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REVIEW ARTICLE

DICOUMAROL DRUGS AND THE PROBLEM OF HÆMORRHAGE*

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MODERN pharmacology aims to provide a scientific explanation of the clinical action of drugs. Anticoagulants first developed 25 years ago in Toronto have a well-established place in therapeutics. To understand the clinical problems presented by the use of these drugs requires an understanding of their pharmacology—clinical effects, distribution and metabolism, antidotes and toxicity. The present paper is a description of the pharmacology of dicoumarol and other indirect anticoagulants.

The classical indirect anticoagulant is dicoumarol, discovered by K. P. Link.[1] This and all the many compounds subsequently introduced into medicine are characterized not only by the fact that they have no significant effect on blood clotting when added outside the body, but also that the effect on blood coagulation is demonstrated by the change in the clotting time measured with added thromboplastin, the *prothrombin time*, developed by A. J. Quick. The tremendous developments in the study of blood coagulation in recent years have resulted in a great increase in the number of known factors involved in blood coagulation. While this has made untenable the view that the prothrombin time is a measure of the concentration of prothrombin itself, it has left unchallenged the view that increases in the prothrombin time are due to decreases in the concentration in plasma of proteins closely related to prothrombin and associated with it in its activity in coagulation. For simplicity, we can refer to this as the prothrombin complex and to these drugs as prothrombopenic drugs—drugs which cause an increase in the prothrombin time.

The effect on prothrombin time does not appear immediately after administration of these drugs. When a single dose of dicoumarol is given, it requires 24 hours for it to cause an increase in prothrombin time and the effect of a single dose of the drug on the prothrombin time will persist for five days. If we are to consider we understand the action of this drug, we must be able to explain the prolonged lag in the appearance of the effect of the drug on the blood, the increased prothrombin time, and the persistence of the effect, including the slow return of the prothrombin time to normal levels. It has been widely held that the lag represents the time required for the circulating prothrombin complex to be used up, and the time to return to normal as the time required for its replacement. A great number of prothrombopenic drugs are available today. Many of these, such as Tromexan (ethyl biscoumacetate), warfarin and Marcumar (phenyl-hydroxycoumarin) are related to dicoumarol, being also substituted hydroxycoumarins. On the other hand, phenylindanedione (introduced on the North American continent after work in our laboratory)[2] is not a coumarin; it and a series of related compounds such as Dipaxin (diphenylacetylindanedione) are also active. When these compounds are given to animals or patients there are significant differences in the response obtained. When dicoumarol and phenylindanedione are given in single doses approximately the same increase in prothrombin time can be obtained, but the prolongation of prothrombin time is much greater with dicoumarol. Many chemical compounds closely related to dicoumarol or phenylindanedione, however, have no effect on the prothrombin time.

Site of Action of Prothrombopenic Drugs

Jaques and Spinks[3] studied the site of action, using dicoumarol with a radioactive label. Radioactivity was found in blood, urine and gastrointestinal tract, but none was found in skin, muscle or viscera, except the liver. As much as 20% of the dose was found in the liver and by isolation it was demonstrated that the radioactivity was due to unchanged dicoumarol. Jaques and his colleagues[4] compared in a number of species the effect of dicoumarol on the prothrombin time with the length of time dicoumarol remained in the liver. As shown in Fig. 1, the species in which a single dose of dicoumarol causes only a transitory change in prothrombin time show only a minimal amount of dicoumarol present in the liver for only a short time, while larger amounts of dicoumarol are found in the liver for much longer periods

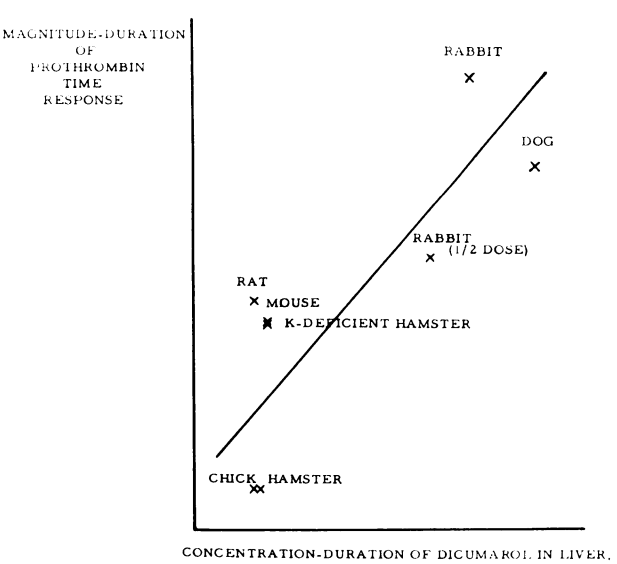

Fig. 1.—*Relation between prothrombin time response and presence of dicoumarol in the liver.* Relative areas of the response curves are plotted (as log values). Dicoumarol—5 mg./kg. Drawn from data in (4).

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in those species where there is marked effect on prothrombin time. Individuals in a given species also show marked differences in the prothrombin time response to a given dose of dicoumarol. Thus in rabbits, some show no change in prothrombin time with doses of dicoumarol which cause a pronounced increase in most animals, and hence rabbits can be divided into two groups, non-reactors with no change in prothrombin time, and reactors. When they were given C^{14}-dicoumarol, the drug in the nonreactor rabbits rapidly disappeared from plasma, blood, liver and muscle in a die-away curve. In reactor rabbits, the dicoumarol persisted longer in blood and tissues. In those animals which showed an increase in prothrombin time, the dicoumarol remained in the liver for three or four days. This difference in the liver was presumably responsible for the difference in concentrations of dicoumarol in the blood. Dicoumarol appears to be metabolized by the liver eventually, and therefore in those animals where there is a hold-up in the liver, its disappearance from the blood and body generally is slower. Van Cauwenberge and Jaques[5] recently made the interesting observation that when such non-reactor rabbits are treated with ACTH, they will show increased prothrombin times with dicoumarol.

Millar *et al.*[6] have studied blood and tissue levels of phenylindanedione (Danilone, Dindivan) in animals. Phenylindanedione disappears from the blood at a surprisingly rapid rate. Like dicoumarol, it can be recovered from the liver, and after intravenous injection much larger amounts of phenylindanedione than dicoumarol appeared in the liver immediately after administration. Up to 18 hours the amount remaining in the liver was about the same as for dicoumarol. On oral administration, absorption from the gastro-intestinal tract was relatively slow, although this may be complicated since intravenous injection showed some excretion of the drug in the bile with possible recycling. However, a very marked difference appeared between blood levels obtained after oral and intravenous administration of the drug. After oral administration, the concentration of phenylindanedione in the plasma was almost negligible, indicating rapid uptake by the liver. As with dicoumarol, the amount of drug fixed in the liver appears to be related to the effect observed on the prothrombin time, but we have not been able to obtain an exact correlation between liver levels and degree of hypoprothrombinæmia. It seems that a certain level or threshold of the drug must be reached in the liver. The fluctuations of the prothrombin time values in the blood do not appear to reflect fluctuations of the amount of the drug in the liver, although our methods of measurement of the latter are much less exact.

Many workers (originally Link) have attempted to identify the active groups in dicoumarol by testing various related compounds. Like Weiner[7] we found that it is not sufficient to study the effect of a single dose of the compound. For example, we found phenylindanedione quite disappointing in our early trials. It was only when we studied repeated doses every eight hours that we got a satisfactory response in dogs and rabbits. Hence a substance can be declared inactive only if no effect on the prothrombin time is detected when adequate blood levels have been demonstrated. Weiner[7] and Pulver[8] have done this for the metabolites of ethyl biscoumacetate (Tromexan) and found both compounds inactive, so evidently as slight a change as introducing a hydroxyl group in the ring, or a carboxyl on the methylene bridge, will render dicoumarol compounds inactive. On the other hand, when compounds as far removed as the indanediones are active, it is evident that considerable variability in chemical structure can still be accompanied by prothrombopenic activity. Link advanced the view that these compounds were degraded to the active compound. Salicylic acid, which he considered to be the active compound, is a weak prothrombopenic agent. It probably can affect prothrombin levels slightly through several actions, one of which is undoubtedly the conversion of small amounts to dicoumarol or a similar compound by bacteria of the gastro-intestinal tract, since Jaques and Lepp[9] showed that in rabbits large doses of sodium salicylate intravenously had no effect on prothrombin time, but did increase it when given orally, and that succinylsulfathiazole abolished the effect.

Dicoumarol presumably inhibits an enzyme system in the liver. Martius[10] has claimed that it inhibits oxidative phosphorylation. Lowenthal[11] in our department has confirmed this but observed that the effect is not shown by all prothrombopenic agents. He found that this action was reversed by cytochrome C but not by K_3, that there was no difference with respect to oxidative phosphorylation, succinic acid oxidase, or cytochrome C oxidase in mitochondria and livers of animals treated with dicoumarol and those not treated, and that dicoumarol did not affect the increase in amount of tryptophan peroxidase produced by sodium salicylate, so that dicoumarol does not affect synthesis of new protein. Probably the effect of dicoumarol on oxidation mechanisms explains the toxic effects of dicoumarol on heart and blood vessels but not its specific effect on prothrombin.

Dicoumarol Drugs and Thrombosis

Dicoumarol drugs are not used simply to increase the prothrombin time of patients but to prevent thrombosis. Our original experiments in Toronto by Murray *et al.*[12] and Dale and Jaques[13] successfully demonstrated that large doses of heparin and dicoumarol could prevent the formation of a thrombus in experimental animals, but evidence that reduction in the incidence of thrombosis depended on the degree to which the prothrombin time was increased has been lacking up to now. To establish a correlation between dose of drug

Canad. M. A. J.
Nov. 15, 1959, vol. 81

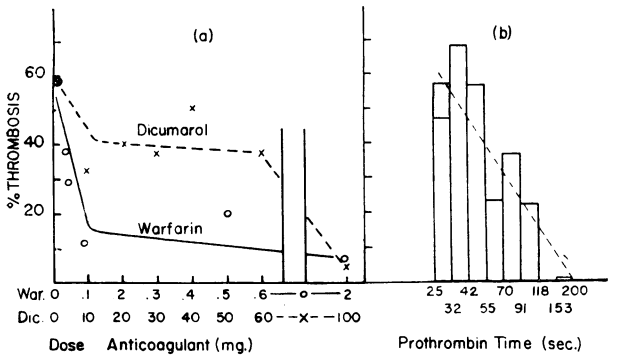

Fig. 2.—*Relation between dose or prothrombin time following indirect anticoagulants and incidence of thrombosis.* Thrombosis produced in jugular vein of rats. Reproduced by permission from *J. Clin. Path.* (14).

(or effect on coagulation) and the effectiveness of the agent in reducing the incidence of thrombosis, it is necessary to use large numbers of subjects with a reproducible incidence of thrombosis. Blake, Ashwin and Jaques[14] have recently worked out a procedure in rats. By simple exposure of the jugular vein and the application of a little 4% formaldehyde to the outside of the vein, closing up the incision and examining it 24 hours later, 70% of the animals consistently developed a thrombus in this vein, readily demonstrated by visual inspection. It is then possible to test the efficacy of an anticoagulant as an antithrombotic agent. As shown in Fig. 2, when dicoumarol and warfarin were tested, warfarin was a much more effective prothrombopenic agent than dicoumarol, but both agents showed a considerable variation with individual animals with regard to the dose increasing prothrombin time. When the incidence of thrombosis was compared with the dose in milligrams of these two agents (Fig. 2a), the highest dose of both drugs reduced the incidence of thrombosis but there was no particular relationship between the degree of reduction and the dosage of drug. When the same animals were grouped on the basis of the change in prothrombin time produced in the individual rat by these drugs (Fig. 2b), a linear relation was obtained between the percentage reduction in thrombosis and the increase in prothrombin time. Therefore an actual linear relationship has at least been demonstrated in the experimental animal between reduction in incidence of thrombosis and increase in prothrombin time with prothrombopenic drugs.

Prothrombopenic Drugs and Vitamin K

The specific antidote for these prothrombopenic agents is vitamin K_1. Vitamin K_3 (menadione) is 2-methyl-1,4-naphthoquinone, while vitamin K_1 is the same with the long phytyl side chain in the 3-position. They have been called the synthetic and natural vitamins, but this differentiation is pointless, as today both compounds are obtained synthetically. When the effectiveness of the two compounds is compared with their ability to reverse the effect of dicoumarol on the prothrombin time in the same patient, menadione has no effect, while administration of vitamin K_1 can result in a prothrombin time close to normal in less than 24 hours. Lowenthal[11] has recently examined this problem from the standpoint of how long it takes K_1 to act. When commercial K_1 preparations are given to rabbits with prothrombin times raised to 100 seconds (normal 15-17 seconds) by warfarin, the prothrombin time returns to a value of 20 seconds in two to eight hours. When K_1 is rendered suitably soluble by using Tween, the prothrombin time is reduced in 40 minutes and a shortening of the prothrombin time can be detected four minutes after the injection. Surely, if the generally accepted view is correct that the time for prothrombin values to return to normal levels after administration of prothrombopenic drugs is due to the synthesis of proteins of the prothrombin complex, then extensive replacement of these proteins in the circulation in 40 minutes means that we must revise our ideas of plasma protein synthesis.

The finding that only vitamin K_1 is therapeutically effective in restoring the prolonged prothrombin time after prothrombopenic drugs, while both K_3 and K_1 are equally effective as dietary supplements in the vitamin-deficient chick, suggests that either these are two fundamentally different actions or that K_3 is converted to K_1 before acting. Jaques and Dunlop[15] showed that when menadione (K_3) is given to dogs simultaneously with dicoumarol it interferes with the rise in prothrombin time. Jaques and Spinks[3] showed that K_3 causes a more rapid disappearance of C^{14}-dicoumarol from the liver of rats, so that although K_3 is not an antidote for dicoumarol, it is an effective antagonist. Dogs with a bile fistula are usually assumed to represent cases of a simple K-vitamin deficiency. After some months the blood of such animals appears to be highly deficient in the prothrombin complex, including proconvertin. Fisher, Millar and Jaques[16] showed that when the vitamins in equimolar doses are given *orally* the prothrombin time returns to normal, and in fact after K_3 administration it persists at normal levels for three weeks. When the blood is examined in the first hours after *intravenous* administration, using the proconvertin test as a sensitive index of changes in the prothrombin complex, the test values become normal in four to ten hours with both K_1 and K_3 and even more rapidly with Synkavite (the phosphate derivative of K_3). Hence the uniqueness of action of K_1 versus K_3 as an antidote for dicoumarol does not hold for other conditions of hypoprothrombinæmia. We earlier concluded that the effect of prothrombopenic drugs is due to their fixation in the liver. While dicoumarol acts in the liver, it does not necessarily follow that the antidotal action of vitamin K_1 is at the same site. Jürgens[17] observed in cats that after *removal* of the liver in dicoumarolized animals, K_1 rapidly reversed the prothrombin time. This suggests that K_1 can exert its effect outside

the liver. The rapidity of action of K_1 in the prothrombinopenia due to dicoumarol suggests an effect on cell permeability with release of the proteins of the prothrombin complex.

Side Effects and Toxicity of Dicoumarol Drugs

As these drugs accumulate in the liver, one would expect to see some evidence of disturbance of liver function, but the ordinary liver function tests all appear to give normal results. Irish and Jaques[18] demonstrated that the plasma concentration of fibrinogen (the most sensitive test of hepatotoxicity) is affected by dicoumarol. In this respect, the latter is certainly a very mild liver toxin because an average dose will cause an increase in plasma fibrinogen, as for minimal doses of most hepatotoxins, and it takes abnormally large doses to cause the typical fall. Van Cauwenberge and Jaques[19] observed in animals receiving dicoumarol, together with other drugs, an apparent reinforcement of drug action by dicoumarol. When using Dial (diallylbarbituric acid) in rats, good anæsthesia was obtained with no deaths in control animals receiving Dial alone, but rats on dicoumarol died before recovering from the anæsthesia. When rats received dicoumarol and reserpine, as judged by their general behaviour, the dose of reserpine had a much greater tranquillizing effect in the dicoumarolized rats than in the controls receiving reserpine alone. Finally, adrenalectomized animals maintained on saline all died of adrenal insufficiency in four days when given dicoumarol, suggesting an increased requirement for corticosteroids after dicoumarol. Jaques *et al.*[4] found a specific uptake of dicoumarol by heart muscle. Kubo[20] and Lowenthal[11] have found that dicoumarol is toxic to the isolated rabbit heart and this probably explains the symptoms of right heart failure observed by the early workers (cf. 13) in rabbits receiving extra large doses of dicoumarol.

Spontaneous Hæmorrhage

The major sign of toxicity with anticoagulants is spontaneous hæmorrhage. In our early experimental work with anticoagulants, we *never* saw animals develop hæmorrhage. In fact, it is amazing how completely some of these drugs can interfere with the blood coagulation system without any symptoms of hæmorrhage. Using phenylindanedione, we have maintained the prothrombin time at a level of 10 *minutes* (normal 10-12 seconds) for three and four months without any signs of hæmorrhage. A prothrombin time of 10 minutes must surely represent a complete blocking of coagulation and is much beyond values established clinically. The fact that hæmorrhage is a not too uncommon complication of clinical use of anticoagulants suggests that some important factor or factors in the production of hæmorrhage have been overlooked. Studies in our laboratory[21] have demonstrated that stress constitutes such a hæmorrhagic factor. When rabbits receiving dicoumarol were exposed to the stress procedures of frostbite, insulin convulsions, or injection of 10% NaCl intraperitoneally, 50% died 60 to 72 hours later. On post-mortem examination, hæmorrhage could be demonstrated in most animals. We have termed this phenomenon death from spontaneous hæmorrhage, and have found that it can be produced by various combinations of treatment. The extensive hæmorrhage usually found post mortem might take the form of an extensive subcutaneous hæmorrhage. In some animals the pleural cavity was found to be filled with blood. Many animals showed marked pulmonary congestion and hæmorrhage, which on occasion appeared as patches of hæmorrhage over the lung. A few animals showed hæmaturia before death. Ecchymotic areas were frequently observed in the kidneys. Hæmorrhage has been observed in the peritoneum, in the intestine (sometimes due to a perforation), in the pericardium and in the uterus. One rabbit developed a hemiplegia of the left fore and hind quarters and there appeared to be a light hæmorrhage into the internal capsule upon examination of the fixed brain tissue. Bleeding from the nose and mouth was not common; when it did occur, the blood loss was certainly not sufficient to explain the marked paleness of organs found on post-mortem examination. In some animals, no frank hæmorrhage could be found. As the time and nature of death were the same and the extreme paleness of the organs indicated severe anæmia, we concluded that they also died from generalized blood loss.

The incidence of death from spontaneous hæmorrhage in rabbits when treated with anticoagulants together with stress procedures is remarkable. No animals died of hæmorrhage when given phenylindanedione alone. The degree of stress used was just below the M.L.D., so that about 10% of animals died immediately from the effects of stress. These did not show signs of hæmorrhage and there were no later deaths at the time when other animals died from hæmorrhage. In contrast to this, when rabbits received both indirect anticoagulants and stress 40-70% died 60-70 hours later. This was true with both phenylindanedione (Danilone) and dicoumarol and with all three types of stress.

The same phenomenon was observed in rats.[19] When rats were given dicoumarol daily for five days, only 6% died, but when subjected to stressful procedures during this period, 50% of the rats died 24 hours later. As in the rabbits, little external hæmorrhage was observed but subcutaneous hæmorrhage was observed. The most common finding post mortem was hæmorrhage in the intestine and congestion and possible hæmorrhage in the lungs. Hæmorrhage was also observed in some animals in the peritoneum, kidney and adrenals and on the under surface of the brain. Other treatments than the 10% NaCl, used in doses known to deplete adrenal ascorbic acid and chol-

Canad. M. A. J.
Nov. 15, 1959, vol. 81

TABLE I.—RELATION OF PRODUCTION OF SPONTANEOUS HÆMORRHAGE TO HÆMOSTATIC MECHANISMS

(1) Blood coagulation (fibrin formation) (2) Clou hémostatique (platelet plugging)

(3) Vascular integrity and response (capillary resistance, vasoconstriction)

Treatment	*Known effect of treatment*	HÆMORRHAGE EXPERIMENTS				
		Dic.	*Res.*	*Stress*	*Adr.*	*Hep.*
		Death from spontaneous hæmorrhage†				
Dicoumarol, Danilone	anticoagulant	1	+	+	+	−
Reserpine	removes platelet serotonin	1:2	2	+	+	+
Frost bite, 10% NaCl i.p., Insulin convl.	decreases capillary resistance	1:3	2:3	3	−	−
Adrenalectomy, ACTH	decreases capillary resistance	1:3	2:3	3:3	3	+
Heparin	anticoagulant and antistress	1:1	1:2	1*:3	1:3	1
		Hæmostatic mechanisms affected				

*But antistress. †30-100% mortality.

esterol, to increase steroid levels in blood and to decrease the circulating eosinophils, also caused the same type of hæmorrhagic death when combined with dicoumarol. About 50% mortality from spontaneous hæmorrhage was found on administering sodium salicylate, adrenaline and histamine with dicoumarol.

Trauma and adrenalectomy were introduced as factors in some experiments. Trauma increased mortality but did not change the conclusions. Thus, dicoumarolized rats showed 30% mortality on cardiac puncture, compared with a very low mortality with untreated rats, but the mortality was raised to 70% if the rats were also subjected to the stress of electroshock before cardiac puncture. When adrenalectomized rats maintained on 1% NaCl were given dicoumarol, they died within a week of adrenal insufficiency. If the rats received desoxycorticosterone, the signs of adrenal insufficiency did not develop but the rats still died within six days. In this case the rats died of hæmorrhage identical with that of intact dicoumarolized rats subjected to stress. Mortality was reduced slightly by whole adrenal cortical extract and prevented almost completely when these dicoumarolized adrenalectomized rats were maintained on cortisone or a somewhat larger dose of hydrocortisone.

It was possible to produce identical death from spontaneous hæmorrhage in animals without the use of anticoagulants and with no change in prothrombin time.[22] When rabbits or rats subjected to the stress of 10% NaCl intraperitoneally were also given reserpine, 30% of the animals died of hæmorrhage 65-90 hours after the stress and reserpine, without any significant change in prothrombin time.

How do these treatments lead to hæmorrhage? In the dicoumarolized subject, is it due to the dicoumarol producing a greater effect on the prothrombin time? Prothrombin values were determined in all these experiments, and while sometimes an increase and sometimes a decrease occurred in the mean value, there was no relation between this and the mortality figure. The answer is actually one that has been known to workers on coagulation for many years—the multiplicity of factors in hæmorrhage and hæmostasis. Roskam[23] in particular has written on this but most authorities in the field have recognized it to a greater or lesser degree. Hæmostasis does not depend on any one single mechanism. There are at least three definite mechanisms (Table I)—the coagulation system, the platelets, the vascular component (vascular integrity and vascular response). Tocantins[24] has indicated that the relative importance of these three mechanisms is different at different levels of the vascular tree. Spontaneous hæmorrhage does not result if only one of these mechanisms of hæmostasis is blocked. For example, individuals with the rare condition of afibrinogenæmia may live for many years in spite of the fact that there is no possibility of the blood clotting. Patients on anticoagulants may shave without difficulty from hæmorrhage. These examples may be replicated many times. They emphasize that for such a serious physiological function as hæmostasis there is a very great physiological reserve. Hence, when animals bleed after treatment with dicoumarol and stress, it is due to the effect of the stress on a hæmostatic mechanism other than the coagulation system which has already been deranged by dicoumarol. Kramár[25] has demonstrated that stress

and adrenalectomy have a very marked effect on the ability of blood vessels to maintain their integrity as judged by the capillary resistance test. Hæmorrhage results from combined treatment with dicoumarol and stress because after stress there is marked impairment of vascular integrity.

Our experiments on spontaneous hæmorrhage are summarized in Table I. The various treatments to which experimental animals have been subjected are listed on the left-hand side and again across the top of the Table. In the upper right side is scored the occurrence of spontaneous hæmorrhage. Along the diagonal corresponding to treatment with a single procedure, all values are negative (-); i.e., spontaneous hæmorrhage does not occur or only to a slight degree (<10%). Away from the diagonal corresponds to treatment with a combination of procedures. Some of these show +; i.e., 30-100% mortality from spontaneous hæmorrhage. Numbering the hæmostatic mechanisms (1), (2) and (3) for blood coagulation, platelet plugging and vascular integrity, we can then indicate the hæmostatic mechanisms blocked by the given procedure and this is entered in the lower left half of the Table. Dicoumarol as an anticoagulant blocks (1). Reserpine by removing serotonin from platelets presumably affects (2). Stress and adrenalectomy reduce the effectiveness of (3). No spontaneous hæmorrhage results from these individual effects. When (1) and (2) are both disrupted by dicoumarol and reserpine together, hæmorrhage occurs. When (1) and (3) are damaged by dicoumarol and stress together, or dicoumarol and adrenalectomy, spontaneous hæmorrhage results. When (2) and (3) are damaged by reserpine and stress, hæmorrhage occurs. On the other hand, stress and adrenalectomy act on a single mechanism or through a common pathway, and combining these does not result in hæmorrhage. Finally, heparin acts as an anticoagulant but it does not cause spontaneous hæmorrhage when the animals are subjected to stress. This presumably is related to the finding that heparin interferes with certain effects of stress.[26] It does produce spontaneous hæmorrhage in adrenalectomized rats and in normal rats which have been treated with reserpine.

You may ask why we do not get 100% mortality from hæmorrhage. In some experiments we do but there appears to be a large biological variation in response to the procedures used. For example, with dicoumarol we find reactor and non-reactor animals and the degree of mortality can be correlated with the severity of the hypoprothrombinæmia due to dicoumarol. When one gives a standard dose of a stress agent, it is quite evident that the strength of stimulus is different for different individuals and this is responsible for variation. There also appear to be different levels of interference with vascular integrity. There is also the possibility of one treatment interfering with the effect of the other treatment, since it is probable that fibrin formation is involved in platelet clumping, platelet serotonin in vascular contraction, etc. However, we have found this rather coarse classification of mechanisms of hæmostasis to stand up to experimental trial. As an operational principle, the manipulation of multiple factors to give an easily measured indicator—death from spontaneous hæmorrhage—makes possible the assessment of the physiological factors governing hæmostasis, including the hormonal and nervous components controlling the vascular factor, and the development of assay procedures to assess hæmostatic agents. Equally important is the application of the principle in clinical medicine. More specifically, *spontaneous hæmorrhage is not the natural accompaniment of anticoagulant therapy but rather a warning of the presence of some pathological process. Stress through its effect on blood vessels is one of the most common exciting causes of hæmorrhage.*

This is a very quick survey of our recent contributions to this interesting field. The advances made could not possibly have been accomplished without the work of loyal colleagues and students. Owing to shortage of space it is not possible to mention them by name, but I would like to make special mention of Professor G. J. Millar, Dr. J. Lowenthal, our Professor of Chemistry, Dean J. W. T. Spinks, and Dr. H. van Cauwenberge, a visiting worker from Professor Roskam's department at Liége. His visit and most of this work were sponsored by the National Research Council of Canada. The work on thrombosis and the initial work on hæmorrhage were supported by the Defence Research Board of Canada.

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Association Notes

SUBSCRIPTIONS TO BRITISH MEDICAL JOURNAL

The British Medical Association informs us that the subscription rate to the *British Medical Journal* for members of the Canadian Medical Association has been raised from 2 guineas to 2½ guineas (£2.12.6d) as a result of revisions of subscriptions decided on by the representative body of the B.M.A. at the Edinburgh meeting. This low subscription rate, available to C.M.A. members, is the rate charged to B.M.A. members residing within the British Commonwealth.

MEDICAL SOCIETIES

THE AMERICAN ROENTGEN RAY SOCIETY

The 60th Annual Meeting of the American Roentgen Ray Society was held in Cincinnati, Ohio, September 22-25, at the Netherland Hilton Hotel. This meeting of the oldest scientific radiological organization in the United States attracted about 1500 radiologists from the U.S.A. and Canada.

The presidential address was given by Dr. Edward Neuhauser of Boston who succeeded Dr. B. R. Young of Philadelphia as president. Dr. Neuhauser made a sound plea for smaller meetings in medicine. He said that unless the numbers attending meetings were kept down and ample opportunity was given for discussion, the postgraduate education involved could not be effectively carried on. He added, "For years the major societies in medicine have been burgeoning in attendance; many take pride in the number of registrants. Unfortunately, more registrants don't necessarily mean a better meeting. . . . Smaller meetings usually held on an informal basis can have free discussion of completed studies or work in progress. Comment and criticism are invited. It is hoped that these scientific organizations will be kept small by firm and hard-minded admission committees."

A scientific highlight of the meeting was the annual Caldwell Lecture, honouring the memory of the late Dr. Eugene W. Caldwell of New York City, a pioneer in medical radiology. This year's lecturer was Dr. Donald L. McRae, associate professor of radiology, McGill University, who spoke on the significance of abnormalities of the cervical spine. Another striking feature of the meeting was the presentation of a very comprehensive motion picture on the medical use of radiation. This picture, "Radiation; Physician and Patient", had been shown at the scientific assembly of the American Medical Association in June. The film is available for showing from the American Medical Association Film Library, the United States Public Health Service or the American College of Radiology, Chicago.

LETTERS TO THE EDITOR

DR. W. E. GALLIE

To the Editor:

It is well known to many of your readers that Dr. Gallie initiated the first formal training program for surgeons in Canada. Not so well known however is the fact that over the past 25 years the graduates of this training program have gathered once a year for a meeting with Dr. Gallie at which original work done by the former residents was presented to the group. For many of those participating this afforded them an opportunity to present their work; for all it was an opportunity to renew old friendships; however, for most of us who lived at a considerable distance from Toronto, it meant something far more than this. It was a sort of pilgrimage to be with our former Chief for two days.

Repeatedly I have thought about the profound influence exerted by this great man, not only on trainees in surgery, but also on students in medicine and surgeons in general throughout Canada and the world. I have tried to analyze what he meant to me particularly. Now that he has gone, it is prudent and timely to reflect on the great influence which he had on my own career. I would say that it was not that he was such a great surgeon, not that he was such a profound investigator and contributed many procedures of great importance to surgery in this world, nor that he was such a great teacher. What then are the influences that he had upon me in particular? He had attracted good teachers under his professorship who taught us much of our knowledge of surgical technique, diagnosis, and surgical patient care, but I think his greatest influence was "the man himself". His honesty, integrity and humility were qualities which one did not learn from his lectures or writings. These were qualities which we all strove to emulate but which few of us have been able to develop to anywhere near the degree possessed by him. One could not be in his presence without feeling his influence in these respects, and even to feel them once a year at our annual meeting served as a great stimulus for the ensuing 12 months until we would gather again. He was forthright in his opinions, but he was also kindly. He was a friend to anyone who had even slight contact with him. On the one hand he was regarded as "God himself" and on the other hand, "father confessor and a true friend". He was never too busy to talk to one of his trainees and his words were always compassionate and never berating. His tireless energy and great kindliness towards his patients were something that you could not help but absorb as you made rounds with him.

He taught all of us to be good teachers and good surgeons but by simple example he also taught us the finest qualities of man. I am sure these will be enduring even though he has passed on. I am sure they will