HÆMORRHAGIC EFFECT OF ACTH WITH ANTICOAGULANTS*

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IN THE experimental development of anticoagulants, it was early remarked that hæmorrhage was hardly ever observed in normal animals. This was true even with values of the prothrombin time much beyond any encountered clinically. In view of the not too uncommon complication of hæmorrhage with the clinical use of anticoagulants, this suggests that some important factor or factors in the production of hæmorrhage have been overlooked. Recent studies[1] in the laboratory at Saskatoon have demonstrated that stress constitutes such a hæmorrhagic factor. When rabbits receiving dicoumarol, etc., are exposed to such stress as frost-bite, insulin convulsions, and injection of 10% sodium chloride intraperitoneally, 50% will die between 60 and 72 hours later. At postmortem, hæmorrhage can be demonstrated in many animals. This may be subcutaneous, or into the pleural or other cavities, externally or at other sites. This phenomenon has been termed hæmorrhagic death and can be produced by various combinations of treatments. In the present experiments, the effect of combining treatment by pituitary hormones and corticosteroids with treatment by dicoumarol has been studied. Two cases are presented which appear to illustrate the corresponding clinical problem.

Methods‡

Rabbits from the normal colony stock of 2-4 kg. body weight were used. Dicoumarol was given in a single oral dose of 5 mg./kg.; phenylindanedione as an initial dose of 100 mg./kg. followed by 25 mg./kg. three times a day for 5 days; ACTH, somatotrophin, cortisone and desoxycorticosterone were administered intramuscularly as a single dose of 5 mg./kg. at the same time as the first dose of anticoagulant. In one experiment the ACTH was repeated daily for five days. Prothrombin times were carried out by the Quick technique using commercial rabbit brain thromboplastin.

RESULTS

Hæmorrhagic death in rabbits.—Forty-one rabbits were treated with 5 mg./kg. of dicoumarol and the prothrombin time was followed. One of these rabbits died from hæmorrhage on the fifth day. Blood from the intestine was found in the cage, but lungs and other viscera appeared normal. After the prothrombin time returned to normal and after a further rest period of several weeks, the treatment with dicoumarol was repeated and at the same time ACTH was injected. Ten of these animals died. Fig. 1 shows the lungs of one of these animals compared with those of a normal rabbit. Marked congestion and œdema can be observed. Tissues from three other rabbits dying with hæmorrhage are shown in Figs. 2 and 3.

TABLE I.—INCIDENCE OF HÆMORRHAGIC DEATH IN RABBITS RECEIVING ANTICOAGULANTS AND ACTH

Dicoumarol alone	1/41
" + ACTH	10/40
" + somatotrophin	1/11
" + desoxycorticosterone	0/7
" + cortisone	0/9
Phenylindanedione alone	1/7
P.I.D. + ACTH	4/6
Dicoumarol + ACTH repeated daily	0/13

Of the animals receiving dicoumarol and ACTH, one animal died within 24 hours with hæmorrhage in the kidneys and lungs; one died in 48 hours with hæmorrhage in the kidneys, and one in 72 hours, again with hæmorrhage in the kidneys and lungs. Three animals died on the sixth day. One showed the typical picture of hæmorrhage and congestion in the lungs. One showed slight bleeding only from the nose and ears but post mortem all the organs were quite pale, indicating that extensive hæmorrhage had occurred. The other

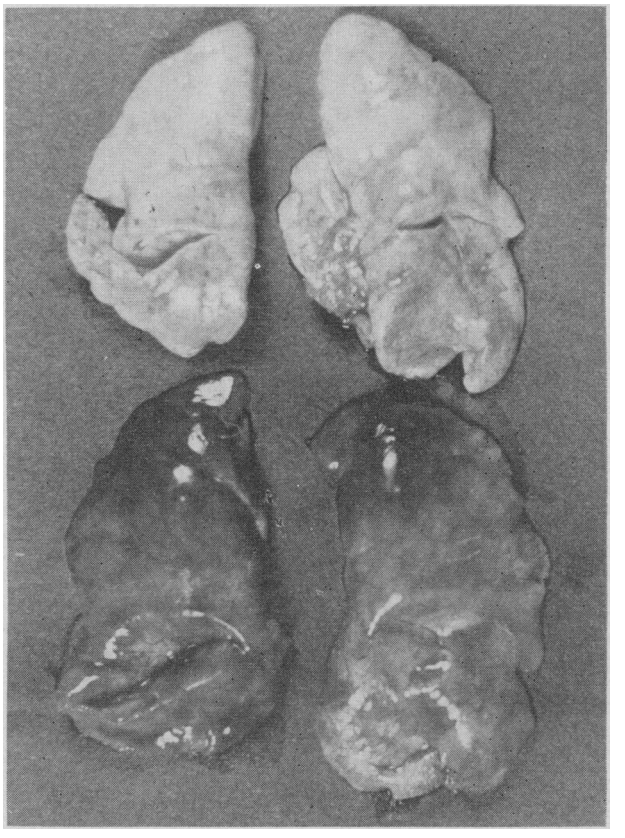

Fig. 1.—Lungs from normal, control rabbit above; lungs from rabbit dying of hæmorrhage after dicoumarol and ACTH below. Marked congestion and œdema.

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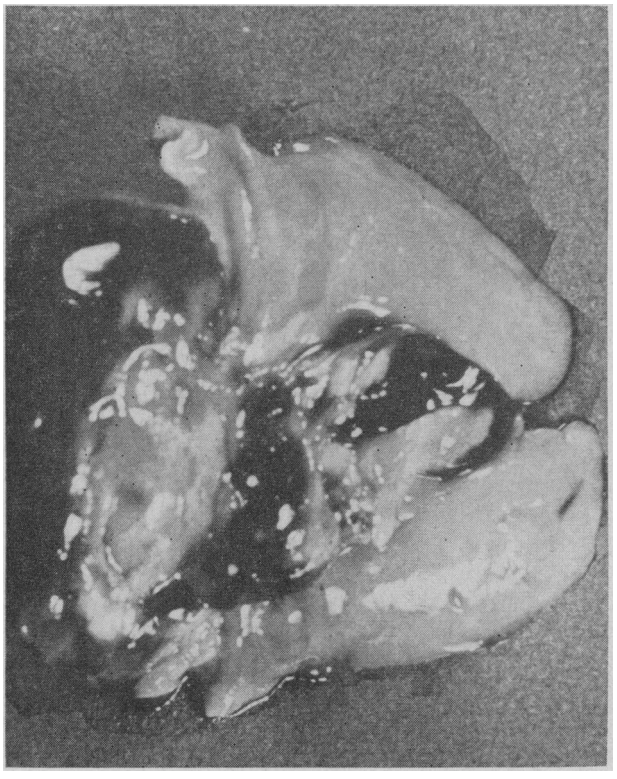

Fig. 2.—Lungs and heart from rabbit dying of hæmorrhage after dicoumarol and ACTH. Death on seventh day. Extensive hæmopericardium and congestion.

showed intestinal hæmorrhage. Three rabbits died on the seventh day. One showed hæmorrhage and congestion in the lungs and kidneys, while the third showed an extensive hæmopericardium. One animal died on the eighth day and showed patchy hæmorrhage in the lungs, hæmorrhagic areas in the intestine and blood in the peritoneum. Another animal showed bleeding from the mouth and nose on the third day but survived. Only one animal died of hæmorrhage on receiving dicoumarol and somatotrophin and no animals died after treatment with cortisone or desoxycorticosterone with dicoumarol. The animal receiving somatotrophin died on the third day with intestinal and peritoneal hæmorrhages.

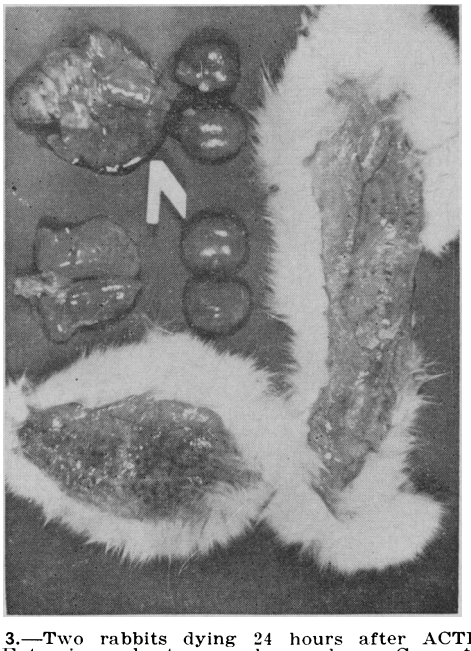

Fig. 3.—Two rabbits dying 24 hours after ACTH and P.I.D. Extensive subcutaneous hæmorrhage. Congestion of lungs. Ecchymotic spots on surface of kidneys.

A small series of animals was tested with phenylindomedione (P.I.D.) and ACTH. Two died 24 hours after ACTH with hæmorrhages in lungs, kidneys, uterus and subcutaneous tissue. One rabbit was found dead on the fifth day with hæmorrhage in the uterus and diffuse hæmorrhage in the left lung. One rabbit was found dead on the eighth day with blood in the urine and patchy hæmorrhage in the lungs. The very high incidence of hæmorrhage and death following ACTH in animals receiving P.I.D. is striking. Actually hæmorrhage from this anticoagulant alone is quite rare in rabbits. When it occurs, it is due to the trauma to the mouth involved in giving the drug in capsule form three times a day, as was the case with the single animal which died after P.I.D. alone. This animal died on the sixth day after bleeding from the jaws and ears from the second day. No lesions were found in the organs but these were very pale.

Finally a small series of rabbits received dicoumarol and 5 mg./kg. of ACTH daily for five days, starting with the administration of dicoumarol. No deaths occurred in this series.

Prothrombin time in rabbits.—Prothrombin times were determined on the animals before the administration of dicoumarol and one, three and five days thereafter. As has been reported by Link[2] and further studied by Jaques *et al.*,[3] rabbits show the phenomenon of resistance, so that rabbits can be divided into reactive and non-reactive rabbits (those showing an increase in prothrombin time and those showing no increase in prothrombin time after dicoumarol). On the basis of the results obtained, animals were sorted out into reactors and non-reactors. The mean prothrombin times are reported in Fig. 4 for all the animals. With the very wide spread in prothrombin times resulting after the administration of dicoumarol, arithmetic means of the values themselves have not a great deal of meaning. It has been pointed out by Mogenson, Fisher and Jaques[4] that if log values of the prothrombin times are taken this gives an approximately normal frequency distribution curve and therefore some meaning to the ordinary statistical procedures such as standard deviation. The prothrombin times were therefore transposed to corresponding logarithmic values, and the mean and standard error calculated for each set of data. Examination of Fig. 4 suggests that ACTH was successful in converting non-reactor rabbits to reactor rabbits. There is a suggestion, though, that the prothrombin time in the reactor rabbits returns to normal more rapidly after ACTH and the prothrombin time was not sustained as long in the ACTH-treated non-reactor rabbits.

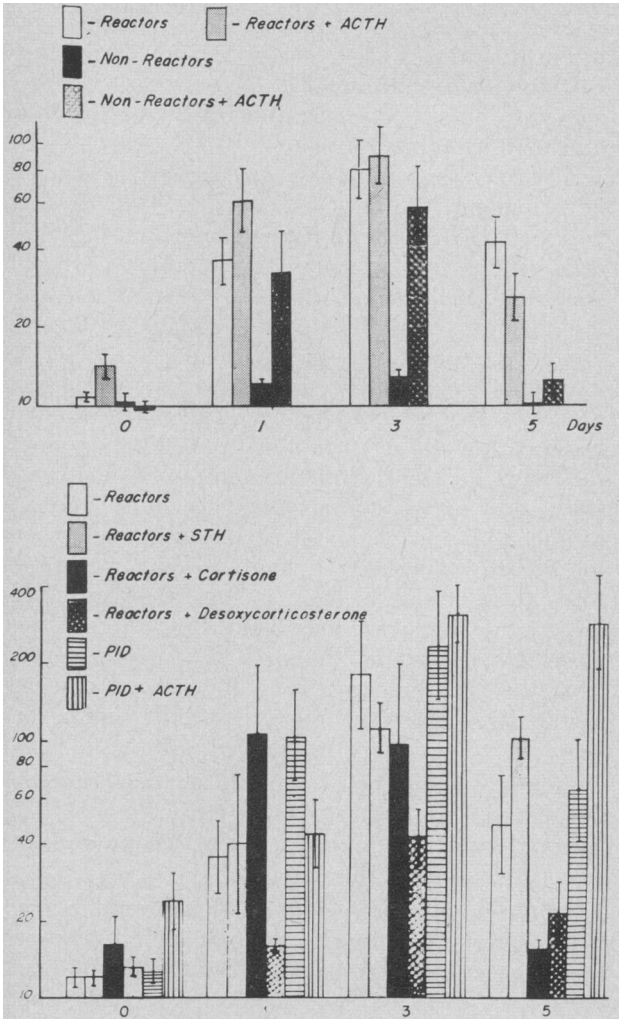

Fig. 4.—Prothrombin time response of rabbits to dicoumarol when treated with ACTH, etc. Anticoagulant and hormone both given on Day O, and prothrombin times determined as shown. Prothrombin times plotted as the mean of the log values of prothrombin time in seconds with standard error. P values were calculated comparing mean values of prothrombin time for the same rabbits receiving dicoumarol with and without the hormone, not against the mean value for all reactor animals shown in figure.

The t test was applied to determine the significance of differences in the mean values. In reactor rabbits, there was no significant difference in the mean prothrombin time on days following dicoumarol, with and without ACTH. On the other hand, there was a marked increase in the prothrombin time of the non-reactor rabbits receiving dicoumarol and ACTH. This, of course, is highly significant when compared with the normal values seen for the same animals with dicoumarol alone on the first and third day after dicoumarol; in fact, the mean values are the same as for reactor rabbits on dicoumarol alone. There is, however, one difference. The mean prothrombin time on the fifth day after dicoumarol is not significantly greater than normal, and hence much less than for reactor rabbits five days after dicoumarol. Presumably this is due to disappearance of the injected ACTH. To test this, another series of animals were given 5 mg./kg. of ACTH each day for five days. Only three proved to be non-reactors. These last three were converted to reactors by ACTH, but the continued daily administration of ACTH following dicoumarol did not maintain the prothrombin times at high values.

Somatotrophin, cortisone and desoxycorticosterone also did not significantly affect the increased prothrombin time induced by dicoumarol in reactor rabbits. The apparent difference seen in the graph with desoxycorticosterone is due to the fact that the group of reactor rabbits used did not give as long prothrombin times with dicoumarol alone as the other groups used. Values were therefore compared for the same animals with and without DOCA. There was no significant difference. Unfortunately, non-reactor rabbits were not available in adequate numbers for this experiment. Desoxycorticosterone and somatotrophin were each given to one non-reactor rabbit without any increase in prothrombin time being observed with dicoumarol. One non-reactor rabbit received cortisone and then showed an increase in prothrombin time ($>$ 480 sec. on the first and third days and 15.6 sec. on the fifth day), while a second non-reactor rabbit gave the same prothrombin times after dicoumarol and cortisone as after dicoumarol alone. We do not find rabbits which are non-reactors to P.I.D. The injection of ACTH did not change the prothrombin time response to P.I.D.

Case Reports

The association of hæmorrhage with the combined treatment of animals with dicoumarol and ACTH suggests the need for examining this as a possible source of clinical bleeding. Two cases which occurred in the Medical Clinic A, University of Liège, are reported.

1. D . . . Jeanne, suffering from rheumatoid arthritis for more than 12 years, was admitted to the medical ward on August 1, 1952, with phlebitis of the right leg with œdema. She was treated with ethyl biscoumacetate (Tromexan) and penicillin for three weeks without any other therapy. The prothrombin level was continuously controlled at between 25 and 45% without any sign of hæmorrhage on one tablet of Tromexan a day. By August 20 the phlebitis was ameliorated but her rheumatoid arthritis was very painful, with increased sedimentation rate and high temperature. ACTH was administered intravenously (10 mg. in 500 ml. of 5% dextrose twice daily) and Tromexan and penicillin were continued. After three days of this treatment with ACTH associated with Tromexan and penicillin, frank hæmorrhage was observed in the stool, the benzidine test for blood in the urine was positive and microscopic examination revealed red cells. The patient was anæmic (Hb. 6.5 g. %; 10.5 g. % before treatment with ACTH). Both drugs were discontinued and 1500 ml. of blood was transfused over a period of five days. The patient recovered from the effects of this hæmorrhage. A barium series proved to be normal.

2. L . . . Marie, a married woman, 61 years old, was admitted to the Liège University Hospital on

March 3, 1953. She was suffering from subacute lupus erythematosus with skin manifestations on the face, the hands, the feet and the neck, and also with pleural effusions, bronchopneumonia in the right lower lobe, albuminuria and fever. There was an increased sedimentation rate (56 mm./1st hour) and raised γ-globulin level. On March 5, administration of penicillin and 40 units a day of Cortrophin-Zinc (long-acting delayed-action ACTH) was begun. On March 8 the temperature was normal and the sedimentation rate decreased to 27 mm./1st hour. On March 10 some ecchymotic lesions appeared on the arms and the legs. The next day new ecchymotic lesions appeared on the trunk and the limbs, accompanied by gross melæna with severe anæmia. The fever reappeared, and in spite of transfusion the melæna and anæmia increased (Hb. 4 g. %) with an increase in the hæmorrhagic lesions over the whole body. The number of platelets was 175,000/c.mm., the prothrombin level 42% and the mean bleeding time 4 min. 24 sec. The patient died March 13/14.

Discussion

As reported in previous papers, mortality due to hæmorrhage is quite small with these doses of anticoagulants in rabbits. However, when ACTH was given with dicoumarol or phenylindanedione, a considerable number of animals died of hæmorrhage, the pathological picture being similar to that previously observed in animals receiving these anticoagulants and subjected to stress. The first case reported is remarkably similar to our animal experiments. The patient was maintained on Tromexan for three weeks without any sign of hæmorrhage. When she was given ACTH, severe hæmorrhage developed in three days, as in the rabbits. Withdrawal of drugs and transfusion saved the patient. The second patient illustrates how severe hæmorrhage can be with ACTH. Here anticoagulants had not been administered but the patient had a correspondingly low prothrombin time, presumably due to the accompanying clinical pathology affecting the liver. The administration of ACTH then precipitated a most extensive hæmorrhagic episode which resulted in death.

Cosgriff *et al.*,[5] Smith *et al.*[6] and others have drawn attention to the problem of thrombosis with ACTH. Bounameaux, van Cauwenberge and Roskam[7] suggested that thrombosis with ACTH is found in those diseases where there is damage to vessels, particularly vascular endothelium, such as lupus erythematosus, periarteritis nodosa, endoarteritis obliterans, Buerger's disease, etc. Here there is present an endothelial lesion tending to thrombosis and it is not surprising that thrombosis then occurs, in view of Cosgriff's finding of increased coagulability with ACTH and cortisone. Stefanini and Rosenthal[8] and others have reported cases of hæmorrhage with ACTH and cortisone. Cheymol and Leroux[9] conclude on the basis of an experimental and clinical study of the effect of ACTH and cortisone on coagulation, platelets, etc., that ACTH will tend to promote hæmorrhage or tend to promote thrombosis, since it causes important modifications of hæmostasis and coagulation, which are markedly different in different patients owing to differences in diathesis. It is evident from our results that treatment with anticoagulants can in itself be one of the factors leading to hæmorrhage with ACTH.

The effect of ACTH in converting rabbits which were previously refractory to dicoumarol to reactors is unexpected. Presumably this is due to the known influence of ACTH on protein metabolism,[10] particularly in the liver. It is interesting that the converted rabbits showed the same mortality with dicoumarol and ACTH as the original group of reactor rabbits.

Why does the combined administration of dicoumarol and ACTH lead to hæmorrhage? It is evident that as the latter does not increase the effect of dicoumarol on the blood prothrombin in reactor rabbits, the ACTH must have some other effect. ACTH causes an increase in the number of platelets[11] but it also decreases their adhesiveness.[7] Roskam, Jaques, MacFarlane, and Tocantins in their respective writings have for many years emphasized that hæmostasis depends on three mechanisms—blood coagulation, platelets, and vascular integrity. Interference with a single mechanism does not result in hæmorrhage. Interference with several mechanisms simultaneously results in hæmorrhage. Dicoumarol interferes with blood coagulation. The similarity of the effects of ACTH to those of stress suggests that, like the latter, ACTH lowers vascular resistance in addition to affecting platelets. The relation of this action of ACTH to corticosteroids is under investigation. However, the observation that hæmorrhagic death did not occur when ACTH was administered daily following dicoumarol is in agreement with other experiments that suggest that ACTH does not have a direct effect but rather that the hæmorrhage is related to levels of circulating corticosteroids below normal, after the initial rise due to administration of ACTH. With damage to two hæmostatic mechanisms, hæmorrhage results. The fact that this occurs in only 20% of animals suggests that not every animal shows the same degree of damage with the dose of ACTH used.

Summary

A significant number of rabbits treated with both dicoumarol and ACTH died of hæmorrhage. No animals died on ACTH treatment alone and only one in 33 died of hæmorrhage with dicoumarol.

Rabbits which failed to show any increase in prothrombin time with a standard dose of dicoumarol showed an increased prothrombin time after treatment with ACTH.

Administration of somatotrophin, cortisone and desoxycorticosterone did not cause death in animals receiving dicoumarol.

A case is reported of gross phlebitis occurring in a patient suffering from rheumatoid arthritis and treated with Tromexan and ACTH. When the two drugs

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were given simultaneously, extensive hæmorrhage was observed, particularly from the gastro-intestinal tract. On cessation of the combined therapy, the patient recovered and no other cause of hæmorrhage could be discovered. A second case is reported of extensive, fatal hæmorrhage following treatment with ACTH.

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RÉSUMÉ

L'administration concomitante de dicoumarol et d'ACTH chez le lapin entraîne la mort d'un certain nombre d'animaux à la suite d'hémorragies viscérales (pulmonaires, rénales et intestinales). L'ACTH par lui-même ne provoque aucune mortalité. Un des 33 lapins traités par le seul dicoumarol a succombé. Dans nos essais les lapins chez lesquels on n'observa aucun accroissement du temps de prothrombine à la suite de l'administration orale d'une dose standard de dicoumarol réagirent normalement à l'anticoagulant lorsqu'ils furent traités à la fois par dicoumarol et ACTH. L'administration de somatotrophine, de cortisone ou de désoxycorticostérone à des lapins traités par dicoumarol n'entraine aucun accroissement de la léthalité.

Les auteurs rapportent deux cas cliniques illustrant leurs observations expérimentales 1) chez une malade souffrant de polyarthrite chronique évolutive compliquée de phlébite, l'administration simultanée de Tromexan et d'ACTH entraîna des hémorragies importantes, particulièrement au niveau du tractus gastrointestinal alors que l'anticoagulant administré seul préalablement à ce traitement combiné avait été parfaitement toléré pendant plus de trois semaines. A l'arrêt de la thérapeutique associée les hémorragies cessèrent, aucune autre cause de saignement ne put être découverte. 2) chez une malade souffrant de lupus érythémateux aigu disséminé avec hypoprothrombinémie des hémorragies généralisées apparurent au cours d'un traitement par ACTH.

SYMPOSIUM ON THE MANAGEMENT OF CORONARY HEART DISEASE*

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[*Each of the authors had undertaken to deliver a 20-minute paper on a broad aspect of coronary heart disease, after a luncheon at the annual meeting of the Canadian Medical Association, Quebec Division. At their first session to consider their tasks, they chose to use a novel technique to present the subject of the management of coronary heart disease. This method is to be found applied to the subject of the rehabilitation of cardiac patients in a recent book edited by Dr. Paul D. White and his confreres.*[1] *Moreover, as both French and English were used by both speakers, a version was prepared in each language; the French version is to be published in* l'Union Médicale.]

1. *How important is coronary heart disease in the daily work of the general practitioner?*

DR. SEGALL: Two elements join to make coronary heart disease of primary importance in the general practitioner's daily work. The total number of men and women in the susceptible age group, i.e., over 50 years, has been and is steadily increasing because of improved public hygiene, life-saving antibiotics and life-saving, life-prolonging surgery. This is one element, the greater number of candidates for the disease. The other is the improved medical knowledge which has made every physician and surgeon acutely aware of the clinical pictures of the disease so that it is recognized more readily in all its varied appearances. The availability of the portable electrocardiograph apparatus has greatly strengthened the physician's diagnostic power. Public education has made lay people fully aware of the wide prevalence of coronary heart disease, its recognition by the physician is not surprising, and lay people tend to give better co-operation in its management because they bring an informed intelligence to bear on the problem.

2. *What guidance does the clinical history provide in recognizing coronary heart disease?*

DR. DAVID: With the exception of rare instances, the diagnosis of coronary heart disease remains based on the *clinical history*. Therefore, the practitioner or the heart specialist must not hurry in taking the history of a disease that will reveal itself by the answers of the patient. What are the clues to be recognized by the examining physician?

First.—It seems to be an established fact that coronary disease is associated with some genetic factors which make it more frequent in certain families and rare in others. Therefore, it is not without interest to know the family history of the parents, brothers and sisters.

Second.—A higher incidence of coronary disease has been observed with certain entities such as hypertension, diabetes, xanthomatosis, familial or essential hypercholesterolæmia, myxœdema, etc.

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