Combined Deficiencies of PTA and AHG with Vascular Fragility

By Seymour Perry, Richard Oppell and Mary Baker

With the development of more refined methods of studying defects in coagulation, there have been a number of reports in the recent literature of multiple congenital deficiencies of clotting factors occurring in the same individual. However in spite of these newer technics, the incidence of reported clinical cases remains very low in respect to total population. Therefore it is to be expected that the frequency of multiple defects in one person would be remarkably low. For example, it has been estimated that the incidence of classic hemophilia, the most common of this group, is $1 \times 10^{-4}$ and of parahemophilia, $2.5 \times 10^{-7}$. Granted a number of genetic assumptions, the chances that these two particular defects would occur together is $0.9 \times 13 \times 10^{-11}$. The expected incidence of combined AHG and PTC deficiency would be one in ten million. There are no available data for the incidence of PTA deficiency in the population, but based on studies which have shown that these cases constitute about one-tenth of all hemophiliacs, the expected frequency of combined PTA and AHG deficiency would be about $7 \times 10^{-10}$. The purpose of the present communication is to report a patient with this combination and to detail the analysis of the kinship in which clinically diverse hereditary defects of coagulation occur frequently enough to suggest a single genetic basis for all, namely, a single gene with pleiotropic effects or linked genes.

On review of the available literature we have been able to find eleven reports of multiple defects. These include combined hemophilia and parahemophilia; PTA and factor VII deficiencies; hemophilia and PTC deficiencies. However, the patients of Hill and Speer have been re-studied and found to have only a single defect. Only one instance of combined PTA and AHG has been recorded, but the evidence presented is not conclusive.

Studies of patients with multiple clotting defects are important in increasing our understanding of the mechanism of congenitally acquired hemorrhagic disorders and their patterns of inheritance. The studies in the patient reported here are valuable since he appears to be a combined PTA–AHG deficiency with vascular fragility and the results are of further interest because many of his immediate and distant relatives were available for investigation.

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CASE HISTORY

Mr. W. W., a 22 year old Caucasian, was referred to the University of California Medical Center, Los Angeles, in October, 1956, by one of us (R.O.) for the investigation of a bleeding diathesis. His father had previously been found to have a coagulation defect (see below) and this was part of the family study.

The patient had been relatively free of coagulation difficulties except for a 3 week bleeding episode following a tonsillectomy at the age of 9. He had bruised readily but never bled excessively after trauma. There had never been hemarthrosis, extensive ecchymoses, epistaxis, or other severe manifestations to indicate the presence of a coagulation defect. He had never had a surgical procedure or a tooth extraction. However, in July 1959, 2 teeth were extracted without difficulty after preoperative transfusion of fresh plasma.

Physical examination was completely negative. Routine laboratory studies such as hemoglobin, white and red blood counts, urinalysis and chest film were all normal.

METHODS

Many of the methods used in this investigation have been published previously.

Siliconed or plastic tubes, siliconed needles and syringes were used unless otherwise specified. The two syringe technic was used to obtain blood.

Coagulation tests were done concurrently on at least two normal controls on the days that patients were being investigated. It should be particularly noted that all studies were done on fresh blood, plasma or serum unless otherwise indicated.

Clotting times, platelet counts, prothrombin times, prothrombin consumptions, and the thromboplastin generation test (TGT) were performed as previously described. The initial TGT in every patient was done using his own substrate. If thromboplastin generation were abnormal, the test was repeated using normal substrate. Anti-hemophilic globulin levels were determined according to the method of Pool and Robinson. Assays for prothrombin, proconvertin and accelerator globulin were done as described by Lewis and Didisheim.

Recalcification times and tests for circulating anticoagulants employing varying proportions of normal and patient's plasma were performed in the usual manner. To eliminate the possibility that an anticoagulant of low titer was responsible for some of the results additional studies were performed. These included thromboplastin dilution and thromboplastin inactivation tests. Thromboplastin generation was studied using mixtures of normal and patient's reagents undiluted and also after incubation at 37 C. This is thought by many to be the most sensitive means available for the detection of anticoagulants acting in the first phase of coagulation. Tests for the circulating anticoagulant of the antithrombin type were also done.

In order to exclude a Hageman factor deficiency, glass activation studies of plasma were done according to the method of Margolis. Highly centrifuged citrated plasma in siliconed glassware is exposed to glass microspherules for 20 minutes at room temperature. This plasma is then diluted with normal plasma (collected in siliconed glassware) and recalcified with a calcium chloride lysed-platelet reagent. Undiluted test and normal samples of plasma are used as controls. Clot promoting activity in plasmas was studied using the procedure described by Margolis. This is similar to the glass activation test except that as the plasma is exposed to the microspherules, aliquots are removed at intervals, mixed with intact normal plasma and recalcified with the calcium chloride containing lysed platelets. Hageman trait plasma shows little or no activity in contrast to normal or PTA-deficient plasma.

RESULTS

Routine Studies

Results of routine coagulation studies are shown in table 1. The clotting time was normal in glass but prolonged in siliconed glass. The tourniquet
test was moderately positive after 5 minutes. Assays for prothrombin, accelerator globulin and proconvertin were normal. Assays for antihemophilic globulin were done on seven separate occasions with an average of 10.8 per cent and a range of 3.4 per cent to 15 per cent. On one other occasion a value of 38 per cent was obtained. The TGT was normal on that day. This will be discussed below.

**Thromboplastin Generation**

Thromboplastin generation using normal substrate was poor as shown in figure 1. The curve obtained using the patient's own substrate plasma was somewhat worse, maximum generation being 39 seconds at 6 minutes. There was complete correction when normal adsorbed plasma was substituted. Normal serum substituted for the patient's effected incomplete correction. Thromboplastin generation was normal when 1:1 mixtures of normal adsorbed plasma and the patient's adsorbed plasma were used. Again, 1:1 mixtures of his serum with normal serum alone resulted only in some improvement of thromboplastin generation without complete correction. Equal dilutions of the patient's plasma and AHG deficient plasma did not correct the plasma defect.

These results and the low AHG assay levels are consistent with a defect in the adsorbed plasma but they also suggest the presence of a serum defect. Various substitutions and mixing experiments were performed in an attempt to delineate the serum defect. Dilution with normal and PTC deficient sera corrected the serum defect in the TGT. However, thromboplastin generation was poor when fresh known PTA deficient serum was used with the patient's BaSO₄ treated plasma (fig. 2). There was no improvement in the thromboplastin generation when the patient's serum was used in a system containing known PTA deficient plasma (fig. 3). Similar results were obtained with blood freshly obtained from two other PTA deficient individuals. These findings indicate that the serum defect is probably a deficiency of PTA.

*These studies were confirmed by Dr. Arthur J. Seaman, Associate Clinical Professor of Medicine, University of Oregon Medical School.

†Confirmed by Dr. Seaman and also by Dr. Samuel Rapaport, University of Southern California School of Medicine, Los Angeles, Calif.
Fig. 1 (top, left).—Normal thromboplastin generation was obtained when BaSO₄ treated normal plasma was used with the patient's serum. However, when the patient's adsorbed plasma was used with normal serum, correction was negligible.

- patient's adsorbed plasma plus patient's serum; ○ normal adsorbed plasma plus patient's serum; ● patient's adsorbed plasma plus normal serum; × normal control.

Fig. 2 (top, right).—Improvement in TGT was obtained when known PTA-deficient adsorbed plasma was used with patient's serum. However, thromboplastin generation was poor when known PTA-deficient serum was substituted for that of the patient's.

● patient's adsorbed plasma plus patient's serum; ○ PTA-deficient adsorbed plasma plus patient's serum; ● patient's adsorbed plasma plus normal serum.

Fig. 3 (bottom).—Substitution of the patient's serum for the serum of a known PTA-deficient individual in a system containing the latter's adsorbed plasma and normal platelets did not improve thromboplastin generation.

○ known PTA-deficient adsorbed plasma plus PTA deficient serum; ● PTA-deficient adsorbed plasma plus patient's serum; ● PTA-deficient adsorbed plasma plus normal serum.
Investigations for a Circulating Anticoagulant

Since the recalcification time was normal, ordinary mixing experiments therefore would not be expected to demonstrate anticoagulant activity.

The presence of a circulating anticoagulant of the antithrombin type was thought unlikely and this was confirmed as shown in table 2.

The possibility of an antithromboplastin was eliminated by several studies. Thromboplastin generation was abnormal with the patient's reagents regardless of whether patient's or normal substrate was used. We were not able to repeat the experiments demonstrating the presence or absence of the so-called Bridge anticoagulant which has been postulated in hemophiloid disorders.27 This has not been confirmed.28 Thromboplastin dilution and inactivation studies were both normal as shown in tables 3 and 4.

No anticoagulant activity was demonstrable when mixtures of the patient's serum with normal serum and the patient's adsorbed plasma with normal adsorbed plasma were used undiluted in the thromboplastin generation test. (fig. 4).

The incubation studies using mixtures of patient's adsorbed plasma with normal adsorbed plasma and patient's serum with normal serum were designed to investigate the possibility of an inhibitor acting early in the first phase of coagulation. However, control studies using normal plasma alone

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PTA and AFG Deficiencies with Vascular Fragility

Fig. 4A: ○——○ normal serum plus normal adsorbed plasma (undiluted); ○——○ normal serum plus patient's adsorbed plasma and normal adsorbed plasma 1:3 (undiluted).

Fig. 4B: ○——○ normal adsorbed plasma plus normal serum (undiluted); ○——○ normal adsorbed plasma plus patient's serum and normal serum 1:1 (undiluted).

Incubation Time in Minutes

Fig. 4.—Undiluted mixtures of normal adsorbed plasma with the patient's adsorbed plasma and normal serum with the patient's serum did not reveal the presence of any inhibitory activity.

Demonstrated a deterioration of thromboplastin generation even after 2 hours' incubation. Apparently, exposure to 37°C for this period of time is adequate to inactivate some coagulation factor(s) necessary for good thromboplastin generation. Hence, modification of the test in this manner is probably not valid for the demonstration of anticoagulant activity.

Finally, figure 5 shows that increasing dilutions of the patient's serum in the TGT failed to improve thromboplastin generation. Ordinarily, an anticoagulant might be expected to be diluted out so that at first there would be a marked increase in thromboplastin formation.

Experiments with Stored Plasma and Serum

Since Rosenthal[29,30] and others[31] have reported that PTA deficient plasma and serum seem to gain in activity after storage in glass, these were retested in the TGT. Serum and BaSO₄ treated plasma had been stored at 4°C in glass tubes after aliquots of each had been used in the TGT and found abnormal. These were retested 3 months later. The patient's serum was now completely normal (fig. 6) and there was improvement in the activity of his adsorbed plasma (fig. 7). As far as is known, a PTA deficiency is the only one which will behave this way on storage and this constitutes further evidence that a deficiency of PTA is present.[32]

Differentiation from Hageman Factor Deficiency

A Hageman and a PTA defect may appear alike superficially; even mixing experiments may be confusing.[32] so that it was felt that additional studies would be of value.
Fig. 5.—Effect of increasing dilutions of the patient’s serum. Dilutions of the serum were used with normal adsorbed plasma and platelets. In contrast to serum containing an inhibitor, this serum did not permit improved thromboplastin generation with progressive dilution.

- Serum diluted 1:10; - - - - diluted 1:50; - - - - - - diluted 1:500.

Hageman factor deficiency is a major defect from the laboratory standpoint but produces no clinical bleeding. In contrast, PTA deficiency often demonstrates only a minor defect, as shown by coagulation tests, but may produce significant clinical bleeding. Hageman deficient plasma is not activated by glass and has no clot promoting activity. PTA deficient plasma (as well as PTC and AHG deficient plasma) and normal plasma are activated by glass.

This patient’s plasma after exposure to glass microspherules gave normal glass activation times. The clotting times for both the patient’s plasma and normal plasma were 3 minutes. Clot promoting activity was almost identical with that in the normal control (fig. 8). This differs from the results reported by Margolis, who noted that normal and PTA deficient plasma showed a leveling of activity whereas the normal continued to increase for 5 to 10 minutes. Unfortunately, no Hageman factor plasma was available to us for testing.

**Family History**

The family tree is shown in figure 9. Results of clotting studies are summarized in figure 10. It should be noted that II-6, II-9 and II-11 were brothers and married 3 sisters (II-7, II-8, and II-10, respectively) of another unrelated family. Both families are of Anglo-Saxon descent.
PTA AND AHG DEFICIENCIES WITH VASCULAR FRAGILITY

Fig. 6.—Patient's serum when retested after 3 months' storage was quite normal.

- - - - - patient's serum plus adsorbed normal plasma in November 1958; - - - - - curve obtained in February 1959 using the same serum after storage at -4 C. for 3 months.

Fig. 7.—After 3 months' storage, patient's adsorbed plasma was much more effective in thromboplastin generation although still not normal.

- - - - - patient's adsorbed plasma plus normal serum in November 1958; - - - - - curve obtained in February 1959 using same plasma after storage for 3 months.

Fig. 8.—Clot-promoting activity of the patient's plasma was quite normal. As his plasma was rotated with glass microspheres, aliquots were removed and mixed with intact normal plasma and recalcified with a calcium-platelet preparation (semi-log).

- - - - - patient; - - - - normal.

Pertinent details of the family history are as follows:

II-8.—Bled excessively after minor cuts.

II-10.—Bled severely after tooth extractions and small cuts. Died early in life of a cerebral hemorrhage.
Fig. 9.—Family tree of patient W. W., indicated by arrow in generation IV. Squares are males; circles are females. Black symbols indicate those with positive history of a bleeding diathesis (see text for details).

Fig. 10.—Summary of clotting studies in family of propositus (indicated by arrow).

Although not shown in the chart, studies were not adequate in IV-8 to establish unequivocably an AHG deficiency. Similarly, PTA deficiencies were not clearly proved in III-3 or V-1. However, there was enough evidence to strongly suspect the presence of these deficiencies. Also, it should be noted that tourniquet tests were not done in all available members of the family (see text).

III-3.—First seen in 1955 at the age of 63 at the University of California Medical Center upon referral by one of us (R.O.) for investigation of a hemorrhagic diathesis. He had been fairly well most of his life except for excessive bleeding after tooth extractions. In 1954, he had a transurethral resection and required 25 transfusions because of bleeding over a 3 month period. In 1956, he was again hospitalized for 3 months after a transurethral resection because of unusual bleeding. This time 11 pints of blood were required.
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Clotting studies revealed a positive tourniquet test, and slightly abnormal prothrombin consumption. Thromboplastin generation tests were done on 3 occasions. There appeared to be a defect in both the plasma and serum in two tests, one of these being also associated with a qualitative platelet defect. On the other occasion, only a plasma defect was found. Unfortunately, at the time, facilities for more extensive studies were unavailable to us. It is of interest to note that this patient died at the age of 65 of thrombotic thromocytopenic purpura and bronchogenic carcinoma.

III-4.—Seen in 1955 at the age of 60. Bled severely after a transurethral resection. Developed a very large subcutaneous hematoma after herniorrhaphy.

Clotting studies revealed only a defect in his adsorbed plasma in the TGT. AHG assay was 22 per cent.

III-6.—Extensive bleeding after each of two tonsillectomies and required multiple transfusions. Died of uncontrolled bleeding from a duodenal ulcer at the age of 35.

III-9.—Severe bleeding after tooth extractions. Died at 45 of cerebral hemorrhage.

III-11.—This man gave a life-long history of ready bruisingability. At age 10 he almost bled to death after a tonsillectomy. At age 30 he bled for 8 days following the extraction of 5 teeth. At 51, he sustained a laceration of a finger and subsequently developed a hematoma which dissected up to the elbow. At 56, he had a hemorrhage of one ankle after trauma. Upon examination, he had a positive tourniquet test and a plasma defect in the TGT.*

III-12.—History of hemarthroses, hematomas, and severe bleeding after tooth extractions. Bleeding time was normal but a plasma defect was demonstrable in the thromboplastin generation test. AHG assay was 8.7 per cent.

III-13.—A "bleeder" all her life particularly after tooth extractions. Said to have had hypertension. Died in middle age of a cerebral hemorrhage.

IV-1.—Nose bleeds as a child but no other bleeding. Family history completely negative. Coagulation studies, including TGT, were normal. AHG assay 62 per cent.

IV-3.—25 years old when studied in 1958. No history of bleeding but has always bruised readily. Never had surgery or tooth extractions.

We are grateful to Dr. David S. Fischer and Dr. Clement A. Finch, Professor of Medicine, University of Washington School of Medicine, Seattle, Washington, for being kind enough to study this patient, his son, and his grandchildren.

We are greatly indebted to Dr. Arthur J. Seaman, for studying this individual as well as his niece and her children.

Had normal bleeding time but clotting time in silicone was prolonged and prothrombin consumption was poor. No tourniquet test was done. Thromboplastin generation tests were not conclusive. On one occasion both normal adsorbed plasma and serum were able to correct his abnormal curve (see figure 11). However, when studied again, a defect could only be demonstrated in his plasma. AHG assay was 20 per cent.

IV-4.—Epistaxis as a child and bled after a tonsillectomy but had two dental extractions, plastic removal of a scar, and sustained multiple lacerations without excessive bleeding. Bleeding time was prolonged and AHG assay was 27.7 per cent.* The TGT was slightly abnormal but was corrected by both normal plasma and serum. Correction (by a 1:1 mixture of the patient's plasma with normal adsorbed plasma), was far from complete. Unfortunately, no PTA deficient plasma was available for mixing experiments.

IV-8.—Required two transfusions because of excessive bleeding during an elective appendectomy. No other history is available. Coagulation studies revealed a positive tourniquet test and a poor TGT with defects in both plasma and serum.

*We are grateful to Dr. Paul M. Aggeler, Children's Hospital, San Francisco, California, for his cooperation in the study of this patient.

V-1.—Enlarging scalp hematoma for 2 months at age 2 which had to be evacuated. Ready bruisingability.

Prolonged bleeding time and positive tourniquet test. Poor prothrombin consumption and abnormal TGT. Definite plasma defect but questionable serum defect. AHG assay 47 per cent.

V-2.—Ready bruisingability but no other manifestations. Bleeding time prolonged with positive tourniquet test. Prothrombin consumption poor and thromboplastin generation
slightly abnormal. Correction by both normal plasma and serum. AHG assay 80 per cent.

V-4, 5.—Slightly prolonged bleeding and clotting times (glass). V-5 had a slightly positive tourniquet test. Both had poor thromboplastin generation with correction by normal plasma and to a lesser extent by normal serum. Unfortunately, PTA deficient plasma was not available for mixing experiments.

**DISCUSSION**

The data obtained in the present study demonstrates that various members of this family may have deficiencies of AHG or PTA, vascular fragility, or some combination of the three. There is little doubt that the propositus, at least, has all three. Although it would have been desirable to do mixing studies on more members of the family, it was unfortunately not possible. However, if the propositus is accepted as having a deficiency of PTA (as well as AHG) it seems quite likely that those members of the family having both a plasma and serum defect also have a PTA deficiency.

The presence of a mild anticoagulant acting in conjunction with a factor deficiency may account for some of the cases of double deficiencies which have appeared in the literature. This possibility is always difficult to eliminate but with the various techniques used in this investigation no such anticoagulant was revealed.
Vascular fragility and a clotting factor deficiency in the same individual is not a frequent occurrence. Even less common is the association of a capillary disorder with more than one defect in coagulation. In a recent comprehensive review of so-called vascular hemophilia, Valberg and Brown could find only three such instances. Ingram has added another.

Hemorrhagic disorders involving defects of clotting factors with vascular fragility constitute a very confused area in coagulation, partly because of the great number of terms being used. However, there seems to be general agreement that the inheritance pattern may be accounted for on the basis of a simple autosomal dominant. Recently, Graham has suggested that the genetics of syndrome may be much more complex. He is of the opinion that vascular hemophilia is due to a polygenic situation. One gene results in a low AHG level and another is responsible for the vascular defect. However, Nee is of the opinion that cases in which an individual demonstrates 2 or more defects in the coagulation mechanism are beginning to appear with such frequency that it would be almost inconceivable statistically that these are due to unrelated genetic alterations. A single gene with variable penetrance and expressivity is a more likely possibility.

The hemorrhagic disorder described by Rosenthal and presumably due to a deficiency of PTA has been accepted with some reluctance. This is due to the fact that PTA has several unusual features such as the resemblance in some respects to both AHG and PTC. The explanation has been advanced that “PTA deficiency” may only be a combined mild deficiency of both AHG and PTC. Studies in the family reported lend support to the contrary. The presence of both defects, PTA and AHG, in the propositus with the demonstration of these defects separately in other members of the family is also an important piece of evidence in this regard. As has been reported, the inheritance pattern of PTA deficiency appears to be autosomal probably dominant.

There is apparently only one report in the available literature of a combined PTA and AHG deficiency. Unfortunately, this is based on evidence which is questionable and consists solely of mixing experiments done in glass tubes. The improvement in prothrombin consumption which was obtained with normal plasma as contrasted with that following mixing with PTA deficient or hemophilic plasma does not appear significant.

There has been insufficient emphasis on the difficulties which may be encountered in conducting the type of study reported here. Results in an individual may fluctuate widely if he is studied repeatedly over a period of years. This has been noted previously. Frick in reporting a case of PTA deficiency with a vascular anomaly noted variation in the serum defect between normal and slightly pathologic. The propositus in the present report was tested many times over a 4 year period. On one occasion he showed only a mild deficiency of AHG and on another occasion he was completely normal. The serum defect showed similar fluctuations. The thromboplastin generation curve, although always abnormal, varied significantly in configuration from time to time.

Although nothing can be done about fluctuations inherent in the patient, meticulous attention to certain details will decrease the likelihood of induced
changes. Samples which are frozen and stored for any length of time should not be considered valid in this type of study particularly when a PTA deficiency is suspected. Mixing experiments require the presence of both the patient under investigation and the individual with the known deficiency so that the bloods may be drawn simultaneously. Finally, all samples should be collected under identical conditions especially in view of the effects of glass activation.

**SUMMARY**

Coagulation studies in a 22 year old Caucasian male have revealed the presence of combined deficiencies of PTA and AHG with vascular fragility. Members of his family have been shown to have isolated deficiencies of PTA, AHG, vascular fragility and various combinations of all three defects. The family studies indicating segregation of the PTA and AHG deficiencies lend support to the concept that these two are clinically separate entities.

The inheritance patterns of PTA deficiencies and AHG deficiencies with vascular fragility are discussed.

The problems encountered in this type of study are mentioned, and the precautions to be observed are indicated.

**SUMMARIO IN INTERLINGUA**

Studios del coagulation in un mascule de racia caucasian de 22 annos de etate ha revelate le presentia de un combinate carentia de antecedente de thromboplastina del plasma (PTA) e de globulina anti-hemophilic (AHG) con fragilitate vascular. Altere membros del mesme familia esseva recognoscite como distinguite per isolate carentia de PTA o de AHG o fragilitate vascular o per varie combinationes del tres defectos. Le studios familial indicante un seggregation del carentias de PTA a de AHG supporta additionalmente le notion que iste duo entitates es clinicamente separate.

Es discutite le genetica de carentias de PTA e de carentias de AHG con fragilitate vascular.

Le problemas incontrate in iste typo de studio es mentionate, e le mesuras de precaution a prender es indicate.

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This paper reports a rapid method of measuring the labile fibrinolytic activity of whole blood, in which the rate of lysis is followed by means of hourly estimations of the hemoglobin content of the clot; the 50 per cent fibrinolysis time is then determined from a graph of the results. The authors emphasize the importance of strict attention to details of technic.

The existence of a diurnal variation in lysis times was confirmed; this variation was significant only in ambulant subjects. The mean 50 per cent lysis time of 17 normal ambulant subjects after a fat-free breakfast was 3.18 hours (σ = 1.09) at 9:30 a.m. and 2.54 hours (σ = 0.63) at 11:30 a.m. In 6 healthy volunteers exercise was found to shorten fibrinolysis times considerably, although the effect was transient. A fatty meal lengthened fibrinolysis times, but this effect was abolished by exercise; there was a rough correlation between lipemia and lysis times.—R. M. H.


This paper describes experiments on the in vitro effect of suspensions of cholesterol and its oleate, stearate and acetate, and of emulsions of neutral fats, on the clot lysis time of normal human plasma. Cholesterol oleate suspensions inhibited fibrinolysis significantly; the other substances did not. —R. M. H.
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SEYMOUR PERRY, RICHARD OPFELL and MARY BAKER