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SALICYLATES IN RELATION TO  
RHEUMATIC FEVER.

Thesis for the degree of M.D.

by

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M.B., Ch.B.

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"An inquiry into the mode of action of Salicylate  
of Sodium in Acute Rheumatic Fever."

The chief reasons which have influenced me in selecting the subject referred to in the title of this thesis are two in number. Firstly that we have a distinct, and common pathological condition, secondly that the ameliorating influence of the drug selected upon the symptoms of this disease is such as to suggest a definite drug action upon a definite organism, and its toxins.

Introduction. "The Disease". As far back as 1642 Bullonius gave the name Rheum to an unknown substance which he thought flowed from the brain, and settled in the affected part causing a variety of bodily symptoms suggestive of what we now differentiate into the various degrees, and varieties of Rheumatism. Sydenham's genius at a later date established Acute Rheumatism, and Gout as clinical entities. His description leaves no room for doubt as to the accuracy of his observations. "It is prominent in Autumn attacking the young and vigorous and rarely kills the patient".

Within the last few years Bacteriologists have made strenuous efforts to establish the cause of this/

this disease, and thereby place it upon a firm pathological basis. In brief review Achajine holds that Rheumatic Fever is due to a specific anaerobic bacillus. Singer maintains that Rheumatic Fever is simply an attenuated form of pyemia due to a staphylo-coccal, or strepto-coccal infection while Ellenger holds the wider view that Rheumatic Fever is not due to any particular microbe, but is a reaction in predisposed persons to various microbes; more especially those of streptococcal origin.

Payton, and Payne have isolated, and specially investigated a diplococcus Rheumaticus. (2)

Their conclusion as to this being the causal origin of Acute Rheumatic Fever has been confirmed by Beattie. (3) Beattie meets those who hold that the causal agency in Acute Rheumatic Fever is a streptococcus by asserting that his Diplococcus Rheumaticus is a streptococcus, but that it is one of a particular form, and reaction which is always present in the vast majority of cases of Acute Rheumatic Fever.

"Its Treatment." Although Willow Bark has been advocated from time to time during the last 100 years for the treatment of fevers in which must have been/

been included Acute Rheumatic Fever various less salutary forms of treatment have from time to time held the field until Buss of Basle introduced salicylic acid as a specific in 1875.

Rheumatic subjects did not escape the prevailing lancet in Sysdenham's day whose dietary treatment was as beneficial as his medicinal was bad, for he says "That with young persons who have not over-indulged in wine, Rheumatism may be dispelled by spare and cooling diet provided that it be moderately home". The Alkaline treatment at one time in universal use has still not a few advocates while the Mercurial, and Lemon Juice treatment of Rus have been abandoned.

The year 1875 saw the introduction of salicylic Acid treatment in Traubes Clinique. During the same year MacLagan introduced Salicin in Great Britain quickly to be followed on the Continent by Germain who gave to the profession Salicylate of Soda. Recently Aspirin has come into the market.

Since the introduction of these Tar Derivatives 32 years ago no better or more efficacious drug has been found to replace them,

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Granting to himself the hypothesis than an organism is the causal agency in Acute Rheumatic Fever and that its toxines are responsible for the symptoms/

symptoms which occur therein, the writer has paid special attention to those agencies which are likely to militate against these agencies, therefore he has asked himself what effect has the administration of Salicylate of Soda upon,

1. Leucocytosis.
2. Opsonines which according to Wright are chiefly concerned with No. 1 in phagocytosis.

Further coming to the fons et erigo mali.

3. The organism itself.
4. Its toxins.

1. The effect of the administration of Salicylate of Soda upon leucocytosis in a healthy person.

Note. It would seem probable that if Salicylate of Soda affects leucocytosis in health that such a change if any will occur also under pathological conditions. In considering this problem it must be borne in mind that in Acute Rheumatic Fever a leucocytosis manifests itself independently of any drug which may be administered, and thus masks observations. Thus Cabot<sup>(4)</sup> states that "All observers agree that leucocytosis is the rule" during the course of Acute Rheumatic Fever. He has collected in all 83 cases.



Of these:-

Cases.		between	6000 and 8000	W B C
4				per cub. mil.
9	"		8000 and 10000	"
12	"		10000 and 12000	"
14	"		12000 and 14000	"
21	"		14000 and 16000	"
(5) 23	"		16000 and 18000	"

It is necessary before proceeding further to have a clear conception of what Leucocytosis really is. Cabot is happy in his definition:- (6)

"An increase in the number of leucocytes in the periphral blood over the normal number in the individual case, this increase never involving a diminution in polymorphonuclear varieties, but generally a marked absolute and relative gain on the number previously present".

He further adds, " Thus defined Leucocytosis is of (7) two kinds, (1) that in which the relative proportions of the different varieties to each other is unchanged. (2) That in which the increase is made up solely, or largely by a gain in the polymorphonuclear leucocytes."

It is with the second variety of leucocytosis that the writer has concerned himself with as the polymorphs are the instruments in phagocytosis.

I. Does the administration of Salicylate of Soda affect ~~produce~~ Leucocytosis in a healthy person.

In order to investigate this the writer made counts of his white blood corpuscles on three consecutive days, the diet being of an ordinary nature and as far as possible of the same nature and partaken off at the same time on each successive day.

Method of Investigation.

Blood. The writer's own which on examination was found to contain no abnormal constituents.

R. B. C. 5,000,000

W. B. C. 7,000

Note. The R. B. C. were well formed and of good colour.

Salicylate of Soda. Only the pure national variety was employed as distilled from Willow Bark in doses of grains XX.

Mode of counting W. B. C. Thoma Zeiss' method

Instruments. Thoma Zeiss' haemo cytometer.

Diluting Fluid. Dilute solution of Methylene green.

Establishment of Standard. Counts were taken at intervals of an hour for eight consecutive hours on two/



two consecutive days.

Diet. Light. Breakfast. 9 a.m.

Dinner. 1-45 p.m.

As far as possible same on each day.

Result. As in column I. and II. of table.

The mean results of Day I and Day II. are tabulated in column III.

Administration of Salicylate of Sodium on Day III.

Grains XX were taken at 10 - 45 a.m.

Grains XX were taken at 3 - 45 p.m.

Excretion of Salicylate of Sodium. The writer found ~~by~~ evidence of the drug in the urine five minutes after administration. Excretion was still continuing four hours after the time of second administration.

Test employed. A few drops of ~~weak~~ aqueous solution of Perchloride <sup>of</sup> Iron were added to freshly passed urine in a conical glass vessel. A dark violet colour denoted the presence of Salicylinic Acid.

Notes. Soullier found Salicylinic Acid in the urine after a dose of grains XV in ten to twenty minutes after administration and after a dose of grains XXX in/  
in/

in five minutes.

Diet. Same as on Day I., and Day II. and at same hour of day.

Note on results.

Count of W. B. C. on day I, and day II. It will be noticed that the digestive leucocytosis was declining at 10 a.m. one hour after breakfast, falling at 11 a.m. to 5500 per cub. mil. on day I and 6500 per cub. mil. on day II remaining stationary after dinner at 1 - 45 in the case of day I, and slightly rising at 3 p.m. to fall to 6500 at 5 p.m. In the case of day II there was a fall from 7500 per cub. mil. to 5500 per cub. mil. at 3 p.m. to be followed by a sharp rise at 4 p.m. to 11,500 per cub. mil.

Count of W. B. C. in Day III when Salicylates were given.

It will be noticed that Day III commenced as Day I, and II with digestive leucocytosis on the decline. One and a quarter hours after dosage the count had fallen as low as 2500 per cub. mil., and never rose above 4000 per cub. mil. until 3 p.m. After dosage at 3-45 p.m. W. B. C. rose to 6000 per cub. mil. at 4 p.m. and 9500 per cub. mil. at 5 p.m.

Table of Blood Counts.

	Day I.	Day II.	Average. I & II	Day III during which Salicylate of Sodium was taken.
9 a.m.		meal at 9 a.m.		
10 a.m.	10625	10000	10312	10000
11 a.m.	5937	9375	7450	Salicylate of soda 7500
12 p.m.	5500	6565	6032	2762
1 p.m.	7812	9375	8598	4062
		Meal at 1-45 p.m.		
2 p.m.	6875	7812	7343	3750
3 p.m.	6800	5625	6212	4375
4 p.m.	7500	11562	9531	Salicylate of soda 6250
5 p.m.	6875	10937	8906	9687

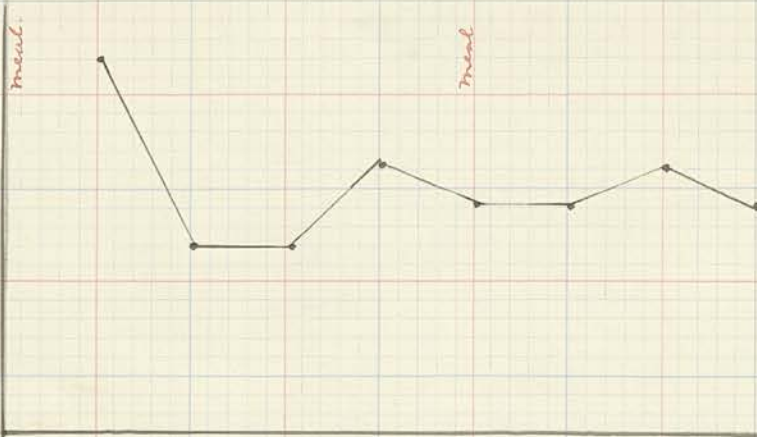
Chart. See Description.

before p 10

9am 10am 11am 12pm 1pm 2pm 3pm 4pm 5pm

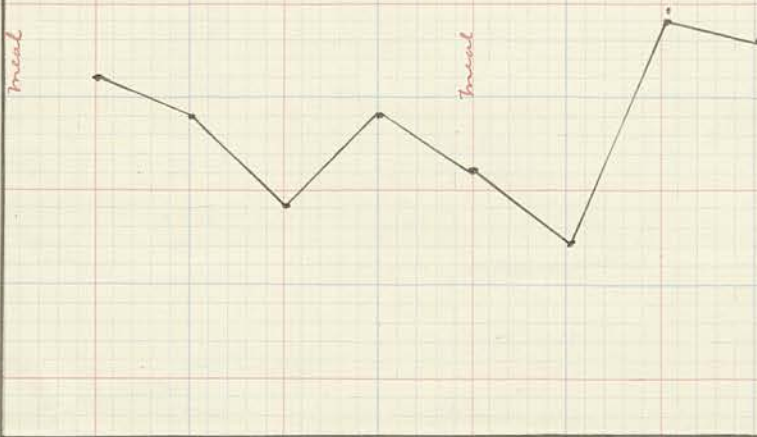
Day I.

1500  
1000  
10500  
10000  
9500  
9000  
8500  
8000  
7500  
7000  
6500  
6000  
5500  
5000  
4500  
4000  
3500  
3000  
2500  
2000  
1500  
1000  
500



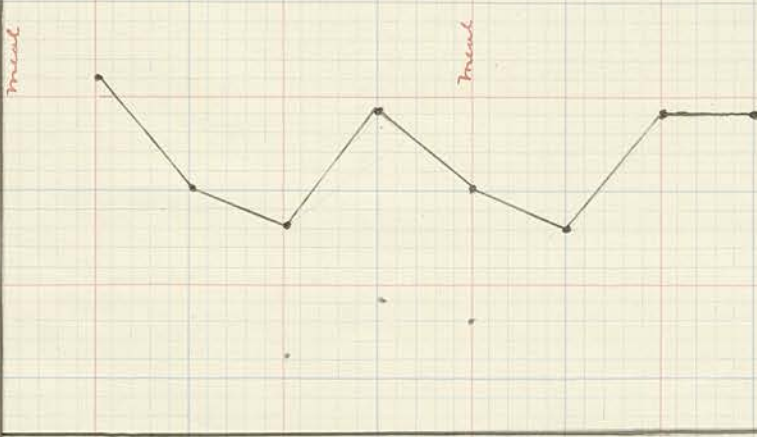
Day II.

1500  
1000  
10500  
10000  
9500  
9000  
8500  
8000  
7500  
7000  
6500  
6000  
5500  
5000  
4500  
4000  
3500  
3000  
2500  
2000  
1500  
1000  
500



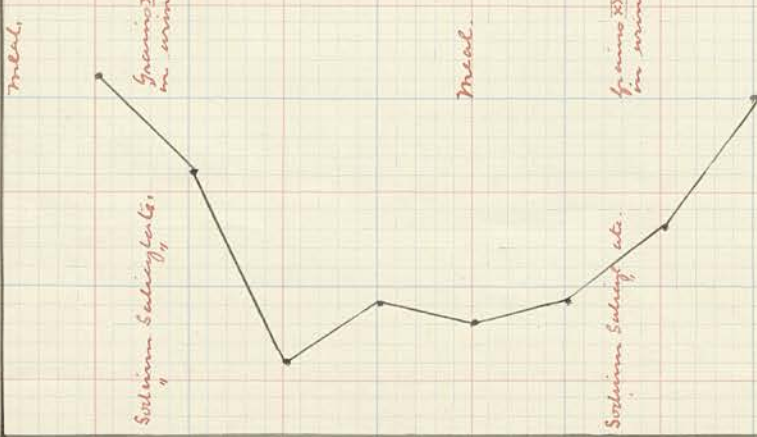
Day I + Day II is average.

1500  
1000  
10500  
10000  
9500  
9000  
8500  
8000  
7500  
7000  
6500  
6000  
5500  
5000  
4500  
4000  
3500  
3000  
2500  
2000  
1500  
1000  
500



Day III

1500  
1000  
10500  
10000  
9500  
9000  
8500  
8000  
7500  
7000  
6500  
6000  
5500  
5000  
4500  
4000  
3500  
3000  
2500  
2000  
1500  
1000  
500



Sodium Salicylate  
in urine.

Sodium Salicylate  
in urine.



Conclusions.

It would thus appear that no immediate rise in the Leucocytic count occurred after the exhibition of grains XX of Salicylate of Soda by the mouth but rather a sharp temporary decline.

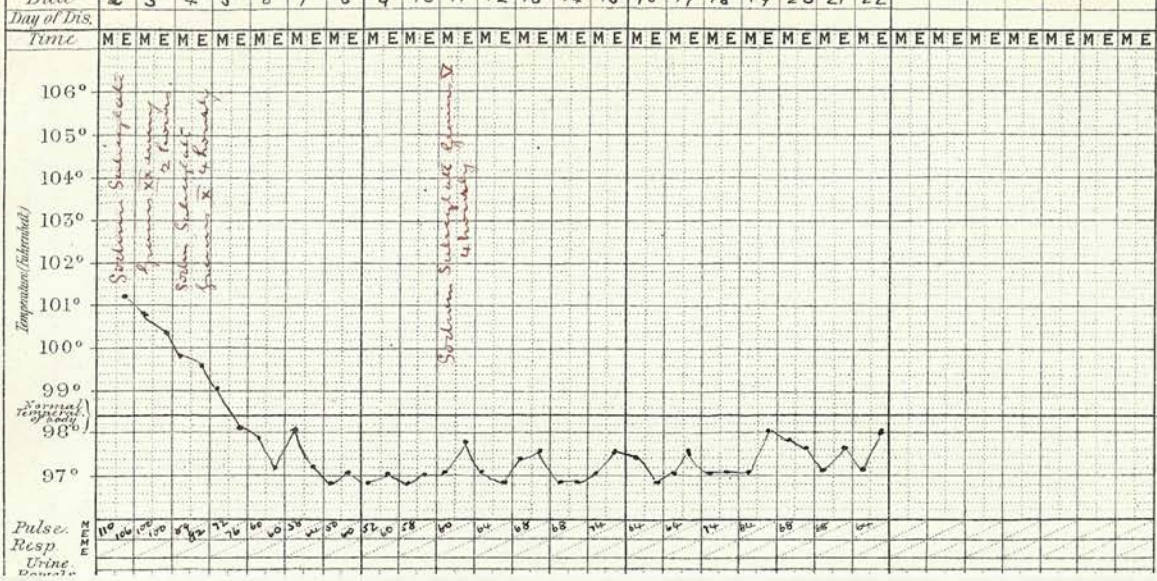
It is worthy of notice that during the six hours on Day III in which Salicylate of Soda was being given the counts were comparatively lower than those of Day I and Day II.

At 5 p.m. the last observation on Day III the Leucocytic count was again rising.

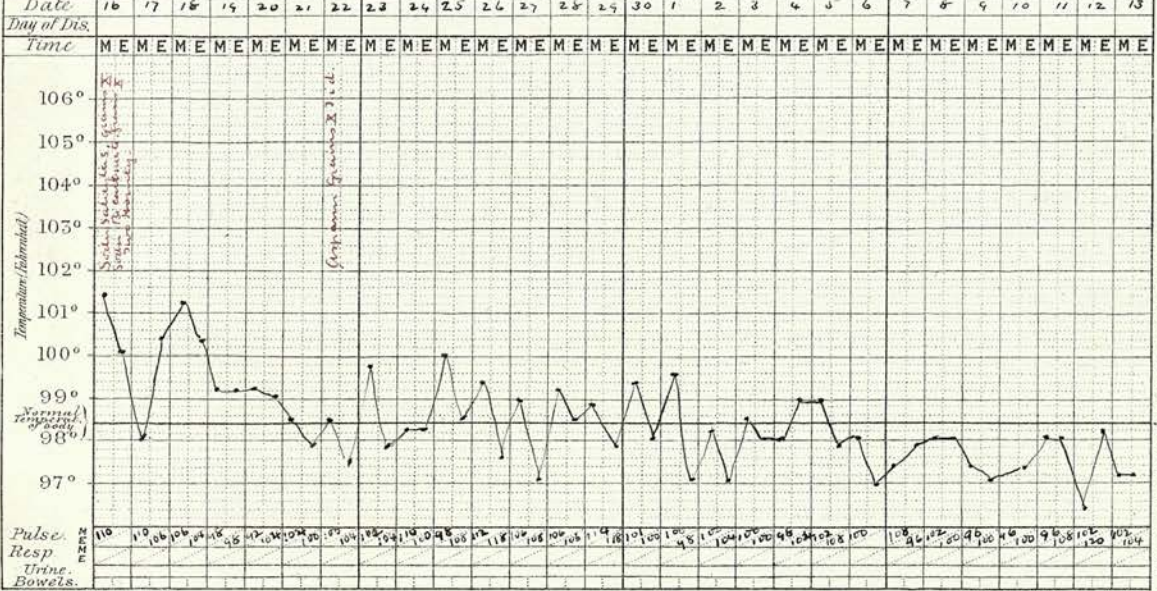
The writer thus thinks that the immediate effect of the administration of Sodium Salicylate is to cause a temporary decrease in Leucocytosis, after which the count slowly rises but not to such an extent or with such rapidity as to justify the statement that Salicylate of Soda takes a part in the Leucocytosis which occurs in Acute Rheumatic Fever.



Name Robert Kemp Age 30 Disease Acute Rheumatic Fever Case I. Result



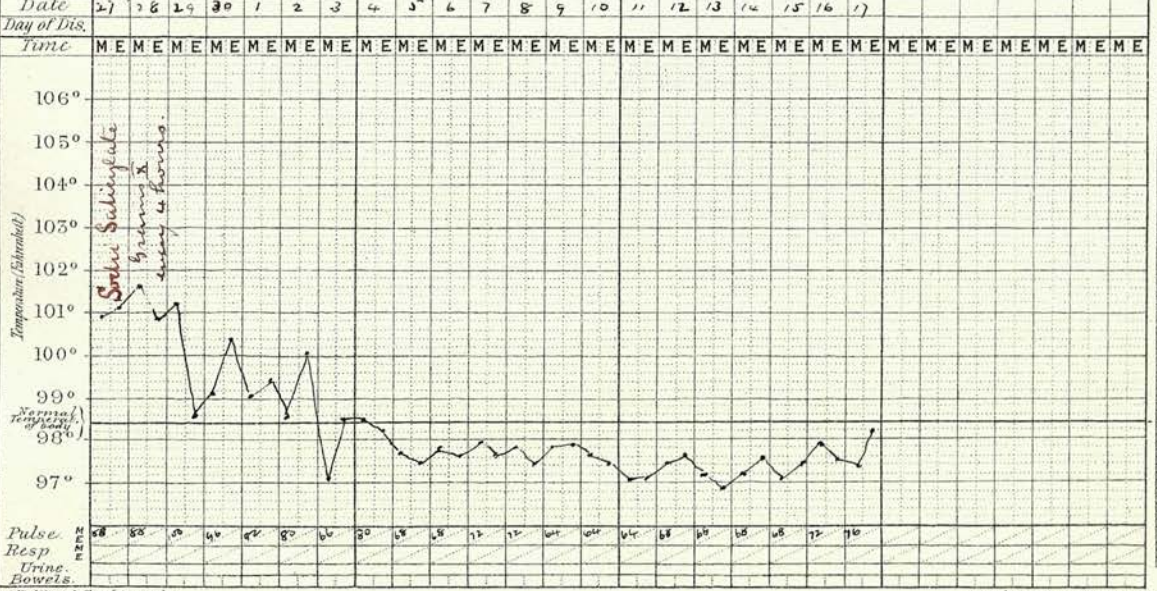
Name Wm Douglas Age 12 Disease Acute Rheumatic Fever Case II. Result



W. Saville 'Clinical Chart' Copyright. No. 7.

H. Silverlock, 92, Blackfriars Road, London.

Name Ellery Taylor Age 22 Disease Acute Rheumatic Fever Case III. Result



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Case I.

R. K. aet. 30.

Occupation Cooper.

Admitted. November 2nd 1906.

Complaint. Pain in joints of all limbs and across  
small of back. Swelling of knees. and  
right shoulder joint.

History. Patient became ill October 28th. Own  
doctor gave medicine which made him sweat  
(Probably Salicylate of Sodium). Patient  
did not improve. So admitted to Hospital.

Previous Health.

Rheumatic Fever eight years previously. No  
other serious illness.

Social condition. Good food in abundance.

Habits. Non smoker. Alcohol in moderation.

Family History. Father and Mother in good health.

Four sisters healthy.

One sister died of Bronchitis.

Children. Three alive and well.

State on Admission. Patient well developed.

Temperature 102. Pulse 110. Respirations 32

Patient perspires freely. Knees slightly swollen  
and tender. Thyroid and spleen not enlarged.

Urine. Specific gravity. 1022 acid.

No abnormal constituents. Nervous system. Sleeps  
badly.

Circulatory System. Nothing to note

Respiratory System. Nothing to note.

Treatment and Progress.

Nov. 2 Patient in bed between blankets.

Diet. Milk. Sodium Salicylate grains XX, two  
hourly.

Nov. 3. Temperature falling. Pain less.

Nov. 4. Sodium Salicylate grains X, four hourly.  
right shoulder still painful.

Nov. 5. Temperature 98.

Nov. 6. Milk diet. Sodium Salicylate grains X

Nov. 7. Diet Fish. Sleep good. No pain.

Nov. 8. Light diet.

Nov. 11th Sodium Salicylate grains V.

Nov. 16th Some pain in right arm in deltoid region.

Nov. 23. Temperature remains sub-normal. Still  
pain in right arm.

Quinine Sulphus grns. II

Phenacitine " II

Sodium Salicylate " II

*D. i. d.*

Dec. 1. Still pain in right arm.

Dec. 8. Free from pain. Left Hospital.

## Case III.

Mary Taylor. Age 28 Single Domestic Servant.

Admitted. 27/11/06.

Complaint. Pain in back, legs and right arm for  
a week before admission.

Family History. Father well. Mother died of  
Eczema. Four brothers alive and  
well. Five dead, cause unknown.

Social condition and Habits. Good situation. Worked hard  
has worked in country where  
she often got wet.

Previous Illnesses. Measles as a child. Frequently  
sore throats and colds.

Present Illness. One week before admission patient  
was seized with sudden pain in left  
ankle, which during week gradually  
developed in legs, arms and back.

Present Condition. Patient is well nourished, and  
has no morbid appearance.

Bowels. Constipated.

Haemopoietic System. Spleen, and thyroid not enlarged.

Circulatory System. Slight pain over praecordia.  
Palpitation, and breathlessness  
on exertion. No faintness.

Suspection. Chest well developed, and normal.  
Apex beat in 5th, left interspace  
just internal to mammary line.

Auscultation. Slight systolic murmur is heard over aortic-valve. All other valves closed. Arterial coats are not thickened.

Locomotor System. Patient has pain in all joints of her body except her left arm. Both feet are slightly swollen, and hands are swollen, stiff and painful to the touch. Patient can only move fingers slightly.

Progress.

Patient made an uninterrupted recovery

Case II.

W. D. Age 13. Occupation School-boy.

Family History. Father, and mother alive and well.

Three sisters, and one brother alive, and well. One sister died of inflammation of lungs.

Social Condition and Habits. Comfortable home. Food good.

Previous Illnesses. Began with pains in both legs.

These spread all over body.

On Admission. Marked dyspnoea. Great pain in all joints and also over left side in 4th interspace in left mammary line.

There was redness, swelling and pain of left ankle joint. Wrists, hands, and knees were painful, but not swollen. There was no serous effusion in either of knee joints.

Circulatory System.

Subjective. Great pain and dyspnoea in left mammary region. Occasionally palpitation on exertion.

Objective Inspection. <sup>beat</sup> Apex, two inches external to mammary line in 5th, and 6th interspaces.

During systolè the interspaces are drawn in a manner to/

to suggest adherent pericardium. There is well marked venous pulsation in neck. Also pulsation in epigastrium.

Palpation. Well marked systolic thrill over apex.

Percussion. Heart markedly enlarged to left.  
Apex in 6th interspace six inches from middle sternal line.

Auscultation. High pitched systolic murmur at apex. **Second** sound closed. Aortic first and second sound closed.

Pulmonary. 2nd sound accentuated and reduplicated.  
No pericardial function.

Progress. Nov. 18th. Patient improved. Pain in joints disappeared.  
Nov. 28th Patient improved and looking better.  
Dec. 1st. Patient still improving.  
Dec. 14th Slight pain in knee.  
" 22nd " " " " and hand  
" 24th Pain in knee and hand disappeared.  
" 26th Patient getting up.



Note on cases.

Sufficient particulars have been given of those cases to show that in their commencement, and subsequent course they were typical cases of Acute Rheumatic Fever.

Case I. had no cardiac complications.

Case II. had previous endocarditis which continued during present attack.

Case III. had slight affection of Aortic Valve.

All cases yielded satisfactorily to Salicylate treatment.

Opsonines.                      Method.

That devised by Sir <sup>ξ</sup>Alworth Wright was employed. (8)

The Diplococcus Rheumaticus as used in suspension appeared to be much smaller than during life which rendered counting extremely difficult.

In order to endeavour to ascertain if opsonines were in any manner affected by administration of Salicylates it was necessary to procure a case, observations of which could be taken before and after treatment. Such a case was No. II. who as far as could be ascertained had received no such treatment before admission.

Experiment No. I.

Blood taken 11 a.m. on admission.	Opsonic Index. 3.16
" " " 2 a.m. after grains XX.	
" " " 12 hours after.	
Sodium Salicylate every two hours	2.83
Control taken as	1.

Experiment No. II.

Owing to lack of another case such as above observations were taken on Case I. during treatment in Hospital, the blood being taken just before administration of Salicylate of Soda by the mouth, and then one hour afterwards.

Case II. A.K.	Opsonic Index.			
	Day 1.	Day 2.	Day 3.	Day 4.
Before salicylate of Soda, grains X.	1.70	1.36	1.10	1.36
After ditto ditto.	3.10	.89	.67	.89

Experiment III. was undertaken to find out whether opsonines specially acted upon the Diplococcus Rheumaticus.

1. Case I.	Sodi. Salicylus given one hour previous to observation	2.07 M. C. R. .72 Staphlococci
2. " I.	ditto ditto ditto	1.44 M. C. R. 1.12 Staphlococcus
3. " II.	" " "	1.27 M. C. R. .85 staphlococcus
4. " III.	" " "	1.65 M. C. R. .92 Staphlococcus

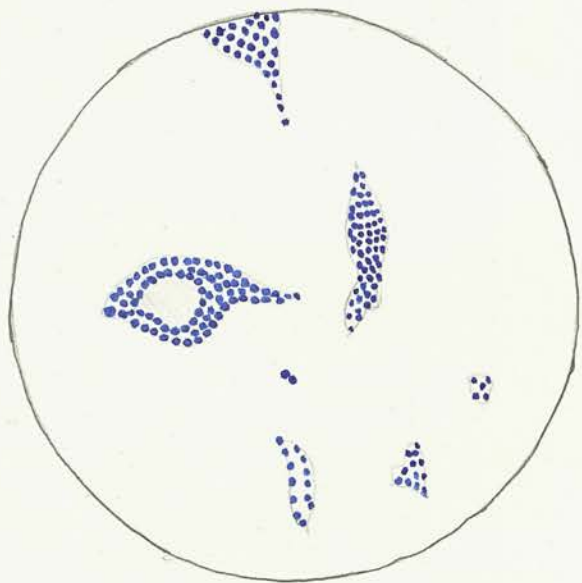
Note on experiments.

No. 1. As only one observation was possible no definite conclusion is justified. It will be noticed that in this case the administration of Salicylates lowered the Opsonic Index.

Experiment No. II. It will be noticed that in Day 1 the Opsonic Index was raised by giving Sodium Salicylate/

Salicylate and in the following three days the Opsonic Index was lowered by administration of same drug, which result is in confirmity with result of Experiment No. 1.

Experiment No. 3. It will be noticed that in all four observations that the leucocytes as influenced by the Opsonines showed a preference for the Diplococcus Rheumaticus as compared with Staphlococcus Pyogenes..



The *Diploleues Rhenanensis*  
from culture. 1 day <sup>old</sup> Oil Emersion.  $\frac{1}{12}$  th  
Stain. Methylene Blue.

Bacteriology of Diplo-Coccus Rheumaticus.

The rapid advances made in Bacteriology within recent years have led to the almost universal opinion that Acute Rheumatic Fever is of bacterial origin. This had long been surmised by clinicians who compared the clinical course of this disease and noted the similarity there-to with the course and symptoms of such a disease as Acute Croupous Pneumonia which was known to be of undoubted bacterial origin. Different observers have observed different organisms and the difficulty appears to be to assign to each its proper place in the course of the disease.

After careful study of the literature upon this subject the organism which appears to the writer to be in the ascendant and to be the primary causal agent in Acute Rheumatic Fever is the Diplo-Coccus Rheumaticus. This small Diplo-Coccus first observed by Triboulet and later by West Phal. (1) has been the subject of careful investigation on the part of Messrs Payton and Payne and later Beattie. (2) (3)

They have isolated this organism in eight successive cases of Acute Rheumatic Fever and obtained pure cultures from the blood during life and/



Cole's Experiment No. 2228.

Series III.

Streptococcus No. 2228.- In one of these rabbits there was no arthritis. Of the other three, two showed a purulent exudate in the joints, and the third, excess of turbid fluid in two joints, and a third joint was distended with fluid but was not opened. One showed endocarditis. These need no comment. They are cases of ordinary pyemia.

and from some of the lesions, post mortem.

Microscopic examination also revealed it in all the important lesions after death. Cole asserts (11) that the intravenous injection of streptococci from various sources will cause arthritis and endocarditis of a similar nature to those caused by the intravenous injection of the *Diplococcus Rheumaticus*, but Cole's experiments with streptococci other than *Diplococcus Rheumaticus* go to show that the endocarditis and polyarthritis was of such a nature as might occur in the course of any pyaemia.

His experiment in series III. streptococcus No. 2228 shows this well. In one of these rabbits, *See slip insertion etc.* This experiment is typical of fifteen others. In these the streptococcus was derived from such various sources as Puerperal Septicaemia, Empyema, Appendicitis, and Scarlet Fever.

The characteristic lesion was an acute purulent poly-arthritis, which cannot by any means be reconciled with the arthritis which commonly occurs in Rheumatic Fever.

(11) Beattie's experiments (fourteen in number) with the *Diplococcus Rheumaticus* produced lesions which were precisely similar to those found post mortem/

mortem in cases which have died of Acute Rheumatic Fever. In no case was there a purulent exudate, and the arthritis if such occurred partook of a thickening of the synovial membrane with exudation of a clear serous fluid. In one case Beattie produced Choreaiform movements such as might have been caused by a localized abscess, but post mortem examination failed to reveal any abscess.

It is on account of the evidence as set forth above that the writer has focussed his work upon the Diplococcus Rheumaticus. Microscopic examination shows this to be a minute coccus about five inches in diameter.

Ordinary basic dyes stain it easily, but it loses its stain by Gram's method.

Formation, and staining.

It occurs in both tissues, and cultures in pairs, many such pairs forming a chain giving the appearance of a chain which is characteristic. On the other hand it may occur in dense clumps, some cocci still retaining the Diplococcal formation, others not so.

There are great variations in size according to/

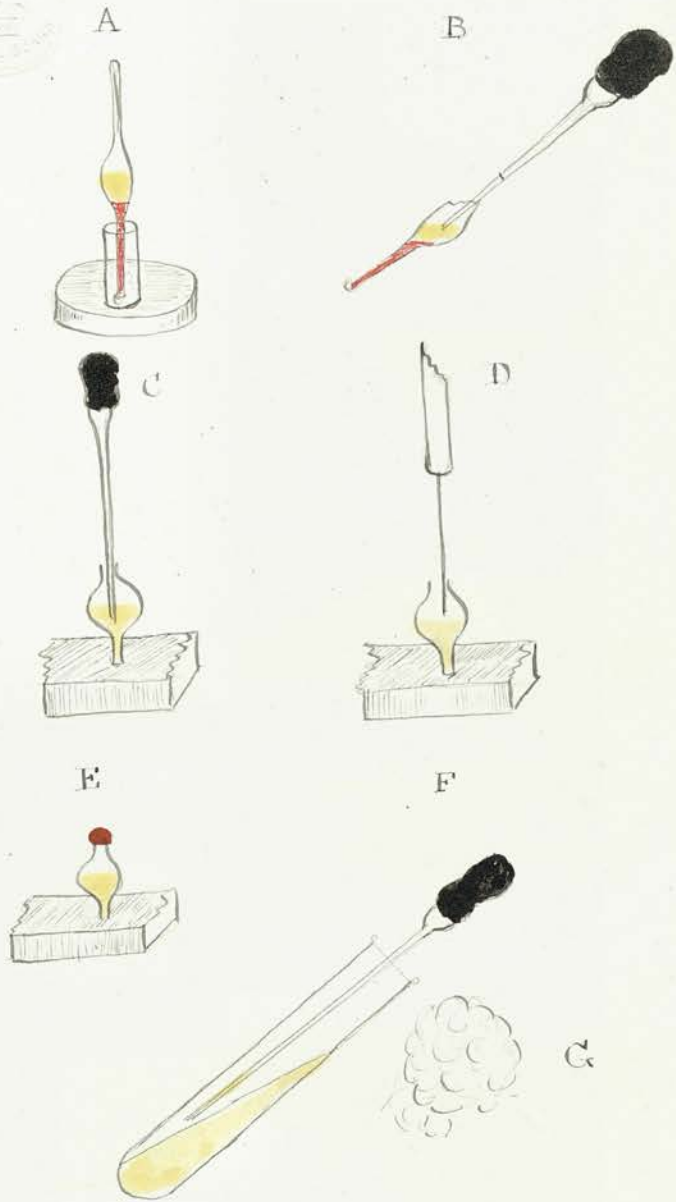
to age, and media on which it is grown.

Dead, or degenerated cocci occur in shrunken tangled masses of streptococcal formation, in patches where the single formation is retained, or singly and alone. Dead, or degenerating cocci appear to stain much more intensely than the healthy cocci.

Cultures. Beattie emphasises the longevity, and durability of its growth as typical. It grows well on blood agar which 12 hours at 35°C. after inoculation shows growth by, small, circular, yellowish white colonies in some cases discrete, but more often the growth takes on a spreading concrete formation appearing when held to the light as a delicate smear.

The writer found this formation common in all his cultures. Colonies appear on microscopic examination under low power as slightly granular masses with clearly defined, but irregular edges.

Grise  
before p. 25.



Illustrating method. Page 25 + 26.

Does the administration of Sodium Salicylate in any way affect the growth of the Diplo-Coccus Rheumaticus?

With a view to determining this the following series of experiments were undertaken.

These if necessary were performed outside the body. Bloods were taken at various intervals after the exhibition of Sodium Salicylate by the mouth. The effect of these bloods which contained Sodium Salicylate was noted upon the growth of the Diplo-Coccus Rheumaticus on Agar, Culture<sup>incubated</sup> at 35 degrees centigrade, for twelve hours.

Bloods. These were taken in most cases from the ear with antiseptic precautions.

Method. The blood after having been drawn off into aseptic glass capsules such as Wright uses in his Opsonic Index work, the glass tubes were immediately sealed.<sup>A</sup> These were then placed in anelectric centrifuge for five minutes each. Such a time was found sufficient to separate the serum from the remaining elements of the blood. This serum was then carefully drawn up into pipettes in as nearly as possible equal quantities.<sup>B</sup> The pipettes which were made of glass tubing drawn to a point were previous to use rendered aseptic by dry heat at 150 degrees centigrade for one hour, the narrow ends being/p



being placed in an aseptic test tube, and the broad ends plugged with wool.

The blood serum now in the pipettes was transferred to a further set of aseptic glass capsules. C

Innoculation. In experiment No. I. the serum contained in the glass capsules was then inoculated by touching a six days' colony of *Diplococcus Rheumaticus* with an aseptic platinum needle, and then transferring needle to serum. D The organisms were then thoroughly mixed with the serum by stirring of needle, the open end of the capsule sealed with wax, E and the whole placed in an incubator for 30 minutes at 35 degrees centigrade in order to allow of thorough mixing.

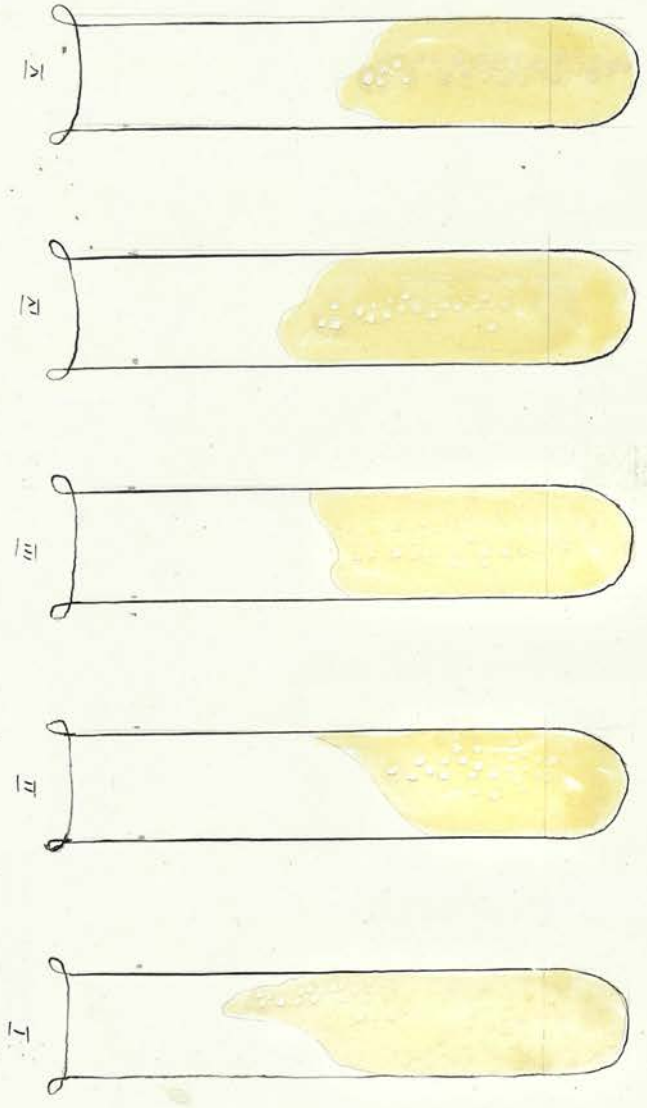
After this time the glass capsules were removed from the incubator, the sealing wax nipped off with pincers, and the serum (intermixed with *Diplo-Coccus Rheumaticus*) carefully pipetted off with a fresh set of aseptic pipettes, Sloped Agar tubes were then inoculated with this serum from the pipettes in as nearly as possible equal proportions. F

Thus each test tube contained:-

- (1) Agar Culture media.
- (2) Blood serum containing Sodium Salicylate as circulating in the blood.
- (3) *Diplo-Coccus Rheumaticus*.

In ~~nearly~~ all cases the purity of cultures was tested microscopically.

Experiment No I.



Experiment No. I.

In all, five bloods were taken as follows:-

	Sodium Salicylate given	Blood taken	
I Case III	3 p.m.	5 p.m.	= 2 hours
2 T. R. S.	5-35 p.m.	5-55 p.m.	= 20 minutes.
3 "	"	6-15 p.m.	= 70 "
4 "	"	7 p.m.	= 85 "
5 Control		7-15 p.m.	

All bloods centrifuged five minutes.

Innoculation. Direct - by touching Colony on Agar tube of Diplo-Coccus Rheumaticus six days old, and innoculating directly into serum.

Mixing. In incubator at 35 for 35 min.

Culture. Five sloped Agar tubes innoculated direct with serum, and organisms by pipette. Placed in incubator at 35° at 11 p.m.

Result of examination after 24 hours after 35.

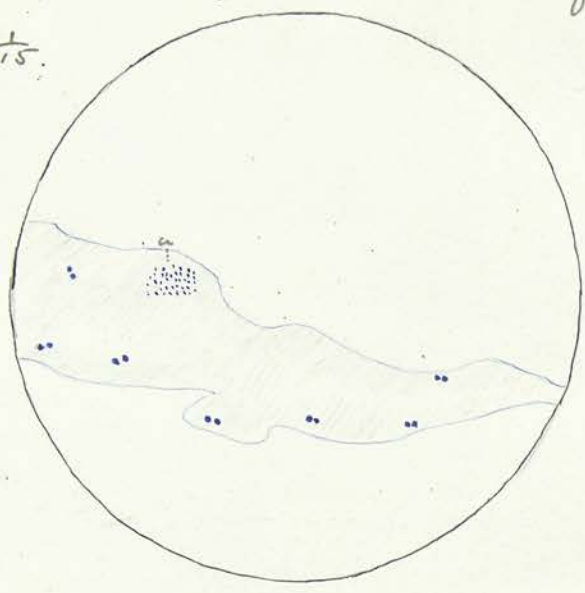
All tubes showed growth by colonies.

1. Colonies plentiful, small discrete, and slight spreading growth.
2. Colonies few in number, and small diameter.
3. Colonies young. Few in number, slight spreading growth.
4. Colonies discrete larger than (3), some spreading growth.
5. Colonies plentiful, large some spreading growth.

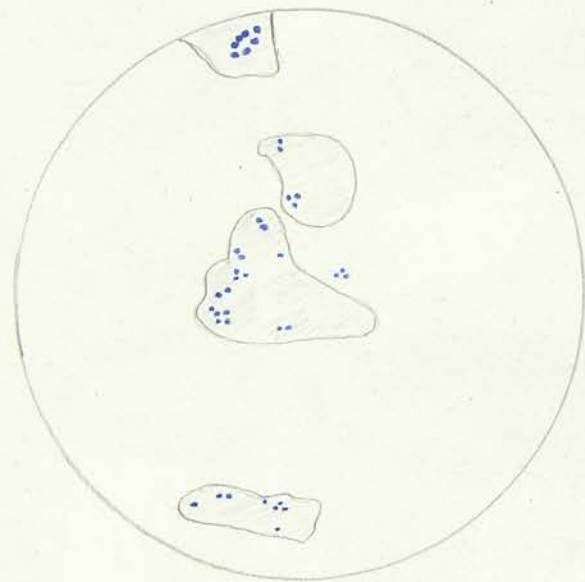
Series of slides taken from cultures of *Expermia*  
oil Emulsion  $\frac{1}{5}$ .

No. I

Dead Cocci. (a)

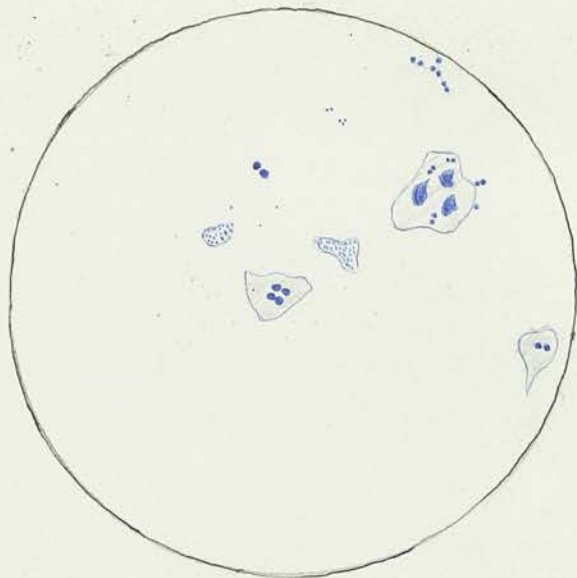


I



II

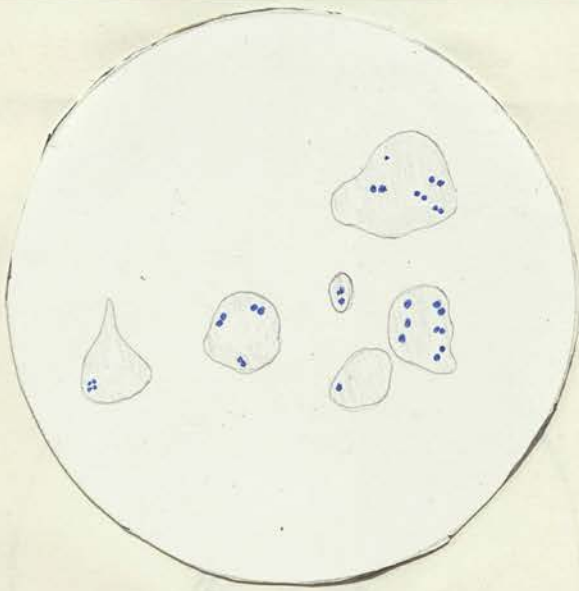
III



Showing Rhizopus Coloni in various sizes of growth.



IV



V





Note on Experiment No. 1.

Blood A. This is the blood of a Case II who was reacting clinically to Sodium Salicylate.

The blood was taken two hours after exhibition of the drug. As compared with Tube No. V. (Control Blood E.) there is no inhibition of growth.

Blood B. C. and D. These were taken at intervals of 20, 35, and 85 minutes after exhibition of the drug. Although there was no inhibition of the growth of *Diplo-Coccus Rheumaticus* as compared with control still the colonies in D. Tube exhibited more growth than in B.

Blood E. That of control. The blood of a person who had taken no Salicylate of Sodium. It will also be noticed that serum of Case I. presented a more favourable media than either that of the control, the or a non-pathological case, the case which was taking Salicylate of Soda.

Experiment No. II.

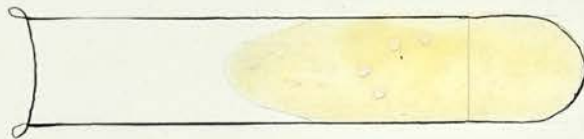
This was conducted on similar lines except that another case of Rheumatic Fever was added, a fresh control replaced that of Experiment No. I.

In all five bloods were taken as follows:-

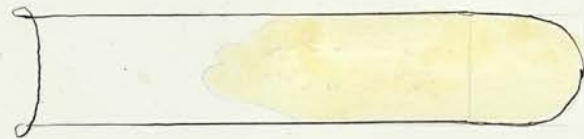
- |    |              |  |
|----|--------------|--|
| 1. | Case No. III | Blood taken 30 minutes after Sodium Salicylate by mouth. |
| 2. | " II.        | " " 25 " " "   |
| 3. | T.R.S.       | " " 30 " " "   |

Experiment No II

III



II



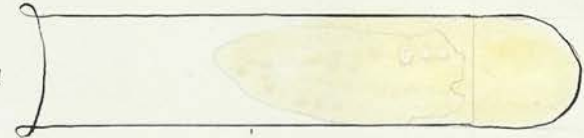
IV



I



V



4. T. R. S. Blood taken 120 minutes after Sodium Salicylate by mouth.
5. Control. No Salicylate given.

Method. This was precisely similar to that carried out in Experiment No. 1. with this difference, namely, that in inoculation one loopful of culture was mixed with one cubic centimetre of sterile water. This was with equal proportions mixed with the blood serums.

Result of examination after twelve hours in incubator at 35 degrees centigrade.

<sup>or culture</sup>  
(Case) I. Growth plentiful and diffuse but weak.

<sup>culture</sup>  
(Case) II. Colonies young and fairly numerous. Some diffuse growth.

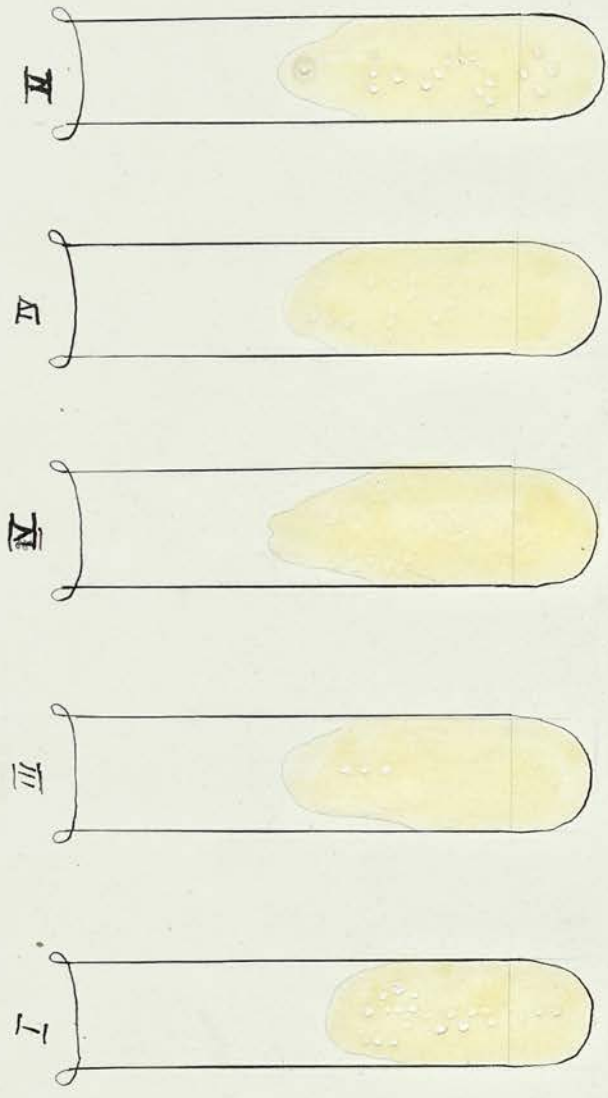
<sup>culture</sup>  
(Case) III. Colonies discrete and strong. Some diffuse growth.

<sup>culture</sup>  
(Case) IV. Colonies strong. Slight diffuse growth in bottom of tube.

<sup>culture</sup>  
(Case) V. Colonies weak and strong, intermixed.

Note on Experiment No. II. In no tube was there complete inhibition of growth. In the cultures of the bloods of the two pathological cases there certainly was younger, and weaker growth than in the control. On the other hand the growth on Cultures III and IV showed little difference as regards rapidity of/

Experiment No. III.



of growth, <sup>but</sup> were much stronger than the two pathological blood cultures and were of equal strength as compared with the control.

The Salicylate of Sodium as circulating in the blood seemed to make no difference in inhibition as regards time when blood was taken, e.g. at 30 minutes and 60 minutes after.

Experiment No. III.

Conducted in similar lines as Experiment No. II.

A. KEMP

Case No. 1 Blood taken 120 minutes after Sodium Salicylate had been taken by mouth.

"	WM DOUGLAS	No. II	"	"	120	"	"	"	"
"		III	"	"	30	"	"	"	"
"		IV	"	"	60	"	"	"	"

Control V No. Salicylate of Sodium given.

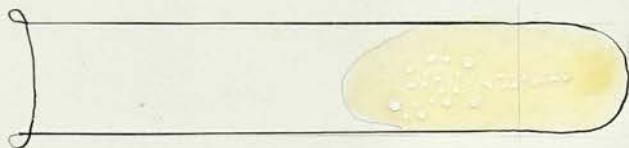
Method. Same as in Experiment No. 2.

Note on Experiment No. III. In no case was there marked inhibition of growth of Diplo-Coccus Rheumaticus as compared with control. Of the cultures on non-pathological which contained Sodium Salicylate culture No. IV. 60 minutes showed more growth than Culture No. III. 30 minutes. Both cultures I. and II. on pathological bloods of cases which were reacting clinically to Sodium Salicylate/

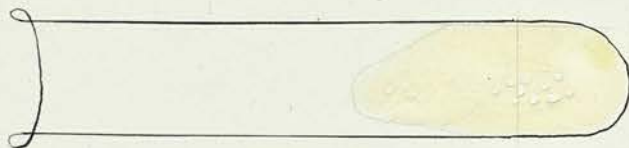


Experiment No. IV

I



II



III



IV



V



VI



Salicylate showed well marked growth.

Conclusions with regard to experiments I, II and III.

1. In no case does the Salicylate of Sodium circulating in the blood in any marked degree inhibit the growth of Diplo-Coccus Rheumaticus.
2. Although the bloods of (a) normal persons were taken at varying intervals after the exhibition of Sodium Salicylate and (b) the blood of cases suffering from Acute Rheumatism under similar circumstances as regards medication, in no case was there enough dissimilarity of growth to assume that either the time which had elapsed since the or the drug itself as circulating in the blood drug was given, presented any cultural difficulties to the growth of the organism.

Experiment No. IV.

This was undertaken to determine at what time after the exhibition of Sodium Salicylate by the mouth its action if any, towards inhibiting the growth of Diplo-Coccus Rheumaticus through the blood stream was greatest in a healthy person. Excretion of Sodium Salicylate in urine occurred five minutes after exhibition of the drug by the mouth.

In all six bloods were taken as follows:-

Case I.	Control.	Blood taken	minutes	after giving	Sodium Salicylate				
					Grains XX by mouth.				
"	II.	T. R. S.	"	"	5	"	"	"	"
"	III.	T. R. S.	"	"	10	"	"	"	"

Case IV. T. R. S. Blood taken 15 minutes after giving  
Sodium Salicylate  
" V. T. R. S. " " 20 " " " " " " grains XX by mouth.  
" VI. T. R. S. " " 25 " " " " " "

Method. Same as followed out in Experiments I. II.  
and III.

Dilution of a Diplo-Coccus Rheumaticus.

Two loopfuls in two cubic centimetres of sterile water.

Incubation. One hour at 35 degrees centigrade.

Result. Examination of cultures after 11 hours incubation as described above. All have small colonies appearing.- 22 hours after incubation as above.

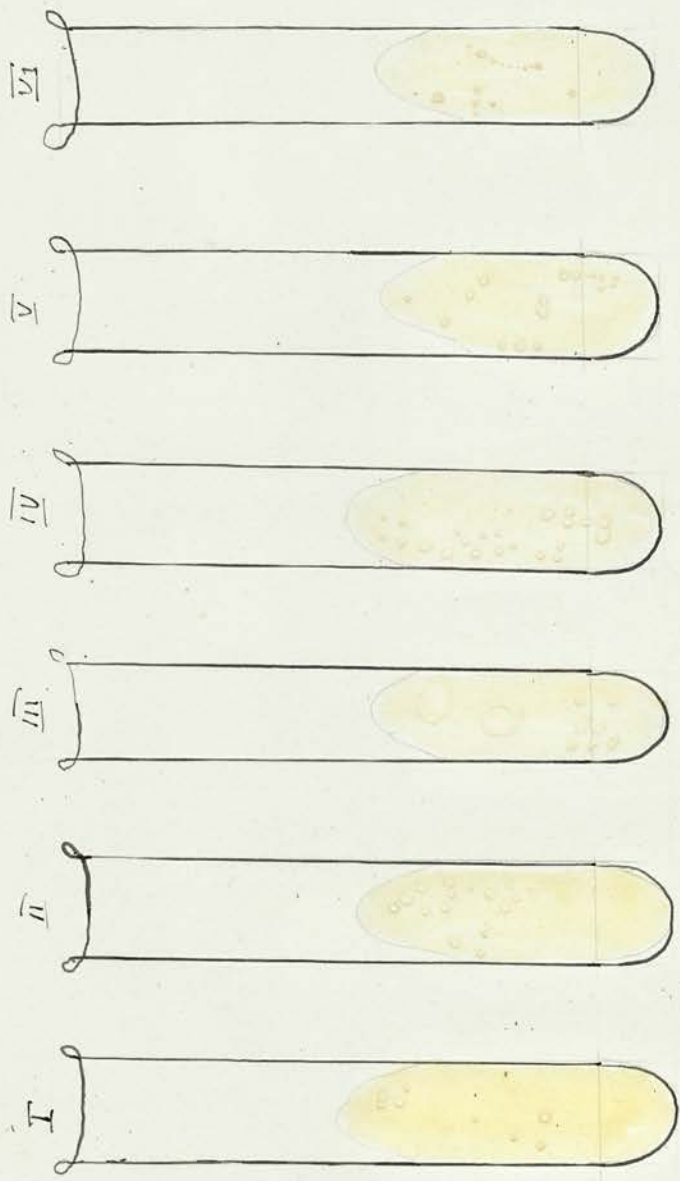
In all cultures showed marked growth of colonies.

Note. On Experiment No. IV. Cultures IV. and V. certainly showed less growth than II, III and VI. as compared with control, but not sufficient to justify any conclusion as to Salicylate of Sodium causing any inhibitory action at any particular interval after exhibition of the drug.

Experiment No. V. This experiment was undertaken with the object of showing what strength of solution of Sodium Salicylate would inhibit the growth of Diplo-Coccus Rheumaticus.

Method A standardized solution containing 25% of

Experiment No. V.



of Sodium Salicylate was prepared..

Six blood serums were also prepared, and respectively mixed as follows:-

Blood Serum I. 25 per cent Sodium Salicylate.

"	"	II. 8.3 "	"	"	"
"	"	III. 6.1 "	"	"	"
"	"	IV. 5. "	"	"	"
"	"	V. 4.25"	"	"	"
"	"	VI. 3.57"	"	"	"

Results after 12 hours incubation at 35 degrees  
centigrade.

All cultures showed plentiful and typical growth  
by colonies.

Note on Experiment No. 5.

It is thus certain that in the blood serum of  
a healthy person innoculated with a 25% solution of  
Sodium Salicylate spread in an Agar tube is still a  
favourable medium in which the Diplo-Coccus  
Rheumaticus grows vigorously.



The Toxines of Diplococcus Rheumaticus.

The method by which the writer had hoped to investigate this was to inject three rabbits

A. B. & C. as follows:-

A. with toxines.

B. " " an injection of Salicylate of Soda

C. " " which had been previously mixed with  
Salicylate of Soda.

Unfortunately lack of time and material which was unavoidably caused him to postpone this part of the research.

Conclusion.

The results obtained in the foregoing observations leads the writer to believe that the field of usefulness of Salicylate of Sodium in Acute Rheumatic Fever lies in their power of neutralizing the toxins of the causal microbe either through causing some change in the metabolism of the body or directly as Salicylate of Sodium inoculating in the blood. No one who has investigated a series of cases of Acute Rheumatic Fever which have been treated with Salicylate of Soda can fail to have impressed upon him that their beneficial action is an altogether striking one and does not depend upon the relief of a simple symptom but upon some specific action upon the last line of defence of the causal organism.

The evidence in support of this statement may be conveniently taken under three headings.

I. Clinical Observations

II. Haematological.

III. Bacteriological.

I. Clinical Observations.

These may be furthered identified as follows:—

1. Reduction of Temperature.
2.       "       "       Pulse, rate.

3. Relief of Pain.
4. Arrest of Blood destruction.
5. Persistence of Endocarditis.
6. Resistance to joint affections.
1. Reduction of Temperature.

This follows administration of Salicylate of Sodium with such unvarying regularity that any case which does not benefit in such a manner is regarded as exceptional.

Salicylate of Soda appears to share this property in common with other kindred derivatives of the tar aromatic series such as Phenacetin<sup>e</sup>; Antipyrine. All of these will reduce temperature in any feverish state which depends upon an organism and its toxins. It is worthy of note however that while Salicylate of Soda can take the place of such things as Phenacetin and Antipyrine in reducing temperature in feverish states the last two mentioned drugs cannot with any satisfaction replace Salicylate of Soda in Acute Rheumatic Fever.

On forming an opinion upon this question much depends upon the view taken as to whether Salicylate of Soda acts upon the cause of the temperature, viz. toxins which are influencing the heat centre, or simply mechanically by providing a readier exit for the/

the out flow of heat produced. Cushney states that <sup>(12)</sup>  
"Salicylates have been said to lower normal temperature,  
but this seems to be erroneous,  
(The writer found no reduction in temperature after  
taking 20 grains of Sodium Salicylate ) except where  
large quantities produce a condition akin to collapse.

Some of the results may be due to impure  
preparations. In fever patients, however, it often  
causes a marked fall in temperature and it was formerly  
used as an antipyretic for this reason.

The action is probably explained by the dilation  
of the cutaneous blood vessels and increase in the  
out put of heat. Dilation of the skin blood vessels  
also occurs in normal persons after Salicylates but  
this is probably counter balanced in them by  
increased heat production."

It would thus appear that the mechanical and  
metabolic increase cannot of themselves be entirely  
responsible for the striking reduction in temperature  
which occurs. Neither must the diuretic action of  
the Salicylates be lost sight off, but the same  
result may be obtained with every diuretic The  
writer therefore looks upon these as contributory  
causes which assist in lowering temperature.

Coming/

Coming to the supposition that Salicylates either as Salicylate of Soda circulating in the blood or by means of some change in the metabolic processes of the body neutralizes the toxins it is somewhat hard to separate the clinical from the bacteriological. Clinically however we observe that

1. Salicylate of Soda has a selective action in reducing the temperature in Acute Rheumatic Fever.
2. That it affects this rapidly in the great majority of cases.
3. That if treatment with Salicylates be discontinued at too early a date the pyrexia and other unfavourable symptoms recur with a severity which equals that of the beginning of the attack.

## 2. Reduction in Pulse Rate.

This would appear to fall in proportion with the temperature. It is here again a question as to whether slowing occurs on account of neutralization of toxins or simply to the depressing effect which the tar derivatives have upon the heart's action.

The writer holds the same view as under previous heading.

## 3. Relief of Pain.

Here/



Here again the same line of argument may be followed. The Salicylates may be looked upon as analgesics in common with the other Tar Derivatives of the same series, but Phenacetine cannot replace the Salicylates in relieving the pain of Acute Rheumatism. Further Salicylate of Soda cannot be looked upon as a good substitute for Phenacetine in neuralgia or <sup>migrane</sup> unless these be of Rheumatic Origin.

Again the writer believes that their analgesic action is only a contributory factor in the relief of pain which follows the exhibition of Salicylate of Soda and <sup>this</sup> cannot alone be accredited to the analgesic properties of the Salicylate

#### The Arrest of Blood Destruction.

The writer regards the progressive anaemia which is the rule in cases of Acute Rheumatism as of <sup>an</sup> cardinal importance, Exactly how Salicylates act in such cases is not known. One may assume however that such blood destruction is caused by the toxins of the Diplococcus Rheumaticus; for this anaemia is quite similar in nature to that which occurs in any pyemic infection where toxins are at work.

(13) Cabot says, "Hayem and Osler state that the poison of Acute Rheumatism is a powerful and rapid destroyer/

destroyer of red cells. In acute cases, according to Hayem<sup>n</sup>, the red cells lose at least 1000000 of their number and in cases which may along and relapse the loss is from 1,500,000 to 2000,000. When an attack is cut short by Salicylate treatment the drain on the corpuscles is stopped. "Turck's careful studies led him to the same conclusions." Cabot dissents from the view that progressive anaemia occurs in all cases.

Persistence of Endocarditis.

Clinical Authorities differ widely regarding the extent to which the exhibition of Salicylate of Soda limits the endocarditis of such frequent occurrence in Acute Rheumatic Fever. Some go the length of saying that it sets no limit at all.

Pathologists have found post mortem the Diplococci<sup>s</sup> Rheumaticus in the vegetations growing on the heart valves. Although such organisms are within the full range and force of the whole blood stream which contains Salicylate of Soda yet it would appear they continue to flourish and to secrete their toxins back into the delicate connective tissue of the heart valves.

Such <sup>connective</sup> ~~fibrous~~ tissue being poorly supplied with blood/

blood the Salicylate of Soda has little chance of reaching the toxins secreted therein, hence neutralization is incomplete, irritation of the connective tissue cells ensues, and fibrous tissue is formed. (15)

#### Remittance of joint affections.

The Diplococcus Rheumaticus had also been isolated post mortem from the synovial membrane of joint cavities.

In contrast to the heart valves we have here an altogether different arrangement.

1. A plentiful supply of blood pouring in all sides with Salicylate of Soda to the capsule of the joint.
2. An actively secreting synovial membrane pouring with its secretion Salicylate of Soda into the joint cavity, which may be compared to a reservoir thus allowing the Salicylates the most favourable conditions for action.

#### 1. Leucocytosis.

Haematological. The writer has endeavoured to estimate the part which Salicylates play in the blood with regard to their beneficial action in Acute Rheumatic Fever. It would appear that far from supplementing the pathological leucocytosis to any marked/

marked extent, they actually depress it for several hours after exhibition by the mouth.

## 2. Phagocytosis.

The Opsonic Index was obtained in order to investigate the effect of Salicylates upon Opsonines.

### Bacteriological.

Experimental evidence has been adduced to show that the Diplococcus Rheumaticus is in no way itself affected by the Salicylate of Soda either as circulating in the blood of a person who was suffering from Acute Rheumatic Fever or of a healthy person. Further it is shown that the Diplococcus Rheumaticus grows well in a 25% solution of Sodium Salicylate spread upon a blood agar culture medium.

In support of these statements clinical evidence is as follows:-

1. If Salicylate treatment be stopped at too early a period in the disease a relapse inevitably occurs with full intensity which would appear to show that the Diplococci Rheumaticus still remains unaffected as far as they themselves are concerned. If their toxins are neutralized then to a certain extent their multiplication is held in check as the pabulum which the toxins would otherwise provide is/

is restricted.

2. Salicylates are frequently given to patients who suffer from recurrent tonsillites supposed to be of Rheumatic origin. Some writers hold that it is by way of the tonsils that the Diplococcus<sup>a</sup> Rheumaticus enters the body. Such history of recurrent sore throats often is the ~~pre~~lude to an attack of Acute Rheumatism and it is conceivable that by the timely administration of Salicylate of Soda the Diplococcus Rheumaticus is prevented from proceeding into the general circulations, because if toxins are neutralized this is a less favourable pabulum, death of the individual cell is prevented and suppuration does not occur.

(4) Hare holds that the administration of Salicylate prevents such tonsillites proceeding to suppuration.

In conclusion the writer feels assured that when the part which Salicylates play in regard to the causal agent of Acute Rheumatic Fever has been fully disclosed that the rules for treatment founded in the clinical experience of the past will receive ample confirmation.