damaged capillaries protein leaves the blood, entering the tissue, where it is stored. Jantz confirmed this theory by experiments on dogs. The animals showed nitrogen retention when they received mescaline but massive excretion of nitrogen on those days when the drug was withheld. Pathological studies revealed capillary damage in the liver, a picture described by Roessle under the term of "serous hepatitis."

The comparison of these findings with Gjessing's in periodic catatonia is close, but Jantz mentions it with due caution. His findings certainly need confirmation by other workers.

The intermediary role of the liver as a site of pathology in mental disorders has an unfortunate history in ancient and modern medicine. Its latest abdication was in the field of alcoholic psychoses. Delirium tremens and Korsakoff states, after having been hypothetically ascribed to hepatic dysfunction for many years, are now recognized as due to nutritional deficiencies. The mescaline-like effect of 30–50 μg. of lysergic acid diethylamide taken by mouth makes it very doubtful if the liver has any share in the symptoms of the intoxication.

Future Research

Within the last ten years much has been learned about metabolism of the central nervous system that can be applied to experimental psychoses. We can expect the biochemist to give us more information on the action of these drugs *in vivo*, especially if full use is made of parallel experimental studies in animals. Here histopathological and histochemical methods, which have recently widened the field of investigation in the central nervous system, should elucidate the rather special interference with oxidation which one can suspect to be taking place. Finally, the new electro-physiological methods will have their place in this experimental work. So far the standard electroencephalogram taken in mescaline and other intoxications has not revealed any characteristic changes; but with the new method of carefully dosed stimulation—for example, in the visual field—and with electrodes to record the less accessible and more remote electrical discharges some insight into the action of the intoxicants can also be expected.

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SODIUM γ-RESORCYLATE IN RHEUMATIC FEVER

BY

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Salicylate has an established place in the treatment of rheumatic fever, though the dose required for full therapeutic action may also give rise to undesirable effects. A drug with a greater safety margin might improve treatment of rheumatic fever, and this paper describes an attempt to find such a substance.

Our starting-point was the observation that salicylic acid, which is *ortho*hydroxybenzoic acid, has a therapeutic action in rheumatic fever, yet its isomers—the *meta*- and *para*-hydroxybenzoic acids—are inactive (Stockman, 1920). The physiochemical properties of salicylate and its isomers were examined for some essential difference which might explain why the first is effective and the others are not. A notable difference is that salicylic acid is a much stronger acid; this has recently been attributed to its ability to form an additional or chelate ring, a property not possessed by the isomers (Baker, 1936). The chelate or claw-like ring is known to chemists, but is perhaps not so familiar to clinicians. It is formed by virtue of the hydroxyl group of salicylic acid sharing its hydrogen ion with the ketone of the carboxyl group (Fig. 1).

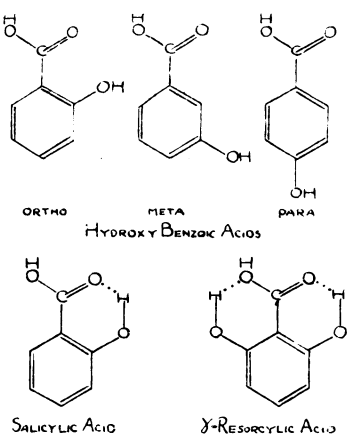

FIG. 1.—Showing the formation of a chelate ring by salicylic acid and of a double chelate ring by γ-resorcylic acid. The isomers of salicylic acid do not chelate because the distance between the hydroxyl and carboxyl groups is too great.

A comparison of the structure of salicylic acid and its isomers shows that the formation of a chelate ring depends on the respective positions of the carboxyl and hydroxyl groups. If the hydroxyl group is in the ortho position, as in salicylic acid, a chelate ring may be formed because of the proximity of the reacting groups to one another. If the hydroxyl groups are in the meta and para positions chelate rings cannot be formed, as the active groups are too far apart (Fig. 1).

If the formation of this special type of ring structure is responsible for the therapeutic action of salicylate, then it might be possible to enhance this action by increasing the chelation effect. This possibility has been explored by investigating the pharmacological properties and therapeutic action of 2:6-dihydroxybenzoic acid, or

γ-resorcylic acid, which was specially selected to test the hypothesis, as it can form a double chelate ring and is in consequence a much stronger acid than salicylic acid. (Fig. 1). The mono-sodium salt of γ-resorcylic acid, henceforth referred to as γ-resorcylate, was prepared, and, when animal toxicity tests indicated that it was safe to give to man, its effect in healthy volunteers was investigated and then a preliminary trial of its action in rheumatic fever was carried out.

The purpose of the clinical trial was to compare the action of γ-resorcylate and salicylate in rheumatic fever, and just before this work started Hench and his colleagues (1949) reported the dramatic effect of cortisone and A.C.T.H. in rheumatoid arthritis and rheumatic fever. The general similarity in the clinical, biochemical, and side-effects of cortisone, A.C.T.H., and salicylate in rheumatic fever (Cochran, Watson, and Reid, 1950) seemed to warrant an extension of our work. Pharmacological investigations of the effect of salicylate and γ-resorcylate on the one hand, and A.C.T.H. and cortisone on the other, were thus carried out by Professor Buttle and by Dr. Prunty and Dr. Clayton. Their findings will be reported separately. In this paper the effect of γ-resorcylate in healthy individuals and its excretion in the urine after a single oral dose are described and an account of its action in rheumatic fever is given.

Sodium γ-Resorcylate in Healthy Individuals

Eight healthy adult males having the same diet and fluid intake were given single doses of 200 mg. of sodium γ-resorcylate by mouth to investigate the clinical reactions to the drug and to study its excretion in the urine. The dose was given in water at 10 a.m., and urine was collected at two-hourly intervals for six hours, then at the thirteenth hour, and, finally, after 24 hours. A simple colorimetric method for estimating γ-resorcylate in the urine was evolved: 1 ml. urine was made up to 25 ml. with a *p*H 2 buffer and 0.1 ml. of a saturated aqueous solution of ferric chloride added. The presence of γ-resorcylate is indicated by the development of a blue colour, the intensity of which varies with the amount of the substance in the urine. The blue colour is not stable and it quickly turns mauve and then brown, but satisfactory results, as judged by addition of known amounts of γ-resorcylate to urine, are obtained if the colorimeter reading is taken immediately after the iron solution has been added.

No serious reactions followed the administration of 200 mg. of γ-resorcylate by mouth to healthy men; the excretion of the drug in the urine is shown in Table I. Considerable quantities (average 21 mg.) appeared in the urine in the first two hours after the dose, and the average peak excretion (35 mg.) was reached between the second and fourth hours. Thereafter the rate of excretion steadily fell until at 24 hours only small quantities were present. The average amount excreted in 24 hours was 134 mg.—that is, about 67% of the dose given.

TABLE I.—*Urinary Excretion of Sodium γ-Resorcylate by Healthy Males*

Case	Urinary Sodium γ-Resorcylate (mg.) at Intervals after 200 mg. by Mouth					
	0 to 2 hrs.	2 to 4 hrs.	4 to 6 hrs.	6 to 13 hrs.	13 to 24 hrs.	Total mg./24 hrs.
1	19	30	27	45	14	135
2	23	46	36	41	13	159
3	33	60	43	36	18	190
4	13	18	24	34	0	89
5	22	41	37	54	8	162
6	23	33	31	—	—	—
7	18	34	27	10	10	99
8	20	19	24	32	10	105
Range ..	13–33	18–60	24–43	10–64	0–18	89–190
Average	21	35	31	36	10	134

These results indicate that γ-resorcylate is rapidly absorbed and that peak blood levels are probably attained between two and four hours after oral administration.

Sodium γ-Resorcylate in Rheumatic Fever

The effect of γ-resorcylate has been investigated in seven patients with rheumatic fever. All the patients had fever, tachycardia, and a migrating polyarthritis on admission to hospital. Further particulars of the sex, age, and clinical state of the patients are shown in Table II. A standard diet containing 60 g. of protein, 70 g. of fat, 250 g. of carbohydrate, 3–5 g. of salt, and 2 litres of fluid was given to each patient, and the intake of fluid, protein, and salt was checked each day. The output of urine every 24 hours was measured and its nitrogen and chloride content were estimated to allow restricted fluid, nitrogen, and chloride balances to be carried out.

TABLE II.—*Clinical Particulars of the Patients*

Patient	Age in Years	Sex	No. of Previous Attacks	On Admission to Hospital			
				Temp.		Pulse Rate (per min.)	Cardiac Involvement*
				°F.	°C.		
J.H. ..	14	M	1	101	38·3	100	0
J.K. ..	16	M	0	101	38·3	100	0
J.S. ..	44	M	0	102	38·9	100	+
M.McK. ..	14	F	1	101	38·3	98	+
H.McI. ..	13	F	3	101·6	38·7	100	+++
S.M. ..	27	F	0	104·2	40·1	120	0
M.J. ..	12	F	0	102·8	39·3	136	++

* Cardiac involvement was assessed from the general condition of the patient, the size of the heart, the presence of murmurs, and electrocardiographic changes.

γ-Resorcylate was administered by mouth to all patients, and, as we were employing a compound which to our knowledge had not previously been given to man, the dosage had to be arbitrarily chosen and cautiously increased, so that it tended to vary from patient to patient. Six received amounts varying from 1.8 g. in three days to 10 g. in 10 days, an average of 0.8 g. a day. The seventh patient, a man of 16 stone (101.6 kg.), was given the comparatively large dose of 7 g. a day for four days. The total daily dose was usually divided into five equal portions and given at four-hourly intervals, omitting one dose in the middle of the night. The average dose in six patients was thus about one-tenth of the usual therapeutic dose of salicylate. The amount given to the seventh patient was about equal to that of salicylate.

The object of the investigation was to compare the effect of comparatively small doses of γ-resorcylate with the known effect of therapeutic doses of salicylate (1) on acute rheumatic manifestations, such as arthritis, fever, and tachycardia; (2) on the E.S.R.; and (3) on fluid, nitrogen, and chloride balances, which show striking changes during salicylate therapy (Reid, Watson, and Sproull, 1950). The results are described under these headings.

γ-Resorcylate and Acute Rheumatic Manifestations

Arthritis was relieved in one to four days after γ-resorcylate administration in all seven patients. The promptness of relief in three was almost incredible, as a few hours after the first dose was given they were able to move acute joints which had been practically immobile.

Relief in the other four patients was less dramatic in the sense that joint pain continued for two to three days and then suddenly disappeared. However, between the fourth and seventh days from the first dose of γ-resorcylate six of the seven patients had recurrence of muscle and joint pain involving the neck muscles and knee-joints particularly. In five patients pain was not accompanied by swelling and was quickly relieved by movement of the affected part. The sixth patient developed a diffuse painful swelling of both hands. All the fingers were symmetrically swollen and tender, and resembled the appearance in acromegaly. After discontinuing γ-resorcylate the swelling and pain in this patient quickly subsided.

The effect of γ-resorcylate on temperature and on pulse and respiration rates, illustrated in Fig. 2, was not

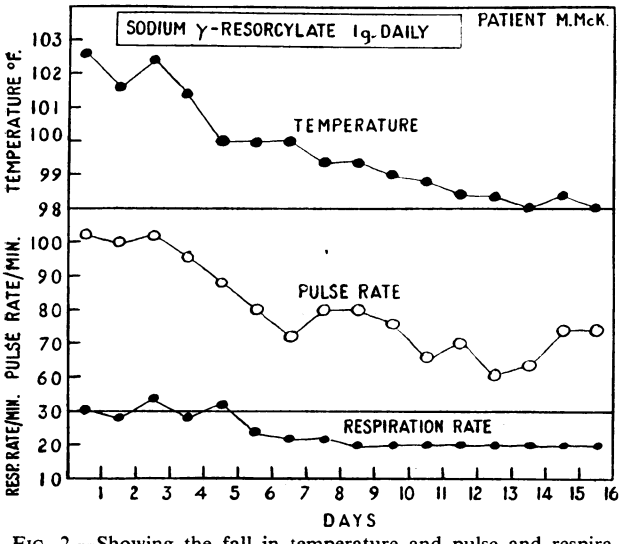

FIG. 2.—Showing the fall in temperature and pulse and respiration rates during γ-resorcylate administration.

quite so spectacular as with salicylate. After a slight initial rise in some patients the temperature and pulse and respiration rates settled gradually in the course of the first five to seven days. The fall in temperature by "lysis" rather than by "crisis" may be due to the fact that profuse sweating, which often occurs with salicylate, was not observed with γ-resorcylate. Other clinical changes noticed after the third day were: (1) Emotional instability and mental confusion in four patients, associated with muscular weakness, myalgia, arthralgia, slight fever, tachycardia, rapid respirations, and a dry tongue. This resembles the "dehydration syndrome" which we have previously described as resulting from overdosage with salicylate (Reid, Watson, and Sproull, 1950). (2) Puffiness of the face in two patients accompanied by acne-like pustules on the face and front and back of the chest, increased hair growth on the back, diminished carbohydrate tolerance, and the development of a "dorsal fat pad" in one patient. This combination of signs and symptoms closely resembles a mild Cushing's syndrome, which has also been observed during salicylate treatment (Cochran, Watson, and Reid, 1950). (3) The development of pericarditis immediately after arthritis had been relieved in one of the two patients who later showed signs of mild Cushing's syndrome.

All these clinical changes disappeared after γ-resorcylate had been discontinued and the attack of acute rheumatism had subsided. Glucose-tolerance tests before, during, and after γ-resorcylate in one of the patients who developed a mild Cushing's syndrome are recorded in Fig. 3.

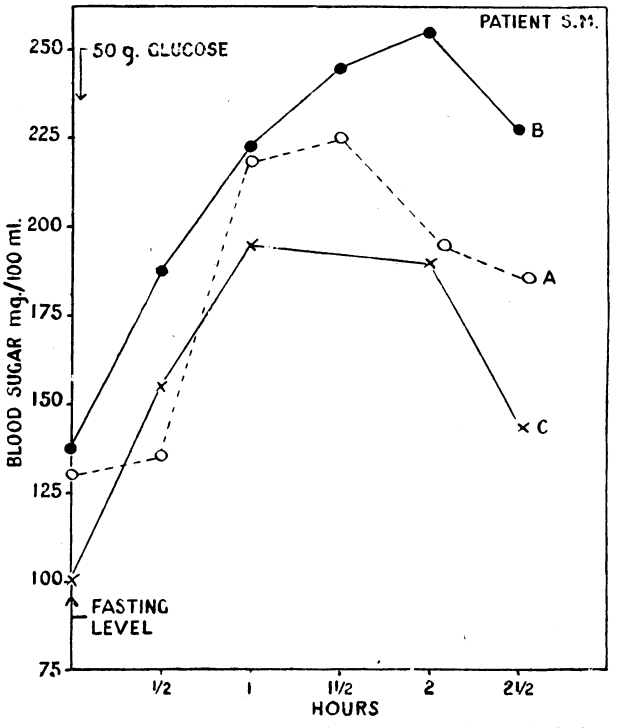

FIG. 3.—Blood-sugar curves (A) immediately before, (B) during, and (C) six days after γ-resorcylate administration in a patient who developed a mild Cushing's syndrome.

Another clinical observation of note was the absence of tinnitus and deafness in the patients treated with γ-resorcylate; in this respect it appears to differ from salicylate.

γ-Resorcylate and the E.S.R.

The changes in E.S.R. in the seven patients after administration of γ-resorcylate were compared with the results obtained in seven other patients previously treated with salicylate (7.5–10 g. daily for 9–19 days). The results are shown in Table III. The average value before

TABLE III.—*Effect of Salicylate and γ-Resorcylate on the E.S.R.*

Case	Sodium Salicylate Group E.S.R. mm./hr.			Sodium γ-Resorcylate Group E.S.R. mm./hr.		
	Immediately Before Salicylate	Peak Value During First Week	Value After 24–31 Days	Immediately Before γ-Resorcylate	Peak Value During First Week	Value After 25–32 Days
1	125	117	51 (28)	111	117	54 (27)
2	118	104	35 (31)	95	125	58 (29)
3	111	119	8 (28)	92	92	54 (29)
4	107	121	40 (24)	90	110	73 (28)
5	105	100	46 (28)	85	91	—
6	81	117	66 (24)	74	75	34 (32)
7	60	108	71 (24)	71	106	11 (25)
Average ..	101	112	45	88	102	47

The number of days from the start of treatment is shown in parentheses.

treatment was a little lower in the γ-resorcylate group, and, after an initial rise in both groups to about the same level during the first week, the average value in the γ-resorcylate group fell to 47 mm./hr. as compared with 45 mm./hr. in the salicylate group at the end of the fourth week. This difference is probably not significant, so that both drugs have about the same effect on the E.S.R.

Unusual changes in the E.S.R. were observed in two patients who were given γ-resorcylate. Within the first three days of administration of the drug the E.S.R.s of both patients fell from initial levels of 74 and 95 mm./hr. to 10 and 30 mm./hr. respectively, and then increased again to the original levels. These sudden and unexpected changes are not common in our experience, but their significance will require further investigation.

Biochemical Changes and γ-Resorcylate

Changes in water, protein, and chloride metabolism during γ-resorcylate administration were assessed by restricted fluid, nitrogen, and chloride balances. The pattern of the changes in all seven patients was more or less the same, though they differed in degree. The patient who received the largest doses of the drug showed the greatest changes. The administration of γ-resorcylate to all seven patients was quickly followed by an increase in nitrogen output in urine, which reached a peak value and then slowly returned to normal. The early changes in water and chloride balances in five of the seven patients suggested chloride and water retention which coincided with the increased nitrogen output. Later, when nitrogen output was returning to normal, a choride and water diuresis developed in all seven patients. These results are illustrated in Fig. 4, in which the early increase

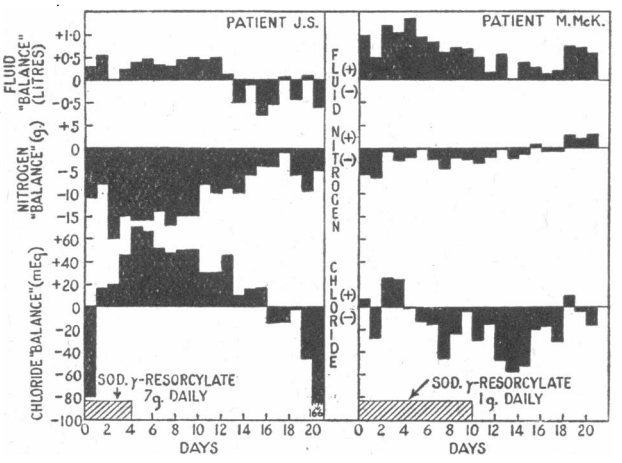

FIG. 4.—The changes in restricted fluid, nitrogen, and chloride balances following γ-resorcylate administration are shown in two patients, J. S. and M. McK., who received large and small doses respectively. The trend of the changes, particularly in nitrogen and chloride balances, was the same in both patients, but was much more pronounced in the patient who received the larger dose.

in nitrogen output and the later chloride diuresis are shown in two patients, one receiving comparatively small doses and the other large doses of the drug.

The changes in fluid, nitrogen, and chloride balances following γ-resorcylate are thus similar to those previously reported with salicylate (Reid, Watson, and Sproull, 1950).

Urinary Excretion of γ-Resorcylate

The amounts of γ-resorcylate excreted in the urine of three of the seven patients with rheumatic fever were estimated during the period of administration by the method previously described. The results, shown in Table IV, indicate that between 63% and 73% of the dose given is excreted in the urine. This amount falls within the limits excreted by healthy individuals after a single oral dose.

TABLE IV.—*Urinary Excretion of Sodium γ-Resorcylate in Rheumatic Fever*

Day	Patient M.McK. Sodium γ-Resorcylate			Patient M.J. Sodium γ-Resorcylate			Patient S.M. Sodium γ-Resorcylate		
	Dose g.	Urine mg. %	Urine mg./24hrs.	Dose g.	Urine mg. %	Urine mg./24 hrs.	Dose g.	Urine mg. %	Urine mg./24 hrs.
1	0·8	46	466	0·4	42	193	1·0	66	732
2	1·0	52	702	0·5	47	338	0·8	76	167
3	1·0	73	588	0·5	41	375	0·8	71	426
4	1·0	81	580	0·4	25	256	0·8	68	537
5	1·0	87	538	0·3	36	263	0·6	68	559
6	1·0	60	625	0·1	18	148	0·6	67	207
7	1·0	64	675	—	3	23	0·1	50	600
8	1·0	52	726	—	—	—	—	19	137
9	1·0	46	588	—	—	—	—	9	74
10	1·0	55	713	—	—	—	—	—	—
11	0·2	7	103	—	—	—	—	—	—
12	—	0	0	—	—	—	—	—	—
Total	10·0 g.		6·3 g.	2·2 g.		1·6 g.	4·7 g.		3·4 g.
	% dose excreted = 63%			% dose excreted = 73%			% dose excreted = 72%		

Summary of Results

Oral administration of comparatively small doses of γ-resorcylate to seven patients with rheumatic fever was followed by relief of acute arthritis and by a fall in temperature and pulse rate. Minor joint and muscle pains, relieved by movement, developed after the third day of dosage in five patients and a diffuse painful swelling of the fingers and hands, resembling the appearances in acromegaly, were observed in another patient. About the same time emotional instability, mental confusion, slight fever, and a dry tongue were observed in four patients. Two others developed puffiness of the face, acne-like pustules on the face, neck, and chest, increased hair growth on the back, and diminished glucose tolerance, which suggested a mild Cushing's syndrome. One of these patients developed pericarditis immediately after arthritis had been relieved. All these side-effects disappeared after γ-resorcylate was discontinued.

After a temporary rise during the first few days of γ-resorcylate administration the E.S.R. began to fall, and the main biochemical changes were an immediate increase in nitrogen excretion in the urine followed later by a chloride and water diuresis.

Discussion

The clinical effects and side-effects of γ-resorcylate in rheumatic fever, and the changes in E.S.R. and in restricted fluid, nitrogen, and chloride balances, are similar to the effects previously reported in this disease with salicylate. γ-Resorcylate in doses of about one-tenth the usual therapeutic dose of salicylate has thus about the same action as salicylate in rheumatic fever, and so far as can be judged from this preliminary trial it would appear that it is more powerful than salicylate in the sense that it induces clinical effects and side-effects for which much larger doses of salicylate are required. From the practical point of view this suggests that γ-resorcylate may have little or no advantage over salicylate in treatment of rheumatic fever, as beneficial and undesirable effects seem to be equally potentiated; but further study will be required for a final decision on this point, especially as the lethal dose of γ-resorcylate in animals is less than that of salicylate (Buttle, 1951).

The importance of the observation that γ-resorcylate is more powerful than salicylate is thus not in the practical application to treatment but in the fact that it offers an explanation of how salicylate and γ-resorcylate may

act in rheumatic fever. The evidence so far is that the isomers of salicylate, which do not chelate, have no antirheumatic action (Stockman, 1920). Salicylate, which does chelate, possesses antirheumatic properties, and γ-resorcylate, which chelates to a greater degree, is as effective as salicylate in much smaller doses. Furthermore, gentisic acid, another dihydroxybenzoic acid recently employed in treatment of rheumatic fever, is also claimed to be as effective as salicylate but less toxic in about the same dose (Meyer and Ragan, 1948; Camelin, Accoyer, Pellerat, Lafuma, and Coirault, 1949). This is consistent with the chelation hypothesis, as gentisic acid chelates to about the same degree as salicylic acid, as indicated by the similarity in their dissociation constants, which may be employed within this series of compounds as an index of chelation (Baker, 1936).

The evidence, though still not conclusive, suggests that the therapeutic action of hydroxybenzoic acids, such as salicylic, gentisic, and γ-resorcylic acids, depends on chelate ring formation. If this view finally proves to be correct, then a valuable lead for the preparation and trial of new antirheumatic compounds will have been obtained. Furthermore, since chelation is not confined to organic acids but is also shown by certain organic bases and other compounds, the variety and number of substances will be great. Finally, the hypothesis may also offer an explanation of the long-standing pharmacological puzzle of certain drugs composed of different elements having similar clinical and pharmacological actions.

Another aspect of this investigation is the general similarity in the clinical effects and side-effects of salicylate, γ-resorcylate, A.C.T.H., and cortisone. All relieve the acute manifestations of rheumatic fever and may give rise to a mild Cushing's syndrome as well as leading to the same general metabolic changes. The pharmacological investigations of Buttle (1951) and of Clayton and Prunty (1951) also indicate that in the particular tests carried out γ-resorcylate is more powerful than salicylate, and that its action resembles that of A.C.T.H. and cortisone in suppressing acute inflammatory reactions after the introduction of chemical irritants into the tissues of rats and mice and in delaying wound healing in mice.

Campbell and Wybar (1951) have also observed that it delays healing of burns in the cornea of guinea-pigs, mainly by inhibiting the formation of new fibrous tissue. The dose of γ-resorcylate required to produce these effects in animals is in the same range as that of A.C.T.H. and cortisone. This at once raises the question of how γ-resorcylate acts. The possibilities are: (1) that it acts on the anterior pituitary; (2) that it acts on the adrenal cortex; (3) that it conserves, directly or indirectly, naturally produced cortisone by preventing its destruction within the body; and (4) that it has the same action on tissues as cortisone. Clayton and Prunty (1951), using the Sayers test (Sayers, Sayers, and Woodbury, 1948), failed to observe adrenocorticotrophic activity with γ-resorcylate in hypophysectomized rats. This seems to rule out a direct action of the substance on the adrenal cortex, though the effect on the latter may be indirect through the pituitary. On the other hand, naturally produced cortisone may be conserved or both substances may have the same effect on tissues.

This last possibility is at present under investigation, and as it is probable that γ-resorcylate owes its action to chelate ring formation it is conceivable that this may also apply to cortisone. The fact that a comparatively simple substance like γ-resorcylate should have similar biological effects to the complex cortisone molecule may at first sight seem unlikely, but a precedent for this has already been established by Dodds, Golberg, Lawson, and Robinson (1939) in the similarity in action of their comparatively simple stilboestrol and the complex steroid structure of natural oestrogens. However, further discussion of the relations between salicylate and γ-resorcylate on the one hand, and A.C.T.H. and cortisone on the other, would serve no useful purpose until more information has been obtained on the mode of action of salicylate and γ-resorcylate and direct clinical comparison of the results of treating rheumatic fever with the drugs and hormones has been made.

Summary

The physiochemical properties of salicylate and its isomers are compared in an attempt to explain why salicylate has a therapeutic action in rheumatic fever yet its isomers have none. A notable difference is that salicylate forms an additional or chelate ring, a property not possessed by the isomers.

The possibility that the therapeutic action of salicylate may depend on chelate ring formation has been examined by investigating the antirheumatic action of γ-resorcylic acid, a dihydroxybenzoic acid which chelates to a greater degree than salicylate.

γ-Resorcylate in much smaller doses has been found to be as effective as salicylate in treatment of rheumatic fever as judged by the clinical, biochemical, and side-effects following its administration. The evidence, though still not conclusive, favours the suggestion that the therapeutic action of salicylate and γ-resorcylate is related to their common property of chelate ring formation.

The general resemblance in clinical, biochemical, and side-effects of salicylate and γ-resorcylate on the one hand, and A.C.T.H. and cortisone on the other, has been discussed with special reference to the possible mode of action of the drugs.

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NOTE ON THE PHARMACOLOGY OF SODIUM γ-RESORCYLATE BY PROFESSOR G. A. H. BUTTLE

Toxicity.—The acute toxicity of the substance given by the oral route is low—5 g. per kg. is tolerated by mice. By the subcutaneous route 1 g. per kg. is tolerated whereas 2.5 g. per kg. kills all the animals. A quantity of 1 g. per kg. a day mixed with the food is well tolerated by mice for a period of three weeks, but doses of this order produce some

cloudy swelling of the tubules of the kidney; this change was not so marked, however, as with corresponding doses of salicylate.

Absorption and Excretion.—The absorption and excretion of this substance are rapid; after a subcutaneous 10-mg. dose in the rat the substance appears in the urine in one hour and is nearly all eliminated three hours after injection. After administration by mouth the quantity in the urine is smaller than after a similar dose given subcutaneously, indicating that the absorption is not so complete by the oral route.

Reduction of Formalin-induced Swellings.—If 4% formalin is injected into the pad of the foot of a mouse a swelling of the lower part of the leg results which is maximal at the end of seven days. If the animal is treated with A.C.T.H., 1 mg. equivalents twice daily, from the time of the injection this swelling is considerably reduced. Treatment with γ-resorcylate, 5 mg. daily in the diet or 0.5 mg. daily by subcutaneous injection, produced a reduction of swelling of the same order as that found with the A.C.T.H. Similar doses of sodium salicylate do not produce an appreciable effect.

APPENDIX

BY

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AND

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Through the courtesy of Dr. J. Reid a sample of sodium γ-resorcylate was received.

It has been shown that A.C.T.H. causes a depletion of the adrenal ascorbic acid of hypophysectomized rats, and the test is regarded as highly specific (Sayers, Sayers, and Woodbury, 1948). We used a group of four hypophysectomized rats and an intravenous dose of γ-resorcylate in saline as high as 2.5 mg. per 100 g. rat, but no adrenocorticotrophic activity could be detected. Though unlikely, this does not rule out the possibility of γ-resorcylate acting on the pituitary gland of the intact animal. Owing to difficulties in obtaining the large number of rats required to test this, the experiment was not performed.

We described a method for consistently producing granulation tissue on the anterior abdominal wall of mice, and showed that its formation could be completely inhibited by A.C.T.H. (Clayton and Prunty, 1951). A similar effect was obtained with cortisone acetate, the dosage necessary varying with the mode of administration. Apparently γ-resorcylate under the right conditions has similar properties.

The experimental details are summarized in the Table at the foot of the preceding column.

In addition Professor Buttle has found that equivalent doses of salicylate had no effect on healing.

Thus γ-resorcylate resembles cortisone in its effect on healing. The dosages required are not very dissimilar. This may be deceiving, as γ-resorcylate is so very rapidly absorbed and excreted compared with cortisone acetate suspensions.

Dose	Mode of Administration	No. of Mice	No. of Ulcers		
			Inhibited	Impaired	Healing
Cortisone acetate					
4 mg.	Merck's suspension subcutaneously two hours before making ulcer ..	11	11	0	0
4 ,,	Merck's suspension subcutaneously, divided into two injections, six hours before and one hour after cutting	3	3	0	0
2 ,,	Merck's suspension subcutaneously six hours before cutting	3	0	3	0
2 ,,	Merck's suspension subcutaneously 17 hours before cutting	2	0	2	0
2 ,,	Suspended in propylene glycol and saline, as two intraperitoneal injections, two hours before and one hour after cutting ..	2	2	0	0
1 ,,	,, ,, ,,	2	0	0	2
Sodium γ-resorcylate					
2 mg.	Solid implanted six hours before cutting	2	0	0	2
4 ,,	,, ,, ,,	2	0	2	0
6 ,,	,, ,, ,,	2	1	0	1
4 ,,	Suspended in arachis oil, and given subcutaneously six hours before cutting	2	2	0	0
3 ,,	Aqueous solution given as a series of repeated subcutaneous injections ..	2	2	0	0
1·5 ,,	,, ,, ,,	2	0	2	0
3 ,,	Aqueous solution as two subcutaneous injections, two hours before and one hour after cutting ..	2	0	0	2
3 ,,	In propylene glycol and saline, as two subcutaneous injections, two hours before and one hour after cutting	2	0	0	2

Controls: With each experiment, controls were cut, and received cortisone diluting fluid, arachis oil, or propylene glycol and saline as necessary.

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TREATMENT OF SOME BULLOUS ERUPTIONS WITH AUREOMYCIN AND CHLORAMPHENICOL

BY

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Following the preliminary report of the treatment of pemphigus vulgaris with "aureomycin" (Bettley, 1950) we are now in a position to record some further experience with aureomycin and chloramphenicol in pemphigus vulgaris and certain other bullous eruptions.

The results obtained by others with similar treatment of comparable cases have shown a surprisingly variable response to this form of chemotherapy. Brainerd *et al.* (1949) treated three cases of pemphigus—one underwent a temporary remission, one was improving spontaneously at the time of treatment, while the third proved unresponsive. Spink and Yow (1949) observed no amelioration in two cases of pemphigus. Beinhauer (1950) treated seven cases of pemphigus vulgaris, all showing a uniform failure to improve. Philip (1950) recorded 19 cases: two passed into a long-standing remission, in seven there was transient improvement only, while in 10 there was no response. Combes and Canizares (1950) likewise reported only temporary remission or complete unresponsiveness in 12 patients. Barber and Yorke (1950) noted a short-lived remission in a case of pemphigus vegetans. Mathieu (1950) obtained a more favourable response, a case of pemphigus vulgaris being checked and being subsequently maintained in remission by maintenance therapy. This consisted of 2 g. of aureomycin daily, a smaller dosage being followed by relapse.

Likewise, diverse responses have been observed in the treatment of dermatitis herpetiformis. Robinson *et al.* (1949), Tzanck and Meyer (1949), Graciansky and Hardouin (1949), and Degos *et al.* (1949) recorded