

PN-ABC-889

AGENCY FOR INTERNATIONAL DEVELOPMENT  
WASHINGTON, D.C. 20523

DATE:

7/7/88

MEMORANDUM

TO: AID/PPC/CDIE/DI, room 209 SA-18  
FROM: AID/SCI, Victoria Ose  
SUBJECT: Transmittal of AID/SCI Progress Report(s)

Attached for permanent retention/proper disposition is the following:

AID/SCI Progress Report No. C 7 - 128  
Interim Report  
rec'd 7/7/88

Annual Report - Jan 1989

Attachment:

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AID-CDR grant/ # C7-128 entitled:

Protein Binding of Drugs in Malnutrition and  
Parasitic Disease

Annual Scientific Report

Submitted by

Abraham Danon, M.D., Ph.D.

January 1989

FEB 23 1989

This report supplements the Interim Report submitted last summer.

We have studied 43 plasmas from pediatric patients with marasmus. Plasma albumin concentration was  $42.9 \pm 1.1$  mg/ml, not different from control levels of  $43.8 \pm 1.2$ . Alpha 1 acid glycoprotein (AGP) concentrations in marasmus were three-fold larger than in controls, namely  $2.49 \pm 0.2$  mg/ml, compared with  $0.85 \pm 0.1$  ( $p < 0.008$ ). The drug protein binding profile of these plasmas exhibited normal binding of the antiepileptic drug phenytoin (DPH) ( $87.5 \pm 0.4\%$ ), which is predominantly albumin-bound, while binding of the beta blocker propranolol was much tighter ( $90.8 \pm 0.6\%$ ) than in controls ( $83.0 \pm 2.4\%$ ). Propranolol is known to bind principally to AGP. Regression analysis surprisingly showed complete lack of correlation between propranolol binding and AGP concentration in this group of patients ( $r = 0.04$ ).

In 10 patients with active malaria plasma albumin concentration and DPH binding were normal, namely  $45.4 \pm 1.8$  mg/ml and  $85.3 \pm 1.4\%$ , respectively. AGP concentrations were elevated to  $1.59 \pm 0.3$  mg/ml ( $p < 0.05$ ), and propranolol binding was greatly increased, to  $91.2 \pm 1.7\%$  ( $p < 0.05$ ).

Guinea worm infection (7 patients) also did not alter plasma albumin concentration or DPH binding ( $40.4 \pm 0.6$  mg/ml and  $85.8 \pm 0.3\%$ , respectively). Again, AGP concentrations rose to twice normal ( $1.64 \pm 0.2$ ) and

propranolol binding was significantly higher than normal (91.7 ± 0.4%).

One patient with onchocerciasis had extremely high plasma albumin concentration, 61.8 mg/ml, and exhibited correspondingly exceedingly high DPH binding, 97%. His AGP level was not elevated and propranolol binding was in the normal range.

### Discussion

We measured the plasma concentrations of the two major binding proteins, namely albumin and AAG, and the actual binding to plasma proteins of two model drugs. DPH was chosen to represent a drug that is exclusively bound to albumin, while propranolol was used because it binds extensively to AGP.

As expected, the AGP concentrations were high both in malnourished children and adults suffering from parasitoses. In both groups of patients propranolol binding was significantly increased over controls, leaving only half of the free drug (< 10%) as in controls (19%). As we have discussed it in the Research Proposal, this very significant difference in the plasma binding of basic drugs may have obvious pharmacokinetic and therapeutic consequences.

The non-correlation between AGP levels and propranolol binding in marasmus patients is intriguing. Although the reason for this situation is not obvious, one may consider several possibilities: First, there may be more than one molecular species of AGP, which contribute differently to propranolol binding. Alternatively, there may be competing ligands for AGP in marasmus plasma. Such ligands could be products of protein or lipid metabolism, the concentrations of which may be elevated in patients with malnutrition. These possibilities will be further investigated in the near future.

We are awaiting the shipment of additional material from Nigeria.

TABLE 1. Protein and drug binding parameters (mean  $\pm$  SEM)

Group (n)	Albumin (mg/ml)	binding DPH %	AGP (mg/ml)	binding Propranolol %
Normals (8)	43.6 $\pm$ 1.2	86.0 $\pm$ 0.7	0.85 $\pm$ 0.1	83.0 $\pm$ 2.4
Marasmus (43)	42.9 $\pm$ 1.1	87.5 $\pm$ 0.4	2.49 $\pm$ 0.2	90.78 $\pm$ 0.6
Malaria (10)	45.4 $\pm$ 1.8	85.3 $\pm$ 1.4	1.59 $\pm$ 0.3	91.15 $\pm$ 1.7
Guinea worm (7)	40.4 $\pm$ 0.6	85.8 $\pm$ 0.3	1.64 $\pm$ 0.2	91.7 $\pm$ 0.4
Onchocerca (1)	61.8	97.0	0.21	81.7
Ascaris	43.0	87.3	> 1	87.0

AID-CDR grant # C7-128 entitled:

Protein Binding of Drugs in Malnutrition and  
Parasitic Disease.

Interim Report

Submitted by

Abraham Danon, M.D., Ph.D.

Rec'd In Sci: JUL 7 1988

1. We started work on the project since Aug. 24, 1987.
2. Dr. Emudianughe of Ilorin has joined us here in Beer-Sheva since October 1st, 1987, and is expected to stay through the end of August, 1988. He is taking active part in the planning, methodology and actual implementation of the project.
3. We have nominated, with your approval, Dr. Paul Alade of Ilorin as co-investigator with the view that he will take care of the Nigerian side, particularly while Dr. Emudianughe is in Beer-Sheva.
4. I visited Ilorin, Nigeria, from March 15th through March 28th, 1988. The goals of this visit were: to establish personal contacts with the Nigerian scientists and administrators; acquire first-hand knowledge and feeling of the collaborative possibilities, problems etc.; make the initial arrangements for the field work i.e., identification of patients, sample collection and handling ; and carry some specimens back to Beer-Sheva for analysis. All objectives were successfully met. More specifically, the reception was very warm and effective, both on the part of the co-investigator and the University officials, particularly the dean and vice-chancellor. The need and willingness for further collaboration through similar research projects, was stressed on several occasions. The fact that both our medical schools belong to the WHO network of

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community-oriented medical schools was repeatedly mentioned as a basis for fruitful relationship. The latter fact was also important in that it provided the scenario for patient identification and sample collection, because the faculty had established relationships with numerous community clinics. During my visit we have been able to identify patients with malnutrition, malaria and guinea-worm (Dracunculus), and managed to collect and carry back some 60 samples.

5. We have developed and perfected the following methodologies: spectrophotometric method for albumin determination ; immunoelectrophoresis for alpha-1 acid glycoprotein and prealbumin; equilibrium dialysis for drug-protein binding. We have started analyzing the patient samples. Preliminary data indicate very low prealbumin levels in malnourished children with very high alpha acid glycoproteins. Surprisingly, propranolol binding in these patients seems not to correlate with alpha acid glycoprotein levels. More data are required to draw firm conclusions.

6. Work is still underway on perfecting the methodologies for equilibrium electrophoresis and equilibrium gel filtration for drug binding.

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