Pharmacology. — *The effect of medicines on auricular fibrillation.* I. *Experimental researches on the influence of hydroquinine, hydroquinidine, quinine and hydroquinidine-free quinidine on auricular fibrillation of cats*[1]). By S. DE BOER and H. H. J. HOLTKAMP. (Communicated by Prof. C. U. ARIËNS KAPPERS.)

(Communicated at the meeting of January 25, 1936).

In 1914 WENCKEBACH published two cases of auricular fibrillation in man which were cured by means of quinine. Later, however, he had little success with this method. In 1918 FREY found quinidine to be more active. From that time onward quinidine is commonly used in special cases of auricular fibrillation.

We examined the effect of 27 different compounds of the cinchona alkaloids on auricular fibrillation of the heart of cats. These substances were prepared for us in the research department of the "Amsterdamsche Chininefabriek".

The experiments were carried out as follows : The cat was narcotized with ether, artificial respiration was applied, the thorax and the pericardium opened. Then the ventricular frequency was determined and the minimum faradic stimulation which produced after-fibrillation for the auricles. Subsequently 1—5 mgr. of the preparation was injected into the vena jugularis externa and we observed whether during faradic stimulation of the same strength still auricular fibrillation set in and also whether after-fibrillation manifested itself. If no fibrillation arose, the stimulus was increased and it was observed at which strength of the stimulus it still occurred. Then every 5 minutes 5 mgr. of the substance per kilogramme of the cat was injected intravenously and each time the frequency of the ventricular beats was observed and stated whether, and if so at which *coil-distance*, still fibrillation and after-fibrillation respectively arose.

In our experiments we obtained the best results with hydroquinine, while hydroquinidine also produced a very good effect. A far less favourable result was obtained with common commercial quinine which now only contains traces of hydroquinine and the hydroquinidine-free quinidine.

Common commercial quinidine, which contains about 20 % of hydroquinidine, ranges in its effect on experimental auricular fibrillation between hydroquinidine and hydro-free quinidine. Of all substances the hydrochloric salts were used in 1 % solution.

The following tables may illustrate this.

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[1]) These experiments were made between June 1935 and February 1936 in the Pharmacological Laboratory of the University of Groningen.

HYDROCHLORIDUM HYDROQUININAE.
Weight of the cat 3500 Gr.

Mgr. per kg. cat intravenously	Ventricular frequency	Coil distance	Fibrillation during stimulation	After-fibrillation
0	200	120	+	constantly
5	144	0	0	0
10	140	0	0	0
15	136	0	0	0
20	136	0	0	0
25	120	0	0	0
30	112	0	0	0
35	104	0	0	0
40	112	0	0	0
45	104	0	0	0
50	100	0	0	0
55	96	0	0	0
60	92	0	0	0
65	76	0	0	0
70	72	0	0	0
75	68	0	0	0
80	68	0	0	0
85	64	0	0	0
90	†			

The first 5 mgr. were injected during constant after-fibrillation, with the result that 30 seconds after the injection the auricular fibrillation gave way to the normal rhythmic activity. This same phenomenon was also observed in four other cases. We even were able in several cases to make constant after-fibrillation disappear several times by means of 1 mgr. of hydroquinine, injected intravenously.

HYDROCHLORIDUM HYDROQUINIDINAE.
Weight of the cat 3100 Gr.

Mgr. per kg. cat intravenously	Ventricular frequency	Coil distance	Fibrillation during stimulation	After-fibrillation
0	152	155	+	5 sec.
5	140	155	+	0.5 „
10	140	140	+	0
15	140	0	0	0
20	60	0	0	0
25	24	0	0	0
30	†			

In this experiment the 2—1 ventricular rhythm set in after injection of 20 mgr. of hydroquinidine, the 4—1 ventricular rhythm after injection of 25 mgr.

HYDROCHLORIDUM QUININAE.
Weight of the cat 3300 Gr.

Mgr. per kg. cat intravenously	Ventricular frequency	Coil distance	Fibrillation during stimulation	After-fibrillation
0	200	155	+	5 sec.
5	140	155	+	1 „
10	152	155	+	0
15	128	110	+	0
20	84	0	0	0
25	44	0	0	0
30	†			

HYDROQUINIDINE-FREE QUINIDINE
Weight of the cat 3100 Gr.

Mgr. per kg. cat intravenously	Ventricular frequency	Coil distance	Fibrillation during stimulation	After-fibrillation
0	128	155	+	1/2 sec.
5	160	155	+	1 min.
10	140	140	+	2 sec.
15	120	0	+	0
20	120	0	0	0
25	†			

HYDROCHLORIDUM QUINIDINAE (common commercial).
Weight of the cat 2500 Gr.

Mgr. per kg. cat intravenously	Ventricular frequency	Coil distance	Fibrillation during stimulation	After-fibrillation
0	200	155	+	3—5 sec.
5	132	140	+	1—2 sec.
10	112	90	+	constantly
15	140	0	0	0
20	60	0	0	0
25	†			

It should be remarked here that the quinine prepared according to the Pharmacopeia Neerlandica V only contains traces of hydroquinine and that formerly far more by-products were present. The quinine prepared according to the Pharmacopeia Neerlandica II, for example, contained 3 % of hydroquinine and 5 % of cinchonidine.

Completely hydroquinine-free quinine will yet be prepared, so that we shall be able to experiment with it later.

The question now presents itself why the hydro-compounds produce a better effect than the hydro-free compounds. This phenomenon may perhaps be wholly or partly explained by the fact that the hydro-compounds are far stronger, more stable compounds than the hydro-free ones. The latter may already be partly decomposed in the body before they could have any effect. In experimental malaria hydro-compounds also have a stronger effect than hydro-free compounds. In all probability this factor plays a part here also.

In our experiments, at any rate, we could in case of bird's malaria obtain a far stronger reaction with hydroquinine than with quinine. We even were able to sterilize infected canaries completely by means of hydroquinine, so that a new infection was once more effective.

Consequently we have obtained in hydroquinidine and hydroquinine two substances which, at any rate on auricular fibrillation of cats, produce a much better effect than quinidine and quinine.

We therefore determined the toxicity of these two substances with regard to quinine and quinidine. In the first place we experimented on mice and determined how much of the substance to be investigated was maximally tolerated after subcutaneous injection. The results are the following :

Hydrochloridum quininae.	200 mgr. per kg. mouse subcutaneously. 4 mice ..... 1 dead.
Hydrochloridum quininae.	300 mgr. per kg. mouse subcutaneously. 4 mice ..... no dead.
Hydrochloridum quininae.	400 mgr. per kg. mouse subcutaneously. 4 mice ..... 3 dead.
Hydrochloridum quinidinae.	300 mgr. per kg. mouse subcutaneously. 4 mice ..... 1 dead.
Hydrochloridum hydroquinidinae.	200 mgr. per kg. mouse subcutaneously. 4 mice ..... no dead.
Hydrochloridum hydroquinidinae.	300 mgr. per kg. mouse subcutaneously. 4 mice ..... 4 dead.
Hydrochloridum hydroquininae.	200 mgr. per kg. mouse subcutaneously. 8 mice ..... 1 dead.
Hydrochloridum hydroquininae.	300 mgr. per kg. mouse subcutaneously. 11 mice ..... 3 dead.

After that experiments were made on canaries. Here it appeared that of

the hydroquinidine, administered per os, 2½ mgr. per 20 gr. of the bird was just tolerated.

Of hydroquinine and quinine, administered per os, 5 mgr. per 20 gr. of the bird was just tolerated.

In these observations also it appeared that hydroquinidine is much more toxic than hydroquinine or quinine. These results also show that hydroquinine seems more suitable to repress auricular fibrillation than hydroquinidine.

Conclusions.

WENCKEBACH had no great success with quinine in the treatment of auricular fibrillation. In his book of 1914 he mentioned only two cured cases, though he used it several times. It lasted till 1918, when FREY found that quinidine had a far better effect. Now it is obvious that the results of FREY and WENCKEBACH are largely due to the by-products and less to the substances themselves. Common commercial quinidine namely, contains about 20 % of hydroquinidine, while the hydroquinidine-free quinidine shows a far weaker reaction than the hydroquinidine. The effect of the quinidine, therefore, would for the greater part be caused by the presence of hydroquinidine. But also the poor results obtained with quinine by WENCKEBACH before 1914 can, in our opinion, be better understood in the light of our researches. Nowadays only traces of hydroquinine are present in quinine, but in the quinine prepared in former days far more byproducts occurred. Thus the quinine prepared according to the Pharmacopeia Neerlandica V only contains traces of hydroquinine, whereas in quinine prepared according to the Pharmacopeia Neerlandica II and corresponding pharmacopeiae 3 % of hydroquinine and 5 % of cinchonidine is present. Now hydroquinine produces a very good effect on experimental auricular fibrillation and in two experiments made with cinchonidine we likewise obtained a very good anti-fibrillation reaction. It is likely, therefore, that the presence of the by-products hydroquinine and cinchonidine in the quinine have contributed to WENCKEBACH's — though small — success. According to this explanation FREY would, therefore, have obtained a good success with his quinidine because so much hydroquinidine (20 %) was present in it. The less great success of WENCKEBACH should then be attributed to the fact that in the quinine also active by-products were present, but in a far smaller percentage (8 %).

In the light of these researches we also understand why WENCKEBACH sometimes saw effect and at other times he did not. The preparations, namely, may have varied as to their content of by-products.

It may also be better understood now why often such large doses of quinidine are required to stop auricular fibrillation. Indeed only $^1/_5$ of this substance produces a good effect, $^4/_5$ has a far weaker effect.

On account of the researches described above it is obvious that in future

quinidine probably will have to give way to hydroquinine or hydroquinidine in the treatment of auricular fibrillation and perhaps also of corresponding affections, such as flutter, paroxysmal tachycardia, extrasystole.

At our request it will already now be used in the clinic in case of auricular fibrillation.

Embryology. — *Gebiss- und Zahnentwicklung bei der Irisforelle (Salmo irideus).* III. *Oberkiefer.* Von B. VAN DER EYKEN. (Communicated by Prof. M. W. WOERDEMAN.)

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Auf die Zähne des Zwischenkiefers folgen, mit einem kleinen Zwischenraum, die Elemente des Oberkiefers, mit welchen wir uns in dieser dritten Mitteilung beschäftigen werden.

Das Embryo *E* [1]) besitzt beiderseits eine einzige Oberkieferzahnanlage, welche sich noch im Papillenstadium befindet und kein Dentin zeigt.

Im nächst älteren Stadium *F* sind links zwei Elemente vorhanden, von denen das mesiale schon ein Scherbchen Dentin besitzt und das distale eine kleine, auf zwei Schnitten sichtbare, Papille darstellt. Rechts im Oberkiefer fehlt die distale Anlage und ist nur das mesiale dentinhaltige, Zähnchen angelegt.

In der Larve *H* ist die Oberkiefergebissanlage links und rechts ebenfalls ungleich schnell verlaufen, weil wir auf dem linken Maxillare drei Elemente antreffen, während rechts schon vier vorhanden sind.

Links enthält der meist mesiale Zahn schon einen derben Dentinmantel, der mittlere ist auch schon gut entwickelt und es wäre zu erwarten, dass seine Odontoblasten bald mit der Dentinbildung angefangen hätten. Das distale Zähnchen ist nur eine winzig kleine Papille, welche sich gerade erst angelegt haben muss.

Rechts werden die Elemente von mesial nach distal auch allmählich jünger, das älteste besitzt ein wenig Dentin, das distal folgende Zähnchen ist eine gut entwickelte Papille, während die meist distal gelegenen zwei Anlagen von sehr kleinen Papillen dargestellt werden. Die drei Elemente links liegen in einer geraden Linie und folgen einander mit genau gleich grossen Zwischenräumen auf; sie gehören also ohne Zweifel einem Odontostichos an.

Ferner ist rechts keine Spur von Alternation zu bemerken, nur sind hier die Zwischenräume ungleich gross, sei es durch eine wirkliche Unregelmässigkeit in der Gebissanlage dieses Teiles, sei es weil eine mangelhafte Technik bei diesem sehr schief geschnittenen Präparate abweichende Verhältnisse vortäuscht. Dass die Elemente des rechten Oberkieferteiles ebenfalls einem Stichos angehören, darüber besteht kein Zweifel.

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[1]) Nähere Angaben betreffs Grösse und Alter der Larven, und Weise der Untersuchung, wird man in den Proc. Royal Acad. Amsterdam, **38**, N°. 8 und 10 (1935) finden.