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## TOLYSIN IN SUBACUTE RHEUMATIC CARDITIS<sup>1</sup>

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Tolysin, which is the ethyl ester of para methylphenyl cinchoninic acid, has recently been added to the list of remedies said to be useful in rheumatic fever. In the present study the effect of this drug was observed<sup>2</sup> in cases of juvenile rheumatic fever, in which it is well known that joint symptoms are often minimal and that the carditis may be the most prominent feature. Its antipyretic and analgesic action in acute arthritis has been frequently observed and has been reviewed by Hanzlik (1). Of the many workers cited by him, Barbour, Lozinsky and Clements (2), and Miller and Boots (3) have in particular, given instances of the satisfactory clinical action of tolysin on the acute phases of this disease. The latter authors present among their cases four of juvenile rheumatic fever with serious cardiac involvement but little or no arthritis, which are somewhat similar to the cases reported in this paper. Poynton (4) has been favorably impressed by its effects in children with rheumatic carditis.

The action of salicyl in rheumatic fever, including its effects on the cardiac manifestations, has been extensively studied and is completely described by Hanzlik as mentioned above. From this review we quote a few words concerning the relationship of the salicylates and cinchophen, which summarize our knowledge of the pharmacology of these drugs, although the statement about the absorbability of neocinchophen might have to be revised since the recent work of Spurling and Hartman (10).

<sup>1</sup> This work has been done under the Morris W. Stroud, Jr. Fellowship in Cardiology of the Pennsylvania Hospital.

<sup>2</sup> We are indebted to the Calco Chemical Company for the supply of this drug.

They (the cincophen derivatives) are chemically related to salicyl and their structure indicates the presence of the quinoline ring which acts as an antipyretic. Obviously, important factors with all the compounds are general solubility and absorbability. The poor solubility and absorbability probably explain the innocuousness of neocincophen. . . . Finally, the combined use of morphine and quinine, both of which are chemically different from all the drugs thus far mentioned but which are nevertheless therapeutically efficient in rheumatic fever, indicates the relative unimportance of chemical composition and structure of these therapeutic drugs and of the specificity of salicyl in this disease. The speculations on the chemical side of the question have not led to anything definite pertaining to the mechanism of anti-rheumatic action.

Since this review Masters (5) has shown that sodium salicylate has no effect on the normal human electrocardiogram and therefore does not account for any of the electrocardiographic changes noted in rheumatic fever. Furthermore, Levy and Turner (6) have shown that following salicylate therapy, in addition to the usual anti-symptomatic effect, there was a gradual reduction of the P-R interval to within normal limits in patients with rheumatic heart disease. On withdrawing the drug a prolongation of the conduction time recurred. We know of no such studies with tolysin.

Because we had under observation carefully controlled cases of juvenile rheumatic fever with no arthritis but with an active infection evidenced by fever, loss of weight and leucocytosis, we were interested in observing the action of tolysin on this phase of the disease.

#### METHODS

In selecting the cases it was necessary to know that an active infection was present and demonstrable, and careful allowance was made for the natural course of the disease. It is well known that the acute forms may subside more or less completely regardless of treatment although subject to recurrences over a period of years. Chronic rheumatic carditis manifests too few signs of infection to be good material for study. We have, therefore, selected six carefully controlled cases from the Children's Heart Hospital of Philadelphia all of the subacute type. In these, three well-recognized criteria of infection were present, viz.: fever, leucocytosis and loss of weight, all of which had been stationary for several months previous to treatment. It is to be noted that during treatment none of these cases had arthritis or chorea, but that all had definite active cardiac lesions.

TABLE 1

Num-ber	Age	Sex	First rheu-matic mani-festa-tion	Time in hos-pital before treatment	Dosage, 1928		Signs of infection before treatment: T = temperature (mouth), W = weight, L = leuco-cyte count, (a) range, (b) before therapy	Signs of infection after treatment	Toxic effects	Time of discharge and end results
					Grams	Days				
I	9	F.	1925	11	32	8	T-98.6 W-53½ L-(a) 8,-11,000 (b) 11,000	Same -½ lb. 11,000	None	April, 1928 T, W and L approximately unchanged
II	9	M.	1924	12	24	6	T-98.6 W-52½ L-(a) 9,-11,500 (b) 11,500	Same -½ lb. 12,500	Vomited once	April, 1928 T, W and L approximately unchanged
III	8	M.	1923	16	16	4	T-100.6 W-53½ L-(a) 6,-7,000 (b) 7,000	Same +½ lb. 7,000	Vomited once	April, 1928 T, W and L approximately unchanged
IV	8	M.	1924	14	32	8	T-100 W-53½ L-(a) 7,-18,000 (b) 7,000	Same -½ lb. 7,200	None	April, 1928 T, W and L approximately unchanged
V	8	M.	1923	1½	35	17	T-100 W-53½ L-(a) 8,-10,000 (b) 8,300	Same -½ 8,000	None	May, 1928 T, W and L approximately unchanged
VI	6	M.	1926	7	17	8	T-100.4 W-45½ L-(a) 9,-14,900 (b) 14,900	Same Same 16,000	None	May, 1928 weight 47½ T and L approximately unchanged

The administration of the drug was oral and the dosage is shown in the table. This has exceeded in our children the efficient therapeutic dose recognized for adults by Hanzlik (1).

#### TREATMENT AND RESULTS

Six children with rheumatic heart disease were treated with tolysin and the results are shown in table 1. The diagnosis in all these cases was rheumatic heart disease (active) with mitral stenosis and insufficiency, and enlargement of the heart. There were no arrhythmias and although the lesions were fairly severe, none of these patients showed failure of compensation. The pulse rate was not affected by treatment in any of these patients.

The absence of any demonstrable effect of tolysin upon the weight, temperature and leucocytosis in this type of rheumatic heart disease is evident from the above data.

#### *Toxicity*

Toxic symptoms of the drug were not found, although sought for in every case. Two children each vomited once during the course of treatment but as they were not sick before or after the vomited dose, and as the trouble was very obviously due to the mechanical difficulty of children swallowing pills, the form of administration and not the action of the drug was blamed for this. None of the cases showed tinnitus aurium, or other toxic effects and from clinical observations we agree with Barbour and Lozinsky (7) that tolysin is non-toxic.

#### *Comment*

It is evident that such cases are a very severe test of any drug therapy. The low grade fever of chronic tuberculosis would perhaps be a comparable condition.

The failure of tolysin to act on this condition is presumably due to the fact that these patients with very low temperatures are not suitable subjects for its antipyretic effects. Hanzlik (1) makes it quite clear that whatever action these drugs may have on arthritis or carditis, the results are almost entirely accounted for by antipyresis and analgesia. In Miller and Boots (3) cardiac series where the fever was

high, favorable results were obtained. We hold with such authorities as Swift (8) and Carey Coombs (9) that a degree of fever such as that exhibited by our series is significant of infection, but it is evidently below the threshold of these drugs. The importance of their pharmacological action cannot be too greatly emphasized in interpreting any clinical study of them.

The weights for many weeks before and after the administration of tolysin were practically constant and there was no effect good or bad on the patients' weight. This is of particular significance in children.

The failure of the leucocytes to fall is contrary to the action of the salicylates and it has been shown that they depress the leucocyte count which rises after the cessation of therapy unless the infection has really subsided. We cannot interpret this from clinical observation alone.

I am indebted to Dr. W. D. Stroud for the privilege of reporting these cases.

#### SUMMARY

In carefully selected and controlled cases of subacute rheumatic heart disease in children, no effect whatever of tolysin has been observed on the infectious process as measured by the fever, weight and leucocytosis.

No toxic action was noted in any of the cases.

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