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Accidental Ingestion of Anticoagulant Resulting in a Severe Hemorrhagic Diathesis*

by

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This case history of a 45-year-old woman, who had been issued Dicumarol instead of Dronactin in a pharmacy-filled prescription, describes an emergency therapeutic program to control hemorrhage with vitamin K, adrenal corticosteroids, and the giving of fresh blood. In a patient with a bleeding disorder, unintentional ingestion of oral anticoagulants is to be suspected if the prothrombin time is markedly elevated, if the patient has been previously treated with an oral anticoagulant, or is engaged in a medical or paramedical occupation. Diagnosis is confirmed by finding a deficiency of factors II, VII, IV, and X, and by the presence of anticoagulant in the plasma through chemical analysis.

Dr. Raymond W. Monto: On the second of September at 12 noon, I received an urgent call from a physician in the Upper Peninsula of Michigan stating that a patient, who exhibited a severe hemorrhagic diathesis, had already been placed aboard an airplane and would arrive at the Henry Ford Hospital in approximately three hours. Doctor Williams will relate the history.

Dr. E. R. Williams: Mrs. M., a housewife, age 45, stated that her present illness began eight days prior to admission when she first noticed ecchymoses on her right arm, and within the next several days similar lesions appeared on the other extremities. She contacted her physician and, although initial "blood tests" were said to be normal, hospitalization was advised. Two days prior to admission at this hospital (H.F.H.), attempted venepunctures resulted in massive hematomas of both arms. On the morning of her flight to Detroit, she collapsed while walking to the bathroom. Neither the pulse nor blood pressure could be obtained. A saline intravenous infusion was started, 100 mg. of hydrocortisone was administered, and the patient was flown to Detroit.

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*Abridged from a transcript of the Tuesday Morning Medical Conference presented 20 September, 1966, in Buerki Auditorium. Edited by W. S. Haubrich, M.D.

**All participants from the Division of Hematology.

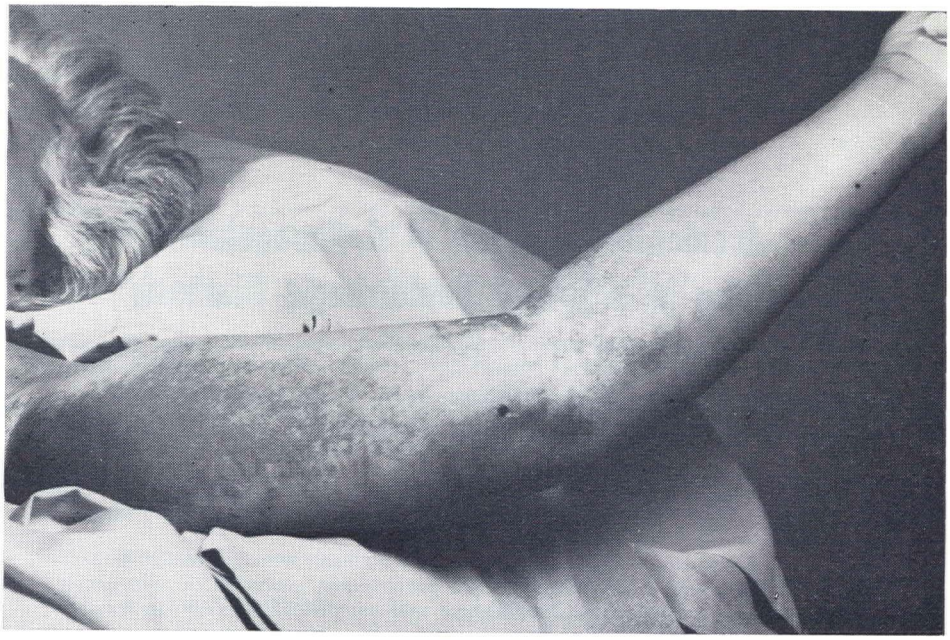

Figure 1

Illustrates a massively swollen arm due to subcutaneous hemorrhage caused by Dicumarol intoxication.

The past history was negative, but for the past seven months she had been treated for a dermatitis of the external auditory canals. The eruption later spread to involve the skin of the face. Oral treatment consisted of Librium (chlordiazepoxide hydrochloride) and Dronactin (dexamethasone and cyproheptadine hydrochloride) in addition to topical preparations.

When seen initially in the Emergency Room, the patient presented the clinical signs and symptoms of shock. She was conscious but very weak. The pulse was 132 per minute and regular, and the blood pressure was 96/60.

Her left arm was massively swollen and ecchymotic (Fig. 1). Large ecchymoses were present over other areas of the body, (Fig. 2). The right arm and leg were similarly involved, but to a lesser degree, and she was bleeding vaginally. The initial laboratory studies included a hemoglobin of 4.6 gms. per 100 ml. and a blood smear which demonstrated adequate platelets and was otherwise normal. The prothrombin time was indeterminable with no end point. A correction mixture using one part normal and one part patient's blood gave a prothrombin time of 14 seconds. The factor II and factor VII and X assays resulted in values too low to measure. Other coagulation tests included a normal fibrinogen level and no evidence of fibrinolysis.

The patient received three units of *fresh* whole blood and intravenous hydrocortisone 100 mg. every four hours. The following morning she was dramatically improved, with a hemoglobin of 10.4 gms. per 100 ml. and a prothrombin time of 25 seconds.

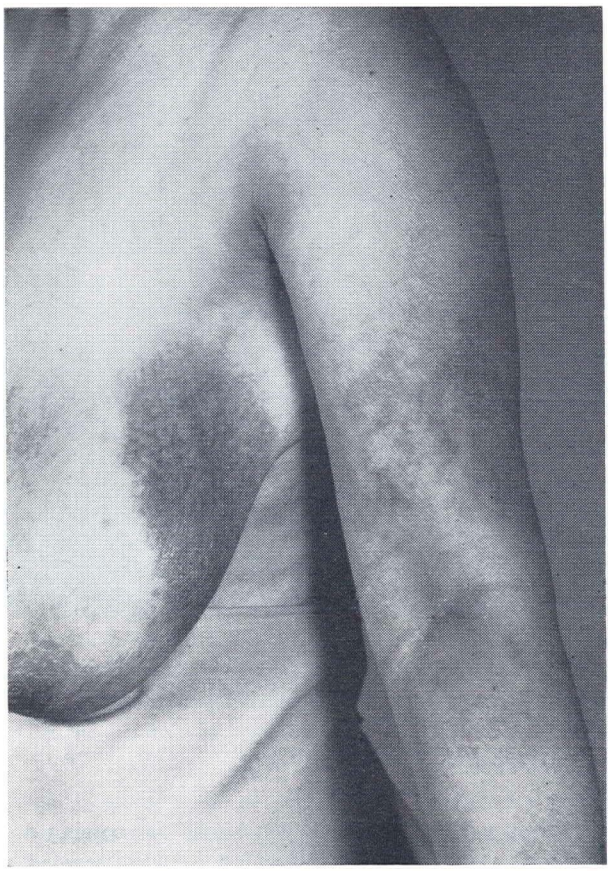

Figure 2

Note large ecchymosis on the lateral aspect of the arm, antecubital area and breast in patient who accidentally received excessive amounts of Dicumarol.

Blood was drawn for analysis of exogenous anticoagulants and the Dicumarol level was later reported to be 19.44 mg. per liter. Further therapy included 80 mg. of I.V. Vitamin K in divided doses and two additional units of *fresh* whole blood. The prothrombin time on the morning of the third hospital day was 15 seconds (control 13 seconds). Her left arm was treated initially with elevation and later with physical therapy. While still ignorant of the results of the chemical analysis of the blood, the patient was exhaustively interrogated for possible exposure to Coumadin-like drugs. At our request, her previous medications were sent from her home. The "Dronactin"* medication bottle contained 59 white tablets which were identified by the pharmacy and the chemical laboratory as 50 mg. Dicumarol tablets (Fig. 3). She had ingested approximately 40 tablets over a period of 18 days prior to admission.

*Dronactin®, for which the prescription was intended, is a combination of dexamethasone and Periactin®.

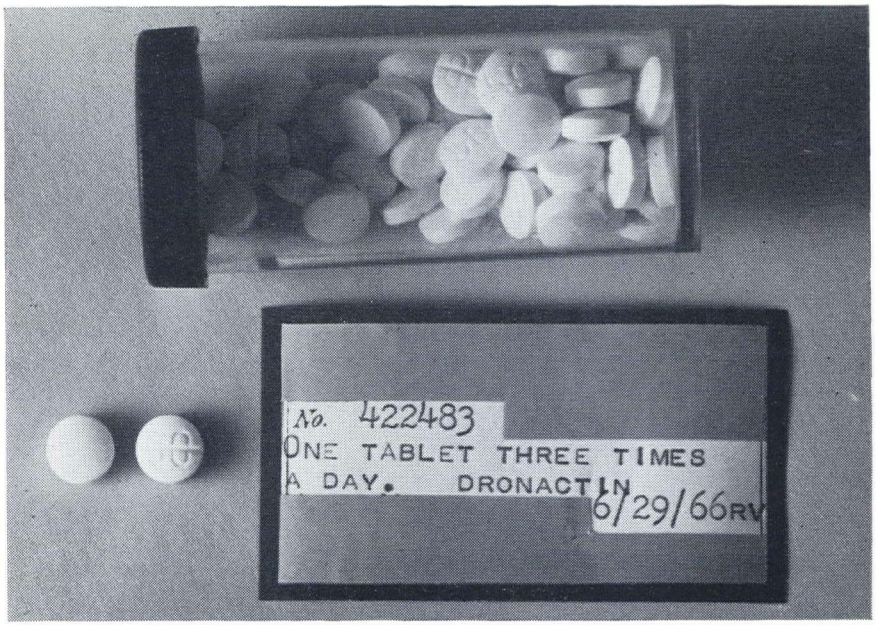

Figure 3

Medicine container labeled Dronactin. Chemical analysis proved the contents to be 50 mg. tablets of Dicumarol.

(The patient is introduced.)

Dr. Monto: Good morning, Mrs. M. Thank you kindly for coming down to share your medical experiences with us. Could you please tell us what seemed to be the earliest manifestations of your illness?

Patient: I noticed bruises on my arms and legs which later spread to other areas of my body.

Dr. Monto: Did you bleed in areas other than the skin?

Patient: My menstrual period was heavy and continuous. When blood was taken from my arms there was difficulty in controlling the bleeding. I lost sensation and use of my left arm and hand. The arm was swollen three times normal size and discolored.

Dr. Monto: Have you bled abnormally in the past?

Patient: No.

Dr. Monto: Do you have any liver disease or have you taken blood thinners for the treatment of blood clots?

Patient: No.

Dr. Monto: Have you experienced a "nervous breakdown"?

Patient: No.

Dr. Monto: Has the strength and sensation in your left arm improved?

Patient: Markedly so — only mild periodic tingling of the finger tips remains.

Dr. Monto: Have you taken medication not prescribed by a doctor or have you been exposed to toxic chemicals?

Patient: No.

Dr. Monto: Thank you very much, Mrs. M., for being with us this morning. (Patient leaves.)

In the past year or two we have encountered several instances of this syndrome, and I have asked Dr. Greidanus to discuss the clinical picture and diagnostic determinations in accidental anticoagulation.

Dr. T. H. Greidanus: Unsuspected ingestion of oral anticoagulants presents a difficult diagnostic problem to the unwary physician. It is to be suspected if the prothrombin time is markedly elevated, and particularly if the patient has a medical or paramedical occupation or has previously been treated with an oral anticoagulant. The diagnosis is confirmed by finding a deficiency of factors II, VII, IX, and X, and by the presence of the anticoagulant in the plasma as demonstrated by chemical analysis.

Hypoprothrombinemia is generally defined as a deficiency in the factors involved in the one stage prothrombin time and indicates a reduction in factors II, V, VII, and X. Vitamin K deficiency is the most commonly encountered clinical state apart from the use of oral anticoagulants. This occurs in biliary obstruction or biliary fistula, in sprue, and in prolonged therapy with certain antimicrobial drugs, any of which may lead to a significant decrease of factors II, VII, IX and X. Oral anticoagulants are believed to produce a competitive inhibition of Vitamin K so that the liver fails to manufacture the Vitamin K-dependent clotting factors. Severe liver disease is also associated with a reduction of the Vitamin K-dependent factors and, in addition, of factor V. Usually, in parenchymal liver disease, the prothrombin time is less than 1½ times the control, and there is little or no improvement with intravenous Vitamin K therapy.

Circulating anticoagulants and fibrinolysis may also elevate the prothrombin time. Several drugs have a similar but weaker effect than Coumadin on clotting factors. These include salicylates and phenylbutazone in large amounts. Heparin may also produce mild hypoprothrombinemia. Congenital absence or deficiency of factors II, V, VII, or X occur also, but are rare.

We would like to emphasize that the oral anticoagulants are not circulating anticoagulants. Their action is upon the liver and they are inactive *in vitro*.

Dr. Monto: Our case presentation this morning aims to illustrate two major points: (1) the diagnostic procedures in a major bleeding disorder, and (2) the emergency therapy used to combat a severe hemorrhagic diathesis. It is apparent by reason of the critical nature of this syndrome that both functions must operate simultaneously.

The first therapeutic measures must be both local and systematic in order to combat the immediate effects of exsanguination. Local measures include use of tourniquets, pressure, rest, cold and the search for a possible bleeding large vessel, the latter of particular importance in the post-operative patient. Systemic emergency therapy includes:[1]

1. Freshest available whole blood (preferably aged less than 24 hours).

2. 150 mg. of hydrocortisone intravenously every six hours.

3. If bank blood is aged more than 48 hours, administer alternate units of fresh frozen plasma.

4. Fresh blood or platelet-rich plasma if platelet count is under 30,000/cu.mm.

5. 10 mg. Vitamin K, intravenously every six hours.

The above therapy continues around the clock until hemorrhage has been controlled for at least 24 hours. Cardiovascular overload is monitored by periodic hemoglobin and hematocrit determinations as well as by clinical observation of venous pressure, including the occasional placing of an intravenous central control device.

Immediately prior to the above program and while replacement therapy is being secured, the following measures are suggested:

1. Brief clinical survey of patient regarding clinical disease status, prior therapy, bleeding history, liver disease, other systemic disease, or previous use of anticoagulants.

2. General examination of patient for evidence of abnormal bleeding from other sites or orifices (drainage tubes, urine, mucus membranes). In a systemic bleeding disorder, abnormal bleeding is rarely limited to one area or orifice.

From the Audience: What is the rationale for the use of corticosteroids in patients with severe hemorrhagic diathesis of unknown etiology?

Dr. Monto: The suggested emergency therapeutic program is designed to meet a life endangering medical emergency. Bleeding in systemic hemorrhagic disorders occurs from small blood vessels. This results in clinically uncontrollable ooze. Adrenocorticosteroids are known to shorten the bleeding time in platelet and vascular bleeding diseases. The mechanism for such action is not proven, but assumed to be on the basis of increased reactiveness and contractibility of the muscled vessels in the terminal vascular bed.[2] In idiopathic thrombocytopenic purpura the therapeutic effect is quite striking. I know of no contraindication for intense short term steroid therapy under these emergency conditions.

From the Audience: What is the explanation of the pharmacist's error?

Dr Monto: Most drugs are shelved alphabetically. Note *D*ronactin and *D*icumarol. In another recent case Dicumarol was dispensed in place of Dramamine. Most pharmacists attempt to avoid this error by not placing similarly appearing medications in sequence, i.e., utilization of formulation in tablets, capsules, or alternate colors. I believe we would be alarmed by the true incidence of drug errors both in hospitals and pharmacies, as well as by patients themselves. I am a firm believer that in most instances medication diagnostic procedures?

From the Audience: Would intensive early treatment interfere with eventual specific diagnostic procedures?

Dr. Monto: This is possible. I have already emphasized the importance of obtaining initially a blood smear, plasma, and serum for study. In event the coagulation laboratory is not operating, plasma and serum can be frozen for later analysis. Our first responsibility is to assure the survival of the patient, and diagnostic procedures may have to be deferred until a later date.

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