dicoumarol and its catabolism is more rapid. Its actions would place it somewhere in between heparin and dicoumarol though its properties are more closely allied to dicoumarol.

It is my belief that this anticoagulant is deserving of clinical trials in a larger number of cases.

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REFERENCES

1. SOULIER AND GUEGUEN: *Compt. rend. Soc. biol.*, 141: 1007, 1947.
2. JAQUES, L. B.: Personal communication.

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THE PATHOGENESIS OF SECONDARY ANÆMIAS*

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THE term "secondary" anæmia is loosely used but it is a convenient name for that large group of anæmias which occur in association with some other disease. It has been commonly believed that these anæmias are dyshæmopoietic in nature and that the disturbance of erythropoiesis is merely part of a general toxæmia or disturbance of metabolism. The anæmias which complicate those infections due to organisms which produce hæmolysins have been the only widely accepted exception to that general proposition. It is the purpose of this communication to put forward evidence that excessive hæmolysis and sometimes abnormal hæmolysis may frequently play a part in the pathogenesis of the anæmia which complicates carcinoma, the reticuloses and also sepsis due to organisms which do not produce hæmolysins in large amounts.

METHOD

Hæmolysis has been studied in these cases by determining the rate of destruction of transfused erythrocytes. The patients are transfused with whole blood or with erythrocyte suspensions belonging to a group other than their own, and the rate at which the transfused erythrocytes disappear from the peripheral circulation has been determined by the method of selective agglutination of the circulating erythrocytes by appropriate high titre sera (Ashby,[1] Mollison and Young[10]). By this method the average life of the transfused erythrocytes in a normal person has been shown to be about 60 days (Callendar, Powell and Witts[3]). This means, of course, that the life span of the erythrocyte is about 120 days, and this value corresponds well with the estimations provided by those who have fed man glycine containing N^{15} (Shemin and Rittenberg[13]) and by those who have used pigment excretion studies as the basis for estimation (Hawkins and Whipple[8]).

In a normal person, when the number of surviving erythrocytes is plotted against time the decay curve is linear and reaches the base at about 120 days. In some cases of anæmia two types of abnormal results may be seen. Firstly, the decay curve may remain linear but have an increased slope reaching the base in less than 120 days. Secondly, the plotted results may show considerable curvature as well as reaching the base in less than the normal time. This latter is the case, for example, in frank hæmolytic anæmias such as Lederer's anæmia. When the decay curve is of this type, the results may be interpreted as providing evidence of the operation of a method of hæmolysis not active in health as well as an increase in the rate of hæmolysis. The hæmolytic process which produces a linear decay curve has been called the *linear hæmolytic mechanism* and that which produces curvature in the decay curve has been called the *exponential hæmolytic mechanism* (Brown, Hayward, Powell and Witts[2]).

An attempt has been made to describe the results of this type of experiment numerically (Brown, Hayward, Powell and Witts[2]), working on the hypothesis that two processes of cell destruction can be distinguished. The simplest algebraic equation which reasonably fits the data in these cases is:*

$$\frac{N}{No} = (1\text{-Lst})\,\frac{R\exp(\text{-Let}) + 1}{R + 1}$$

which becomes

$$N = No\ (1\text{-Lst})$$

when the decay curve is linear. From these the average life (t) of the transfused erythrocytes can be calculated, and as well the fraction of the transfused erythrocytes (Fe) which has been destroyed by the *exponential hæmolytic mechanism* and a fictitious average life (ts) of the transfused erythrocytes which would obtain if the *linear hæmolytic mechanism* had been acting alone. The results of the present experiments will be described in this manner.

There are two points concerning the method to be mentioned. One concerns its accuracy. Every one is aware of the degree of accuracy in counting erythrocytes. The accuracy in counting inagglutinable erythrocytes is of the same degree and it has been found that the standard error of the difference between dupli-

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* Notation—

N	=	Donor cell count in recipient at time t, million per c.mm.
No	=	Donor cell count in recipient immediately after transfusion, million per c.mm.
t	=	Time measured from transfusion (days).
Ls	=	Constants.
Le	=	Constants.
R	=	Constants.
t	=	Average life of transfused cells measured from t=0 (days).
ts	=	Average life corresponding to linear component (days).

cate observations is of the order of 6% of the inagglutinable count (Brown, Hayward, Powell and Witts[2]). In the present series of experiments, four counts were made on each specimen and each count was plotted rather than just the average count for the day. Counts were made every other day in the initial period and subsequently at about fortnightly intervals.

The second point concerns the delicacy of the method. It has been found that the method provides evidence of increased hæmolysis and/or abnormal hæmolysis in cases where there is no reticulocytosis, no abnormal bilirubinæmia and no increase in excretion of urobilinogen and herein lies the merit of the method. Fæcal urobilinogen was determined by the method of Schwartz *et al.*[12] (Table I).

TABLE I.

SURVIVAL OF TRANSFUSED ERYTHROCYTES COMPARED WITH RETICULOCYTE COUNT, PLASMA BILIRUBIN, AND FÆCAL UROBILINOGEN

Case	*Reticulocytes* %	*Plasma bilirubin* mgm. %	*Fæcal urobilinogen* mgm./day	*Average life* t days	*Average life corresponding to linear mechanism* ts days	*Fraction destroyed by exponential mechanism* Fe
XI	1.1	0.4	12.0	53.0	53.0	0
VIII	1.1	0.4	60.0	40.2	52.5	0.29
XXV	1.0	0.9	130.0	30.0	30.0	0
XVI	1.0	0.5	196.0	21.0	25.0	0.24
XIV	0.8	0.3	20.0	16.8	32.5	0.38
VII	0.6	0.5	0.3*	8.0	8.0	0

*0.3 units in 2-hour urine specimen.

THE ANÆMIA OF INFECTION

The anæmia associated with infections due to organisms other than those which produce hæmolysins in large amounts is usually normocytic and normochromic, but on occasion it may be slightly microcytic and hypochromic. There is as a rule no accompanying reticulocytosis and this with the absence of an increase in the plasma bilirubin and the absence of an increase in the excretion of urobilinogen has led many to the conclusion that it is a dyshæmopoietic anæmia. Vaughan and Saifi[16] concluded on these grounds that there was no evidence of hæmoglobin breakdown in excessive amounts but because of an increased excretion of coproporphyrin I and III they did suggest that there was disturbance of hæmoglobin synthesis. Robscheit-Robbins and Whipple[11] had suggested the same thing some three years earlier. It was a conclusion that was concurred in by such standard authors as Whitby and Britton.[17] Cartwright[4] and his colleagues brought forward in 1946 the hypothesis that the anæmia is due to a disturbance of iron metabolism. They had found that in the anæmia of infection there is a low concentration of iron in the serum, that the iron absorption curve is low, and that iron given intravenously quickly disappears from the blood stream. They suggested that the anæmia of infection is due to a disturbance of hæmopoiesis, the result of a failure to form heme because of the lack of iron to incorporate into the protoporphyrin molecule. Hemmeler[9] in the same year also concluded that this anæmia was due to disturbed erythropoiesis.

In my own experience the examination of sections of bone marrow of the ribs of six patients with empyema has led to the finding of a hyperplastic marrow with a proportionate

TABLE II.

SURVIVAL OF TRANSFUSED ERYTHROCYTES IN CASES OF ANÆMIA OF INFECTION

Case	*Diagnosis*	*Average life* t days	*Average life corresponding to linear mechanism* ts days	*Fraction destroyed by exponential mechanism* Fe
I.	Septic arthritis	50.0	50.0	0
II.	Pneumococcal empyema	60.0	60.0	0
III.	Pneumococcal empyema	41.5	41.5	0
IV.	Pneumococcal pneumonia	46.0	46.0	0
V.	P. vulgaris abscesses	23.0	23.0	0

increase in the erythroid series. The bone marrow is at least active, even if not efficient.

Study of a group of these cases by the method of transfusion which has been described has led to evidence which suggests that as well as a disturbance of erythropoiesis there is in some cases excessive blood destruction. Table II shows the rate of destruction of transfused erythrocytes in this series, in all but one of which the streptococcus could be excluded. In Case V, a diabetic with multiple *Proteus vulgaris* abscesses, the rate of destruction of the transfused cells was more than twice that of normal. It should perhaps be noted that in this group there was evidence of activity of the *linear hæmolytic mechanism* alone. Similar evidence of excessive blood destruction has been found in an earlier group of cases of infection (Brown, Hayward, Powell and Witts).

THE ANÆMIA OF MALIGNANT DISEASE

The rôle of excessive hæmolysis in the anæmia of malignant disease has been studied in those cases where the issue was not complicated by blood loss, and where the neoplasm did not involve the gastro-intestinal tract. Three of the series were cases of carcinomatosis

TABLE III.
SURVIVAL OF TRANSFUSED ERYTHROCYTES IN CASES OF CARCINOMA WITH ANÆMIA

Case	*Diagnosis*	*Average life t days*	*Average life corresponding to linear mechanism ts days*	*Fraction destroyed by exponential mechanism Fe*
X.	CA of lung	39.0	48.0	0.22
XIII.	CA of parotid	33.0	33.0	0
XI.	Carcinomatosis (prostate)	53.0	53.0	0
XII.	Carcinomatosis (breast)	33.0	33.0	0
XIV.	Carcinomatosis (uterus)	16.8	32.5	0.38

with widespread secondaries, including involvement of bone. In these cases it is commonly held that the anæmias belong to the myelophthisic group and that it is due to a disturbance of erythropoiesis. A case of bronchogenic carcinoma and a case of carcinoma of the parotid gland completed the group.

All five patients destroyed the transfused erythrocytes at more than the normal rate (Table III). In the patient with carcinoma of the lung and in one of the patients with carcinomatosis there was evidence of activity of the *exponential hæmolytic mechanism* as well as activity of the *linear mechanism.* Stats *et al.*[15] have also remarked on the presence of hæmolytic anæmia in a single case of colloid carcinoma probably arising from the colon.

THE ANÆMIA OF THE RETICULOSES

Collins and Rose[5] recently reviewed the problem of the anæmia of leukæmia and came to the conclusion that disturbed erythropoiesis is an essential feature of the disease. Some earlier workers (Jaffé and Kress) had concluded, on the basis of the hæmosiderosis which they found, that excessive blood destruction was the principal factor in the pathogenesis of the anæmia and even suggested that excessive hæmolysis might play a part in the pathogenesis of the leukæmic process. However, Whipple and Robscheit-Robbins found only a little more iron in leukæmic livers than in

TABLE IV.
SURVIVAL OF TRANSFUSED ERYTHROCYTES IN CASES OF THE RETICULOSES

Case	*Diagnosis*	*Average life t days*	*Average life corresponding to linear mechanism ts days*	*Fraction destroyed by exponential mechanism Fe*
VI.	Acute lymphatic leukæmia	23.3	23.3	0
VIII.	Chronic lymphatic leukæmia	40.5	52.5	0.29
IX.	Chronic lymphatic leukæmia	18.0	24.0	0.34
VII.	Chronic myelogenous leukæmia	8.0	8.0	0
XVI.	Hodgkin's disease	21.9	25.0	0.24
XVII.	Hodgkin's disease (a)	63.0	63.0	0
	(b)	40.5	40.5	0
XV.	Plasma cell myeloma.	28.0	28.0	0

normal human liver, and Forkner suggested that the hæmosiderosis reported by Jaffé and Kress in acute leukæmia might have been due to the hæmorrhagic tendency their cases showed. The occasional occurrence of hæmolytic anæmia in the course of the reticuloses has been remarked on by Singer and Damshek[14] and by Stats *et al.*[15] The present work suggests that excessive hæmolysis may be present more often than is commonly believed.

In the four cases of leukæmia which have been studied by means of transfusion, there has been evidence of increased blood destruction (Table IV). In three of these cases the increase was marked and in two there was evidence of activity of the *exponential* as well as the *linear hæmolytic mechanism.* Two cases of Hodgkin's disease have been studied. In one of them, the average life of the transfused erythrocytes was greatly reduced, and the decay curve was curved. In the other, the cells of the first transfusion survived for the normal time, whereas a year later the cells of the second were destroyed by the *linear hæmolytic mechanism* at an increased rate. A patient with a plasma cell myeloma also showed excessive activity of the *linear mechanism.*

COMMENT

The results of this experimental method suggest that in three groups of cases, a hæmolytic factor plays a part in the pathogenesis of the accompanying anæmia. This is a view which is contrary to the commonly accepted views concerning the pathogenesis of these anæmias and the results gained by the method perhaps need validation. First of all it can be said that in those cases where there is other evidence of excessive blood destruction, transfused erythrocytes are destroyed more rapidly than normal except in familial hæmolytic anæmia (Dacie and Mollison[7]) and in nocturnal hæmoglobinuria (Dacie and Firth[6]). Secondly, it can be pointed out that there is no evidence from the work with the MNO and Rh groups that cells of Group O are destroyed more rapidly than the patient's own cells when he belongs to another group, and as already mentioned, the figures arrived at for the average life of the erythrocyte correspond well with the estimates provided by means not involving the use of cells of another group. Finally, the conclusions put forward here were arrived at after comparison of results obtained in normal subjects with the results obtained by the same method in the patients involved.

The results show the importance of hæmolysis in the three anæmias considered, and in some of the cases the excessive hæmolysis demonstrated was sufficient to account for the anæmia found. It is to be emphasized that the cases in this series were studied as they became available and were not chosen because a hæmolytic anæmia was suspected on the usual grounds. If study of a larger series provides the same results as the study of this group of 17 cases, it will be apparent that excessive hæmolysis plays a more frequent part in the pathogenesis of these anæmias than is at present recognized. In the majority of cases there was no evidence that there was at work any hæmolytic mechanism other than that seen in the normal subject, even though in these cases there was evidence of increased activity of that process. In the other cases there was evidence of a hæmolytic process not seen in health. This process which has been called the *exponential hæmolytic mechanism,* has not so far been seen except where the *linear mechanism* shows increased activity. The physiological basis of these two mechanisms remains a matter for speculation.

Unfortunately neither the results of this work nor the results of previous work provide any better suggestion for therapy than transfusion. Provision in excess of the known factors required for erythropoiesis has no beneficial effect, and all that remains is to do what can be done about the primary condition and to transfuse when the amount of circulating hæmoglobin is reduced to the point of embarrassment.

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REFERENCES

1. ASHBY, W.: *J. Exper. Med.*, **29**: 267, 1919.
2. BROWN, G. M., HAYWARD, O. C., POWELL, E. O. AND WITTS, L. J.: *J. Path. & Bact.*, **56**: 81, 1944.
3. CALLENDAR, S. M., POWELL, E. O. AND WITTS, L. J.: *J. Path. & Bact.*, **57**: 129, 1945.
4. CARTWRIGHT, G. E., LAURITSEN, M. A., JONES, P. J., MERRILL, I. M. AND WINTROBE, M. M.: *J. Clin. Investigation*, **25**: 65, 1946.
5. COLLINS, D. H. AND ROSE, W. M.: *J. Path. & Bact.*, **60**: 63, 1948.
6. DACIE, J. V. AND FIRTH, D.: *Brit. M. J.*, **1**: 626, 1943.
7. DACIE, J. V. AND MOLLISON, P. L.: *Lancet*, **1**: 550, 1943.
8. HAWKINS, W. B. AND WHIPPLE, G. H.: *Am. J. Physiol.*, **122**: 418, 1928.
9. HEMMELER, G.: *Helvet. med. acta.*, **13**: 20, 1946.
10. MOLLISON, P. L. AND YOUNG, I. M.: *Quart. J. Exper. Physiol.*, **30**: 313, 1940.
11. ROBSCHEIT-ROBBINS, F. S. AND WHIPPLE, G. H.: *J. Exper. Med.*, **63**: 767, 1936.
12. SCHWARTZ, S., SBORROV, V. AND WATSON, C. J.: *Am. J. Clin. Path.*, **14**: 598, 1944.
13. SHEMIN, D. AND RITTENBURG, D.: *J. Biol. Chem.*, **166**: 621, 1946.
14. SINGER, K. AND DAMSHEK, W.: *Ann. Int. Med.*, **15**: 544, 1941.
15. STATS, D., ROSENTHAL, N. AND WASSERMAN, L. R.: *Am. J. Clin. Path.*, **17**: 585, 1947.
16. VAUGHAN, J. M. AND SAIFI, M. F.: *J. Path. & Bact.*, **49**: 69, 1939.
17. WHITBY, L. E. L. AND BRITTON, C. J. C.: Disorders of the Blood, Philadelphia.