Discussion. From Tables I and II it is apparent that the smoke from certain types of cigarette tobaccos tends to be lower in edema-producing irritants than that from other types, and that in a blend of these tobaccos these irritants appear to be additive.

In our original description of the method here used[1] and throughout the presentation of the present study, we have stressed the fact that the only irritants measured by this technic are those that produce edema. That this is not necessarily related to the sensations of subjective irritation experienced by a smoker was strikingly brought out in the present study in the case of the cigarettes made from Burley tobaccos alone. As measured by edema-producing irritants alone this cigarette was not significantly more irritating than the blended cigarette, yet the sensations experienced by the smoker were quite the opposite. Whereas, the average smoker had no difficulty in making a deep inhalation of the smoke from the blended cigarette, a similar inhalation of smoke from the Burley cigarette left him unable to draw a second breath for an uncomfortably long period. It is apparent from this that substances which produce a degree of subjective irritation disproportionately greater than that which might be expected on the basis of their edema-producing properties, may be present in cigarette smoke. Development of a method capable of quantitative measurement of the subjective sensation of irritation to complement the measurement of edema-producing irritants so that a more complete picture may be obtained is greatly to be desired.

Conclusions. 1. Smoke from different types of cigarette tobaccos may differ significantly in edema-producing irritants. 2. Constituents are present in cigarette smoke, from at least certain types of tobaccos, which produce a degree of subjective irritation disproportionately greater than that which might be expected on the basis of their edema-producing properties.

We are indebted to Mrs. Sarah Guerry for technical assistance in performing the reported experiments.

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New Formula for Dilution Curve of Plasma Prothrombin. Normal Standards and Changes in Pathologic Conditions.

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The various one-stage methods for the measurement of prothrombin time used at present, differ little from the procedure originally employed.[1] They are based on the assumption that the clotting time of plasma is dependent solely on its prothrombin content, if an excess of thromboplastin and optimal amounts of calcium are provided; constancy of the rate of conversion of prothrombin to thrombin is assumed. As source of thromboplastin an extract of rabbit brain, or the venom of the Russel viper, are most commonly used.

In all procedures the quantitative comparison of abnormal with normal plasma meets with as yet unresolved difficulties, which have occasioned a variety of methods of assay. The simplest assumption,[2] that the clotting

[1] Quick, A. J., Stanley-Brown, M., and Bancroft, F. W., *Am. J. M. Sc.*, 1935, **190**, 501; Quick, A. J., *J. A. M. A.*, 1938, **110**, 1658.

[2] Ziffren, S. E., Owen, C. A., Hoffman, G. R., and Smith, H. P., *Am. J. Clin. Path., Tech. Supp.*, 1940, **4**, 13; Ziffren, S. E., Owen, C. A., Hoffman, G. R., and Smith, H. P., PROC. SOC. EXP. BIOL. AND MED., 1939, **40**, 595; Govan, C. D., *J. Pediat.*, 1946, **29**, 629.

time of plasma is linearly proportional to its prothrombin content, is obviously incorrect,[3] since it can be shown that the clotting time of normal plasma on dilution follows a curve resembling a hyperbola in shape.[1,4] This curve shares with the hyperbola the property that the product of the 2 coordinates, clotting time in seconds and percentage of plasma concentration, tends to be constant but differs from a hyperbola in 2 respects: (1) a plasma percentage over 100 *a priori* cannot exist, and (2) the approach to infinity of clotting time in the region of low plasma concentrations is not truly asymptotic; beyond a certain dilution, plasma will no longer clot at all. In comparing abnormal plasma with the normal, generally the assumption has been made, either expressly or implicitly, that the clotting properties of abnormal plasma can be expressed in terms of a dilution of normal plasma. Often the prothrombin content has been expressed as per cent of normal, based on a curve established for serial dilutions of normal plasma. If the assumption underlying such a procedure were correct, dilution curves of normal and abnormal plasmas could be made to coincide by proper linear shifting of their curves along one of the coordinates. For instance, an abnormal plasma which undiluted might have a clotting time corresponding to a 50% concentration of normal plasma, on dilution with an equal volume of saline should give a clotting time corresponding to a 25% concentration of normal plasma. Serious doubts concerning the validity of this premise have been expressed, and it has been demonstrated that the dilution curves of pathic and normal plasmas usually cannot be superimposed, indicating that not only their starting points, but also their slopes differ.[5,6] One group of investigators, for purposes of assay of prothrombin-lowering substances, plotted the logarithm of the clotting time versus the logarithm of plasma concentration.[5] This method also is based on the assumption that the curves of normal and abnormal plasma have the same slope. No proof was adduced for this premise.

Some observers have preferred either a 12.5 or a 25% concentration of plasma for the routine measurement of prothrombin,[6,7] since in states of prothrombin deficiency the clotting time of plasma increases more on dilution than normally. One investigator,[8] noting considerable variation in the difference between the clotting times of undiluted plasma and a 1:8 plasma dilution in various clinical conditions, proposed that this difference was a more reliable index of the prothrombin activity than the clotting time of either undiluted or diluted plasma alone; when the difference between undiluted and diluted plasma was increased a state of hypoprothrombinemia was indicated, and either hyperprothrombinemia, or an increase of coagulation-inhibitors, when the difference was reduced.

Finally, a formula describing the dilution curve of normal plasma of rabbit and man has been given as follows:[9]

$$t = a + k/c$$

where t is the clotting time of any given concentration of plasma, c is the concentration of plasma, and a and k are constants. a is the intercept at infinite concentration, while at 100% concentration $t - a = k/100$. a was found to be 5.1 for rabbit and 10.3 for human plasma, while the k values were 139 and 354, respectively. This formula, indicating direct proportionality between the clot-

[3] Quick, A. J., *The Hemorrhagic Diseases and the Physiology of Hemostasis*, Springfield, Ill., 1942, C. C. Thomas.

[4] Page, R. C., de Beer, E. J., and Orr, M. L., *J. Lab. and Clin. Med.*, 1941, **27**, 197; Quick, A. J., *Am. J. Physiol.*, 1941, **132**, 239.

[5] Campbell, H. A., Smith, W. K., Roberts, W. L., and Link, K. P., *J. Biol. Chem.*, 1941, **138**, 1.

[6] Overman, R. S., Stahmann, M. A., Sullivan, W. R., Huebner, C. F., Campbell, H. A., and Link, K. P., *J. Biol. Chem.*, 1942, **142**, 941.

[7] Brambel, C. E., and Loker, F. F., PROC. SOC. EXP. BIOL. AND MED., 1943, **53**, 218.

[8] Shapiro, S., *Exp. Med. and Surg.*, 1944, **2**, 103; Shapiro, S., Sherwin, B., Redish, N., and Campbell, H. A., PROC. SOC. EXP. BIOL. AND MED., 1942, **50**, 85.

[9] Quick, A. J., and Leu, M., *J. Biol. Chem.*, 1937, **119**, LXXXI; Quick, A. J., PROC. SOC. EXP. BIOL. AND MED., 1939, **42**, 788.

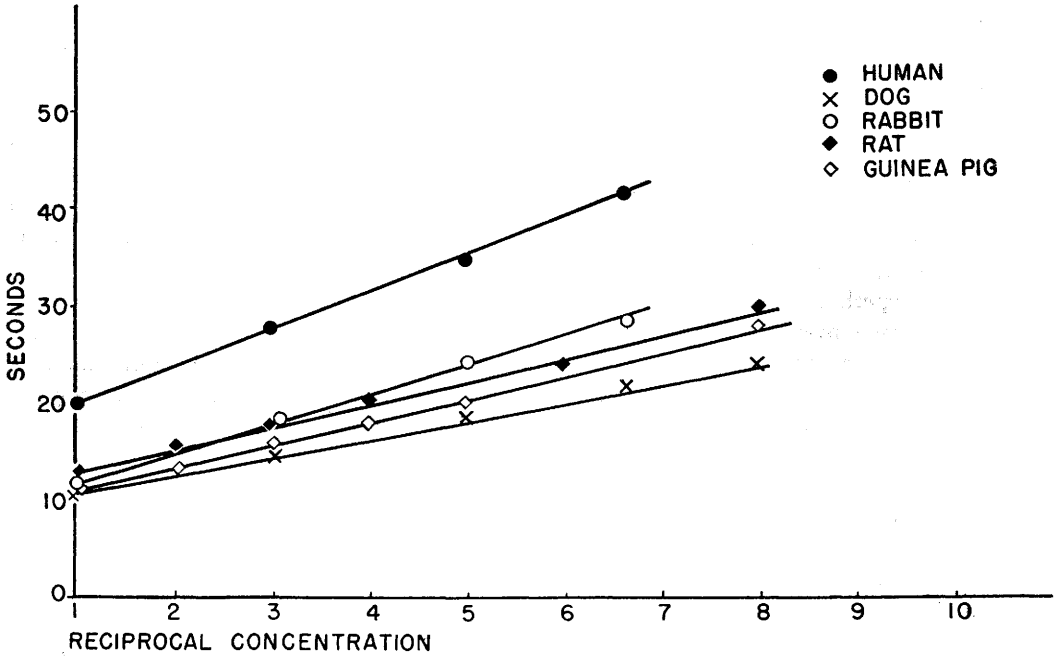

Fig. 1.
Prothrombin time and dilution constant of the blood plasma of man, dog, rabbit, rat and guinea pig.

ting time and $1/c$, the reciprocal of the concentration, fits the experimental finding that for any given plasma the product of clotting time and dilution tends to be constant. The authors did not use the formula for the description of abnormal plasma.

In the following it will be shown that the prothrombin time of normal as well as abnormal plasma of man, dog, rabbit, rat and guinea pig may be expressed by the following formula:

$$t = t_1 + k/(\text{dilution}^* - 1)$$

where t is the clotting time in seconds of any given plasma dilution,* t_1 that of undiluted plasma, and k is a proportionality factor, the dilution constant, which indicates the increase of clotting time per unit increment of reciprocal concentration. This formula, the equation of a straight line, indicates as do some formulas previously mentioned, direct proportionality between the reciprocal of plasma dilution and the clotting time but differs from them in the choice of the constants.

* Dilution = the ratio of the final volume of the plasma-saline mixture to the original volume of plasma.

Both t_1 and k are constants for any given plasma, but vary among different samples and under pathologic conditions. Considered analytically the 2 constants, representing the intercept and the slope of the line, are sufficient to describe the values of serial dilutions of any given plasma. In this communication are presented the normal standard values of t_1 and k for human, dog and rabbit plasma, 2 examples of the behavior of the constants in experimentally-produced hypoprothrombinemia, and a survey of their variations in clinical conditions.

Experimental. Freshly drawn blood, collected by venipuncture with precautions to avoid hemolysis and foaming, was delivered into test tubes measuring 10 x 75 mm and graduated at 1 cc, which contained 0.1 cc of 0.1 molar sodium oxalate. After gentle but thorough mixing the tubes were centrifuged for 5 minutes at 2000 r.p.m. The supernatant plasma was drawn off and the prothrombin time was determined according to the slightly modified method of Fullerton[10] as follows: an 0.15 cc aliquot of the oxalated

[10] Fullerton, H. W., *Lancet*, 1940, **2**, 195.

TABLE I.
Mean Normal Values for the Prothrombin Time of Undiluted Plasma (t_1) and the Dilution Constant of Man, Dog, and Rabbit.

All values are given in seconds.

Species	No. of samples	Undiluted plasma Mean	S.D.*	S.E.*	Dilution constant Mean	S.D.*	S.E.*
Man	37	19.9	1.2	0.2	3.8	0.9	0.2
Dog	22	11.4	1.4	0.3	1.8	0.5	0.2
Rabbit	10	11.4	1.4	0.4	3.2	0.5	0.4

* S.D. = standard deviation; S.E. = standard error.

plasma was measured into a small test tube and placed for one minute in an all-glass water bath permitting close observation at 37°. Then an equal amount of a similarly prewarmed mixture of thromboplastin and calcium chloride was added, and with constant shaking of the tube in the water bath the time for the formation of a solid fibrin clot recorded. Clotting times were also measured on various dilutions of plasma prepared with 0.9% sodium chloride solution. All determinations were performed in duplicate. The mixture of thromboplastin with calcium chloride was prepared by dissolving 0.5 mg of Russel-viper venom (Stypven, Burroughs-Wellcome Laboratories, 9 East 41st Street, New York, N. Y.) in 10 cc of 0.025 molar calcium chloride solution. The mixture was found stable for at least one month when kept in the refrigerator between tests. No significant differences between different batches of venom were ever noted over a period of 4 years, except in 1945-46 when owing to war-time shortages difficulties were experienced by the manufacturer in the preparation of a satisfactory product.

Results. 1. Normal values. In Fig. 1 are presented representative data on individual samples of normal human, dog, rabbit, rat and guinea pig plasma. As can be seen, a straight line relationship obtains for the range of dilutions studied. Fig. 1 also illustrates the fact that there is little relation between the clotting time of undiluted plasma and the dilution constant among different species. For instance it is apparent that the clotting times of the undiluted plasma of dog and rabbit are similar while the slopes of the dilution curves differ widely. On the other hand, rabbit and human plasma give similar dilution constants, despite the difference in the clotting time of the undiluted plasmas.

In Table I are given the mean values of the clotting time of undiluted plasma and the dilution constant, for human, dog and rabbit plasma together with their statistical description. For human plasma, if one accepts the conventional limits of ± 2 standard deviations as the limits of normal variation, a range of 17.5-22.2 seconds for the undiluted plasma and 2.0-5.6 for the dilution constant may be given. A proportional range is found for the plasmas of dog and rabbit.

The formula appears valid over a dilution range up to approximately 1:10 for normal

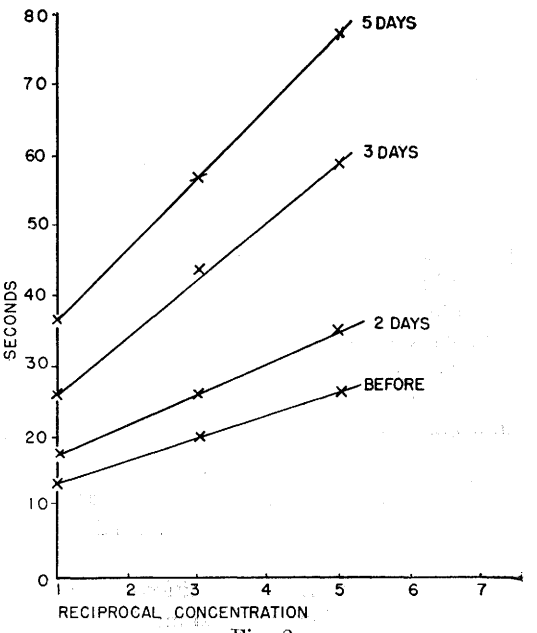

Fig. 2.
The prothrombin time of a rabbit following the subcutaneous injection of 0.5 cc per kg of methyl salicylate.

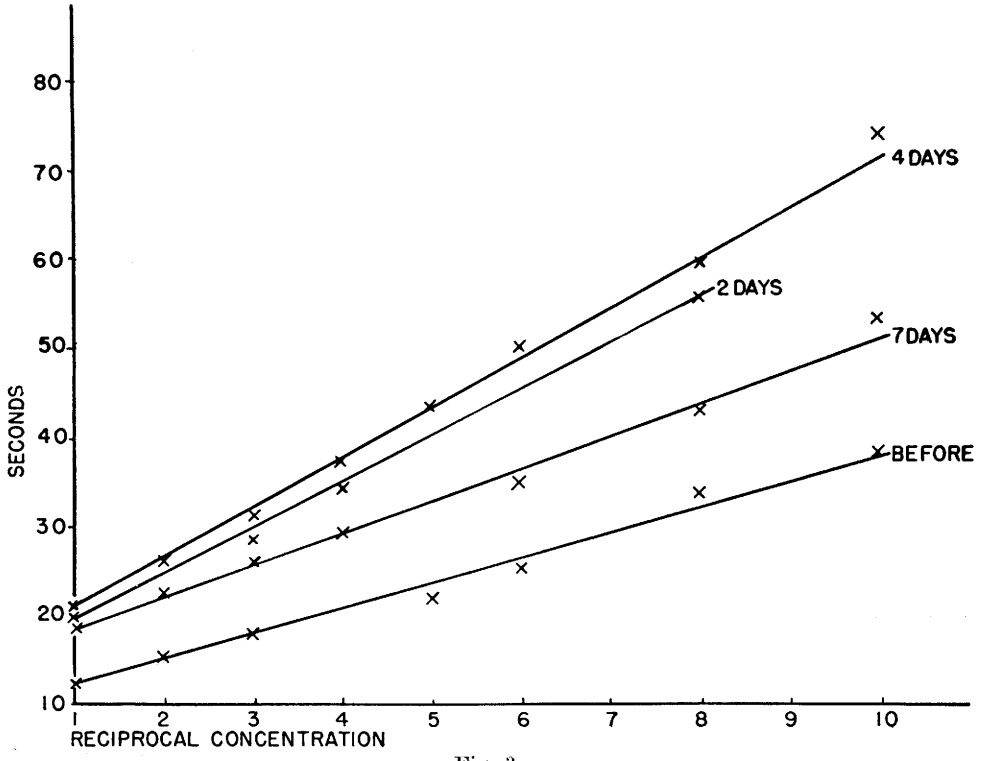

Fig. 3.
Changes of the prothrombin time of a rabbit following the intravenous injection of 2 mg per kg of dicumarol.

human and approximately 1:20 for dog plasma. On further dilution disproportionate lengthening of the clotting time occurs. In plasma with prolonged clotting time the proportionality range is reduced, suggesting the existence of an upper limit of approximately 70-80 seconds for the validity of the formula.

2. Changes in experimentally-produced hypoprothrombinemia. Two examples of hypoprothrombinemia produced in rabbits by the administration of dicumarol and methylsalicylate are presented in Figs. 2 and 3. It may be seen that in both experiments the undiluted plasma clotting time as well as the dilution constant increased. Such data indicate that both indices are related to the prothrombin content of the plasma, and that the curves of abnormal and normal plasma cannot be superimposed.

3. Changes in clinical conditions. The purpose of this section is not so much to present a compilation of changes of prothrombin time in disease, as to indicate the relation of the clotting time of undiluted plasma to the dilution constant. The patients for the most part were children. The data are divided into 2 groups on the basis of the dilution constant. In Table II are presented in order of increasing value cases of elevation of the dilution constant. They are recruited mostly from 3 groups: (1) cases of deficiency of vitamin K, (2) liver damage of various kinds, and (3) bleeding for extended periods of time. A fourth group of cases, patients on salicylate medication, is separately presented in Table IV.

It may be seen that there are interesting parallelisms as well as discrepancies in the behavior of the clotting time of undiluted plasma (t_1) and the dilution constant. In all cases of vitamin K deficiency, with marked prolongation of t_1 the dilution constant also was elevated. On the other hand in patients with severe hepatic damage the dilution constant was increased independently of the changes of undiluted plasma, an observation which has proved to be of diagnostic and prognostic value. The discrepancy between

TABLE II.
Cases of Prolonged Dilution Constant. (Listed in order of increasing value).

Case No.	Plasma prothrombin time: Undiluted plasma (t_1) seconds	Plasma prothrombin time: Dilution constant seconds	Diagnosis
1.	45.5	6.0	Aplastic anemia, bleeding profusely
2.	30.9	6.1	Chronic diarrhea
3.	25.7	7.2	Syphilitic hepatitis
4.	18.4	7.3	Congenital atresia of the bile ducts
5.	36.3	7.3	Lymphosarcoma, bleeding
6.	29.5	7.3	Histoplasmosis
7.	36.1	7.5	Infectious hepatitis, convalescing
8.	28.5	7.6	" " "
9.	33.9	7.6	Chronic diarrhea
10.	35.8	7.7	Intrahepatic biliary obstruction
11.	21.0	8.2	Cirrhosis of liver
12.	26.6	8.6	Rheumatic fever, cardiac decomposition with hepatic congestion
13.	26.7	8.7	Thrombocytopenic purpura
14.	15.0	8.8	Erythroblastosis fetalis
15.	27.2	9.0	Banti's disease
16.	18.4	9.3	Hemophilia, prolonged bleeding from gastro-enteric tract
17.	28.1	9.9	Rheumatic fever with congestion of liver
18.	28.7	9.9	Erythroblastosis fetalis, severe
19.	24.6	10.0	Typhoid fever, severe, 1 day premortem
20.	30.9	10.0	Hemophilia, epistaxis of 5 days' duration
21.	43.0	10.1	Erythroblastosis fetalis, severe anemia
22.	31.2	10.4	Banti's disease
23.	30.1	10.5	Congenital atresia of bile ducts, bleeding
24.	19.6	10.8	Cirrhosis of liver
25.	15.1	10.9	" " "
26.	34.0	10.9	Chronic diarrhea
27.	25.1	11.2	Infectious hepatitis of long duration
28.	23.2	12.4	Diarrhea
29.	21.5	13.8	Hepato-renal syndrome of lupus erythematosus
30.	32.3	14.3	Letterer-Siwe's disease, 1 day pre-mortem
31.	51.2	14.4	Acute infectious hepatitis with subacute liver atrophy
	27.9	15.5	1 day after vitamin K, 1 day pre-mortem
32.	20.0	14.9	Cirrhosis of liver
33.	29.4	16.4	Erythroblastosis fetalis, severe, 8 hours pre-mortem
34.	21.6	19.1	Erythroblastosis fetalis
35.	52.6	≅32	Chronic diarrhea
36.	61.8	≅37	" "
37.	66.8	≅44	Hemorrhagic disease of the newborn
38.	80.2	≅56	Chronic diarrhea
39.	76.8	≅75	" "

the 2 indices in cases of hepatic damage as compared with their parallelism in vitamin K deficiency, suggests that humoral clotting factors other than prothrombin may play a role in hepatic disorders. The data on cases of prolonged bleeding, here presented, indicate that the immediately available supply of prothrombin, or vitamin K, may be exhausted. Thus patients with hemophilia may also develop hypoprothrombinemia (see cases 16 and 20). The data on the effect of salicylate medication in the usual dosage (0.1-0.15 g per kg body weight) on patients with rheumatic fever suggest that with parallel changes of the undiluted plasma and the dilution constant, the latter is a more sensitive indicator of the changes of prothrombin.

The cases of decrease of the dilution constant are drawn from a more heterogeneous material than those of prolongation. In Table III 3 groups appear prominent: (1) cases of infectious hepatitis in an early stage, (2) cases of the nephrotic syndrome, and (3) cases of rheumatic fever. Also represented are cases of purpura, leukemia, and Rocky Mountain Spotted Fever, disorders with bleeding

TABLE III.
Cases of Reduction of the Dilution Constant. (Listed in order of increasing value.)

Case No.	Plasma prothrombin time: Undiluted plasma (t_1) seconds	Plasma prothrombin time: Dilution constant seconds	Diagnosis
40.	17.7	—0.4	Post-infectious state, with high serum agglutinin titer
41.	21.0	0.0	Non-thrombocytopenic purpura
42.	22.5	0.4	Nephrotic syndrome
43.	30.0	0.4	" "
44.	16.0	0.5	Infectious hepatitis
45.	23.8	0.5	Symptomatic purpura
46.	19.9	0.6	Nephrotic syndrome
47.	17.1	0.7	Post-tonsillectomy bleeding
48.	21.7	0.8	Infectious hepatitis
49.	30.6	0.8	Acute lymphatic leukemia
50.	16.4	1.3	Infectious hepatitis
51.	20.7	1.4	Nephrotic syndrome
52.	15.2	1.5	Rheumatic fever
53.	29.0	1.5	Rheumatoid arthritis
54.	18.3	1.7	Nephrotic syndrome
55.	22.5	1.7	Rocky Mountain spotted fever
56.	14.8	1.8	Acute lymphatic leukemia
57.	16.6	1.8	Rocky Mountain spotted fever
58.	21.7	1.8	Infectious hepatitis
59.	14.7	2.0	Sickle cell anemia in hemolytic crisis
60.	19.9	2.0	Rocky Mountain spotted fever
61.	20.8	2.0	Nephrotic syndrome
62.	14.4	2.1	Rheumatic fever
63.	16.1	2.1	" "
64.	16.4	2.1	Infectious hepatitis
65.	22.3	2.1	Rheumatic fever

from the small vessels as a common feature. Another group, cases of patients receiving vitamin K, is presented in Table V.

Again, a widely varying relationship between t_1 and the dilution constant is evident. While both indices changed in a parallel manner in some patients with infectious hepatitis and in those receiving vitamin K, marked discrepancies were found among the other patients. Of particular interest is the combination of a considerable prolongation of t_1 with a marked reduction of the dilution constant (see cases 43, 49 and 53). Whether the reduced dilution constant reflects an actual increase of prothrombin content or is the result of an increase in the amount of auxiliary clotting factors cannot be said at the present. Reduction of both t_1 and the dilution constant suggests strongly the existence of a state of true hyperprothrombinemia but additional effects of activators and inhibitors of clotting have to be invoked in cases where the 2 indices differ from each other.

Discussion. It may be well to point out that no definite independent biological meaning has been assigned to the 2 constants in the expression for prothrombin time. The data on hypoprothrombinemia, experimental as well as clinical, suggest that the constants, not truly independent of each other, change in a parallel manner. On the other hand, the observations on different species and on the clinical material illustrate marked and well defined discrepancies between the 2 indices. These differences may be related to variations in the amount of auxiliary factors of clotting rather than of prothrombin.

Clinically of greatest interest is the apparent usefulness of the dilution constant as an indicator of hepatic damage. In infectious hepatitis decreases as well as increases of the dilution constant occur, suggesting the occurrence of a period of stimulation, followed by suppression, of hepatic function. Similar changes in cases of bleeding may be due to stimulation followed by exhaustion of prothrombin formation. Most of the conditions in which a decrease of the dilution constant was observed are characterized by altera-

TABLE IV.
Effect of Salicylate on Dilution Curve of Plasma Prothrombin.

Case No.	Plasma prothrombin time Undiluted plasma (t_1) seconds	Dilution constant seconds	Comments
66.	20.1	4.9	Before
	26.6	9.1	2 days salicylate
	25.5	9.7	4 " "
	26.8	10.6	6 " "
	25.8	11.5	8 " "
	23.2	9.6	2 " stopped
67.	20.2	5.6	Before
	24.7	6.4	2 days salicylate
	22.9	6.8	4 " "
	22.1	5.7	2 " stopped
68.	16.2	2.2	Before
	24.1	5.0	4 days salicylate
	27.5	6.8	7 " "
	19.6	4.7	5 " after
69.	21.0	3.7	Before
	23.9	5.8	3 days salicylate
	23.9	6.7	6 " "
	20.2	4.7	4 " after
70.	20.8	5.2	Before
	31.1	10.3	4 days salicylate
71.	22.0	4.7	Before
	22.9	7.1	4 days salicylate
	20.5	5.5	2 " after
72.	19.1	4.7	Before
	21.3	6.0	2 days salicylate
	20.3	6.9	6 " "
73.	19.7	3.5	Before
	21.4	6.4	2 days salicylate
	22.6	7.2	7 " "
74.	20.2	2.4	Before
	27.6	9.6	12 days salicylate
	22.0	2.0	10 " after

TABLE V.
The Effect of Vitamin K Medication on Dilution Constant.

Case No.	Plasma prothrombin time Undiluted plasma (t_1) seconds	Dilution constant seconds	Comments
10.	35.8	7.7	Intrahepatic biliary obstruction
	16.1	0.9	2 days after Vit. K
37.	66.8	$\cong$44	Hemorrhagic disease of new born
	16.2	1.4	1 day after Vit. K
39.	76.8	$\cong$75	Chronic diarrhea
	14.7	1.7	2 days after Vit. K
27.	25.1	11.2	Infectious hepatitis of long duration
	19.2	2.0	2 days after Vit. K
75.	15.4	1.4	Erythroblastosis fetalis 1 day after Vit. K
76.	16.3	1.8	Chronic diarrhea 1 day after Vit. K

tions in the distribution of plasma protein and increases of fibrinogen. Such patients may experience a general humoral stimulation in which clotting factors participate.

Summary. A new formula expressing the dilution curve of plasma prothrombin is presented. Normal standards and examples of change in experimental clinical conditions are given.

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Inhibitory Effect of Dibenamine on Vasoconstrictor Substances.

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Recently Nickerson and Goodman[1] reported the results of the study of a new adrenolytic and sympathicolytic drug, dibenzyl-β-chloroethyl amine hydrochloride (dibenamine). They found that after the administration of this agent to dogs and cats, intravenous epinephrine in high doses causes a reversal of blood pressure (a fall of 20 to 40 mm Hg). In addition to the blocking and reversing of the excitatory adrenergic response, dibenamine had the ability to prevent epinephrine-induced cardiac irregularities in dogs sensitized by cyclopropane.[2] Most of the studies on dibenamine reported above deal with responses of heart rate, blood pressure, nictitating membrane, pupillary reactions.

Because of the possible clinical usefulness of dibenamine in angiospastic conditions associated with peripheral vascular diseases, causalgic states or hypertension,† an investigation of vasomotor responses to this agent, as expressed in terms of peripheral blood flow, seemed of interest. The present report deals with a study of the inhibitory effect of dibenamine on vasoconstrictor substances.

Methods. All the experiments reported in this investigation were carried out in the Laewen-Trendelenburg (L-T) preparation in frogs *(Rana pipiens)*. This preparation is a sensitive indicator in testing vascular responses, and offers a simple tool for the analysis of vasomotor agents and their antagonists. The perfusate used was a solution containing 0.65% NaCl and 0.02% KCl. Two Mariotte bottles were connected by a Y-piece with the perfusion system, *i.e.* the rubber tubing leading to the aortic cannula. One bottle contained the plain perfusion solution, the other, added to the latter, dibenamine.‡ This substance was used at various concentrations. Epinephrine hydrochloride, nicotine base (Eastman Kodak) and hypertensin (angiotonin)§ were used in testing the vasoconstrictor-blocking ability of dibenamine. The injections of these vasopressor substances were made through the rubber tubing into the glass cannula inserted into the abdominal aorta of the frog. Their vasomotor activity was evaluated in terms of the output variations of drops per minute.

Results. The injection of a small amount of epinephrine (1/10-1 γ), nicotine (1-10 γ) or hypertensin (0.05-0.5 cc) in the L-T preparation induces a marked vasoconstriction as

* Elsa and William Menke Fellow.

This investigation was aided by a grant from the Peripheral Vascular Disease Research Fund.

1 Nickerson, M., and Goodman, L. S., *Fed. Proc.*, 1946, **5**, 194.

2 Nickerson, M., Smith, S. M., and Goodman, L. S., *Fed. Proc.*, 1946, **5**, 195.

† Clinical investigation of the action of dibenamine in such conditions is now in progress.

‡ Dibenamine was supplied by Givaudan-Delawanna, Inc., Delawanna, N.J., through the courtesy of Dr. W. Gump.

§ Hypertensin (angiotonin) was prepared from the interaction of Renin (Smaco) and sheep serum according to the method described by Sapirstein *et al.*[3]

3 Sapirstein, L. A., Reed, R. K., and Southard, F. D., Jr., *J. Lab. and Clin. Med.*, 1944, **29**, 633.