lytic activity on EA as substrate, the loss exceeds 95%; part of this is accountable as loss of $C'_{a,b}$ (60-90%), as detected with $EAC'_{1,4,2}$ as substrate. Currently, efforts are being made to reduce this loss by modification of the dialysis procedure.

Summary. Fractionation of guinea pig complement by chromatography on diethylaminoethyl cellulose has been explored. C'_2 and C'_4, as well as the components provisionally designated as C'_a and C'_b which convert $EAC'_{1,4,2}$ to E*, can be separated from one another in a single pass, and the fractions so obtained possess good stability.

The authors are indebted to Mr. Louis G. Hoffmann for performing the assays for fourth component of complement and to Dr. Julie Hartmann and Mr. Charles Cook for analytical assistance.

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Received January 26, 1959. P.S.E.B.M., 1959, v100.

Drug-Induced Pulsus Alternans in Dogs.* (24759)

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Pulsus alternans has been recognized as a symptom of considerable clinical importance since it was first described by Traube(1), but the fundamental mechanisms underlying it are not yet clearly understood(2,3,4). Obscurity of mechanism has resulted from want of a reliable method for its experimental induction in laboratory animals. Poumailloux (5) emphasized that most authors before 1930 were satisfied with clinical description neither dependent on nor indicative of any causal relationship. With few exceptions later studies have been limited to observations on occasional patients in whom the condition was discovered at examination. The present paper presents a simple pharmacological method for inducing pulsus alternans in dogs.

Methods. Twenty-five mongrel dogs in apparent good health were used. Electrocardiograms were recorded from limb electrodes through Sanborn preamplifier on either Sanborn Polyviso recorder or on Heiland recording galvanometer. With direct cannulation of vascular structures and appropriate Statham transducers, pressure changes were converted into electrical changes for recording. Femoral arterial pressure was used to represent systemic arterial pressure to avoid interfering with carotid sinus mechanisms. Cannulation of the ventricles was accomplished by direct puncture with 16 gauge needle. Flexible connecting tubing of polyethylene permitted measurement for protracted periods without shifting of needle. Positive pressure artificial respiration was provided when spontaneous respiration was inadequate and in open chest

* Presented in part at meeting of Fed. Soc., Atlantic City, April, 1959.

preparations. Injections of drugs were made into femoral vein *via* an inlying catheter. All animals were anesthetized with pentobarbital sodium (*ca.* 30 mg kg i.p.). The following sympathomimetic amines were used to initiate mechanical alternation of pulse: epinephrine, neosynephrine, ephedrine, methamphetamine and methoxamine. As a matter of convenience methoxamine† was used in most experiments.

Results. The sympathomimetic amines listed above induced mechanical alternation in one or more pentobarbitalized dog; some have consistently resulted in the phenomenon. Predictability of response varied considerably among these drugs. Some compounds had more effect on heart rhythm, making analysis of the alternation difficult. Both "true" pulsus alternans in which interval between weaker and stronger beats is equal, and pseudoalternans in which the interval is unequal because of prematurity of ventricular contraction have been encountered. Neosynephrine, ephedrine, methamphetamine and occasionally methoxamine resulted in bigeminal rhythm, *i.e.*, pseudoalternans. Methoxamine usually did not cause PVC and alternation in pulse pressure was typical of "true" pulsus alternans. Sometimes effects were mixed, and bigeminal rhythm replaced alternation in which no ECG evidences of premature contractions were seen. A 2 μg kg dose of epinephrine, for example, caused a brief period of pulsus alternans which began 16 seconds after injection, but persisted for only 5 seconds (7 heart beats). It coincided with onset of moderate acceleration of sinus origin and with increased systolic and diastolic pressures. About 15 seconds later, a series of PVC alternated with sinus beats. Each PVC caused pulse pressure of smaller amplitude than the preceding beat of sinus origin. The beat which followed each PVC was stronger than those before the bigeminy.

Characteristics of methoxamine-induced alternation. Mechanical alternation resulted from 43 of 55 doses of methoxamine (0.4 mg/kg i.v.). Differences between systolic pressure in weaker and stronger members of paired beats varied from a few mm Hg to the entire pulse pressure when a pulse deficit occurred. The difference is increased by injecting a small additional dose of pentobarbital 1 or 2 minutes before the methoxamine. Onset of alternation usually occurred during first 2 minutes and persisted about 5 minutes, although both longer and briefer intervals were encountered. Three distinct patterns were found, 2 of which were "true" pulsus alternans, the third, pseudoalternans. Fig. 1 illustrates the most common type (26 of the 43 instances) in which onset of alternation was gradual, becoming progressively more marked until frequently a 50% pulse deficit resulted.

† 'Vasoxyl' brand methoxamine hydrochloride, Burroughs Wellcome and Co. (U.S.A.)

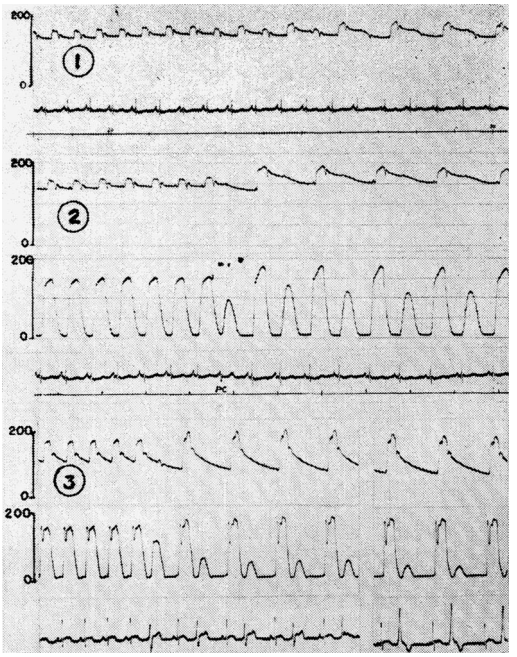

FIG. 1. Pulsus alternans induced by 0.4 mg/kg methoxamine in a pentobarbitalized dog. Upper tracing = femoral arterial pressure in mm Hg. Lower tracing = Lead II ECG. Time = sec. with each 10 sec. interval indicated. Record begins 18 sec. after inj.

FIG. 2. Pulsus alternans induced by 0.4 mg/kg methoxamine in a pentobarbitalized dog. Notice sudden onset following single premature ventricular contraction at PC. Upper tracing = femoral arterial pressure in mm Hg. Center tracing = left ventricular pressure in mm Hg. Lower tracing = Lead II ECG. Time = sec. Record begins 16 sec. after inj.

FIG. 3. Bigeminal rhythm induced by 0.4 mg/kg methoxamine in a pentobarbitalized dog. Traces to be identified as in Fig. 2. First part of record begins 7 sec. and second part, 25 sec. after inj.

ECG showed no indication of drug activity other than slight slowing of sinus rhythm and periodic waxing and waning of amplitude of R associated with respiration. Sometimes a moderate increase in T amplitude in the weaker beats alternated with reduction of T in the stronger ones. Recovery involved gradual strengthening of weaker and weakening of stronger pulsations.

In a second type (Fig. 2), alternans appeared suddenly, apparently the consequence of a single PVC. Except for the PVC the weaker and stronger beats followed one another after identical time intervals. Femoral arterial pulse rate was halved, but left ventricular pressure showed that the ventricle did contract in response to each impulse from the sinus pacemaker On alternate beats intraventricular pressure failed to reach arterial diastolic pressure during the isometric phase and resulted in arterial pulse deficit. Onset of alternans was associated with PVCs in 8 experiments. In one instance alternation followed a premature auricular contraction.

A third type of alternation occurred in 8 of 43 instances, and was associated with not just a single PVC but with coupled premature beats characteristic of bigeminal rhythm in which a secondary ventricular pacemaker alternated with the sinus pacemaker. Fig. 3 shows the definite prematurity of the weaker beats both in ECG and ventricular pressure tracings. The secondary pacemaker shifted considerably before becoming localized at the focus characteristic of the bigeminal rhythm.

Twelve of the 55 doses of methoxamine did not result in alternation of the pulse. Only 4 of these were initial doses.

Discussion. Pulsus alternans has long been recognized as due to alternation in strength of ventricular contractions(6). When, in the weaker beats, intraventricular pressure fails to reach arterial diastolic pressure, aortic or pulmonary valves do not open, ejection is not achieved and arterial pulse deficit occurs. This emphasizes the necessity for recording more than one parameter when assessing drug-induced cardiovascular changes. In the experiments illustrated, the profound slowing of arterial pulse would not have been recognized from the ECG which showed only a very modest bradycardia.

Ventricular pressure tracings indicate cardiac origin of alternans. The weaker beats are not followed by normal beats, but by beats that are stronger than normal(4,5).

Other pharmacological substances have been reported to produce pulsus alternans. Among these are glyoxylic acid(7,8), fluoroacetate(9) and chloroform(10). All chemical substances reported to result in systolic alternation are not listed here, but data are given to indicate that in pentobarbitalized dogs moderate doses of methoxamine hydrochloride will usually induce some degree of pulsus alternans. Unlike glyoxylic acid and chloroform which are hypotensive, methoxamine is hypertensive. Alternation is usually related to the period immediately after peak of pressor response has been reached.

Tachyphylaxis is indicated by frequent failure of repeated doses to cause alternation.

Summary. Single i.v. injections of methoxamine hydrochloride into pentobarbitalized dogs usually resulted in a transient period of ventricular alternans often appearing as 50% pulse deficit. Although pseudoalternans associated with PVC and coupling was seen, the majority of experiments exhibited "true" pulsus alternans in which a regular sinus rhythm was present.

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Received January 26, 1959. P.S.E.B.M., 1959, v100.