III. Original Communications

I. THE ACTION OF CERTAIN SALTS OF FORMIC ACID ON THE CIRCULATORY AND MUSCULAR SYSTEMS

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I. Introductory

The formates at the present time are receiving much notice. Points of interest are associated with their chemistry, and in the realm of therapeutics no up-to-date tonic is complete without them. It has been claimed for them that they stimulate the heart, vessels, bladder, and alimentary canal; that they increase the appetite, abolish fatigue, and exert a tonic influence on muscles. One enthusiast suggests that for the latter reason formic acid should replace alcohol among the working-classes. It has been stated that the formates are powerful diuretics; that they conserve youth, delay senescence, and that they cure rheumatism, tremors, and pneumonia. When administered to rabbits they increase their vivacity, while the endowment of the ant with formic acid explains its industry.

The local application of formic acid is said to cure lupus and inoperable cancer, and it has been recommended as a preservative of food. The physiological action of substances alleged to be possessed of so many of the attributes of an elixir of life seemed to us to be worth investigating.

The literature on the subject is for the most part unsatisfactory. The work of Clément (1) and Garrigue (2) can only be described as that of wild enthusiasts. Huchard (3), however, to a certain extent confirms their results, though he does so in more restrained phraseology.
A much more careful piece of work is that of Fleig (4). In the first part of his paper he criticises his French confrères so unmercifully and so thoroughly that he leaves subsequent critics very little to say. Indeed, had Fleig's paper received the attention it deserves the formates would never have attained the position in fashionable therapeutics they now have. Fleig immersed exposed loops of intestine in animals in Locke's fluid and noted the movements. Formate of soda added in varying proportions never affected the contractions in amplitude, frequency, or rhythm. Experimenting with the isolated heart of rabbits he never obtained an excitor or reinforcing effect due to sodium formate. On the contrary, concentrated solutions caused toxic effects, lessened amplitude, diminished frequency and arhythmia.

In the case of a nearly exhausted heart, however, calcium formate acted as a stimulant, just as any calcium salt would. The contractions of the gastrocnemius of rabbits set up by induction shocks were not affected by sodium formate.

Nerve energy direct and reflex was not stimulated by sodium formate. Ergographic records, carefully carried out, were negative in Fleig's observations, and he ascribes the results of Clément and Huchard to the effects of training and suggestion.

Among the purely clinical records the only observations of importance are those of Croom (5) in 1906, and Ker and Croom (6), published last June. They have given formic acid to patients suffering from diphtheria, and conclude that the results they obtained are distinctly encouraging, particularly in relation to the occurrence of cardiac failure and paralysis. They, however, themselves admit that standards of comparison for its merits are difficult to obtain in such a disease. They cannot confirm the diuretic effect observed by Clément and Huchard, and in this particular standards of comparison are definite. While their general verdict on formic acid is favourable, it is expressed with an amount of Scotch caution which contrasts strongly with the enthusiasm of the French advocates.

The salts we employed in the following experiments were those of sodium, potassium, and calcium. In many instances, however, the action of the two latter was evidently affected, sometimes to a preponderating extent, by the metallic ion, so that the bulk of our later investigations were carried out with the sodium salt.

A few observations were made with formic acid, but its powerful
local nocuous effects in causing tissue necrosis and increasing coagulability of the blood obviously rendered it unsuitable for such investigations as we wished to carry out.

We may note in passing that the formic acid, even in dilute solution, has a local effect on muscle. The muscle becomes more translucent and acquires a curious glazed appearance.

II. Observations on Animals

1. Effects on Blood Pressure.—Observations were made on 14 rabbits, fully anæsthetised with ether. In most cases several salts were employed. Tracings were taken from the left carotid, and the solutions were injected into the left jugular vein. The vagus nerves were cut in the great majority of cases. The doses varied from 10 to 20 m. according to the weight of the rabbits.

Sodium Formate.—
Injection of a 1/500 solution had no effect.
Injection of 1/100 solution in 4 instances, and of 1/50 solution in 2 instances, had no effect.
Injection of 1/25 caused a very slight fall of pressure in 3 cases, but in one instance had no effect.
Injection of 1/10 caused a slight fall, with immediate recovery in 5 cases.
Saturated solution caused a fall of 64 mm. of mercury, followed by a gradual rise to normal.

Potassium Formate.—
Injection of 1/1000 caused a slight fall of pressure, with immediate recovery.
Injection of 1/100 caused a fall of pressure, with recovery in 3 cases, and was negative in 3 cases.
Injection of 1/25 in all of 3 cases caused a very definite fall, with recovery gradual and not always complete.
Injection of 1/10 in all of 4 cases caused a fall practically to zero, and was immediately fatal in 3 cases. The fourth animal recovered only after artificial respiration.

Calcium Formate.—
Injection of 1/500 had no effect.
Injection of 1/250 had no effect.
Injection of 1/100 caused a slight fall in one case, a slight rise
in another, had no effect in a third, and stopped the experiment by clotting in two instances.

Two injections of 1/50 had no effect.

Injection of 1/25 caused a slight fall, with recovery in 2 cases, and had no effect on a third.

Two injections of 1/10 (saturated) solution tended to cause a slight rise. In one case a slight fall was caused. In each case clotting occurred and prevented further observations.

Formic Acid.—Two injections of 1/50 were made. In each case, after a preliminary fall and recovery, there was a long and gradual fall.

These experiments indicate that sodium formate has little effect on the blood pressure, unless it is in fair concentration. Strong solutions are definitely depressor.

Potassium formate is slightly depressor in dilute solutions, definitely depressor in moderate concentration, and usually fatally inhibits the heart in strong solutions.

The experiments with calcium were less definite, but they probably warrant the inference that the more dilute solutions have a slight depressor effect, and that concentrated solutions tend to raise the pressure.
The general effect of the acid in the two experiments was depressor.

The want of similarity in the action of the different salts is to be explained by the influence of the metallic ion. The true formate effect is shown in the case of the soda salt to be depressor. This depressor effect becomes enormous when added to the preponderating potash effect, while it tends to be obscured altogether when opposed by the stimulating action of calcium.

2. Observations on the Blood-Vessels.—These experiments were carried out on pithed frogs. A cannula was tied into the aorta and Ringer's solution was allowed to flow into it from a reservoir in which the fluid was kept at approximately the same level. The salt to be investigated was added to the Ringer's solution in known proportions. After flowing through the vessels the fluid escaped from a cut in the sinus venosus, and eventually dropped from the animal's toes. By such an arrangement any change in the calibre of the vessels affects the rate at which the drops fall. We used a graphic method for recording the drops. They were allowed to fall on a piece of tinfoil attached to the long lever of a receiving tambour. The movements were transmitted to the lever of a recording tambour and were marked on the smoked paper of a kymographion. Time intervals were recorded by means of an electric marker. After a salt had been perfused the vessels were again perfused with Ringer's solution only. Those experiments, in which the return rate most closely approached the original rate, were obviously the most satisfactory, but a failure to obtain a return rate similar to the original does not necessarily invalidate the observation. Sixty-six experiments were carried out. The following is a typical example:

Frog perfused with Ringer's Solution.

Original Rate . . . . 20 per minute.

After the addition of 1 in 1000 Sodium Formate.

In 30 seconds . . . . 22 per minute.
In 60 seconds . . . . 24 "
1 to 3½ minutes . . . . 28 "
3½ to 5½ minutes . . . . 26 "
5½ to 6 minutes . . . . 24 "
6 to 7 minutes . . . . 22 "
7 to 10 minutes . . . . 20 "
10 to 14 minutes . . . . 18 "
Ringer's Solution only.

14 to 19 minutes . . . 16 per minute.
19 to 20 minutes . . . 18 "

With a few exceptions it was found that all the salts in all the dilutions used first caused a dilatation, followed by constriction.

In 15 instances (7 potassium, 4 soda, 4 calcium) there was no dilatation, and in 10 instances (8 soda, 1 potassium, 1 calcium) no constriction occurred. In nearly every case the dilatation began within 3 seconds, never later than 30 seconds, and gradually approached its maximum. The constriction followed in from 17 to 480 seconds, usually about the expiry of a minute and a half. Although the intervals of time at which the dilatation and constriction occurred varied within very narrow limits, it seemed to us that in collating our results to select arbitrary intervals and state the conditions then found would not correctly indicate the result of our experiments. We therefore chose the maximum amount of change in each case.

The results are tabulated as follows.

The number of drops is that counted in 30 seconds.

Sodium Formate, 1 in 1000.

| Experiment | Original Rate | Maximum Dilatation Rate | Maximum Constriction Rate | Return Rate | Percentage Rate |
|------------|---------------|-------------------------|---------------------------|-------------|-----------------|
| | | | | | Dilatation. | Constriction. |
| 1 | 108 | 127 | 99 | 99 | 117 | 91 |
| 2 | 20 | 22 | 14 | 19 | 110 | 70 |
| 3 | 19 | 19 | 14 | 19 | 100 | 73 |
| 4 | 33 | 47 | 16 | . | 142 | 52 |
| 5 | 136 | 151 | 114 | 130 | 133 | 83 |
| 6 | 12 | 16 | 10 | 10 | 133 | 83 |
| 7 | 142 | . | 115 | 171 | 100 | 81 |
| 8 | 38 | 56 | 56 | 56 | 145 | 100 |
| 9 | 34 | 37 | 12 | 12 | 109 | 35 |

Average . . . 118 74
### Sodium Formate, 1 in 500.

| Experiment | Original Rate | Maximum Dilatation Rate | Maximum Constriction Rate | Return Rate | Percentage Rate | Dilatation | Constriction |
|------------|---------------|-------------------------|---------------------------|-------------|----------------|------------|--------------|
| 10         | 99            | 104                     | 77                        | 77          | 110            | 80         | 100          |
| 11         | 19            | 23                      | 19                        | 19          | 121            | 100        | 62           |
| 12         | 19            | 23                      | 19                        | 19          | 121            | 100        | 62           |
| 13         | 8             | 9                       | 5                         | 6           | 112            | 100        | 62           |
| 14         | 68            | 130                     | ..                        | 120         | 191            | 100        | 80           |
| 15         | 10            | ..                      | 8                         | ..          | 100            | 80         | 80           |
| Average    |               |                          |                           |             | 126            | 87         |              |

### Sodium Formate, 1 in 250.

| Experiment | Original Rate | Maximum Dilatation Rate | Maximum Constriction Rate | Return Rate | Percentage Rate | Dilatation | Constriction |
|------------|---------------|-------------------------|---------------------------|-------------|----------------|------------|--------------|
| 16         | 77            | 96                      | 71                        | 71          | 124            | 78         |              |
| 17         | 19            | 26                      | 19                        | 19          | 136            | 100        |              |
| 18         | 19            | 25                      | 16                        | 16          | 131            | 84         |              |
| 19         | 7             | 10                      | 7                         | 7           | 142            | 100        |              |
| Average    |               |                          |                           |             | 133            | 90         |              |

### Sodium Formate, 1 in 100.

| Experiment | Original Rate | Maximum Dilatation Rate | Maximum Constriction Rate | Return Rate | Percentage Rate | Dilatation | Constriction |
|------------|---------------|-------------------------|---------------------------|-------------|----------------|------------|--------------|
| 20         | 20            | ..                      | 2                         | 10          | 100            | 90         |              |
| 21         | 71            | 75                      | 60                        | 60          | 105            | 84         |              |
| 22         | 19            | 25                      | 18                        | 18          | 132            | 94         |              |
| 23         | 16            | 21                      | 5                         | 11          | 131            | 69         |              |
| Average    |               |                          |                           |             | 117            | 84         |              |

### Sodium Formate, 1 in 50.

| Experiment | Original Rate | Maximum Dilatation Rate | Maximum Constriction Rate | Return Rate | Percentage Rate | Dilatation | Constriction |
|------------|---------------|-------------------------|---------------------------|-------------|----------------|------------|--------------|
| 24         | 60            | 180                     | 60                        | 60          | 300            | 100        |              |
| 25         | 18            | 24                      | 10                        | 18          | 133            | 55         |              |
| 26         | 11            | 19                      | 9                         | 9           | 181            | 81         |              |
| Average    |               |                          |                           |             | 204            | 78         |              |

### Sodium Formate, 1 in 25.

| Experiment | Original Rate | Maximum Dilatation Rate | Maximum Constriction Rate | Return Rate | Percentage Rate | Dilatation | Constriction |
|------------|---------------|-------------------------|---------------------------|-------------|----------------|------------|--------------|
| 27         | 60            | 166                     | 60                        | 60          | 276            | 100        |              |
| 28         | 18            | 29                      | 4                         | ..          | 161            | 78         |              |
| 29         | 9             | 11                      | 4                         | ..          | 122            | 56         |              |
| Average    |               |                          |                           |             | 186            | 78         |              |
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Sodium Formate, 1 in 10.

| Experiment | Original Rate | Maximum Dilatation Rate | Maximum Constriction Rate | Return Rate | Percentage Rate |
|------------|---------------|-------------------------|---------------------------|-------------|-----------------|
|            |               |                         |                           |             | Dilatation.     |
| 30         | 5             | 7                       |                           | 6           | 140             |
| 31         | 19            | 39                      |                           | 15          | 200             |
|            |               |                         |                           |             | Constriction.   |
|            |               |                         |                           |             | 100             |
|            |               |                         |                           |             | 63              |
|            |               |                         |                           |             |                 |
| Average    |               |                         |                           |             | 170             |
|            |               |                         |                           |             | 81              |

Potassium Formate, 1 in 1000.

| Experiment | Original Rate | Maximum Dilatation Rate | Maximum Constriction Rate | Return Rate | Percentage Rate |
|------------|---------------|-------------------------|---------------------------|-------------|-----------------|
|            |               |                         |                           |             | Dilatation.     |
| 32         | 188           | ..                      | 125                       | 136         | 100             |
| 33         | 11            | 11                      | 7                         | 10           | 110             |
| 34         | 171           | ..                      | 129                       | 156         | 100             |
| 35         | 56            | ..                      | 48                        | 56           | 100             |
| 36         | 45            | 47                      | 39                        | 42           | 104             |
| 37         | 60            | 67                      | 36                        | 55           | 112             |
| 38         | 33            | 46                      | 17                        | 26           | 139             |
| 39         | 9             | 12                      | 10                        | 9            | 133             |
|            |               |                         |                           |             |                 |
| Average    |               |                         |                           |             | 112             |
|            |               |                         |                           |             | 77              |

Potassium Formate, 1 in 500.

| Experiment | Original Rate | Maximum Dilatation Rate | Maximum Constriction Rate | Return Rate | Percentage Rate |
|------------|---------------|-------------------------|---------------------------|-------------|-----------------|
|            |               |                         |                           |             | Dilatation.     |
| 40         | 6             | 11                      | 5                         | 7           | 183             |
| 41         | 120           | 148                     | 36                        | 120         | 123             |
| 42         | 42            | 44                      | 18                        | 38           | 104             |
| 43         | 44            | 59                      | 36                        | 55           | 134             |
| 44         | 50            | 59                      | 47                        | 50           | 118             |
|            |               |                         |                           |             |                 |
| Average    |               |                         |                           |             | 132             |
|            |               |                         |                           |             | 62              |

Potassium Formate, 1 in 250.

| Experiment | Original Rate | Maximum Dilatation Rate | Maximum Constriction Rate | Return Rate | Percentage Rate |
|------------|---------------|-------------------------|---------------------------|-------------|-----------------|
|            |               |                         |                           |             | Dilatation.     |
| 45         | 8             | 8                       | 3                         | 8           | 100             |
| 46         | 30            | 34                      | 7                         | 26          | 113             |
| 47         | 55            | ..                      | 25                        | 40          | 100             |
| 48         | 50            | 57                      | 39                        | 51          | 114             |
|            |               |                         |                           |             |                 |
| Average    |               |                         |                           |             | 107             |
|            |               |                         |                           |             | 45              |

Potassium Formate, 1 in 100.

| Experiment | Original Rate | Maximum Dilatation Rate | Maximum Constriction Rate | Return Rate | Percentage Rate |
|------------|---------------|-------------------------|---------------------------|-------------|-----------------|
|            |               |                         |                           |             | Dilatation.     |
| 49         | 26            | 34                      | 2                         | 20          | 130             |
| 50         | 40            | ..                      | 21                        | ..          | 100             |
|            |               |                         |                           |             | Constriction.   |
|            |               |                         |                           |             | 17              |
|            |               |                         |                           |             | 52              |
|            |               |                         |                           |             |                 |
| Average    |               |                         |                           |             | 115             |
|            |               |                         |                           |             | 34              |
| Experiment | Original Rate | Maximum Dilatation Rate | Maximum Constriction Rate | Return Rate | Percentage Rate |
|------------|---------------|-------------------------|---------------------------|-------------|-----------------|
|            |               |                         |                           | Dilatation  | Constriction    |
| 51         | 20            | ..                      | 3                         | ..          | 100             | 15              |
| 52         | 25            | 29                      | 13                        | 19          | 115             | 52              |
| 53         | 130           | ..                      | 10                        | ..          | 100             | 8               |
| 54         | 10            | ..                      | 6                         | 8           | 100             | 60              |
| 55         | 156           | 158                     | 65                        | 68          | 100             | 41              |
| 56         | 56            | 4                       | 58                        | 7           | 100             | 7               |
| 57         | 51            | 93                      | 41                        | 52          | 183             | 81              |
| 58         | 50            | 58                      | 37                        | 46          | 116             | 74              |

Average . . 116 45

Calcium Formate, 1 in 500.

| Experiment | Original Rate | Maximum Dilatation Rate | Maximum Constriction Rate | Return Rate | Percentage Rate |
|------------|---------------|-------------------------|---------------------------|-------------|-----------------|
|            |               |                         |                           | Dilatation  | Constriction    |
| 59         | 50            | 60                      | 23                        | 49          | 120             | 46              |
| 60         | 19            | 30                      | 12                        | 15          | 160             | 78              |
| 61         | 27            | 36                      | 24                        | 27          | 133             | 88              |
| 62         | 7             | 10                      | 5                         | 7           | 142             | 71              |

Average . . 139 71

Calcium Formate, 1 in 250.

| Experiment | Original Rate | Maximum Dilatation Rate | Maximum Constriction Rate | Return Rate | Percentage Rate |
|------------|---------------|-------------------------|---------------------------|-------------|-----------------|
|            |               |                         |                           | Dilatation  | Constriction    |
| 63         | 15            | 20                      | ..                        | 15          | 133             | 100             |
| 64         | 8             | 8                       | 3                         | ..          | 100             | 37              |
| 65         | 15            | 19                      | 11                        | 7           | 126             | 57              |

Average . . 120 64

Calcium Formate, 1 in 10.

| Experiment | Original Rate | Maximum Dilatation Rate | Maximum Constriction Rate | Return Rate | Percentage Rate |
|------------|---------------|-------------------------|---------------------------|-------------|-----------------|
|            |               |                         |                           | Dilatation  | Constriction    |
| 66         | 7             | 10                      | 5                         | ..          | 142             | 71              |

These tables show (i) that the sodium salt caused the greatest individual amount of dilatation, that the average amount of dilatation is greater than in the case of the other salts, and that sodium formate has the least constrictor effect.
(2) The potassium salt caused the greatest individual amount of constriction, the greatest average amount of constriction, and the least individual and least average amount of dilatation.

(3) The calcium salt had effects on the vessels intermediate between those of sodium and potassium.

(4) As regards strength of solution it is seen that in the case of soda and calcium the amount of dilatation increases in proportion to increasing strength of solution, and that the amount of constriction diminishes with increasing concentration.

In the case of potassium the amount of dilatation remains constant for all the concentrations used, while constriction increases with increased strength of solution.

3. Observations on the Heart.—(A) Perfusion Experiments.—Frogs' hearts were used. The perfusions were carried out by means of Schafer's heart plethysmograph. In some of the cases instead of using the piston recorder of Schafer's instrument we attached the very delicate and simple volume recorder recently introduced by Dixon (7).

Sodium Formate.—Seven observations were made with 1 in 1000 solution.

In two cases results were negative.

In three instances the heart was slowed and then stopped in diastole.

In two the heart became irregular and was stopped in diastole. In the latter five cases the force of contraction was greatly diminished.

Sodium formate 1 in 100 either perfused through the heart or merely painted on it, rapidly decreased the force of contraction, and in four out of five cases stopped the heart in diastole.

Sodium formate 1 in 100 caused great irregularity, with frequently an increased rate and speedy stoppage in diastole.

Potassium formate 1 in 1000, 1 in 500, and 1 in 100 caused irregularity, diminished force, and stopped the heart in systole.

Potassium formate 1 in 10 immediately stopped the heart.

Calcium formate 1 in 1000 augmented the force of the heart, sometimes caused irregularity, and soon stopped it in systole.

Solutions of 1 in 500, 1 in 100, and 1 in 10, slowed and stopped the heart in systole.

Formic acid 1 in 2000 diminished the force of contraction, and stopped it in systole.
Hearts perfused with formic acid showed a remarkable increase in translucency, in some cases becoming glassy-like and almost transparent.

Some points of interest emerged in the inter-relationship of the action of these salts. Thus a heart stopped in diastole by sodium formate could sometimes be made to beat again by perfusing calcium formate, but only for so long as the calcium formate was perfused.

A heart brought to a standstill by dilute calcium formate could be made to beat again for a brief period by perfusing strong sodium formate through it.

(B) Heart Movements.—These observations were also made on frogs’ hearts. After the frog was pithed a hook was passed through the tip of the ventricle and attached by a pin to an aluminium lever writing against a smoked drum. The salts were applied to the heart by dropping the solutions from a glass pipette. Fifteen such experiments were carried out, the results were confirmatory of the foregoing. Thus, solutions of potassium and sodium formate caused arrhythmia, followed in succession by diminished rate, diminished force with increased rate, diminished force with lessened
rate, and speedy stoppage with strong solutions. The potassium salt acted more powerfully than the sodium. Calcium formate 1 in 100 produced slight slowing of the heart only. Solutions 1 in 10 not only slowed the heart but lessened its force of contraction.

The application of calcium formate in several instances caused a return of contraction in hearts stopped by the application of the potassium or sodium salts. The two series of observations indicate that all three salts are toxic to the heart. In the case of potassium formate the toxic action is practically exclusive. In the case of sodium formate a certain stimulating effect, probably in virtue of irritation, can also be noted. The effect of calcium formate is mainly that of calcium, the toxic effects being secondary.

4. Observations on Muscle Curves and Fatigue.—The gastrocnemius of the frog was used. The muscle of one limb was made to record the simple contraction induced by an induction shock of optimum strength, and was then either injected or painted with a formate. The corresponding muscle of the other limb was treated similarly with Ringer's solution. The same apparatus was used for the two limbs, the order of making the contrasted observations being alternated in successive experiments. In every case the muscle was loaded with 30 grammes.

Fig. 3.—Left figure shows gastrocnemius contraction before and after injection of sodium formate (1 in 100) 3 m. into the muscle. Right figure shows the contraction of the opposite gastrocnemius before and after injection of 3 m. of Ringer's solution. The second curve is the smaller in each case.
It may be mentioned here that in no case did the Ringer's solution materially alter the height of the curve or the length of the latent period. Only the fatigue effects therefore need be stated.

Sodium formate \( \frac{1}{1000} \). Muscle injected with 5 m. Curves before and after were the same height. Completely fatigued after 600 shocks. Ringer preparation fatigued but still active.

\( \frac{1}{100} \). Muscle injected with 5 m. Curve lowered \( \frac{1}{2} \) mm. Completely fatigued after 450 shocks. Ringer preparation showed only lengthening of latent period.

\( \frac{1}{10} \), 5 m. Curve lowered 6 mm. Latent period greatly increased. Fatigued after 200 shocks.

Saturated, 5 m. Curve lowered 8 mm. Latent period increased. Fatigued after 150 shocks. Ringer muscle not affected.

**Potassium Formate.**—

\( \frac{1}{50} \). Curve lowered 2.5 mm.—fatigued after 400 shocks. Ringer preparation—fatigued after 800 shocks.

\( \frac{1}{25} \). Curve lowered 3.5 mm.—fatigued after 250 shocks. Ringer muscle—fatigued after 600 shocks.

\( \frac{1}{10} \). Curve lowered 5.5 mm.—fatigued after 100 shocks. Ringer muscle—fatigued after 600 shocks.

**Saturated.**—No response after injection.

**Calcium Formate.**—The height of the curves was somewhat diminished, but a great prolongation of contraction period became evident, due to calcium effect.

**Formic Acid.**—\( \frac{1}{100} \) painted on the muscle lowered height of curve by \( \frac{1}{2} \) mm. Fatigue occurred after 200 shocks.

Ringer muscle—fatigued after 600 shocks.

These experiments indicate that the effects on skeletal muscle are similar to those on cardiac muscle—namely, that all three are toxic in the order, potassium, sodium, calcium, but that in the case of the latter the toxic effect is subsidiary to the action of the metallic radicle.

**III. Observations on the Human Subject**

Although we now felt convinced that the administration of formates might be harmful, we made some observations upon ourselves, upon a lady student, and a laboratory boy. Conditions as regards work and exercise were practically constant during the experiments. Three of the subjects were habitual abstainers from alcohol and tobacco: the fourth acquired these virtues for a month previous to the experiments, and during their course. Only sodium
formate was used. The dosage was one gramme given thrice the first day, two grammes thrice on the two succeeding days, and once on the morning of the fourth day—a total of 17 grammes.

1. Subjective Sensations.—These were absent, except in the case of the student, who either misunderstood, or disregarded instructions and took the salt in an unduly concentrated form, and, in consequence, experienced an increased sense of thirst. No increase of appetite was noticed.

2. Observations on Blood Pressure.—These were made for a few days before, during, and after the course of sodium formate, by means of the Riva-Rocci instrument, the reading being taken when the pulse became imperceptible at the wrist. The variations gave no indication of action on the part of the salt:

|       | Day before formate taken | Fourth day |
|-------|--------------------------|------------|
| F. W. | 100                      | 114        |
| J. G. S. | 100                  | 90         |
| I. M. | 110                      | 98         |
| A. G. | 110                      | 114        |

3. Ergographic Records.—Mosso’s instrument was used. A weight of 4.5 kilos. was raised over a pulley by flexion of the terminal
phalanx of the right middle finger every two seconds until complete fatigue occurred.

The time was marked by a metronome beating seconds. Three of the subjects of experiment naturally sustained the weight until the intermediate second struck, the fourth relaxed the muscle immediately after the pull. We thought it well not to attempt to alter this arrangement, and have made no attempt to place the records on an equal basis, as each only applies to the individual in question. It is particularly difficult to get satisfactory ergographic records for purposes of comparison. Training undoubtedly, and suggestion in all probability, play an important part. In order to eliminate the effect of training, two of the subjects practised with the ergograph daily until no further improvement occurred. The effects were remarkable. Unfortunately the early records in one case were not kept, but in the other there was an increase to eight times the original capacity for work in three weeks.

In the other two cases a single record was taken immediately before the formate course was begun, and a second record was taken four days later, when stiffness and pain on flexing the arm had disappeared. This method is probably not satisfactory, and it is interesting to note that after the formate course the untrained individuals showed improvement, the trained individuals showed diminution of work capacity.

Results:

|                  | Before | After 2nd day | After 4th day | After 5th day | After 6th day |
|------------------|--------|---------------|---------------|---------------|--------------|
| F. W. (trained)  | 2.28   | 2.0           | 1.78          | 1.19          | 1.79         |
| I. M. (trained)  | 12.68  |               | 10.19         |               |              |
| A. G.            | 4.02   |               | 4.41          |               |              |
| J. G. S. (contractions not sustained) | 10.23 | 21.92         |               |               |              |

Dynamometer Records.—The observations were made with the right arm held at right angles to the body.

|      | Before Formate | After |
|------|----------------|-------|
| F. W. | .              | 30    |
| J. G. S. | .            | 34    |
| I. M. | .              | 30    |
| A. G. | .              | 57    |
These results all tend to show that in healthy human subjects sodium formate, in the doses given, has no appreciable effect.

**Summary**

Formic acid, formate of potassium, sodium and calcium in minimal active doses exert a toxic action on the circulatory and muscular systems. This action is enormously added to by the effect of the metallic ion in the case of the potash salt, and may be obscured by the metallic ion in the case of the calcium salt.

With the exception of calcium formate in strong solution, they all lower blood pressure. They all have a transient vaso-dilator, followed by a vaso-constrictor, action.

They are all toxic to the heart and to skeletal muscle in the order potassium, sodium, calcium, and accelerate rather than retard fatigue.

In the dosage stated, sodium formate has no demonstrable effect on the circulatory or muscular systems, or other noticeable effect on the healthy human subject.

Have the formates a place in therapeutics?

In so far as our experiments afford an answer to this question (assuming that the formates are absorbed) we should say (1) that the medicinal use of potassium formate would be unjustifiable; (2) that the effect of sodium formate might seriously impair the strength of a patient already debilitated; (3) that in calcium formate we have a lime salt, freely soluble, and not too unpalatable, which has an action in coagulating the blood both in virtue of its metallic and basic ion.

We venture to suggest that in cases of remote or intractable hæmorrhage it is worthy of a trial.

**References**

1. Clément. *Lyon Medical*. Aug. 3, 1903; Feb. 19, 1905. *C. R. Soc. de Biol.* March 21, 1904.
2. Garrigue. "Maladies microbiennes, guérison de la tuberculose et du Cancer." 3rd edition. Baillière, Paris. 1903. *C. R. Soc. de Biol.*, 58. 1905. P. 996.
3. Huchard. *Bulletin de l’Acad. de Méd.*, 53. 1905. P. 251.
4. Fleig. *Archiv. Générales de Méd.* 1905. Pp. 2753 and 2817. Also *C. R. Soc. de Biol.* Mar. 1, 1907. P. 298.
5. Croom. *Edin. Med. Journ.* Oct. 1906.
6. Ker and Croom. *Ibid.* June 1907.
7. Dixon. *Journ. of Physiology*, 35. March 1907.