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# The Effect of Persantin on Intercoronary Collateral Circulation and Survival During Gradual Experimental Coronary Occlusion:

## A Preliminary Report

ARTHUR M. VINEBERG, Ph.D., M.D.,* RANGA S. CHARI, M.D.,†
ROQUE PIFARRE, M.D.‡ and CLAUDE MERCIER, M.D., C.M.,‡ *Montreal*

ABSTRACT

**Twenty-five dogs were exposed to gradual coronary occlusion by placing Ameroid constrictors around the origins of the left circumflex and anterior descending coronary arteries. Previous experiments have demonstrated that these constrictors absorb water and, over a period of three weeks, narrow the cross-sectional area of the two arteries to 50% or less, and consequently cause the death of 80% of the experimental animals. Twelve of the 25 animals were fed 50 mg. of Persantin three times a day by mouth commencing one day before the operative procedure. Determinations of the concentration of the drug in the blood revealed a level consistent with that obtained in humans after the administration of therapeutic doses. Eleven of the 13 control animals died in the three-month experimental period while only six of the 12 treated animals expired. Injections of Schlesinger mass in all animals dying or killed following the experimental period demonstrated that Persantin significantly accelerated the development of intercoronary anastomoses in the treated group, and in the surviving animals produced a rich anastomotic network much in excess of that seen in the surviving animals in the control series that were exposed to hypoxia alone. On the basis of these experimental findings, it is suggested that Persantin may favourably alter the prognosis of many patients with coronary artery disease.**

CORONARY artery disease leading to luminal narrowing is found in the majority of males on the North American continent examined during routine postmortem studies.[1] In addition, the commonest cause of *sudden* death is myocardial infarction. It is generally agreed that this sequel of coronary occlusion, particularly in the young adult, is in large part due to the relative absence of an adequate intercoronary collateral circulation. Available evidence indicates that, although intercoronary collaterals can be detected within a few days following an occlusion of a major coronary artery branch, several weeks or months may be required for their full development. The slowness of this development (following rather than preceding the coronary occlusion) emphasizes the need for finding a simple and practical method to encourage the formation of intercoronary collaterals, which can be used prophylactically in susceptible males. This prophylactic enhancement of collateral circulation would provide protection to the myocardium at the time of the sudden occlusion of a major branch of the coronary tree.

The problem of increasing the blood flow to the myocardium in the presence of atherosclerosis has been approached surgically. The Vineberg sponge operation and Vineberg internal mammary artery implant[2] have proved successful in supplying the myocardium with an extra-coronary source of arterial blood in certain patients with severe ischemic heart disease. These surgical procedures are not generally applicable, however, to the individual with mild coronary insufficiency who requires protection of an area of the myocardium threatened by sudden occlusion of a coronary vessel. Physiologic stimuli such as hypoxia have been shown experimentally to enhance the development of functioning intercoronary collaterals, but have no practical value in a clinical setting.

The most useful method of inducing the prophylactic development of intercoronary collaterals would be by means of the administration of drugs. The long-acting nitrates have proved disappointing in this respect.[3] However, initial reports concerning the new "coronary-active" compound called Persantin®* indicate that this drug has many of the properties necessary for the development of adequate intercoronary collaterals.

The present study was carried out in order to determine whether this agent had such properties in view of the potential value of such an action in clinical conditions characterized by coronary insufficiency.

### PHARMACOLOGY OF PERSANTIN

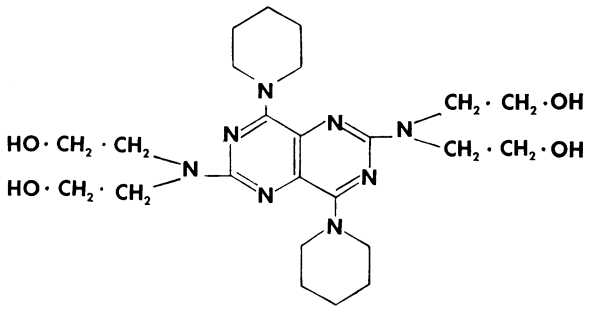
In 1951 Fischer and Roch[4] described the synthesis of a new double ring structure from two

*Associate Professor, Department of Surgery, McGill University, Montreal.
†Present address: Department of Surgery, University of Alberta Hospital, Edmonton, Alta.
‡Research Assistant, Department of Experimental Surgery, McGill University, Montreal.

*Boehringer Ingelheim Products distributed by Geigy Pharmaceuticals, Montreal, Que.

condensed pyrimidine rings. Persantin is one derivative of this series and has the following structure:

2, 6-bis di(2-hydroxyethyl) amino-4, 8-bis (1-piperidyl) pyrimido-(5, 4-d)-pyrimidine.




Elliot[5] has reported that Persantin increases the coronary flow in experimental animals up to 300% of normal. This marked effect of Persantin on coronary flow has been confirmed in the atherosclerotic human by Kinsella, Troup and McGregor;[6] these workers noted increased coronary blood flow in such subjects as evidenced by a decreased coronary arteriovenous oxygen difference. There was no concurrent alteration in cardiac dynamics or blood pressure. Of particular pertinence to the present study was the report of West *et al.*[7] that this compound, in an experimental setting, increased the coronary flow in animals subjected to partial coronary occlusion. Similarly, it has been reported that Persantin augments the coronary flow of animals exposed to marked hypoxia[8] and increases the flow of blood into myocardial tissue rendered ischemic.[9] Experimental evidence suggests[10] that Persantin acts to accentuate the effects of myocardial metabolites, such as adenosine, that have been proposed as the effector substances in the normal coronary response to hypoxia.[11] Persantin, in addition to its coronary effects, has also been reported to influence directly myocardial metabolism in the presence of hypoxia and lead to restoration of myocardial function and contractility.[12]

## METHODS

### 1. *The Experimental Production of Gradual Coronary Occlusion*

In the majority of cases of human atherosclerosis, the location of the grossly visible areas of atheroma and the consequent coronary narrowing follow a fairly constant pattern. The most frequent site of involvement is the proximal one-third of the left coronary artery, primarily the anterior descending branch; there is a lesser degree of involvement of the circumflex artery. In the proximal one-quarter of the right coronary artery, small plaques are commonly encountered, but the degree of morphologic alteration in this artery, particularly during the third and fourth decades of life, is considerably less than that seen in the left coronary system. In the older age groups, the pathologic changes in the right coronary artery increase in frequency and severity and may ultimately produce lesions in that segment comparable to that seen in the anterior descending segment of the left coronary artery.

Because of the early and prominent involvement of the left coronary system, efforts, previously reported,[2] have been made in this laboratory to develop a method whereby gradual coronary narrowing could be accomplished in the anterior descending and circumflex arteries of the left coronary system, thus simulating the progression of disease seen in the human patient. Briefly, this method consists of placing mechanical coronary artery constrictors around the origins of the circumflex and anterior descending arteries. These constrictors are composed of a segment of plastic rod into which a central lumen, communicating with a peripheral slot, has been drilled. This plastic material, Ameroid, is surrounded by a steel jacket. The plastic absorbs water, and in so doing, expands in all directions. Peripheral expansion is prevented by the steel jacket, so that the expansion of the Ameroid is directed towards narrowing of the central lumen in which the coronary artery lies. The rate of absorption, and therefore the rate of expansion, can be controlled by coating the Ameroid with petrolatum jelly. To reduce experimental error to a minimum, Ameroid constrictors are made in batches, mixed up and placed in a dessicator. The lumen is drilled to precision; it measures 0.110 inch and its size is checked before the Ameroid constrictor is placed around the coronary arteries by the insertion of a rod 0.110 in. in diameter.

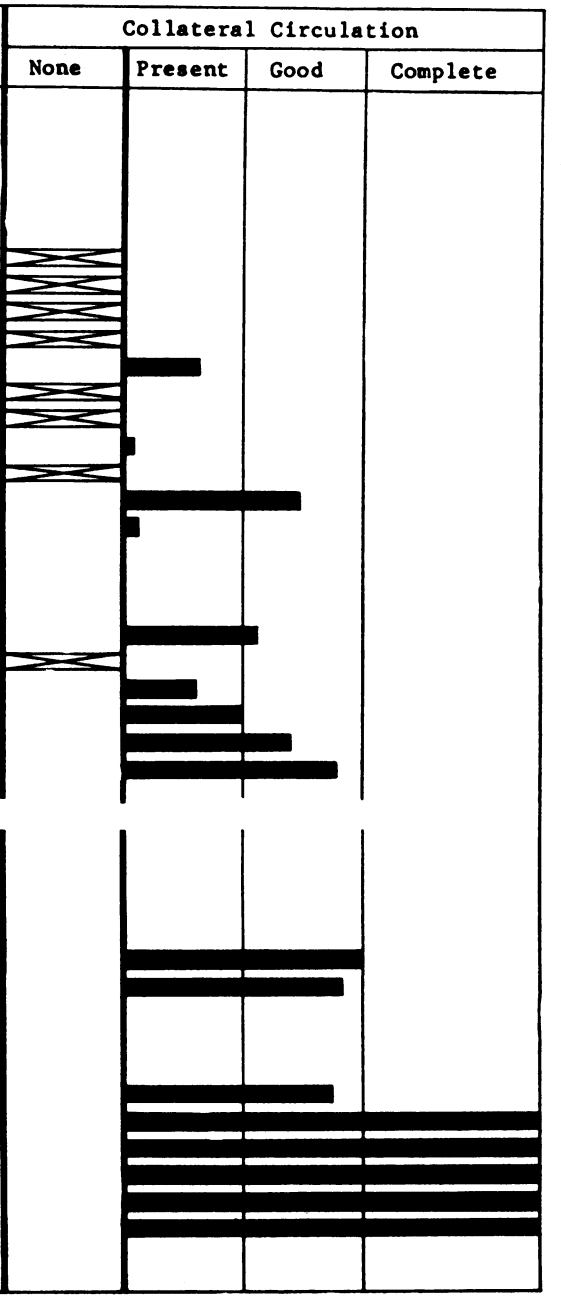
When Ameroid constrictors are placed around the anterior descending and circumflex arteries of the dog, between 80 and 85% of the animals die within 30 days, on the average. It has been noted that such animals die suddenly while fighting, eating or running, and frequently die without any physical evidence of myocardial infarction. On histologic examination of the constrictors, it has been found that the animals die when the combined cross-sectional area of the two coronary arteries has been reduced by an average of 50% or more. These animals, like man, reach a critical point of coronary artery narrowing; at this point a sudden increase in the myocardial demand for blood, which is beyond the capacity of the narrowed coronary arteries, results in death.

### 2. *The Present Study*

A group of 25 dogs, each weighing between 40 and 50 lb., underwent thoracotomy; Ameroid constrictors were placed around the origins of the circumflex and anterior descending coronary arteries. Prior to the operative procedure, 13 dogs were selected to act as a control group and 12 dogs to form the Persantin-treated group. The

TABLE I.—THE SURVIVAL TIME AND THE DEVELOPMENT OF COLLATERAL CIRCULATION IN CONTROL AND PERSANTIN-TREATED ANIMALS SUBJECTED TO THE AMEROID CONSTRICTOR TEST. (SEE TEXT FOR THE DESCRIPTION OF THE CLASSIFICATION OF COLLATERAL CIRCULATION.)

| Animal No. | Survival Time | Collateral Circulation: None | Present | Good | Complete |
|---|---|---|---|---|---|
| **ANIMALS DEAD WITHIN THREE MONTHS** | | | | | |
| **A. Control Series - 11/13 animals** | | | | | |
| 422 | 12 days | | | | |
| 83 | 14 " | | | | |
| 374 | 14 " | | | | |
| 78 | 17 " | | | | |
| 50 | 17 " | | | | |
| 359 | 18 " | | | | |
| 93 | 18 " | | | | |
| 100 | 20 " | | | | |
| 476 | 20 " | | | | |
| 469 | 32 " | | | | |
| 99 | 60 " | | | | |
| **B. Persantin Treated Series - 6/12 anim.** | | | | | |
| 45 | 12 days | | | | |
| 482 | 14 " | | | | |
| 87 | 14 " | | | | |
| 490 | 21 " | | | | |
| 82 | 23 " | | | | |
| 96 | 27 " | | | | |
| **ANIMALS SURVIVING BEYOND THREE MONTHS** | | | | | |
| **A. Control Series - 2/13 animals** | | | | | |
| 94 | Killed (8 months) | | | | |
| 91 | Killed (6 months) | | | | |
| **B. Persantin Treated Series - 6/12 anim.** | | | | | |
| 88 | 4 months (died) | | | | |
| 60 | Killed (9 months) | | | | |
| 97 | Killed (7 months) | | | | |
| 79 | Killed (6 months) | | | | |
| 322 | Killed (7 months) | | | | |
| 381 | Killed (6 months) | | | | |



latter received 150 mg. of Persantin orally each day in the form of two 25-mg. tablets contained in a small meat-ball fed to the animals three times a day. The administration of Persantin commenced two days before the operative procedure and continued until death occurred naturally or the animal was killed. The dosage of the drug was chosen on the basis of the quantity of Persantin necessary, in a single dose, to give a blood level in the dog approximating that obtained in humans from the recommended therapeutic dose. Since in humans administration of the drug is recommended before meals, the drug was given to the dogs in a fasting state and the animals were fed their single daily meal in the evening. The drug was fed to each animal individually by a handler specifically assigned to this duty throughout the course of the experiments.

Two dogs were operated upon each day, one from the control group and one from the Persantin-treated group. Immediately following recovery from the operative procedure, the dogs were removed to the animal farm, where they were housed in one large compound and allowed unlimited exercise. At variable intervals, not more than one week apart, 5 c.c. of blood was withdrawn from each Persantin-treated animal, approximately 60-90 minutes after the feeding of the drug. The blood

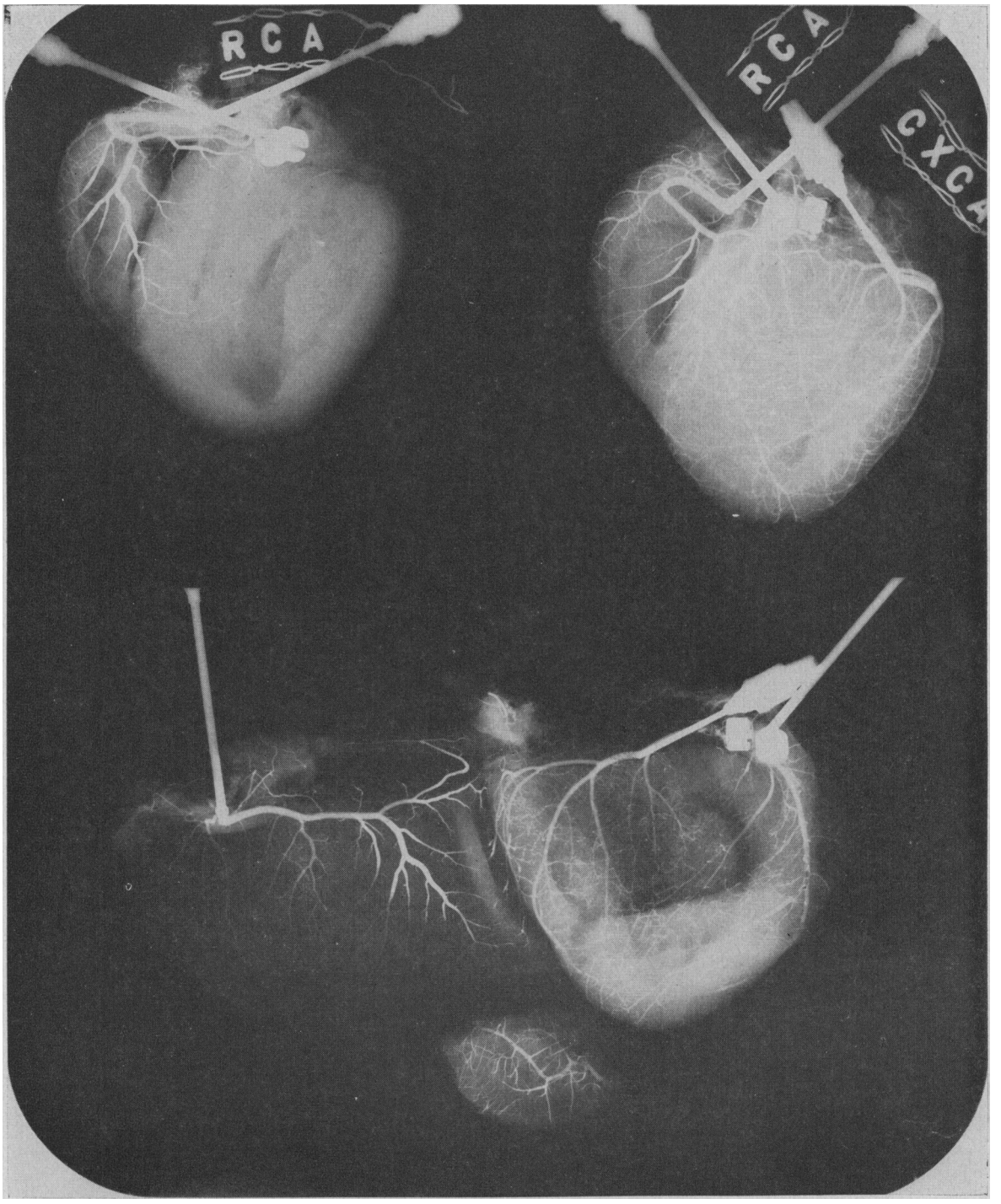



Fig. 1.—Dog No. 476 of the control series died after 20 days. The film (upper left) demonstrates perfusion and filling of the right coronary artery. No right-to-left circulation is seen. The left coronary arteries, perfused separately, are shown in the right upper film. Unrolling of the heart discloses no visible collaterals between the left and right coronary arteries.

level of Persantin was determined by a fluorimetric technique; this allowed a constant check of the effectiveness of the feeding procedure with respect to absorption of the drug.

After the death or the sacrifice of the animals, the heart was removed and placed in an ice chest until rigor mortis had disappeared. Injection studies were then carried out to identify and record the development of collateral circulation. A barium-sulfate-gelatin Schlesinger mass was prepared, and this standard preparation was used for all of the injections. Further variation from animal to animal was minimized by using a standardized injection technique at a constant pressure. First, the right coronary artery was cannulated and the perfusion mass introduced. Following a radiograph of the heart, the mass was introduced through the left coronary artery and a second radiograph was taken. Lastly, the heart was "unrolled" in the manner described by Schlesinger and a third radiograph was taken of the coronary circulation. In this manner, the amount of perfusion mass filling the

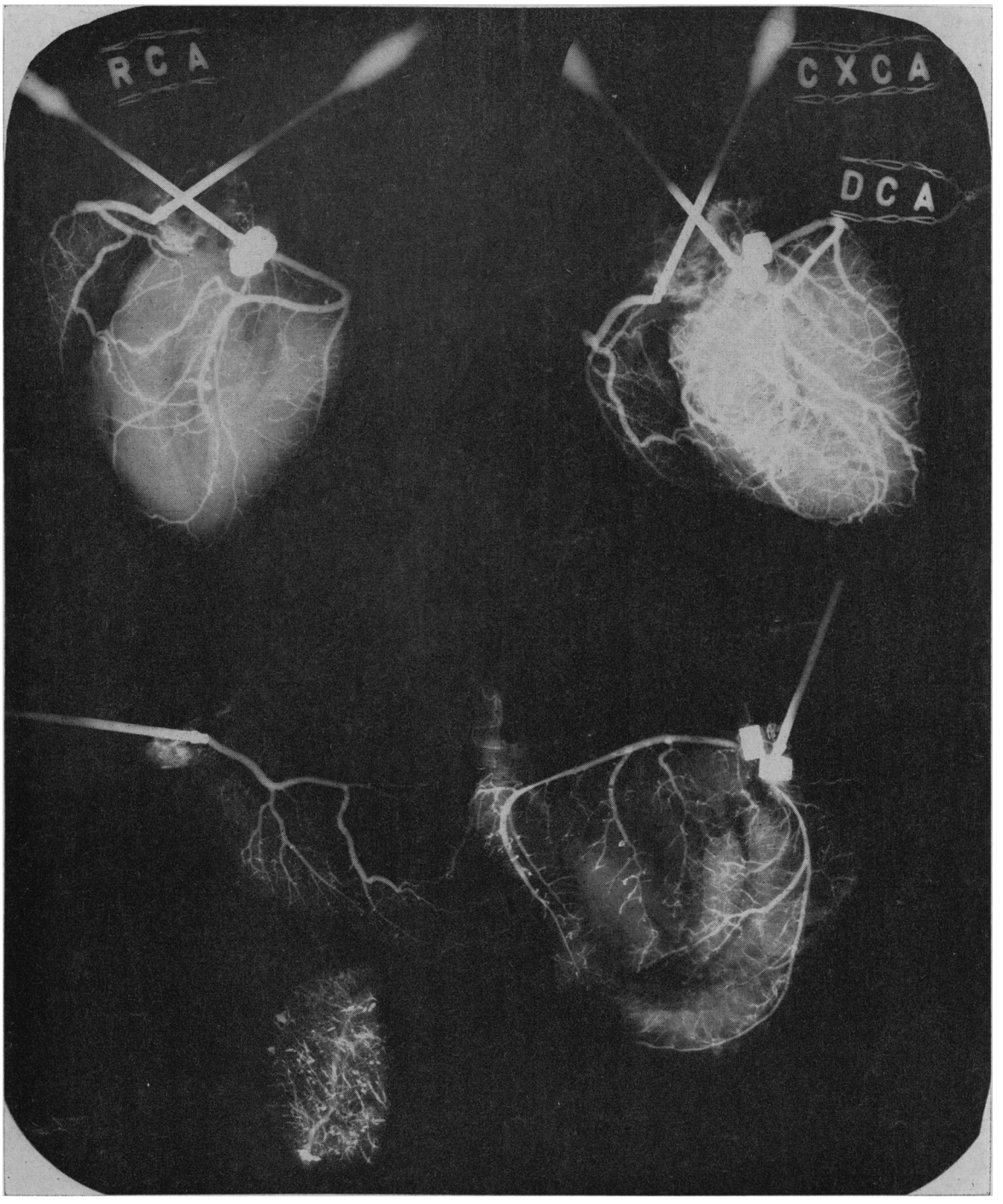



Fig. 2.—Animal No. 94 of the control series survived beyond three months. Perfusion of the right coronary artery (upper left) caused filling of the right coronary system and cross-flow, retrograde filling of the major branches of the left coronary system. There is minimal filling of smaller vessels. The lower picture of the unrolled heart demonstrates the vessels responsible for this right-to-left flow.

left coronary system through collaterals from the right coronary artery could be determined and subsequently compared with the mass in the injected left coronary tree in the same heart. The connecting intercoronary anastomoses responsible for the right-to-left filling can be identified by the unrolling technique. During this study, two hearts injected at the same time showed clear differences in the degrees of anastomoses found. This observation excludes the possibility that differences which will be reported in the anastomoses in the control and Persantin-treated animals were due to differences in technique or in the mass used in perfusion.

## RESULTS

### 1. *Survival*

The survival figures for the 25 animals in this study are shown in the first half of Table I. In the

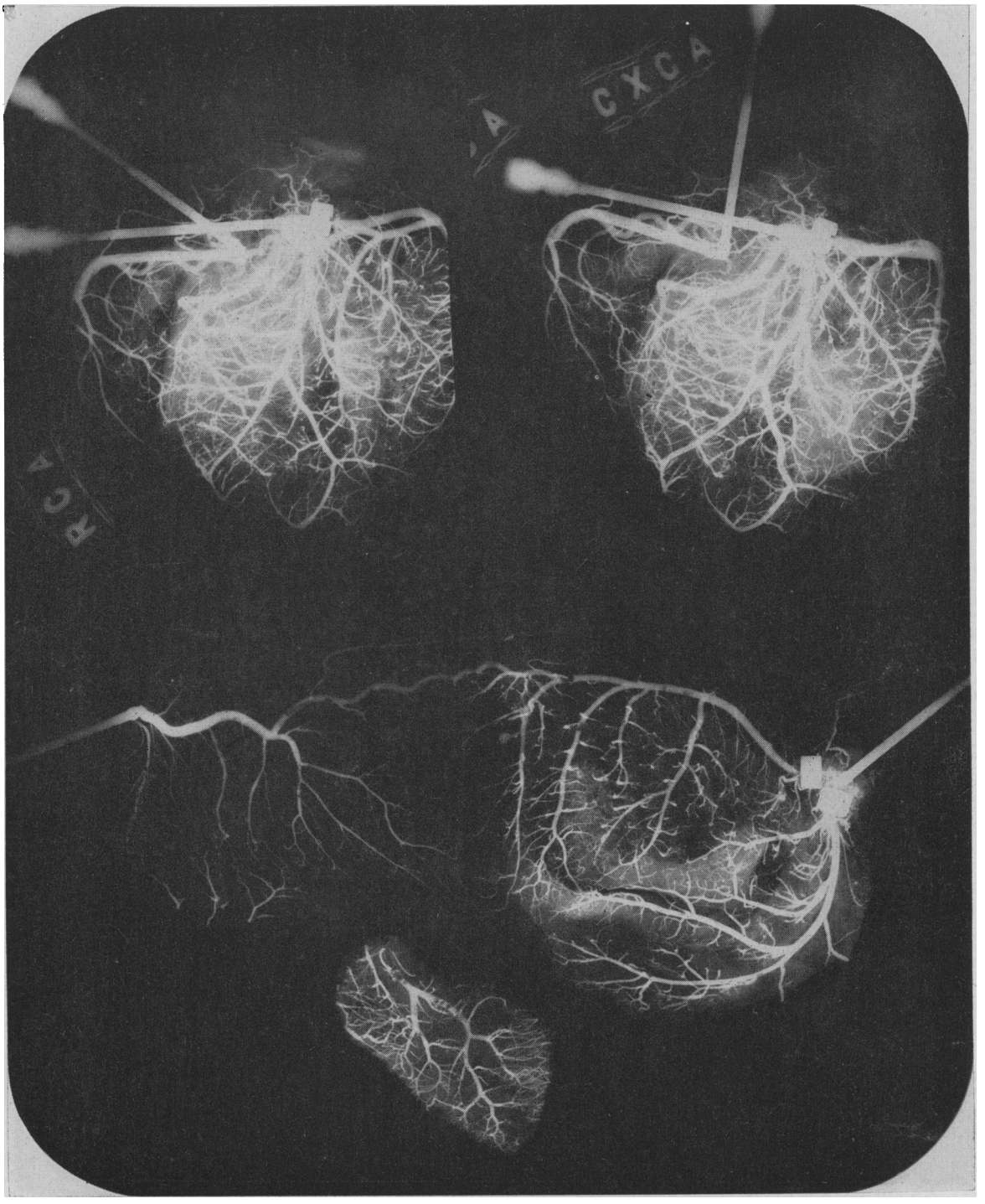



**Fig. 3.**—Animal No. 381 in the Persantin-treated group survived beyond three months. Perfusion of the right coronary artery (upper left) caused complete filling of the right and retrograde filling of the left system. Note the large size of the major vessels and the rich intercoronary anastomoses throughout the entire heart. The intercoronary anastomoses of major vessel size are seen in the unrolled heart.

control series of 13 animals, two animals survived beyond the three-month experimental period and were sacrificed. This 15% survival rate is consistent with the survivals previously reported[2] from this laboratory for similar control groups subjected to the same procedure. In contrast, in the Persantin-treated group the three-month survival rate was more than tripled when compared with the control series. A total of six animals out of the 12 treated with Persantin lived beyond the three-month experimental period and were subsequently killed. This represents a survival of 50%.

### 2. *Development of Collateral Circulation*

The right half of Table I graphically illustrates the degree of collateral circulation which appeared in the control and Persantin-treated animals. In order to provide a rough quantitative estimate of the functional intercoronary anastomoses between the right and left coronary arteries, a system of

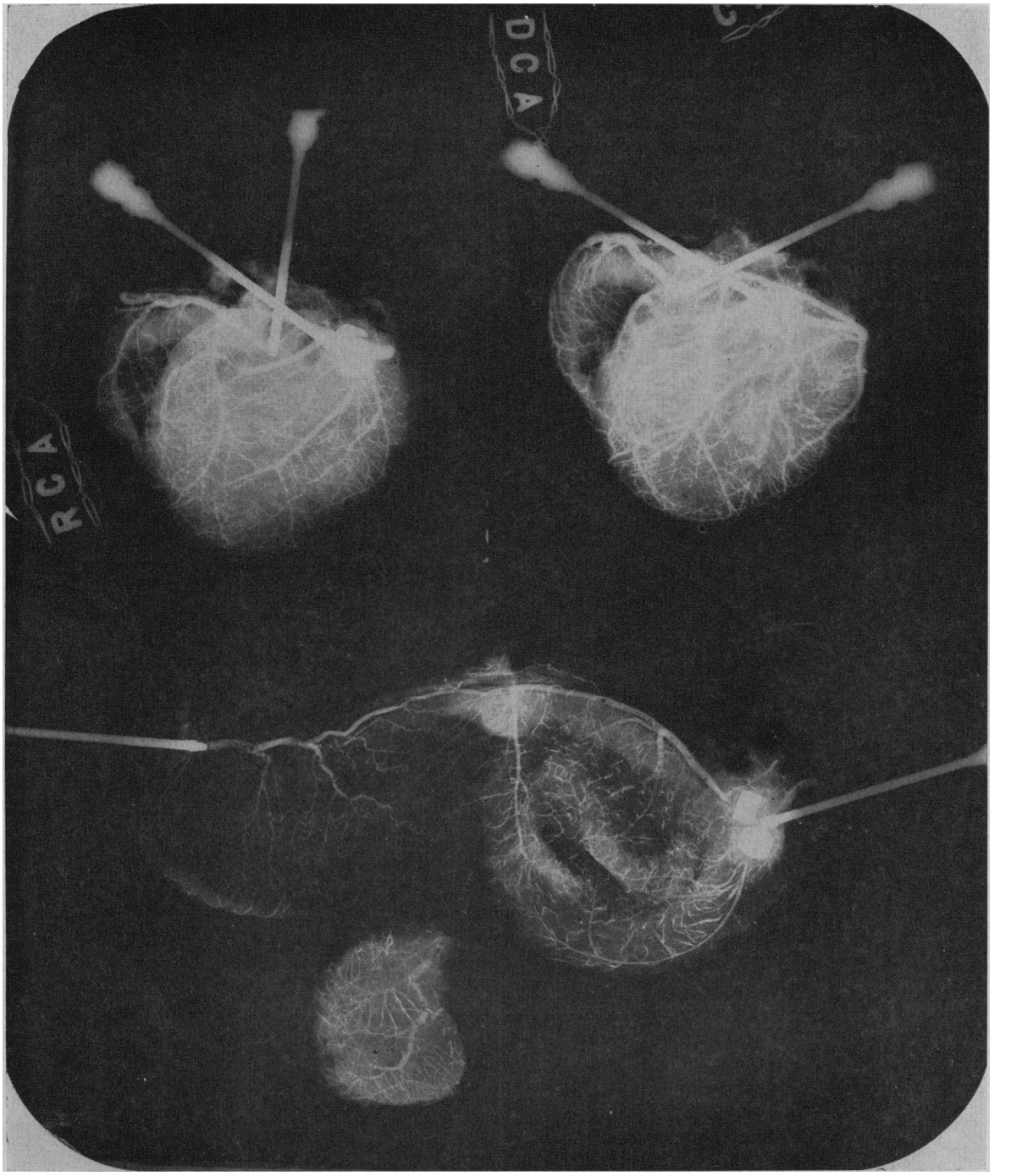



Fig. 4.—Animal No. 322 survived beyond three months. Perfusion of the right coronary artery (upper left) led to complete filling of the right and retrograde filling of the left system. Note the large size of the major vessels and the rich intercoronary anastomoses throughout the entire heart. The intercoronary anastomoses of major vessel size are seen in the unrolled heart.

grading was used. The amount of filling of the left coronary tree following perfusion of the right coronary artery alone was compared with that obtained when the right and left coronary arteries were perfused independently. Thus, the following four grades of collateral circulation were recognized:

(a) *No collateral circulation.*—The radiographs of the heart from dog No. 476 (Fig. 1) are typical of the findings in this category. When the right coronary artery is injected, the perfusion mass remains in the right coronary system; there is no filling of the left coronary tree. Following separate perfusion of the left coronary artery and unrolling of the heart, no collateral circulation can be seen in the boundary between the two circulations. This pattern was seen in seven of the 13 dogs in the control series that died within the three-month period. Only one of the seven Persantin-treated dogs dying within the same period showed a complete lack of intercoronary anastomoses.

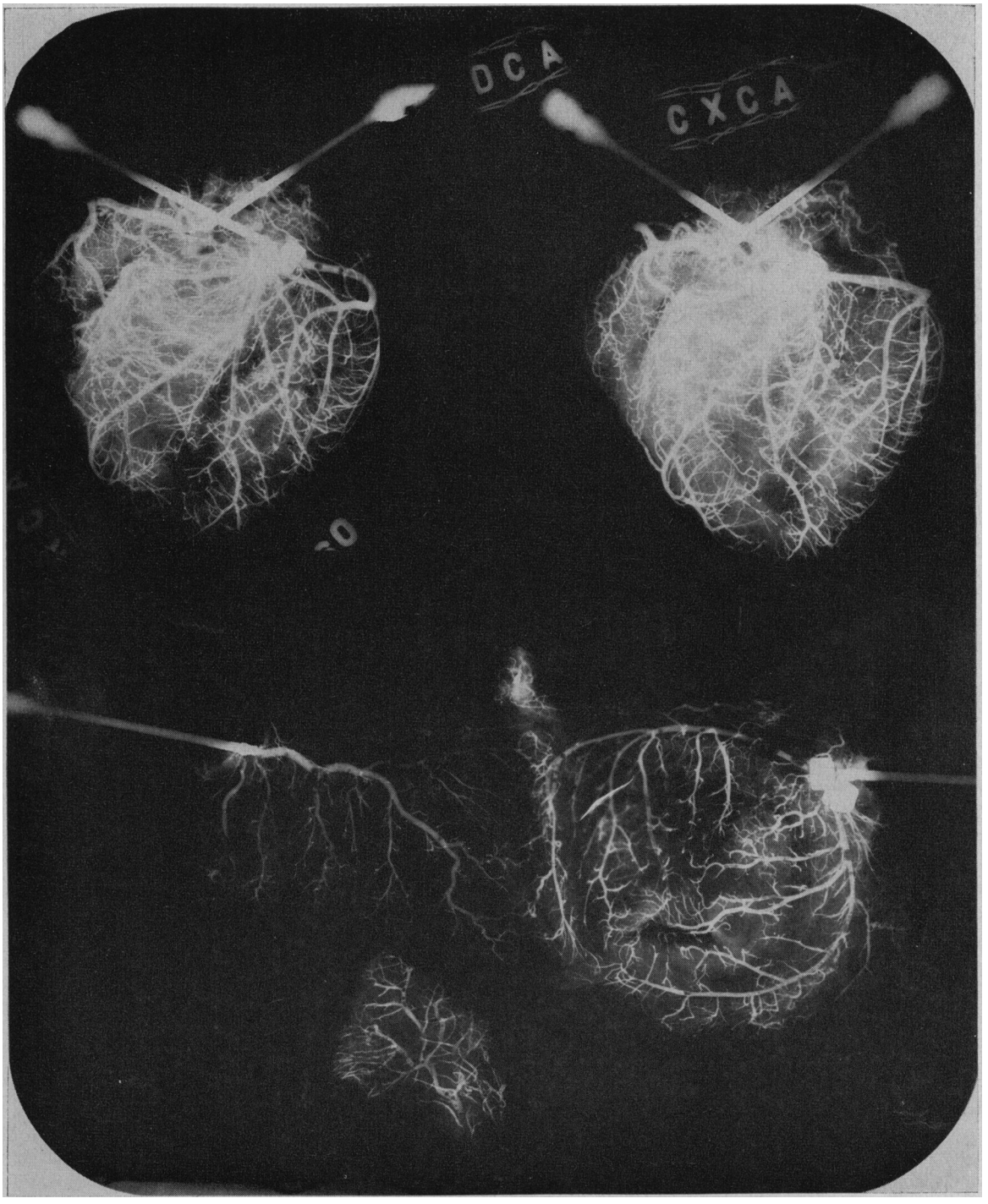



**Fig. 5.**—Animal No. 60 in the Persantin-treated group survived beyond three months. Perfusion of the right coronary artery (upper left) caused complete filling of the right and retrograde filling of the left system. Note the large size of the major vessels and the rich intercoronary anastomoses throughout the entire heart. The intercoronary anastomoses of major vessel size are seen in the unrolled heart.

(b) *Collateral circulation present.*—In this category the development of collateral circulation was sufficient to allow, under the standard conditions of the injection procedure, a variable degree of flow of the radio-opaque mass from the right side to fill portions of the anterior descending and circumflex arteries on the left. If the major arteries and their largest branches on the left side were outlined throughout 50% or less of their extent, the heart was placed in this category.

(c) *Good collateral circulation.*—As in (a) and (b), this category compares the degree of filling of major arteries of the left coronary tree, when the right coronary artery is perfused, with the degree of filling of the left side following perfusion through the left ostium. Animals demonstrating

50% or greater filling of the major arteries, but little or no filling of the smaller vessels, are placed in this category. Fig. 2 demonstrates the radiographic picture obtained from animal No. 94, one of the two control animals that survived the three-month experimental period. It should be emphasized that the degree of collateral circulation seen in this radiograph represents the maximum response of control animals to the hypoxia produced by the Ameroid constrictors in this and previous experiments.

(d) *Complete collateral circulation.*—The fourth category, seen only in the Persantin-treated series that survived beyond the three-month period, represents a state of complete collateral circulation. The intercoronary anastomoses which developed in these animals treated with Persantin allowed free transit of the perfusion mass from the right side; it completely filled both the major and minor arteries of the left side. In these animals perfusion of the right coronary system was followed immediately by a flow of the Schlesinger mass throughout the left system with subsequent backflow through the cannula in the left coronary ostium. The rapidity of filling and the presence of backflow immediately identified the Persantin-treated animals. Figs. 3, 4 and 5 represent the radiographs from dogs No. 381, 322 and 60. A comparison of these three figures (the Persantin-treated survivors) with Fig. 2 reveals immediately the marked difference between the size of the main coronary arteries in the surviving controls and in the surviving Persantin-treated animals. The rich anastomotic bed throughout the entire heart in the latter animals is readily discernible.

In conclusion, the evidence in Table I and Figs. 1 to 5 would indicate that Persantin has tripled the survival rates of animals exposed to the Ameroid constrictor test, by virtue of a profound effect on the development of intercoronary collateral circulation between the right and left coronary systems. It is further evident that even in those animals dying within the three-month period the degree of collateral circulation seen in the Persantin-treated series exceeded that seen in the control series.

## DISCUSSION

In the present state of our knowledge it must be postulated that the beneficial effect of Persantin observed in the present study is due to a profound physical effect of the drug on the coronary arteries and their collateral bed. It matters little to the results of this study whether the collateral channels developed *de novo* or whether Persantin causes the opening up of a non-functioning intercoronary collateral bed. The two dogs surviving in the control group represented in all probability that proportion of animals genetically endowed with the ability to quickly and adequately develop functioning collateral vessels under the stimulus of hypoxia caused by gradual coronary occlusion. However, it is clear that the majority of animals did not have this potential. Previous experimental evidence has demonstrated that Persantin enhanced the effects of hypoxia and greatly increased coronary blood flow. Presumably this additive effect would lead to a more rapid development of intercoronary collaterals; this supposition is borne out by the present study. The rich anastomotic network and the enlarged major vessels seen in the Persantin-treated animals which survived beyond three months was greatly in excess of that seen in the control series killed at approximately the same time.

With regard to the blood levels of the drug obtained in these animals, although some differences in blood levels were found from day to day, no relationship could be found between these levels and the degree of collateral circulation developed. The average blood levels in the Persantin-treated animals which did not survive for three months was approximately the same as the blood levels in dogs that survived beyond this period and that demonstrated complete collateral circulation. These average levels were in turn comparable to those seen in humans to whom the recommended therapeutic dose had been administered. In view of these findings it is reasonable to postulate that animals differ, in all likelihood on a genetic basis, in the rapidity with which collateral circulation develops under therapy with Persantin. It is evident from Table I that the majority of animals in the Persantin-treated series developed collateral circulation in excess of that seen in the control series. There is wide variation in the degree and the speed with which different animals develop collateral circulation. This variation is reflected in the death of animals when a point of critical narrowing of 50% or more of the total cross-sectional area of the two major coronary arteries is reached. If the collateral circulation develops sufficiently rapidly and effectively to give a satisfactory alternate blood supply in replacement of that lost following coronary Ameroid constriction, then these animals do not die.

A final comment should be made regarding the applicability of these findings to a clinical setting. While there is general distrust of the practice of transferring the results of animal experimentation to humans, there is nevertheless a general correlation. Thus, the pharmacologic effects of Persantin, as documented in dogs and reported in the literature, have found general confirmation in human studies reported. The profound effects observed in the present study would indicate that a similar applicability to human collateral circulation development and patient prognosis may also be found. It is obvious that, like the animals in the present experiments, not all patients will receive equal benefit from the use of this drug. In some patients, the coronary arteries will be so severely involved that nothing short of bringing in an extracardiac sup-

ply of blood will relieve the ischemia. To these patients the only hope will lie in surgical revascularization procedures, with perhaps the additional benefits of a compound such as Persantin to redistribute flow from the new vascular source. The more widespread use of coronary angiography as a diagnostic tool in cardiac disease is perhaps timely in this regard. Undoubtedly, the time is near when all patients with coronary artery disease will be treated either by surgery or through the enhancement of collateral circulation by means of a drug such as Persantin. Treatment will be selected on the basis of the extent of the coronary disease as revealed by angiography.

SUMMARY

An experimental investigation is reported of the effect of Persantin on survival and the development of collateral circulation in animals exposed to gradual coronary constriction of both main branches of the left coronary artery. In the control series of 13, two dogs (15%) survived for three months, while six (50%) of the 12 animals receiving 150 mg. of Persantin orally in divided doses survived beyond this period. Schlesinger mass studies performed on the animals would indicate that Persantin significantly accelerated the opening up of the collateral circulation in the treated group. In the surviving animals, the agent seemed to have produced a profound, rich anastomotic network much in excess of that seen in the surviving members of the control series that were exposed to hypoxia alone.

On the basis of these highly significant findings in experimental animals, it is suggested that Persantin may favourably alter the prognosis of many patients with coronary artery disease.

The authors are indebted to Dr. R. J. Efford, Fellow in Medicine at the Royal Victoria Hospital and Medical Adviser to Geigy Pharmaceuticals, for his invaluable assistance in the design of this study. We are grateful to Geigy Pharmaceuticals, Montreal, for supplying us with the Persantin and for the grant-in-aid which made this study possible.

REFERENCES

1. ENOS, W. F., BEYER, J. C. AND HOLMES, R. H.: *J. A. M. A.*, **158:** 912, 1955.
2. VINEBERG, A.: *Progr. Cardiov. Dis.*, **4:** 391, 1962.
3. GREGG, D. E.: *In*: The physiological basis of medical practice, by C. H. Best and N. B. Taylor, 7th ed., Williams and Wilkins Company, Baltimore, 1961, p. 335.
4. FISCHER, F. G. AND ROCH, J.: *Jutras Liebigs Ann. Chem.*, **572:** 217, 1951.
5. ELLIOT, E. C.: *Canad. Med. Ass. J.*, **85:** 469, 1961.
6. KINSELLA, D., TROUP, W. AND MCGREGOR, M.: *Amer. Heart J.*, **63:** 146, 1962.
7. WEST, J. W. *et al.*: *Circulation Res.*, **10:** 35, 1962.
8. BRETSCHNEIDER, H. J. *et al.*: *Arzneimittelforsch.*, **9:** 49, 1959.
9. KIESE, M., LANGE, G. AND RESAK, K.: *Z. Ges. Exp. Med.*, **132:** 426, 1960.
10. BRETSCHNEIDER, H. J.: Action of coronary dilators. Presented at American Heart Association Symposium on Coronary Circulation, Chicago, Ill., March 1962.
11. BERNE, R. M.: *Fed. Proc.*, **20:** 101, 1961.
12. SIESS, M.: *Ver. Deutsch. Ges. Kreislaufforsch.*, **27:** 259, 1961.

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

### RES JUDICATAE—
### A MEDICAL MISSIONARY

To a great extent the revolution and the famine in China have brought out more vividly the "what's the use" of some phases of missionary life, for the missionary has been truly "a very present help in time of trouble". For a nation the size of China, with its immense ignorant population, it is a wonderful, almost incredible, thing that there has been relatively little bloodshed during the civil war; the loss of life has been less than in some single great battles in history. With the exception of the battles at Hankow, there has been very little real warfare, and one can scarcely believe a dynasty has been overthrown and a republic born. No human being can tell what will yet be the outcome; China has given the world many big surprises before this and no doubt there are more "up her sleeve". . .

Whenever we foreigners worked in the famine districts we went in pairs. The need for relief was so urgent that we could not wait until the districts were quiet, so we went without military protection. The whole country was in a state of absolute anarchy. Wholesale, widespread looting, murder, and rapine still continued. Cities and towns were attacked and robbed by the soldiers—robbers whenever or wherever their evil desires dictated. Although the only instance where a foreigner was in imminent danger, as far as we knew, was when his convoy of grain boats was attacked by robbers and one coolie killed, none of us knew for certain when our time might come; so it was a bit nerve racking, especially when the native helpers would themselves get frightened and come to us for courage and comfort.

When morning after morning one finds people lying round dead in a public convenience; when one sees people dying of starvation by the roadside; when one knows positively of a woman burying a still living child because "she had no food and it had to die anyway"; when one knows that dogs dig up the freshly buried and eat them because even they are starving to death; when one knows of people eating a dog that had died; when one sees, handles, and smells food being eaten and that food composed of a cake made of grasses, barks, roots, and weeds, with a few kernels of wheat scattered through it, from all appearance dried cow manure; when one sees every article that the house possesses, even to the roof, either burned or sold for food; when one sees the glossy, pastey, tightly drawn, dark coloured, wrinkled skin, projecting cheek bones, and the teeth covered with sordes, or, on the other hand, the swollen faces, hands, and feet, and even general anasarca, which indicate the person about to die of starvation; when one sees, examines and treats people poisoned by the weeds and grasses they had been forced to eat for food; when one sees thousands of people begging on their knees for a chance to work for food and that food either bean cake, i.e., the remains of beans after the oil has been pressed from them, which are used in normal years principally for manure, or Kao liang, that is a seed of a species of corn used for feeding pigs or making alcohol;—it seems to me there was urgent need of the missionary physician.—W. R. M., *Canad. Med. Ass. J.*, 2: 716, 1912.