# Effect of Cholinesterase-containing Globulin Fraction of Human Plasma in Macrocytic Anemia

ROBERT D. BARNARD and JOHN W. MENTHA[1]

*Terrace Heights Hospital, Hollis, Long Island*

Several patients with gastric carcinoma who received multiple whole blood transfusions preparatory to laparotomy were found, on the advent of the latter, to have such extensive metastases that resection was waived. Nevertheless, presumably because of the multiple transfusions, there was a period of increased strength, abatement of pallor, and remission of macrocytic anemia. The previously low blood cholinesterase ($ChE_b$) established itself at a higher level during this period.

In each patient there was a small transitory rise in blood cholinesterase (confined to the plasma phase and of an extent calculable from the plasma volume and the administered esterase unitage) which subsided before the advent of a more marked secondary rise confined exclusively to the erythrocyte phase ($ChE_e$) occurring in the first and third patients, and which was of a much greater extent than could be accounted for on the basis of the administered unitage. On subsidence of the secondary rise in the first and third patients, there was a fall to normal in the previously elevated icteric index and a reticulocytosis which, while not nearly as marked as that usually obtained by liver extract therapy, appeared to be of a significant degree.

It has been concluded from this and related studies that the height of the blood cholinesterase, and particularly the erythrocyte cholinesterase, level is the determinant (rather than just the accidental concomitant) of remission in macrocytic anemia, and that Davis's (*3*) hypothesis that macrocytic anemia is the result of a cholinergic "brake" on erythropoiesis is correct in its general implications. Davis considers the estrapenia as allowing acetylcholine to act as a marrow vasodilator; we regard the dynamics of this cholinergic "brake" as that of an atopic reaction on the part of the hemopoietic marrow in which the latter participates as the shock organ (*2*).

TABLE 1

EFFECT OF IV-6 PLASMA FRACTION ON THE BLOOD PICTURE IN MACROCYTIC ANEMIA

| Patient | Date | IV-6 administered (gms) | RBC (million) | Hematocrit (%) | Hb* | Icterus index | $ChE_b$ | $ChE_s$ | $ChE_e$† | Reticulocytes (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Go | 9–22 | | | | | 16 | 4.61 | | | 1.0 |
| | 9–23 | 10 ‡ | 3.13 | 30 | 67 | 18 | 4.45 | 2.53 | 8.84 | |
| | 9–23⅔ | 20 ‡ | | | | | | | | |
| | | | 3.20 | 31 | | 16 | 5.15 | 3.27 | 9.24 | 1.3 |
| | 9–24 | | 2.82 | 29 | | 18 | 6.10 | 4.57 | 8.42 | |
| | 9–25 | | 3.09 | 29 | | 16 | 9.33 | 2.80 | 24.32 | 1.1 |
| | 9–26 | | 3.20 | 29 | | 10 | 6.85 | 2.44 | 16.98 | 2.9 |
| | 9–27 | | 3.55 | 31 | 63 | 4 | 5.60 | 3.02 | 11.51 | 3.9 |
| Ra | 10–20 | | 2.40 | 25 | 55 | 12 | | | | 0.6 |
| | 10–22 | 20 | 2.29 | 23 | 52 | 10 | | 1.92 | 6.47§ | 1.1 |
| | 10–23 | | 2.33 | | | 12 | | 3.13 | 6.81§ | 0.8 |
| | 10–24 | | 2.27 | 20 | | 8 | | 1.86 | 14.64§ | 1.0 |
| | 10–25 | | | | | 10 | | 1.77 | 9.02§ | 2.3 |
| | 10–26 | | 2.81 | 25 | 52 | 6 | | | | 6.3 |
| | 10–27 | | | | | | | | | 4.2 |

* Hemoglobin concentrations expressed in decimillimols of iron/liter of blood.

† Erythrocyte ChE calculated from $ChE_b$, $ChE_s$, and hematocrit.

‡ Intravenous infusion of 4% solution in physiologic saline over an 18-hr period. Infusion interrupted after administration of 10 gms for blood studies.

§ Erythrocyte ChE determined by direct measurement.

To determine directly the role of the cholinesterase content of transfusions in the effect produced in macrocytic anemia, three patients with this type of anemia have been given infusions of IV-6 human plasma fraction. This material contains approximately 500 Alles and Hawes (*1*) units of serum cholinesterase ($ChE_s$)/gm. A patient with macrocytic anemia complicating ametastatic right colon adenocarcinoma received the equivalent of 15,000 $ChE_s$ units intravenously in a single administration; another patient with rectosigmoid carcinoma with hepatic metastases received 7,000 units; while the third patient, a case of Addisonian anemia in relapse, received 10,000 units. All administrations were uneventful.

The only patient with macrocytic anemia complicating acute malignant leucoblastosis (acute leucemia) to whom we have administered the IV-6 plasma fraction was a child with malignant lymphoblastosis who evinced some transient clinical improvement but who did not respond to the administration by a rise in erythrocyte cholinesterase or by reticulocytosis. Should this single observation be generally confirmed, it may legitimatize the hypothesis that the gravity of the malignant estrapenic

[1] The writers are indebted to A. J. Aptaker, H. A. Goldberger, M. Newberg, A. N. Saperstein, and J. M. Seibel, of this hospital, for placing clinical material at their disposal and to the Cutter Laboratories, Berkeley, California, for furnishing the plasma fractions after thorough safety and sterility tests.

blood dyscrasias is conditioned by the degree of loss of ability on the part of the erythropoietic tissues to elaborate cholinesterase. Though other cholinergics besides acetylcholine are undoubtedly involved in the production of cholinergic episodes and the maintenance of cholinergic states in the human, the concomitance of blood cholinesterase level depression with morbidity degree in these dyscrasias may indicate a rational approach to control through substitutive enzyme therapy. Such therapy appears to have been successful in an estrapenic condition, experimental surgical shock in dogs (*5*).

The presence in human plasma (which has not had its cholinesterase activity vitiated) of a factor which permits maturation of leucemic myeloblasts (*2, 6*) and of a factor (diminished in the estrapenic plasma of relapsing Addisonian anemia) which causes reticulocyte "ripening" (*4*) would appear to warrant the attempt at isolation and the therapeutic trial of these fractions.


### References

1. ALLES, G. A., and HAWES, R. C. *J. biol. Chem.*, 1940, **133,** 375.
2. BARNARD, R. D. *Med. Rec.,* 1947, **160,** 610.
3. DAVIS, J. E. *Science,* 1946, **104,** 605.
4. JORGENSEN, S., and PLUM, C. M. *Ugesk. Laeger,* 1943, **31,** 787.
5. SCHACHTER, R. J. *Amer. J. Physiol.,* 1945, **143,** 552.
6. SCHWIND, J. L. *Amer. J. med. Sci.,* 1947, **218,** 170.


## Sulfaquinoxaline in the Control of *Eimeria tenella* and *Eimeria necatrix* in Chickens on a Commercial Broiler Farm[1]


L. C. GRUMBLES, J. P. DELAPLANE, and T. C. HIGGINS

*Rhode Island State College, Kingston*


Delaplane, Batchelder, and Higgins (*1*) first reported the use of sulfaquinoxaline in the prevention of *Eimeria tenella* infection in chickens under laboratory and field conditions. Grumbles, *et al.* (*2*) continued these studies and made more extensive observations on sulfaquinoxaline in preventing and treating both cecal and intestinal coccidiosis (*E. tenella* and *E. necatrix*) under field and laboratory conditions.

Sulfaquinoxaline was fed at the rate of 0.05% to chickens subjected to severe exposure of coccidia on a commercial broiler farm. The drug was given 2 days out of 5 (2–3 schedule), 1 day out of 4 (1–3 schedule), 1 day out of 5 (1–4 schedule), 2 days out of 6 (2–4 schedule), 4 days out of 8 (4–4 schedule), and at the rate of 0.0125% fed continuously.

Results of studies on 43,309 sulfaquinoxaline-treated birds and 3,085 untreated controls are shown in **Table 1.** The deaths from coccidiosis among the medicated birds were 1.75, 2.17, 1.80, 0.86, 1.13, and 1.20% as compared to 17.43% in the controls. The birds which died from coccidiosis showing *E. necatrix* infection were 0.63, 0.26, 0.28, 0, 0.13, and 0.12%, respectively, as compared to 7.45% in the controls.

Thus, sulfaquinoxaline used at the rate of 0.05% intermittently and 0.0125% continuously in the feed is effective in the control of *E. tenella* and *E. necatrix* infection in chickens. No symptoms of toxicity were observed in the birds after the use of the drug at the levels cited.

TABLE 1

| Schedule | No. of birds | Coccidiosis mortality (%) | | | |
|---|---|---|---|---|---|
| | | Cecal | *E. necatrix* | Both* | Total |
| Control pens "2–3" | 3,085 | 9.98 | 3.53 | 3.92 | 17.43 |
| .05% S.Q.† "1–3" | 17,699 | 1.12 | 0.51 | 0.12 | 1.75 |
| .05% S.Q. "1–4" | 7,348 | 1.91 | 0.18 | 0.08 | 2.17 |
| .05% S.Q. "2–4" | 5,459 | 1.52 | 0.02 | 0.26 | 1.80 |
| .05% S.Q. "4–4" | 1,043 | .86 | 0 | 0 | 0.86 |
| .05% S.Q. 0.0125% | 1,575 | 1.00 | .13 | 0 | 1.13 |
| continuous | 10,181 | 1.08 | 0.1 | 0.02 | 1.20 |

* Both *E. tenella* and *E. necatrix* infections.
† Sulfaquinoxaline.


### References

1. DELAPLANE, J. P., BATCHELDER, R. M., and HIGGINS, T. C. *N. Amer. Vet.,* 1947, **28,** 19–24.
2. GRUMBLES, L. C., DELAPLANE, J. P., and HIGGINS, T. C. (To be published.)



[1] This study was made possible by a grant from Merck & Company, Inc., Rahway, New Jersey. Contribution #709 of the Rhode Island Agricultural Experiment Station.


## Weed Control in the Tropics


A. S. CRAFTS[1]

*Department of Agronomy, Agricultural Experiment Station, Rio Piedras, Puerto Rico*


The use of cheap labor for hoeing weeds is traditional in the tropics. Only recently have chemicals been given serious consideration. The low cost and great effectiveness of the 2,4-D herbicides have created new opportunities for improvement of cultural methods and conservation of labor. Van Overbeek and Vélez (*4*) and White and Villafañe (*6*) have pointed out the unique value of 2,4-D as a selective weed killer in cane and other tropical crops.

The selective nature of 2,4-D is at once a virtue and a fault. Being relatively nontoxic to cane and coffee (*4*), this herbicide can be used with little or no injury in these crops. On the other hand, being nontoxic to grasses, one of the large and important groups of weeds is im-


[1] On leave from the University of California College of Agriculture, Davis, California.

A. Emanuelli, assistant agronomist with the Puerto Rico Agricultural Experiment Station, has cooperated actively in the conduct of this research.