54. *The Action of Japan Camphor upon the Heart.*

(*Report III.*)

The Fate of Camphor in the Body and its Intermediate Product Acting as a Cardiac Stimulant.

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In our previous reports it has been suggested that Japan camphor as such is to be regarded as a paralysing but not a stimulating agent upon the intact heart; and that the heart seems to be stimulated rather by some of its intermediate products in the body. These suggestions are based on the following facts. Japan camphor in small doses, even when injected intravenously into rabbits, exercises its stimulant action upon the heart only after a latent period, just as when hypodermically given, while its depressant effect is elicited directly after the injection. Camphor, introduced into the perfusion fluid of the isolated rabbit's heart, paralyses the organ immediately after the injection, although rarely its stimulant effect is seen after a while. Moreover, the isolated frog's heart (Straub's method) is wont to be depressed by the introduction of camphor in various concentrations; only in a low concentration the heart beat becomes stronger after an initial passing depression and a rather prolonged latent period; and when this nutrient solution containing camphor, which has been in contact with the heart for a while, is applied to another isolated frog's heart, its beat is sometimes augmented directly after the administration. Probably these facts indicate that camphor can stimulate the heart only after remaining in contact with the tissues for some time.

The substance to which the action of camphor as a cardiac stimulant is to be attributed has not been found among the intermediate products formed or supposed to be formed in the body before being finally excreted as glycuronic acid derivatives. First, campherol, consisting of p- and o-oxycamphors (Asahina and Ishidate), or one of its components (p-oxycamphor) shows the stimulant action only after a latent period, while its depressant action is observed directly after the administration; the fact probably indicating that these oxidation products too do not

stimulate the heart unless after they have remained in contact with the tissues. Secondly, p- and o-oxycamphor glycosides, the probable combinations in the body before being oxidized into the glycuronic acid derivatives, like the final products (p- and o-oxycamphor glycuronic acids), no longer stimulate the heart.

Further tracing possible oxidation products of camphor in the body, the following two substances were prepared and their actions upon the heart examined.

(1) o-OXOCAMPHOR (o-DIKETOCAMPHANE). The fact that campherol contains a minute quantity of o-oxycamphor besides p-oxycamphor (Ishidate) leads us to suppose that o-oxycamphor, being easily oxidized *in vitro*, may partly be oxidized into o-oxocamphor *in vivo*. Thus the cardiac action of o-oxocamphor, prepared by oxidation of o-oxycamphor isolated from campherol, was studied and found to exert some depressant effect alone without stimulating the heart of frog or rabbit, just as in the case of o-oxycamphor.

(2) p-OXOCAMPHOR (p-DIKETOCAMPHANE). p-oxocamphor prepared after Brecht from borneol *in vitro* does not stimulate the intact heart, as has already been reported by Leo. But we thought it worth trying to test how does act p-oxocamphor which may be formed *in vivo* by the oxidation of p-oxycamphor.

In oxidizing the p-oxycamphor isolated from campherol two substances were obtained according to the severeness in the procedure of oxidations; i.e. by using strong oxidizing agents a substance was obtained; identical to Brecht's p-oxocamphor in every respect ($F=209-210^{\circ}\text{C}$; $[\alpha]_D^{20}=+103^{\circ}.6$), while by the mild oxidation the substance obtained was quite different not only in its chemical characters ($F=200-201^{\circ}\text{C}$; $[\alpha]_D^{20}=+81^{\circ}.6$) but also in its cardiotonic action.

These two substances, however, are undoubtedly optical isomers having the same chemical constitution, as the disemicarbazone of the same melting point ($F=295^{\circ}\text{C}$) can be produced from both substances.

The perfusion experiments with isolated frog's hearts. When our p-oxocamphor was injected into the perfusion fluid in such doses as 0.05 c.c. of 1% or 0.2 c.c. of 0.5% solution, without exception, the auricular and ventricular movements became distinctly stronger immediately after the administration.

The perfusion experiments with isolated rabbits' hearts. When our p-oxocamphor was introduced into the perfusion fluid in small doses (from 0.5 c.c. of 0.1% to 0.1 c.c. of 1% solutions), the heart beat

without delay became markedly stronger and the effect continued for a while.

The intravenous injection into frogs. Our p-oxocamphor injected intravenously in small doses (0.1 c.c. of 0.02% solution) produced its stimulant action upon the heart directly after the administration.

The intravenous injection into rabbits. Our p-oxocamphor injected intravenously in small doses (0.1 c.c. of 1% solution) exercised constantly its stimulant action upon the heart directly after the injection and the heart continued to beat very strongly for one hour or more.

*The relation between dose and rate of action of camphor,
p-oxycamphor and p-oxocamphor as
cardiac stimulants.*

When our p-oxocamphor was given to the frog's heart, isolated and prepared after Straub, even in a concentration as low as 1:40,000, the heart beat became stronger directly after the administration, while by p-oxycamphor in a concentration of 1:20,000 or camphor in 1:4,000, the stimulant effect appeared only after a while, preceded first by a slight depressant effect.

(It may be worthy to mention that the action as a respiratory stimulant is manifested much more prominently by p-oxocamphor than either by camphor or by p-oxycamphor).

These facts lead us to the following conclusions:

1) It is not camphor as such but at least one of its oxidation products, e.g. p-oxocamphor, that exerts the stimulant action upon the heart.

2) Camphor and its oxidation products in the body so far examined have only depressant action upon the heart except p-oxocamphor.

3) Camphor, when absorbed in the body, is excreted through the kidney as glycuronic acid derivatives (p- and o-oxycamphor glycuronic acids), except a minute quantity excreted unchanged through the lung. And on the way of oxidation p- and o-oxycamphors are produced and the former seems partly to be further oxidized in the tissues into p-oxocamphor, a genuine cardio-tonic substance.

The fate of camphor in the body and the cardiac action of camphor as well as its intermediate products are shown in the diagram below.

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