontinued for from 3 to 15 months. Of 13 patients, a heart murmur was not heard in seven, and in 11 of these patients there was no evidence of heart enlargement; one patient had had a recurrence of rheumatic fever.

Fifteen patients who had a recurrent attack of rheumatic fever were given 5.2 to 10.4 Gm. of sodium gentisate every 24 hours, with most of them receiving 8.0 Gm. of the drug each day or 1.0 Gm. of sodium gentisate every three hours, day and night; this was decreased as improvement occurred. The drug was given for from 1 month to 24 months but most of these patients were treated for an average of six months. We found it necessary to continue sodium gentisate treatment for a longer time in the recurrent type of rheumatic fever, particularly in several patients who were in older age groups. Two of our patients with persistent rheumatic fever have required continuous therapy for 20 and 22 months to remain symptom free. There was complete relief of symptoms in from 24 hours to 3 weeks following sodium gentisate therapy with an average of 11 days. The blood sedimentation rate returned to normal in from 30 to 120 days with an average of 60 days for 13 of these patients. The disease manifestations have recurred in two of these patients, but 12 patients have remained symptom free for an average of eight months since sodium gentisate treatment was discontinued.

An attempt to evaluate increased cardiac damage in 13 patients after therapy had been discontinued for 3 to 20 months has shown the heart findings unchanged in six, the murmurs decreased in six, with an aortic diastolic murmur, previously present, absent in one; one patient has died.

We have found sodium gentisate to be more generally satisfactory than the salicylates in the treatment of the acute, recurrent and persistent forms of rheumatic fever, but it has two disadvantages. (1) Sodium gentisate is rapidly eliminated from the body, which requires that it be administered at frequent intervals throughout the entire day, and (2) the sodium content detracts from its use in patients with rheumatic heart disease and active carditis who are in a state of congestive heart failure. We have sought to overcome these defects of sodium gentisate in groups of patients treated with special compounds of gentisic acid.

Results of Treatment with "Gen"

Sodium gentisate was combined with a non-absorbable, innocuous acid-absorbing resin to determine whether the speed of hydrolysis in the gastrointestinal tract could be retarded.

Such a combination, prepared under the trade name “Gen,” was given to two patients who had primary attacks and to three patients who had recurrent attacks of rheumatic fever; the latter patients were in congestive heart failure. These patients received 1.0 to 1.2 Gm. of Gen every three or four hours day and night. In one patient who had a primary attack of rheumatic fever, the drug had to be discontinued after four weeks of therapy because of poor response. The second patient who had a primary attack of rheumatic fever required nine months of treatment with Gen before the rheumatic fever manifestations were suppressed. Of the three patients who had recurrent rheumatic fever and who were in congestive heart failure, one showed a minimal reduction in the rheumatic fever manifestations and gradual progression of the congestive heart failure, the Gen being discontinued after six weeks. The other two patients with congestive heart failure were relieved of their rheumatic fever manifestations, but they showed no corresponding improvement of their congestive heart failure which had to be corrected by digitalization and diuretics. The temperature, heart and sedimentation rates were influenced much more slowly with Gen than with sodium gentisate.

Our experience with Gen caused us to believe that this compound reduces the effect of sodium gentisate and that the use of an anion resin in combination with sodium gentisate does not improve the absorption of gentisic acid from the gastrointestinal system nor aid in the treatment of rheumatic fever patients who are in a state of congestive heart failure.

Results of Treatment with Methyl Cellulose–Sodium Gentisate

It is claimed that methyl cellulose delays the absorption of a digitalis glycoside from the gastrointestinal tract and prolongs the effect of the drug.22 We have investigated this effect with a tablet combination of 0.3 Gm. of sodium gentisate and 0.09 Gm. of methyl cellulose. In vitro studies with these tablets had demonstrated that disintegration in gastric and intestinal juices required twice the time for that of regular sodium gentisate tablets. Of six patients treated with methyl cellulose–sodium gentisate tablets, four had a primary and two a recurrent attack of rheumatic fever. Two of these patients were symptom free after four days of treatment, the maximum was two weeks and the average was one week. The sodium gentisate–methyl cellulose therapy was continued for from four weeks to three months, with all of these patients receiving 8.0 Gm. of methyl cellulose–sodium gentisate every 24 hours or 1.2 Gm. every three hours from 7 a.m. to 10 p.m. which avoided interrupting their sleep. The temperature of these patients became normal in an average of six days, and the heart rate was normal in an average of three weeks after therapy was instituted. The blood sedimentation rate became normal within 12 days to six weeks after methyl cellulose–sodium gentisate treatment was started with an average of 28 days. There were no toxic reactions.

An attempt to evaluate heart damage three months after therapy had been discontinued showed the heart size normal in the four patients who had primary attacks of rheumatic fever and the heart enlargement unchanged in the two patients who had recurrent attacks of the disease. The heart murmurs persisted in all patients but in those who had primary attacks of rheumatic fever the murmurs were considerably decreased in intensity. Because of the sodium content, sodium gentisate–methyl cellulose is not satisfactory for patients who are in congestive heart failure but it does permit the use of smaller amounts of drug and it need be given less often, its action being more sustained with lower urinary minute output.

Results of Treatment with Gentisic Acid Ethanolamide

Five patients who had acute rheumatic fever were treated with gentisic acid ethanolamide. The ethanolamide of gentisic acid has been known for several years and has been used as a solubilizing agent for vitamins. No work had been done to evaluate this salt in the treatment of acute rheumatic fever. We were interested in its therapeutic possibilities but particularly for patients with acute rheumatic fever who were
in congestive heart failure. Acute toxicity studies with gentisic acid ethanolamide in mice, rats and rabbits had shown that it was of much lower toxicity than was sodium salicylate. Chronic toxicity studies in young rats who received daily subcutaneous injections of gentisic acid ethanolamide in doses of 100 mg. per kilogram, and 300 mg. per kilogram, for four weeks, had shown no adverse influence on the growth rate or blood picture. The microscopic examination of hearts, livers, kidneys, spleens and femoral bone marrows revealed no pathologic changes. Of the five patients treated, three had a primary and two a recurrent attack of rheumatic fever. All of these patients obtained complete symptomatic relief after two to five days of treatment with 1 Gm. of the drug given every three hours, six times daily, or a total of 6.0 Gm. of gentisic acid ethanolamide in 24 hours. The drug was administered for from 40 to 66 days. The temperature of these patients became normal within 5 to 12 days and the heart rate was normal within 7 to 16 days after gentisic acid ethanolamide therapy was started. The blood sedimentation rate became normal after 12 to 44 days of therapy or an average of 25 days.

These five patients have been examined from four to five months after therapy was discontinued and all have shown a distinct reduction or change in the intensity and character of their former heart murmurs and the heart size has remained normal or unchanged. The state of congestive heart failure that was present in one of these patients was corrected with the suppression of the rheumatic fever, and a similar result has been observed in two other patients who have been followed for less than three months since the drug was discontinued. This limited experience suggests that gentisic acid ethanolamide has qualities which make it superior to sodium gentisate in the treatment of acute rheumatic fever. The gentisic acid ethanolamide therapy gave earlier symptomatic relief and the decline to normal of the temperature and pulse rate was more consistent and somewhat earlier than with sodium gentisate. The gentisic acid ethanolamide suppresses the manifestations of rheumatic fever with less drug than does sodium gentisate and the absence of sodium makes it desirable for patients who are in congestive heart failure.

**Action on Lymphocytes**

Of the 44 patients who had acute rheumatic fever and who were treated with compounds of gentisic acid, 39 had an average rise of 54 per cent and four patients had a distinct fall in their lymphocyte counts. The elevation of the lymphocyte counts occurred within the first 10 days after gentisate therapy had been started and later the lymphocyte counts gradually returned to their former or even lower levels. In some patients, and usually in the latter part of their illness, there was a secondary rise in the lymphocyte counts. An increase of 52 per cent in the lymphocyte count occurred within an average of nine days in 10 patients with acute rheumatic fever whom we treated with sodium salicylate.

**Absolute Eosinophil Counts**

Absolute eosinophil counts were obtained frequently on 23 patients. A more than 50 per cent decline in the absolute eosinophil count was observed in these patients within the first 10 days of gentisate therapy. In most of these patients the greatest decline in the absolute eosinophil count was observed on the sixth or seventh day of gentisate therapy. The absolute eosinophil count dropped from 250 and 800 eosinophil cells to zero cells in three patients after seven days of gentisate therapy and after nine days in another patient.

**The Urinary Excretion of Gentisic Acid Compounds**

Chemically speaking the gentisates are derivatives of 2,5-dihydroxybenzoic acid, and clinical experience had indicated that they were rapidly eliminated from the body. To determine the rates of elimination, the 24 hour urinary outputs were analyzed for the uncombined drug (table 1). The excretion of gentisic acid was not influenced by variations in the total urinary output unless the amount of urine was greatly limited. When this occurred, on the following day there was always an increased urinary output which compensated for the decrease of the previous day. The
different urinary pH levels had no influence on the amount of gentisate excreted.

If we consider only the uncombined form of the drug, the ethanolamide of gentisic acid is excreted to a lesser extent than is the sodium gentisate or gentisic acid, a difference that is statistically significant. The excretion of gentisic acid ethanolamide in children is greater than in adults, while the 24-hour excretion of gentisic acid and sodium gentisate is approximately the same.

In table 2 is given the 24-hour urinary output of gentisic acid when sodium gentisate has been combined with an anion resin or with methyl cellulose and of gentisic acid ethanolamide given with Benemid as a retarding agent.

The adsorption of sodium gentisate on an anion resin does not decrease the amount of gentisate that is excreted through the urine in 24 hours. The same is true for the combination of sodium gentisate and methyl cellulose. The excretion of gentisic acid ethanolamide with Benemid in children and adults appears confusing, but we have tabulated only that portion of the drug that is excreted in the free or uncombined state. The apparent difference in excretion between the sodium gentisate and the gentisic acid ethanolamide is due to a greater conjugation of the latter compound. This ex-

TABLE 1.—Excretion of Gentisic Acid Compounds per 24 Hours

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of Patients</th>
<th>No. of Samples</th>
<th>Aver. 24 hr. Excretion* %</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium gentisate.</td>
<td>8</td>
<td>28</td>
<td>58.3</td>
<td>± 14.8</td>
</tr>
<tr>
<td>Gentisic acid.</td>
<td>4</td>
<td>16</td>
<td>60.9</td>
<td>± 18.1</td>
</tr>
<tr>
<td>Gentisic acid ethanolamide† (adults)</td>
<td>3</td>
<td>19</td>
<td>25.8</td>
<td>± 6.3</td>
</tr>
<tr>
<td>Gentisic acid ethanolamide† (children)</td>
<td>3</td>
<td>29</td>
<td>44.1</td>
<td>± 11.1</td>
</tr>
</tbody>
</table>

* None excreted in stool.
† Excretion of uncombined form.

TABLE 2.—Excretion of Gentisic Acid Compounds with Retarders per 24 Hours

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of Patients</th>
<th>No. of Samples</th>
<th>Aver. 24 hr. Excretion* %</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium gentisate on anion resin</td>
<td>5</td>
<td>33</td>
<td>58.4</td>
<td>± 25.5</td>
</tr>
<tr>
<td>Sodium gentisate &amp; methyl cellulose</td>
<td>4</td>
<td>30</td>
<td>61.7</td>
<td>± 13.9</td>
</tr>
<tr>
<td>Gentisic acid† ethanolamide and Benemid (adults)</td>
<td>2</td>
<td>12</td>
<td>35.5</td>
<td>± 5.9</td>
</tr>
<tr>
<td>Gentisic acid† ethanolamide and Benemid (children)</td>
<td>5</td>
<td>37</td>
<td>23.5</td>
<td>± 9.5</td>
</tr>
</tbody>
</table>

* Uncombined form of drug.
† Benemid: Adults, 2 Gm. per 24 hours; Children, 1 Gm. per 24 hours.

TABLE 3.—Excretion of Conjugates of Gentisic Acid Compounds

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of days</th>
<th>Daily drug intake (millimols)</th>
<th>Aver. output of Ethereal sulfur (millimols)</th>
<th>Aver. output of Glucuronid acid (millimols)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium gentisate.</td>
<td>14</td>
<td>34</td>
<td>3.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Gentisic acid ethanolamide.</td>
<td>34</td>
<td>32</td>
<td>6.0</td>
<td>9.0</td>
</tr>
<tr>
<td>None</td>
<td>5</td>
<td>none</td>
<td>1.0</td>
<td>0.5</td>
</tr>
</tbody>
</table>

TABLE 4.—Blood Levels during a Four-Hour Period between Treatments

<table>
<thead>
<tr>
<th>Drug</th>
<th>0 time</th>
<th>30 min</th>
<th>1 hour</th>
<th>2 hour</th>
<th>4 hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium gentisate.</td>
<td>2.0</td>
<td>9.8</td>
<td>8.0</td>
<td>7.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Sodium gentisate; methyl cellulose</td>
<td>6.0</td>
<td>4.0</td>
<td>5.0</td>
<td>5.5</td>
<td>6.0</td>
</tr>
<tr>
<td>Sodium gentisate with an anion resin</td>
<td>2.1</td>
<td>2.1</td>
<td>2.4</td>
<td>4.2</td>
<td>2.1</td>
</tr>
</tbody>
</table>

These data do not permit a final answer as to the degree of conjugation of these various gentisic acid compounds but it indicates that a great difference does occur. The combination of gentisate compounds with the retarder, Benemid, does not affect the excretion of the free drug but definitely lowers the total excretion of gentisates. We have found, however, that the retarding action of Benemid on the total excretion of a gentisate may be lost after 10 days to two weeks.
Blood Levels of Certain Gentisic Acid Compounds

The gentisic acid compounds suppress the manifestations of rheumatic fever at lower blood levels than are required for the salicylates. A blood level of 3.5 to 5 mg. of gentisic acid per 100 cc. is sufficient to suppress the manifestations of rheumatic fever. Table 4 gives the blood levels of patients receiving 1.0 Gm. of a gentisic acid compound every four hours with zero hour being just before the drug was given.

The combining of sodium gentisate with methyl cellulose retards the breakdown of the tablet in the gastrointestinal tract and produces a more constant and prolonged absorption of the gentisate into the blood stream as compared with the rapid and high absorption and rapid excretion which occurs with sodium gentisate and the limited absorption of sodium gentisate when combined with an anion resin. The total 24-hour urinary output of gentisate is the same for the three gentisate compounds.

We avoided the use of vitamin C with the gentisates so that we might obtain a single drug action on the rheumatic fever patient. This may account for some of the differences in our findings and those reported for other antirheumatic agents.

Discussion

The metabolites of the salicylic acid are probably the substances which act to suppress the manifestations of rheumatic fever in patients receiving salicylate therapy. A mixture of the salicylic acid metabolite, gentisic acid, and hyaluronidase is inactive, but when such a mixture is incubated it becomes an active inhibitor of the depolymerization of hyaluronic acid by hyaluronidase. By means of the turbimetric method, it has been demonstrated that many other aromatic or phenolic compounds are inhibitors of hyaluronidase. The gentisic acid in the body is at least partially converted to the quinone form. It has been found by in vitro studies that the depolymerization of hyaluronic acid by hyaluronidase is inhibited by the quinone of gentisic acid or 2,5-benzoquinone carboxylic acid at a concentration of 0.001 M and higher. We have observed that an impure form of gentisic acid (90 per cent purity) was more effective in acute rheumatic fever patients than was a highly purified form of the drug. This is due to the presence of small amounts of the isomers of gentisic acid (side products of the synthesis of gentisic acid) or of the oxidized form of gentisic acid. The nonspecific hyaluronidase inhibitor in human serum appears to be a homogeneous complex of heparin, polypeptide and lipid which migrates with the albumin, while that which inhibits streptococcal hyaluronidase migrates entirely with the gamma globulin, is not heat-labile and is a true neutralizing antibody. The known property of certain phenols to combine with or precipitate proteins and to block enzyme systems may account for their antihyaluronidase behavior and this ability varies with different phenolic compounds.

The antirheumatic action of salicylates and other phenolic derivatives may be mediated through the pituitary-adrenal axis and be more specific than has been formerly supposed. The specific action of certain phenolic compounds in rheumatic fever may be explained by the "accomplished ability to convert salicylic acid 'in vitro' to diphenic acid and thence to members of the steroid group and the direct action of salicylic acid upon cholesterol and/or cholesteryl esters to influence the concentration of the sterol and its esters and the ratio between the free cholesterol and the cholesteryl ester fraction" as suggested by Tormey and Barnhurst. The inherent inability of the rheumatic fever patient to demobilize the antihemolytic agent cholesterol after a hemolytic attack causes it to be partially demobilized abnormally through conversion to excess desoxycorticosterone. It has been shown that desoxycorticosterone can produce the characteristic changes of rheumatic fever.

The amount of ascorbic acid in the suprarenal glands is a measure of the glands' activity, and the removal of ascorbic acid from the adrenal gland is under the control of adrenocorticotrophic hormone. The giving of preliminary treatment with the adrenal cortical hormone prevents the normal depletion of ascorbic acid by pituitary and adrenal gland activity. The agents which stimulate the adrenocorticotrophic hormone-adrenocortical ac-
tivity probably do so by diminishing the concentration of the adrenal cortical hormone in the blood or by increasing its utilization by the tissues. It has been demonstrated in rats that salicylates cause a definite depletion of the ascorbic acid content of the adrenal glands, the degree of depletion being proportional to the amount of the drug that has been given. This response does not occur in hypophysectomized rats and tends to be inhibited by preliminary treatment with Cortone. In another study with rats, the subcutaneous injection of 400 mg. per kilogram of sodium salicylate produced a pronounced decrease in the ascorbic acid content of the pituitary and adrenal glands which persisted for more than 24 hours. The injection of 0.2 mg. of adrenaline (per rat) produced a similar but less marked effect.

There is a regular and increased excretion of reducing steroids but no regular effect on the excretion of the neutral 17-ketosteroids in humans with rheumatic diseases who are treated with acetyl salicylic acid, but there is no direct relationship between the amount of the reducing steroids excreted and the type of rheumatic disease but each increase in the excreted reducing steroids corresponds to the patient's clinical improvement. A single intraperitoneal injection of a large dose of salicylate into intact rats produced the biochemical, histologic and hematologic picture of stress. After the injection of sodium salicylate into hypophysectomized rats, no significant change was observed in the ascorbic acid or cholesterol content of the adrenal glands nor was there an important decrease in the number of circulating eosinophils. Adrenocorticotropic hormone did produce significant biochemical and hematologic changes in the hypophysectomized rats similar to those observed in intact rats. The integrity of the pituitary-adrenal axis may be essential for effective therapy with phenolic acid derivatives, and where adequate salicylate therapy has been ineffective, as in malignant rheumatic fever, perhaps the hypothalamic-pituitary-adrenal axis has been seriously damaged by the disease.

The reduction of circulating eosinophils by 50 per cent or more after the injection of a fixed amount of adrenocorticotropic hormone proves the integrity of the pituitary-adrenal axis. The administration of salicylates produces a more than 50 per cent eosinopenia in guinea pigs and also in man. Others have been unable to demonstrate eosinopenia in normal humans in whom plasma salicylate concentrations, usually regarded as necessary, had been attained. A review of this negative experience has shown that after a single oral dose of 4 or 6 Gm. of sodium salicylate there is no significant decrease in the absolute eosinophil count during the first four hours, but a significant drop occurs between the fourth and sixth hour due, undoubtedly, to the slow absorption from the intestinal tract. The urinary uric acid-creatinine ratio increased significantly by the second hour. A positive Thorn test has been observed four hours after an intravenous injection of 4 Gm. of sodium salicylate. The pronounced eosinopenia and increase in the uric acid-creatinine ratio are associated with oversecretion of adrenocorticotropic hormone or Cortone, as is the increased urinary excretion of neutral steroids. The salicylates, given in adequate doses, produce these several changes which depend on stimulation of the adrenal cortex by the pituitary gland. In patients whom we have treated with a compound of gentisic acid, we have observed a greater than 50 per cent reduction in the absolute eosinophil count within the first 10 days of therapy and in four patients the eosinophile cells were reduced to zero.

A decrease in circulating lymphocytes has been considered to be a sensitive indicator of extra quantities of adrenocorticotropic hormone or adrenal cortical factors in the blood stream. A significant drop in the lymphocyte count with adequate salicylate therapy has been observed and been attributed to stimulation of the pituitary production of adrenocorticotropic hormone. This action of salicylates on the lymphocyte count is contrary to our experience with patients whom we have treated with salicylates and with the gentisic acid compounds. We observed, usually, a definite rise in the lymphocyte count and within 10 days after salicylate or gentisate therapy had been started.

Of 75 patients, 44 of whom have been ob-
served 3 to 20 months after discontinuing treatment with compounds of gentisic acid, we have found that the gentisates are the equal and in some respects are superior to other forms of therapy in suppressing the acute manifestations of rheumatic fever. The return to normal of the temperature and blood sedimentation rate was earlier with sodium gentisate, gentisic acid ethanolamide and methyl cellulose–sodium gentisate than with salicylates. Most patients treated with these gentisate compounds had normal temperatures in an average of six days and normal blood sedimentation rates in an average of 27 days. The 10 patients with acute rheumatic fever whom we treated with sodium salicylate had normal temperatures in an average of 14 days; others have reported an average of 6.6 days for patients treated with oral and intravenous salicylates. The blood sedimentation rate was normal in an average of 30 days and 54.1 days in other groups of patients with acute rheumatic fever who were treated with the salicylates.

The salicylates are not tolerated by children with the gastrointestinal symptoms of acute rheumatic fever but these patients do tolerate the gentisates. Unlike the salicylates, the gentisates cause no disagreeable or harmful reactions. The gentisates relieve the manifestations of the persistent and cerebral forms of acute rheumatic fever and are well tolerated for many months. We were unable to determine whether these drugs shorten the normal course of the disease. In the 44 patients in whom treatment had been discontinued for from 3 to 20 months, the disease recurred in three patients.

The rapid and complete elimination from the body of sodium gentisate, which necessitates administering this drug at frequent intervals, was materially modified by the use of gentisic acid ethanolamide or a combination of sodium gentisate with methyl cellulose. We believe that the superiority of gentisic acid ethanolamide results from the slower breakdown and utilization of this compound in the body. The combining of sodium gentisate with methyl cellulose delays the absorption of the gentisate from the gastrointestinal tract, for while the 24-hour excretion of the gentisate fraction is the same as with sodium gentisate, the therapeutic blood level was maintained more constantly.

We have observed no important toxic reactions from the gentisates among the 75 patients whom we have treated, and we have given up to 6.0 Gm. in a single dose and as much as 5.2 Gm. a day for as long as 24 months. The two patients who received the drug in capsule form and who complained of nausea were given prompt relief when the gentisate was administered in a liquid vehicle.

**Summary**

The general nature of phenolic acid compounds in the treatment of rheumatic fever has been discussed.

Of 75 patients treated with gentisate compounds, we have discussed 44 who have been observed for from 3 to 20 months after the drug had been discontinued.

The metabolism of salicylic acid in the human body and the therapeutic importance of its metabolites, and, in particular, of gentisic acid, have been reviewed.

The clinical and partial laboratory results have been presented for 28 patients who were treated with sodium gentisate, for five patients who were treated with a combination of sodium gentisate with an anion resin, for six patients who were treated with a combination of sodium gentisate and methyl cellulose and for five patients who were treated with gentisic acid ethanolamide.

It is our impression that gentisate compounds are more effective than other forms of rheumatic fever therapy in suppressing the manifestations of rheumatic fever.

The superior tolerance for the gentisates is impressive and makes the treatment of rheumatic fever easier for the doctor and the patient.

The methyl cellulose–sodium gentisate compound and gentisic acid ethanolamide showed slower absorption or utilization within the body and the sodium gentisate–methyl cellulose compound maintained the most constant therapeutic blood levels.

The gentisates cause a pronounced rise in the lymphocyte count rather than the reduced lymphocyte count observed with cortisone and
adrenocorticotropic hormone therapy. We purposely chose to not use vitamin C in conjunction with the gentisates so as to obtain a single drug response.

A relationship between salicylic acid or its metabolite, gentisic acid, and the cortico-adrenal axis in acute rheumatic fever has been discussed.

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SUMARIO ESPAÑOL

Los compuestos químicos conocidos como supresores de las manifestaciones de la fiebre reumática son revisados y la naturaleza antirreumática de ciertos compuestos fenólicos se discute. Se reporta sobre 75 pacientes con fiebre reumática aguda que fueron tratados con compuestos gentísicos y se discute los records de 44 de los pacientes que han sido observados de 3 a 20 meses después de la droga se disoció. Estos pacientes fueron tratados con gentisato sódico. "Gen," metilo de celulo losa-gentisato sódico y etanolamida de ácido gentilico. La excreción urinaria de estas drogas se informa con niveles de sangre seleccionados. El efecto antihialuronidásico del ácido salicílico y sus metabolitos y la relación de los compuestos fenólicos al eje pituitario-adrenal se discute.

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Phenolic Compounds in the Treatment of Rheumatic Fever: I. A Study of Gentisic Acid Derivatives

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