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THE EFFECT OF PERSANTIN ON CORONARY FLOW AND CARDIAC DYNAMICS*

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IN 1951, Fischer and Roch[1] reported the synthesis of a new series of compounds with a pyrimidopyrimidine ring system. Subsequent pharmacological investigation of one such derivative (RA8) revealed a markedly selective effect on coronary flow and it became available for clinical use in Europe under the trade name Persantin.

The recent interest in this compound on this continent[2] has led us to initiate studies of the effect of this drug on coronary flow and cardiovascular dynamics, utilizing a technique of controlled cardiac output in dogs. It is felt that this report of the marked effect of RA8 on coronary flow will stimulate further studies of its therapeutic efficacy in angina pectoris, and help to resolve the current controversy[3-5] concerning the role of pure coronary dilatation in the alleviation of pain secondary to coronary insufficiency.

EXPERIMENTAL METHOD

The anatomical distribution of the coronary venous system in the dog is such that approximately 95% of the total venous return enters the right side of the heart via the coronary sinus and the anterior cardiac veins.[6, 7] This one-sided distribution of the coronary return allows it to be separated from the rest of the venous return to the heart and permits its accurate measurement by direct means. This has been accomplished by utilizing the complete right-heart bypass preparation.

In this preparation, illustrated schematically in Fig. 1, the blood flow from both venae cavae is diverted into a venous reservoir, from which the blood is pumped back into the pulmonary artery, via a Sigmamotor pump under conditions of controlled flow. It is assumed that equivalent amounts of blood, pumped into the pulmonary artery, will be ejected into the arterial system by the left side of the heart. This is a reasonable assumption, since Seely, Nerlich and Gregg[8] have shown that known amounts of blood pumped into the pulmonary artery correlate well with the estimated cardiac output.

If the pulmonary artery is occluded by a tape preventing any regurgitation of blood into the right ventricle, and if an additional catheter is placed in the right ventricle, as designated in Inset A, all the coronary blood returning to the right side of the heart will be diverted into the small reservoir (see Fig. 1). The coronary venous return,

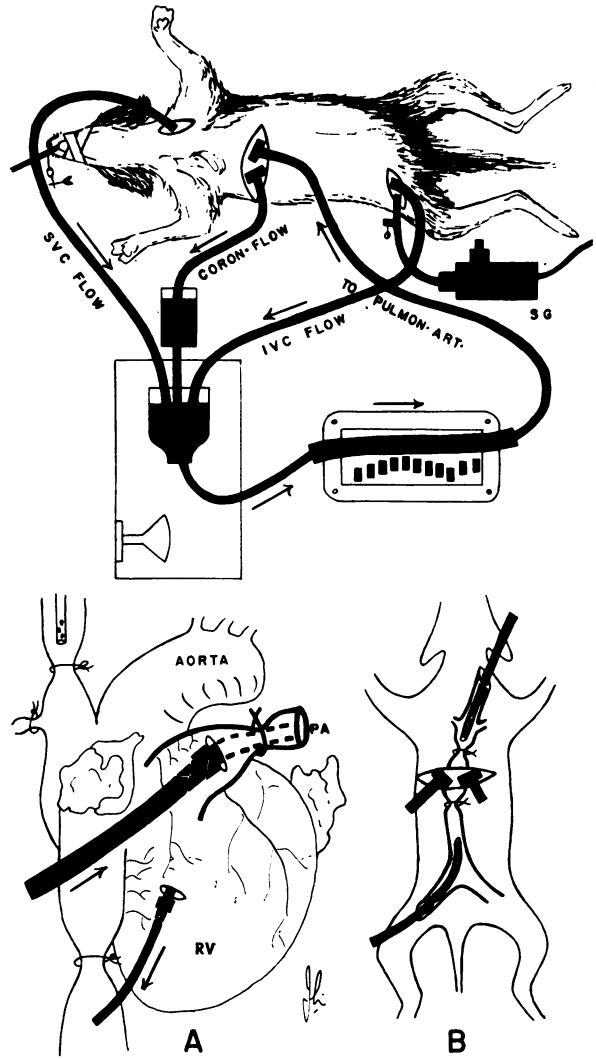

Fig. 1.—This is a diagrammatic representation of the complete right-heart bypass preparation. The main portion of the diagram shows the following: S.V.C. FLOW refers to the conduit which drained the superior venal caval blood into the venous reservoir from the catheter located in the left external jugular vein and superior vena cava; I.V.C. FLOW is the conduit which drained the inferior vena caval blood from a catheter, in the right femoral vein, located approximately at the level of the bifurcation of the inferior vena cava. The location of the catheters in the superior and inferior venae cavae is shown in Inset B. The conduit, marked CORON. FLOW, represents the tube which drained the coronary return from the right ventricle into the small venous reservoir. Line marked TO PULMON. ART. is the tube through which blood was pumped from the reservoir into the occluded pulmonary artery. S.G. stands for strain gauge, which was connected to a catheter in the right femoral artery and to a Gilson recorder. The pump head tubing is seen in the Sigmamotor pump head; the venous reservoir was in a box with a plexiglass front, which had a heat lamp to maintain the temperature at approximately 37° C. Inset (A) shows the catheter in the pulmonary artery (P.A.) with a ligature about it and the smaller catheter in the right ventricle (R.V.); also illustrated are the ligatures about the superior and inferior venae cavae and azygos vein. The tip of the catheter in the superior vena cava is shown as well. Inset (B) shows the location of the superior and inferior venae cavae catheters.

flowing through the catheter per interval of time, is measured by direct collection of such flow in a 100-ml. graduated tube.

The experiment was carried out in 10 dogs that weighed from 11.5 to 17 kg., with an average weight of 13 kg., with a standard deviation of ±1.9 kg. The dogs were anesthetized with sodium pentobarbital, 30 mg./kg. of body weight, and heparinized with 2 mg. of heparin/kg. of body

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weight.* The cardiac cannulations were performed by means of a right unilateral thoracotomy incision in the fourth interspace. During the open-chest period, the dogs received pure oxygen with the aid of a mechanical respirator attached to an endotracheal-cuffed tube. The cautery was used liberally to ensure a minimum of bleeding. The azygos vein was ligated. Drainage of both venae cavae was effected by placing a catheter into the left external jugular vein to the level of the superior vena cava and another into the right femoral vein to the level of the bifurcation of the inferior vena cava. In this way, the number of cannulae passing into and out of the chest cavity was minimized.

When the cannulations were completed, as illustrated in Fig. 1, the bypass was started by removing the clamps on the caval catheters and the pulmonary artery connection and simultaneously starting the Sigmamotor pump. Thus, the transition from the dog's circulation to that of the bypass circuit was effected smoothly.

The rate of the Sigmamotor pump, as noted above, was equivalent to the cardiac output of the dogs. In each of the 10 dogs a different cardiac output was used. It is important to note that the cardiac output, once selected, was maintained at a constant level throughout that particular experiment.

The drug, Persantin, was injected intravenously through the rubber tubing connecting the catheter in the pulmonary artery and the tubing leading from the Sigmamotor pump. It was found that two separate injections of Persantin could be given during each experiment, approximately 30 to 45 minutes apart, thus providing two separate sets of data. A 15- to 20-minute period of stabilization was allowed from the commencement of the bypass, so that a steady state could be reached, prior to the injection of Persantin.

At the end of this period of stabilization, control measurements were recorded for coronary return, mean arterial blood pressure, heart rate and oxygen content of the femoral arterial blood and coronary return blood. The coronary flow measurements were made by putting the catheter from the right ventricle into a 100-ml. graduated tube and measuring the flow over either a 30- or 60-second interval and computing the value in ml./min. The mean blood pressures were measured as follows. A nylon catheter was placed in the right femoral artery and attached to a Statham transducer which, in turn, was connected to an electrically damped Gilson medical electronics minipolygraph recorder. An electrocardiogram was recorded simultaneously on the minipolygraph and was used to observe the heart rate. The oxygen content was determined by means of the Van Slyke apparatus. At least one or two oxygen saturations per experiment were carried out on the arterial blood, to ensure an arterial saturation over 90%, for the coronary vessels are sensitive to hypoxia. The myocardial oxygen consumption was obtained from the formula,

$$\frac{(\text{A-V})\text{O}_2 \text{ difference} \times \text{flow}}{100}$$

which gives the value for myocardial oxygen consumption, in ml. of oxygen consumed per minute.

Persantin, diluted in saline, was administered into the pulmonary artery in a dosage of 0.3 mg./kg. of body weight, over an interval of 50 to 60 seconds. The coronary blood flow was measured at one- to two-minute intervals during the period of major response to the drug and then at intervals of 15 to 30 minutes. During each coronary flow measurement, the mean arterial blood pressure and heart rate were recorded.

After the injection of Persantin, the rate of coronary return visibly increased and the colour changed to resemble arterial blood. The rate of flow usually reached a maximum two to four minutes after the start of the injection. At the time of maximum increase in coronary return, simultaneous blood samples from the femoral artery and from the 100-ml. graduated tube were obtained for the determination of the myocardial oxygen consumption.

This was the general pattern of the experiment. The control values for coronary return, mean arterial blood pressure, heart rate and myocardial oxygen consumption were recorded, and the maximum responses in these parameters following the injection of Persantin were measured for comparison. The control values for the second set of data in each experiment were the appropriate values 30 to 45 minutes after the first injection, at which time the residual effect of the drug was considered minimal.

RESULTS

Data for the ten experiments are presented in Table I and include the control values prior to the injection of Persantin and the maximum responses in mean arterial blood pressure, heart rate, coronary return, $(\text{A-V})\text{O}_2$ difference and qO_2. In addition, the differences between the control values and the maximum responses following administration of the drug are expressed as a percentage decrease or increase from the control values. The pertinent relationships are presented in graph form and in the figures.

In Fig. 2, the results of one additional experimentation are presented graphically. This experiment demonstrates the changes that occurred in the coronary return values, the heart rate and the mean blood pressure, after the injection of Persantin. In Fig. 2, the coronary flow measurements were taken at 30-second intervals and illustrate the pattern of response. Determinations of this rapidity could not be carried out in all experiments. This general pattern was typical, varying in degree from experiment to experiment. In Fig. 2, three minutes

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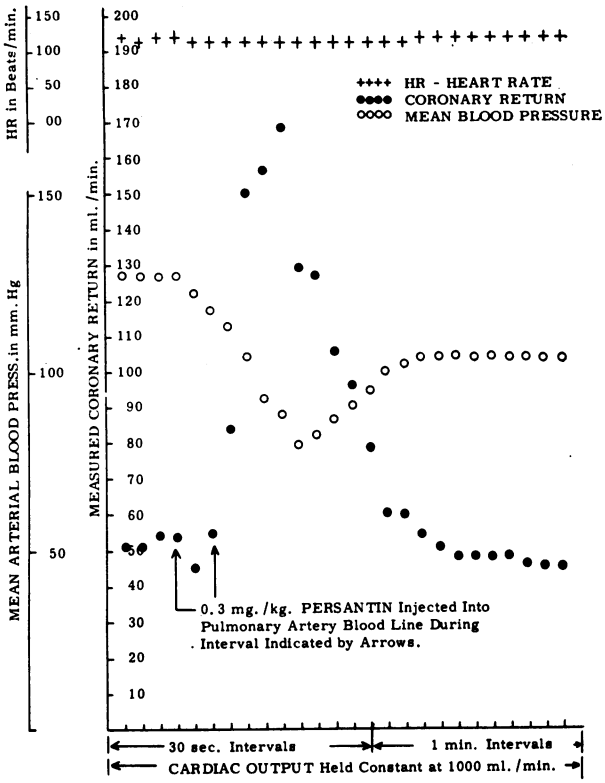

Fig. 2.—This figure is of an additional experiment, in which the coronary flow measurements were made at 30-sec. intervals after the injection of the Persantin. After the maximum response of the drug had occurred, the measurements were made at 1-min. intervals. The cardiac output was constant at 1000 ml./min. throughout this experiment.

after the injection of Persantin, the coronary flow reached its maximum, and simultaneously the mean arterial blood pressure was at its lowest level. It was a common finding in all experiments that the heart rate did not change appreciably. It was also typical that the mean arterial blood pressure did not return to its control value. The coronary return fell to the control values about 15 minutes after the start of the injection. In the experiment illustrated in Fig. 2, the cardiac output was kept constant throughout at a rate of 1000 ml./min.

In each of the 10 experiments, the cardiac output was held constant but, as mentioned above, a different constant was chosen for each experiment. Since mean arterial blood pressure is, to a certain extent, dependent upon cardiac output, different values of mean blood pressure were also obtained in each experiment. The response of coronary venous return to the injection of Persantin, at different mean blood pressures, is shown in Fig. 3. Above 100 mm. Hg there was an obvious increase in coronary flow after the injection of Persantin at any mean arterial blood pressure; but, below 100 mm. Hg, the response of coronary flow to Persantin decreases proportionately. The statistical analysis of this relationship is presented in Fig. 4 and in the appendix of this report.

After the injection of Persantin, the most striking change was the concomitant increase in coronary flow and the reddening of the coronary venous

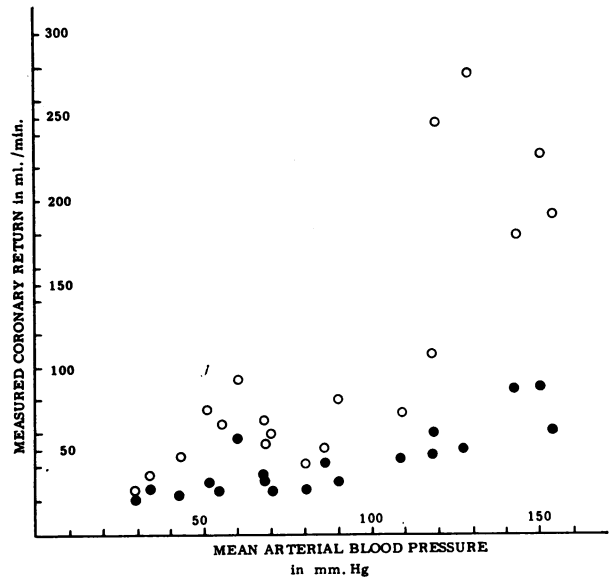

Fig. 3.—The mean blood pressures plotted on the horizontal axis in this graph are the control values (Column 5, Table I) just prior to the injection of Persantin. The black dots are the control values for the measured coronary return (Column 13). The circles represent the maximum response in the measured coronary return (Column 14) after an injection of Persantin. Thus, each dot and the circle directly above it are paired in the above graph. There is an obvious increase in the coronary return above mean blood pressures of 100 mm. Hg. See Fig. 4 and Appendix for statistical treatment.

blood which was grossly visible and indicated the marked increase in residual venous oxygenation. This relationship is illustrated in Fig. 5. The coefficient of correlation between these two parameters, the decrease in the $(A\text{-}V)O_2$ difference and the per cent increase in coronary flow, was 0.83.

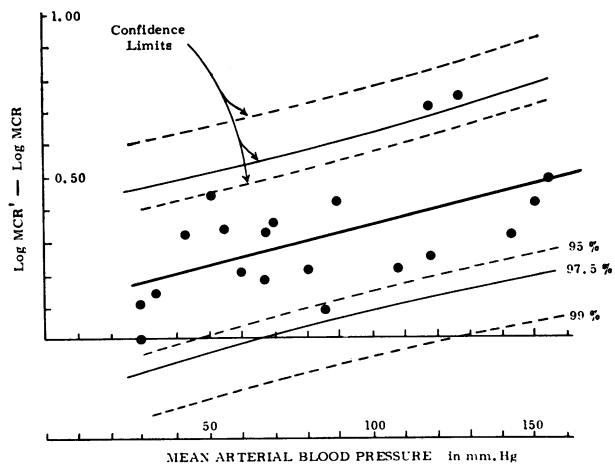

Fig. 4.—This graph is a statistical analysis of Fig. 3. The circles and dots observed in Fig. 3 have been converted into one dot graph by plotting the differences of the $\log_{10}$ values of measured coronary return of Columns 14 and 13 against the corresponding values for mean blood pressure in Column 5. The heavy line in this figure is the regression line for the dot graph and the curved lines the confidence bands for the regression line. Left of the point where the confidence bands intersect the horizontal axis includes zero, while, to the right, is the range of mean blood pressures where a significant increase in the measured coronary return occurred as compared to the control values, after an injection of Persantin. At the 95% level a significant increase took place even when the mean blood pressure was as low as 50 mm. Hg. (See Appendix for further explanation of statistics.)

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TABLE I.

1	2	3	4	5	6	7	8	9	10
Exp. No.	*CO ml./min.*	*Dog wt. kg.*	*Heart wt. (g.)*	*Control MABP*	*Max. resp. after injection of Persantin (MABP)'*	*ΔMABP = (MABP)' − MABP*	*%Δ ±*	*T. max. R. in min.*	*Control HR*
1	400	11.5	68	82	58	24	29 −	4	114
			68	67	46	21	31 −	5	114
2	950	15	109	154	92	62	40 −	3	150
			109	118	96	22	19 −	3	144
3	690	12	91	90	52	38	42 −	3	144
			91	68	52	16	23 −	6	138
4	245	13.4	95	29	22	7	24 −	2	180
			95	29	22	7	24 −	2	192
5	730	12	84	109	74	35	32 −	3	162
			84	86	64	22	25 −	4	156
6	422	16.7		51	32	19	37 —	4	120
				60	29	31	52 −	2	120
7	1040	15	117	143	129	14	10 −	2	180
			117	150	117	33	22 −	2	162
8	418	13.0	82	70	52	18	26 −	2	132
			82	55	34	21	38 −	2	126
9	1090	13.0	74	127	90	37	29 −	2	138
			74	118	85	33	28 −	2	132
10	320	17.0	121.5	43	31	12	28 −	2	120
				34	23	11	32 −	3	120

Average.....13.9 kg.
Standard deviation ..1.9 kg.

	11	12	13	14	15	16	17	18	19	20
Exp. No.	*Max. resp. after injection of Persantin (HR)'*	*T. max. R. in min.*	*Control MCR ml./min.*	*Max. resp. after injection of Persantin (MCR)'*	*ΔMCR = (MCR)' − MCR*	*%Δ ±*	*T. Max. R. in min.*	*Control AO_2*	*Determined at the same time as in Column 14 $(AO_2)'$*	*Control VO_2*
1	104	5	26	42	16	61 +	4	14.4	13.3	2.6
	108		36	54	18	50 +	8	12.7	12.7	2.9
2	126	12	62	192	130	209 +	2	18.9	19.7	3.9
	126	4	60	108	48	80 +	3	19.5	21.0	4.4
3	126	4	30	80	50	167 +	4	22.7	22.4	5.7
	114	6	32	68	36	212 +	5	22.6	21.4	8.4
4	174	6	20	26	6	30 +	4	20.7	21.9	2.8
	186	3	29	29	0	00	8	21.0	21.9	4.0
5	150	6	44	72	28	64 +	2	15.4	18.8	2.7
	150	6	42	52	10	24 +	3	17.4	17.4	3.9
6	104	4	30	84	54	180 +	4	19.9	21.7	5.9
	102	2	48	77	29	60 +	2	21.8		11.5
7	162	15	88	180	92	104 +	2	18.2	17.7	5.7
	162		88	228	160	182 +	2	17.2	19.2	5.9
8	120	5	26	60	34	131 +	2	18.8	18.7	5.4
	120	2	24	66	42	175 +	3	19.9	23.4	7.9
9	132	5	50	276	226	452 +	2	14.4	16.6	4.9
	126	7	48	246	198	412 +	2	14.2	15.3	4.7
10	108	2	22	46	24	109 +	3	23.6	22.0	2.5
	108	3	26	36	10	38 +	7	24.2	27.2	5.7

	21	22	23	24	25	26	27	28	29
Exp. No.	Determined at the same time as in Column 14 $(VO_2)'$	Control $(A-V)O_2$ = Col. 18-Col. 20	$(A-V)'O_2$ = Col. 19-Col. 21	$\Delta(A-V)O_2$ = $(A-V)'O_2-(A-V)O_2$	%Δ±	Control qO_2	Determined at the same time as in Column 14 $(qO_2)'$	ΔqO_2 = $(qO_2)'-qO_2$	%Δ±
1	5.0	11.8	8.3	3.5	30−	3.07	3.49	0.42	13.7+
	7.0	9.8	5.7	4.1	42−	3.53	3.09	0.44	12.5−
2	14.2	15.0	5.5	9.5	63−	12.40	10.45	1.95	15.7+
	12.6	15.1	8.4	6.7	44−	9.06	9.07	0.01	0.1+
3	15.8	17.0	6.6	10.4	61−	5.10	5.28	0.18	3.5+
	15.4	14.2	6.0	8.2	58−	4.54	4.08	0.04	0.8−
4	5.5	17.9	16.4	1.5	8−	3.58	4.26	0.68	19.0+
	4.2	17.0	17.7	0.7	4+	4.93	5.13	0.20	4.1+
5	8.0	12.7	10.8	1.9	15−	5.59	7.78	2.19	39.2+
	8.1	13.5	9.3	4.2	31−	5.67	4.84	0.83	14.6−
6	15.3	14.0	6.4	7.6	54−	4.23	5.38	1.15	27.2+
		10.3				4.94			
7	12.7	12.5	5.0	7.5	60−	11.0	9.0	2.0	18.2−
	13.6	11.3	5.6	5.7	50−	9.9	12.8	2.9	29.3+
8	14.7	13.4	4.0	9.4	70−	3.48	2.40	1.08	31.0−
	16.4	12.0	7.0	5.0	42−	2.88	4.62	1.74	60.4+
9	13.0	9.5	3.6	5.9	62−	4.75	9.94	5.19	109.3+
	14.1	9.5	1.2	8.3	87−	4.56	2.95	1.61	35.3−
10	11.0	21.1	11.0	10.1	48−	4.64	5.06	0.42	9.0+
	12.7	18.5	14.5	4.0	21−	4.81	5.22	0.41	8.5+

Average..... 12.0+
Standard deviation..... 33%

Data for the ten experiments are presented in this table; there are two sets of data for each experiment. Abbreviations are as follows: CO = cardiac output in ml./min.; MABP = mean arterial blood pressure in mm. Hg obtained from the femoral artery; T. Max. R. = time of maximum response in mins. after the injection of Persantin; HR = heart rate in beats/min.; MCR = measured coronary return in ml./min.; AO_2 = arterial O_2 content in volumes per cent; VO_2 = venous O_2 content in volumes per cent of the coronary venous blood; $(A-V)O_2$ = arterio-venous O_2 content difference between the arterial systemic blood and the coronary venous blood; qO_2 = myocardial oxygen consumption in ml. of O_2 consumed per minute, obtained by multiplying the $(A-V)O_2$ difference by the MCR (ml./min.) and dividing by 100. The control values under the columns 5, 10, 13, 18, 20, 22 and 26 refer to the values obtained just prior to the injection of Persantin. The abbreviation %Δ± in columns 8, 16, 25 and 29 means the percentage increase or decrease of the parameter and is the ratio of the difference between the maximum response and the control value, over the control value, times 100.

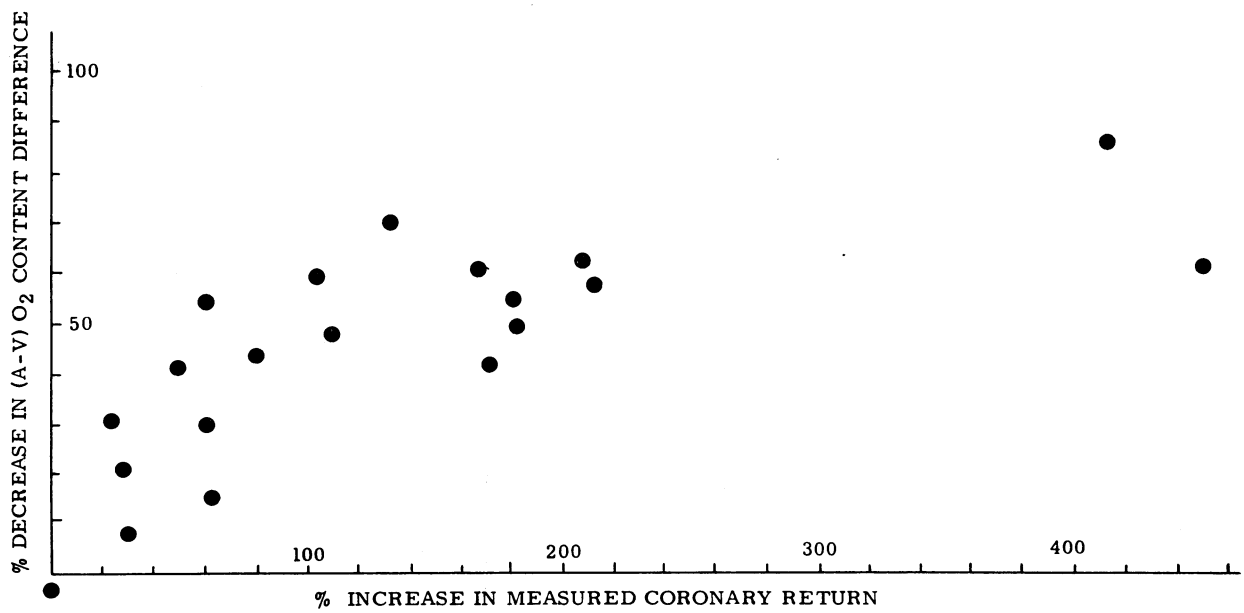

Fig. 5.—Each dot in this graph was determined by plotting the values for the % decrease in (A-V) O_2 content difference (Column 25, Table I) against the corresponding values for the % increase in measured coronary return (Column 16). The maximum % decrease in (A-V) O_2 content difference occurred at approximately 200% increase in measured coronary return.

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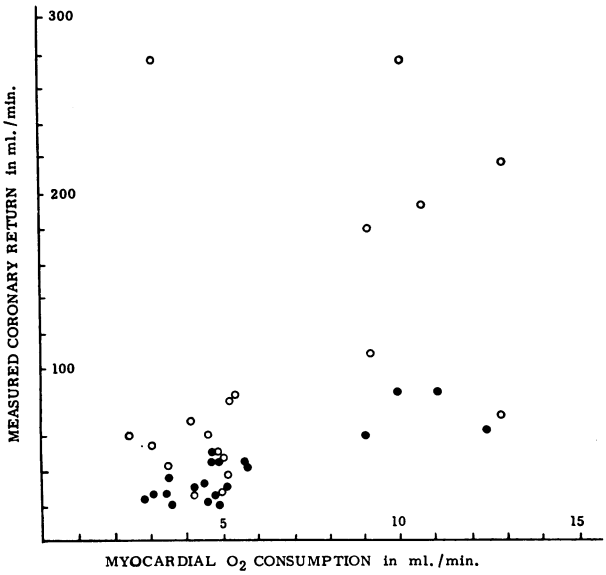

Fig. 6.—The values in this graph represented by the dots and circles are not paired. The circles indicate the values for the maximum measured coronary return that occurred after the injection of Persantin, (Column 14, Table I), plotted against the corresponding values for the myocardial oxygen consumption (Column 27). The black dots refer to the control values of measured coronary return, prior to the injection of Persantin (Column 13), plotted against the corresponding values for the myocardial oxygen consumption (Column 26). There was a more-than-adequate coronary return for any level of myocardial oxygen consumption as a result of the injection of Persantin.

In Fig. 6, the relationship between coronary venous flow and myocardial oxygen consumption is presented. The black dots show the coronary venous return found for each level of oxygen consumption by the myocardium, prior to the injection of Persantin. The circles indicate the coronary return for each level of oxygen consumption by the myocardium after the injection of Persantin. Also (Table I, column 29) Persantin caused an increase in the average myocardial oxygen consumption, when compared with the control values, of 12% (S.D. 30%).

Persantin caused a consistent decrease in the blood pressure of approximately 20% to 30% of the control value. This drop appeared to be the same whether the control value for the mean arterial blood pressure was 50 mm. Hg or 150 mm. Hg, illustrated in Fig. 7, which represents the maximum drop in blood pressure that occurred after the injection of Persantin.

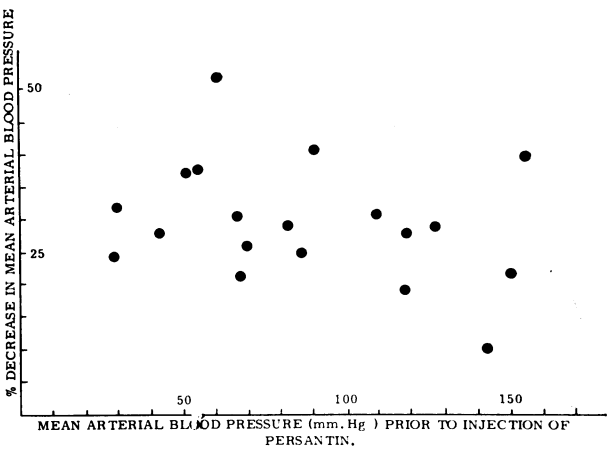

Fig. 7.—The dots in this graph represent the % decrease in mean arterial blood pressure that occurred after an injection of Persantin (Column 8, Table I), plotted against the mean blood pressure prior to the injection ,Column 5).

DISCUSSION

The most striking observation was the obvious increase in flow and venous oxygenation of the coronary blood. This was particularly noticeable in those animals in which the mean blood pressure, prior to the injection of Persantin, was over 100 mm. Hg pressure. These changes are particularly significant because the increase in coronary flow occurred under conditions of constant cardiac output, a depression in the mean arterial blood pressure and a slight reduction in heart rate. Accordingly, the drug must have decreased the peripheral resistance in the coronary vessels to a marked degree.

Much experimental work on the effects of Persantin has been reported in the European journals. In experiments performed on normal dogs, Kadatz,[9] using the Bubble-Flow-Stromuhr, found that the coronary flow increased as much as 123%; Hockerts and Bögelmann,[10] using the Thermo-Stromuhr of Rein, found that it increased 90%; Grabner, Kaindl and Kraupp,[11] using the method of Kety and Schmidt,[14] found the coronary flow 35% greater. Breitschneider *et al.*,[12] using the Stromuhr catheter of Kansow, reported increases in coronary flow up to 400%, with a 200% increase for several hours. In these experiments papaverine was only 50% as effective and theophylline was the least effective when compared with Persantin.

From the experimental work there is a reciprocal relationship between the decrease in $(A\text{-}V)O_2$ difference of coronary venous and the increase in coronary flow after the administration of Persantin.[9, 12] This association was confirmed in our experiments and is shown in graphic form in Fig. 5.

In Fig. 2, the time of maximum decrease in mean arterial blood pressure coincided with maximum increase in coronary flow, which could indicate that the mean arterial pressure was lowered partially by a "shunting" of part of the cardiac output back into the coronary circulation, causing a relative decrease in the flow to the systemic circulation. Further evidence of this "shunt effect" is also provided in Fig. 2, where as the effect of the drug wore off, the mean arterial blood pressure returned to a new level. The difference between the lowest level of mean arterial blood pressure and the new pressure attained after Persantin probably represented the degree of shunting of the coronary flow.

The mean arterial blood pressure did not rise to its control value after the administration of the Persantin, and this seems to indicate a change in the peripheral vascular tone due either to a prolonged effect of the drug or to unknown parameters in the experimental model employed.

Fig. 2 and Table I show that the maximum effect of the drug took place quickly; the main effect lasted approximately 9 to 15 minutes and at the end of 30 minutes the value for coronary return usually returned to the control values. A slight variation in this pattern was seen when the drug was given while the animal's mean arterial blood pressure was low, that is, between the range of 40 and 60 mm. Hg. Under these conditions, the return of coronary flow to normal was slower, and in certain cases the coronary flow did not return to control values, but remained elevated at the 30- and 45-minute intervals. The metabolism of the drug during conditions of hypotension may be retarded.

Determinations of the comparative effects of theophylline, papaverine and Persantin have been made by Breitschneider *et al.*,[12] who found that the increase in coronary flow was in the ratio of 1:1.5:3, respectively, of these drugs.

Doerner and Wick[13] compared Persantin, papaverine and nitroglycerin and found, with respect to potency, duration of effect and uniformity of reaction, that Persantin was definitely and, in some ways, considerably superior to the other compounds.

Brachfeld, Bozer and Gorlin,[3] utilizing the method of Kety and Schmidt,[14] found that in humans after the administration of nitroglycerin, the coronary return flow increased but the $(A\text{-}V)O_2$ difference did not, indicating that myocardial oxygen consumption was increased after the administration of nitroglycerin. In a second paper, Gorlin *et al.*[4] reported that after the administration of nitroglycerin in patients suffering from coronary artery disease, the coronary flow diminished or remained unchanged, indicating that the coronary resistance appeared to remain fixed in these patients. These authors believe that, in normal subjects, the increase in coronary flow from nitroglycerin was caused by dilatation of the coronary vessels by dilator metabolites, whereas, in individuals suffering from coronary artery disease, the apparent lack of increase was due to a fixed resistance of the vessels, a result of pre-existing coronary atherosclerosis.

Remarks which qualify the findings of Gorlin and co-workers have been presented by Honig, Tenney and Gabel.[5] They point out that the originators of the nitrous oxide techniques, Kety and Schmidt,[14] emphasized the importance of the "steady state" during the application of this method. After the administration of nitroglycerin, Honig, Tenney and Gabel[5] remark that "nitroglycerin produces a rapidly fluctuating unsteady state" and, to assess the effects of nitroglycerin, a method must be used which compares a variable with its control value, so that "the time required for its measurement is negligible and a particular point in the sequence of events is specified". The utilization of a complete right-heart bypass preparation in studying the effects of nitroglycerin may fulfil such criteria and give meaningful results in the study of the mechanism of the action of nitroglycerin. Honig, Tenney and Gabel concluded that "nitroglycerin relieves ischemia by enhancing oxygen delivery, rather than by altering load". Honig, Tenney and Gabel, quoting the work of others,[15, 16] thought that it was unlikely that coronary resistance ever "becomes completely fixed". If this thesis is correct, coronary dilator drugs, such as Persantin, may have a real role to play in the treatment of patients suffering from coronary artery disease.

The parameter of mean arterial blood pressure should be used to correlate the effect of Persantin on coronary flow, because coronary flow is dependent upon blood pressure. Braunwald *et al.*,[17] using dogs under controlled conditions, showed that if the cardiac output is kept constant and the blood pressure increased, the increase in coronary flow was much more marked than if the blood pressure was held constant and the cardiac output increased, indicating that the cardiac output probably exerts its influence secondarily through its effect on the blood pressure.

In our experiments, the fall in blood pressure of 25 to 30% of the control value, occurring after the injection of Persantin, may have been due partially to a shunt effect. Also, if the cardiac output had not been held at a constant value, the drop might not have been so marked. The fact that the animals were under the effects of pentobarbital and had thoracotomies may have increased their susceptibility to a fall in blood pressure. The dose of 0.3 mg./kg. used in this study was above the optimum level for coronary dilatation and approached the level known to affect peripheral tone.[12] Kadatz[9] has shown that, in the intact dog, the optimal dose of 0.2 mg./kg. caused an average maximum fall in blood pressure of 12%, while a dose of 0.5 mg./kg. caused an average maximum fall of 25% of the control value. In their studies, the response of the pulse rate was variable; occasional animals showed a decrease, while others showed a slight increase.

The toxicity of Persantin has been tested and found to be low. In the clinical investigations carried out to date, the drug has been well tolerated.[18-20]

SUMMARY

Study of the cardiovascular effects of the synthetic coronary dilator, Persantin, has been reported, utilizing the right-heart bypass, constant cardiac output technique in dogs. This method permits almost complete separation of the coronary venous return from the rest of the venous return to the heart. The general pattern of the experiment, after a period of stabilization of the constant cardiac output, recorded the control values for the coronary return, mean arterial blood pressure and heart rate and then measured the maximum response to the injection of the drug into the pulmonary artery. The maximum effect usually occurred between

two and four minutes after the injection, and the principal part of the response was over in 10 to 15 minutes; after 30 minutes the values for coronary return were at the control levels again. A duration of effect of this length allowed two sets of data to be obtained during each experiment.

The drug appeared to cause a marked increase in the coronary flow. This effect took place during the maintenance of a constant cardiac output, a drop in the mean arterial blood pressure and, essentially, a constant heart rate. Also, an increase in the coronary return was found over a full range of mean blood pressures from normotensive to shock levels. There was a reciprocal relationship between the increase in coronary return and the decrease in $(A\text{-}V)O_2$ content difference (between the arterial systemic and coronary venous blood).

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APPENDIX

This is a further explanation of the statistical treatment used in Figs. 3 and 4. Since the dots in Fig. 3 represented the control values of coronary return measured prior to the injection of Persantin, these values or the plot of these values could be used as the controls in estimating the increase in coronary return (circles in Fig. 3) as resulting from the injection of Persantin. As the mean blood pressure was lowered, however, the increase in measured coronary return became less. The purpose of this statistical study is to show at what mean blood pressure a significant increase in measured coronary return no longer occurred when compared with the control values (black dots).

Both the plots for the circles and dots in Fig. 3 have exponential trends. If these trends were converted to straight lines by taking the logarithms of the ordinates, the equations for the regression lines could be calculated as well as the confidence bands for each equation. The bands, adjacent to each other on either side of the regression lines, would intersect at different points, depending on which limit was used (i.e. 99%, 97.5% or 95%); the area included where the bands overlapped would indicate the range of mean blood pressures where no significant increase in coronary flow occurred; and accordingly, where the bands did not overlap, would indicate the range of mean blood pressures where a significant increase in coronary flow occurred upon the injection of Persantin.

Since each pair of circles and dots were plotted against the same value of mean blood pressure, the step of calculating two regression lines was deleted as follows: the logarithms of the corresponding values in Columns 13 and 14, Table I, were used as equivalent to the logarithms of each pair of values in Fig. 3 (i.e. one dot and one circle). The difference between each set of logarithms was plotted against the corresponding values of mean blood pressure noted in Column 5, Table I; these differences are represented by the dots in Fig. 4. The regression line for these dots was calculated by standard procedures.[21, 23] The confidence bands for the 99%, 97.5% and the 95% limits were determined by the method outlined by Kenney and Keeping,[22] utilizing the one-tailed test for the value of t. The graphic representation of these results is in Fig. 4 (see also legend for Fig. 4).

PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

SIR WILLIAM OSLER

If, at any future time, the framers of the honour list should be at a loss for candidates whose merits they might commend to the notice of His Majesty, we would suggest to them a survey of the field of medicine in Canada. We cannot pretend that Sir William Osler has been chosen from that field, as he has long since belonged to a larger world. Indeed, with possibly one exception, we do not remember that any Canadian has ever been chosen for knighthood on account of his achievements in the medical sciences alone. One or two recipients suggest themselves, but they had a career in the political as well as in the medical world. In 1887 Sir James Grant was created K.C.M.G., but the common belief is that he received this distinction for his personal services towards a member of the royal family, rather than on account of his services, great as they had been, to medicine at large. Many men are yet unmarked, who by their personal distinction and by the inestimable benefits which they have conferred upon humanity, might well be chosen for royal favour, so that their fellow-practitioners might be encouraged to emulate their example.

If our advice were sought by the framers of this list, we could readily suggest the names of physicians and surgeons to our splendid hospitals, and of the deans, past and present, of medical schools which are not excelled in quality by any others within the British Empire. By the elevation of Sir William Osler to the ranks of the nobility, the baronetage receives a new respect in the eyes of all Canadians. His official ennobling is merely a recognition that he has long since ennobled himself and the profession to which he belongs.—*Canad. M. A. J.*, 1: 793, 1911.