The Blood Donor: Detection and Magnitude of Cytomegalovirus Carrier States and the Prevalence of Cytomegalovirus Antibody

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Interest in transfusion-associated Cytomegalovirus (CMV) infections began with the recognition that the overwhelming majority of cases of late-onset postperfusion mononucleosis were heterophile negative (1, 2). In 1965 Klemola and Kääriäinen (3) associated heterophile-negative mononucleosis with CMV infection, and 1 year later the same group documented the association of CMV infection with heterophile-negative posttransfusion mononucleosis (4). Those patients experiencing CMV infection had not undergone extracorporeal perfusion but had been transfused with large volumes of fresh blood, which implied that asymptomatic carriage of CMV might be quite common. This supposition seemed to be borne out by Diosi et al. (5) in work published in 1968 which reported CMV isolation from the peripheral leukocytes of 2 out of 35 healthy blood donors. Since that time peripheral leukocytes from over 1500 blood donors have been inoculated into cell culture for virus isolation, but no CMV has been recovered. This work has been done in various parts of the world including Bristol, England (6), Pittsburgh (7), Cleveland (8), Atlanta (9), Houston (10), Kansas City (11), and Seattle (12).

Prospective studies have examined the incidence of CMV infection by serology in patients receiving multiple blood transfusions. Table 1, taken from Randall and Plotkin (13), lists these studies which have shown posttransfusion infection frequencies ranging from 21 to 38%. It is noteworthy that 10 to 15% of those infected developed the postperfusion syndrome. At this point it is important to emphasize the difference between infection and disease. “Disease” is a very simple English word that means just what it says. . . . dis-ease, or loss of comfort. “Infection”, on the other hand, means the establishment of a host–parasite interaction and need not lead to damage to the host. There are many ways of detecting this interaction, ranging from isolation of the agent to evidence of the immunological response in the host. This table shows evidence of infection.

Table 2 is taken from a paper by Krech (18) and shows the distribution of CMV complement Fixing (CF) antibodies in healthy blood donors in different parts of the world. Antibody prevalences range from 40% in highly industrialized areas to 100% in developing countries. It is interesting that antibody prevalences in Japan and Hong Kong are in excess of 90%, even though they cannot be considered developing areas.

Table 3 is a summary of CMV CF antibody prevalence studies in blood donors living in Europe, Australia, and North America. The low prevalence reported in the study of Monif et al. (24) can be explained by the fact that the majority of the donors in Gainesville are college students, thus young and likely to be middle class. Additional studies reporting low antibody prevalences are those of Jack and McAuliffe
TABLE 1
Incidence of CMV Antibody Rise (CF) in Patients Receiving Multiple Blood Transfusions from Randall and Plotkin (13)

| Study                | Number of patients | Number of patients with rise | Percentage |
|----------------------|--------------------|-------------------------------|------------|
| Prince et al., 1971 (14) | 72                 | 15                            | 21         |
| Henle et al., 1970 (15) | 72                 | 17                            | 23         |
| Stevens et al., 1970 (16) | 41                 | 13                            | 32         |
| Perham et al., 1971 (6) | 55                 | 21                            | 38         |
| Paloheimo et al., 1968 (17) | 63                 | 19                            | 30         |

(19) and Embil et al. (21). Only the study of Mirkovic et al. (10) reported relatively high antibody prevalence. A skewed age distribution of donors does not appear to be the explanation for the low prevalences cited in the two former studies, nor is it responsible for the high prevalence reported in the Houston study. Socioeconomic factors may explain these differences.

From June, 1972 to February, 1973 we conducted a study at the Community Blood Center aimed at defining the epidemiology of CMV infections among blood transfu-

TABLE 2
Distribution of Cytomegalovirus Complement-Fixing Antibodies among Healthy Blood Donors in Different Parts of the World from Krech (18)

| Place where blood was collected | Country code | Number of serum samples tested | Samples with complement-fixing antibody | Number<sup>a</sup> | Percentage |
|--------------------------------|--------------|--------------------------------|----------------------------------------|---------------------|------------|
| Lyon                           | F            | 98                             | 39                                     | 40                  |
| Freiburg                       | D            | 89                             | 37                                     | 42                  |
| St. Gallen                     | CH           | 105                            | 47                                     | 45                  |
| Albany                         | USA          | 98                             | 44                                     | 45                  |
| Melbourne                      | AUS          | 99                             | 54                                     | 54                  |
| Stockholm                      | S            | 99                             | 60                                     | 60                  |
| Manchester                     | GB           | 94                             | 58                                     | 61                  |
| Honolulu                       | USA          | 145                            | 97                                     | 67                  |
| Johannesburg (whites)          | SA           | 96                             | 72                                     | 75                  |
| Houston                        | USA          | 98                             | 77                                     | 79                  |
| Buenos Aires                   | RA           | 43                             | 35                                     | 81                  |
| Bratislava                     | CS           | 100                            | 83                                     | 83                  |
| Port of Spain                  | TT           | 99                             | 86                                     | 86                  |
| Mauritius                      | MS           | 93                             | 83                                     | 89                  |
| Anchorage                      | USA          | 100                            | 94                                     | 94                  |
| Hong Kong                      | HK           | 99                             | 94                                     | 94                  |
| Sendai                         | J            | 99                             | 96                                     | 96                  |
| Greenland                      | DK           | 90                             | 88                                     | 98                  |
| Dar es Salaam                  | EAT          | 117                            | 114                                    | 98                  |
| Morocco                        | MA           | 109                            | 107                                    | 98                  |
| Fiji Islands                   | GB           | 95                             | 95                                     | 100                 |
| Entebbe                        | EAU          | 143                            | 143                                    | 100                 |
| Ibadan                         | WAN          | 95                             | 95                                     | 100                 |
| Johannesburg (Bantu negroes)   | SA           | 112                            | 112                                    | 100                 |
| Manila                         | PH           | 89                             | 89                                     | 100                 |
| Chandigarh                     | IND          | 68                             | 68                                     | 100                 |

<sup>a</sup> ≥ 1 in 4. The tests were performed by the coordinating laboratory.
CMV IN THE BLOOD DONOR

Prevalence of Complement-Fixing Antibodies to CMV in Blood Donors

| Study                      | Year | Reciprocal of lowest serum dilution tested | Geographic region      | Prevalence (%) |
|----------------------------|------|-------------------------------------------|------------------------|----------------|
| Jack and McAuliffe (19)    | 1968 | 8                                         | Melbourne, Australia   | 24             |
| Baron et al. (20)          | 1969 | 10                                        | Pittsburgh, Pennsylvania | 60             |
| Diosi et al. (5)           | 1969 | 8                                         | Timisoara, Rumania     | 65             |
| Embil et al. (21)          | 1969 | 8                                         | Nova Scotia, Canada    | 38             |
| Klemola et al. (22)        | 1969 | 4                                         | Helsinki, Finland      | 66             |
| Collaborative (23)         | 1970 | NS*                                       | Manchester, England    | 56             |
| Mirkovic et al. (10)       | 1971 | 10                                        | Houston, Texas         | 75             |
| Perham et al. (6)          | 1971 | 8                                         | Bristol, England       | 55             |
| Wentworth and Alexander (12)| 1971 | 8                                         | Seattle, Washington    | 52             |
| Monif et al. (24)          | 1973 | 8                                         | Gainesville, Florida   | 21             |
| Kane et al. (11)           | 1975 | 8                                         | Kansas City, Missouri  | 59             |

*NS, not stated.

Attendant to this study we examined the prevalence of CMV antibodies, viremia, and viruria among 223 volunteer blood donors and followed the recipients of blood from infected donors. The donors ranged in age from 19 to 62 with a mean of 37 years. They were 98% Caucasian and 77% were males. No CMV isolations were made from any of the 223 leukocyte-rich plasmas or washed leukocytes inoculated.

| Donor | Age/sex | Time       | Urine culture | Reciprocal antibody titer |
|-------|---------|------------|---------------|----------------------------|
|       |         |            |               | CF<sup>a</sup> | IHA<sup>b</sup> |
| 012   | 25-M    | Donation   | +<sup>d</sup> (23)<sup>c</sup> | 16 | 160 |
|       |         | 6 weeks later | 0<sup>e</sup> | 16 | 160 |
| 025   | 38-M    | Donation   | + (22)        | 16 | 40  |
|       |         | 10 weeks later | 0    | 16 | 40  |
| 029   | 28-M    | Donation   | + (13)        | 32 | 80  |
|       |         | 9 weeks later | 0    | 32 | 80  |
| 123   | 37-M    | Donation   | + (27)        | 8  | 40  |
|       |         | 14 weeks later | 0    | 16 | 40  |
| 162   | 51-M    | Donation   | + (21)        | 64 | 160 |
| 190   | 56-F    | Donation   | + (21)        | 8  | 80  |
|       |         | 8 weeks later | 0    | 16 | 80  |
| 198   | 53-M    | Donation   | + (31)        | 32 | 40  |
|       |         | 8 weeks later | 0    | 32 | 40  |

<sup>a</sup>Complement fixation.
<sup>b</sup>Indirect hemagglutination.
<sup>c</sup>Number of days in culture when viral cytopathogenicity first observed.
<sup>d</sup>+, CMV isolated.
<sup>e</sup>0, CMV not isolated.
TABLE 5
Complement Fixing Antibody Titers of 223 Blood Donors from Kane et al. (11)

| Age          | Number of donors | Positive* (%) | Number of donors with titer |
|--------------|------------------|---------------|---------------------------|
|              |                  |               | < 8 | 8 | 16 | 32 | 64 |
| 19–24        | 26               | 19            | 21  | 1  | 4  | 0  | 0  |
| 25–29        | 46               | 48            | 24  | 2  | 10 | 8  | 2  |
| 30–39        | 68               | 57            | 29  | 7  | 22 | 10 | 0  |
| 40–49        | 45               | 76            | 11  | 8  | 13 | 9  | 4  |
| 50–62        | 38               | 79            | 8   | 9  | 9  | 10 | 2  |
| Total        | 223              | 58            | 93  | 27 | 58 | 37 | 8  |

*Antibody titer ≥ 1:8.

directly onto Wentworth's human fetal tonsil fibroblasts. Seven donors (3%) were cytomegaloviruric, and Table 4 summarizes the laboratory data on these donors. Follow-up blood and urine cultures were taken from six of the seven cytomegaloviruric donors at times ranging from 6 to 14 weeks after donation; none of the cultures was positive for CMV. All viruric donors were antibody positive by CF and indirect hemagglutination (IHA) and their titers remained unchanged in those who were followed after donation. Their titers did not differentiate them from the nonviruric donors. Table 5 shows that 58% of all the donors had CMV CF titers of 1:8 or greater, while Table 6 documents that 59% of this group had IHA antibody titers of 1:10 or greater. When the CF and IHA titers from each donor were compared, the direct correlation illustrated in Table 7 was found. Six of the seven units taken from viruric donors were transfused, but only three of the six recipients lived long enough to be followed for evidence of CMV infection. Table 8 summarizes the laboratory data on the recipients of blood from the viruric donors. Two underwent coronary artery bypass surgery, while the third was transfused during a gunshot wound repair. Each of the recipients showed serologic evidence of CMV infection by a fourfold rise in IHA titer 13 to 16 weeks after transfusion. CMV-specific IgM antibodies were detectable in the posttransfusion sera of two of the recipients. No posttransfusion serum was available for testing from the third recipient. Somewhat puzzling was the fact that CF antibody rises were not detected in the two recipients on whom sufficient quantities of serum were available for testing. CMV was isolated from the urine of one of the recipients 14 weeks after transfusion. No disease attributable to CMV infection was seen in any of the recipients of blood from the viruric donors.

TABLE 6
Indirect Hemagglutination Antibody Titers of 223 Blood Donors from Kane et al. (11)

| Age          | Number of donors | Positive* (%) | Number of donors with titer |
|--------------|------------------|---------------|---------------------------|
|              |                  |               | < 10 | 10 | 20 | 40 | 80 | 160 | 320 | ≥ 640 |
| 19–24        | 26               | 23            | 20  | 0  | 2  | 0  | 3  | 1   | 0   | 0    |
| 25–29        | 46               | 50            | 23  | 0  | 4  | 2  | 7  | 6   | 2   | 2    |
| 30–39        | 68               | 59            | 28  | 0  | 3  | 9  | 16 | 8   | 2   | 2    |
| 40–49        | 45               | 76            | 11  | 0  | 1  | 7  | 10 | 7   | 7   | 2    |
| 50–62        | 38               | 76            | 9   | 0  | 0  | 5  | 8  | 7   | 7   | 2    |
| Total        | 223              | 59            | 91  | 0  | 10 | 23 | 44 | 29  | 18  | 8    |

*Antibody titer ≥ 1:10.
The observation of CMV infection in three recipients of blood from cytomegaloviruric donors prompted us to continue our search for viruric donors in order to see if viruria rather than viremia might be a more reliable indicator of ability to transmit CMV infection via blood. We have followed an additional 420 donors for evidence of CMV infection by urine culture and serology. Only four donors (1%) were excreting CMV in their urine at the time of donation. Antibody prevalence to CMV by CF and IHA was 65% in this cohort. Two of the four units from viruric donors were transfused to patients who could be followed, and the recipients had pre-existing CMV CF antibody titers of 1:8 and 1:16, respectively. Neither recipient showed evidence of infection by virus isolation from the urine or by fourfold or greater rise in antibody titer. Thus, three of five recipients of blood from viruric donors have shown evidence of CMV infection subsequent to transfusion. This study is still in progress and will continue until larger numbers of recipients have been studied. We are also following recipients of blood from nonviruric donors who are matched by age, sex, hospital, and medical history to the patients receiving blood from cytomegaloviruric donors.

The large number of studies cited previously (6–11) which have unsuccessfully attempted to isolate CMV from the leukocytes of normal donors stands in sharp

### TABLE 7
Distribution of 223 Donors by Indirect Hemagglutination (IHA) and Complement Fixing (CF) Antibody from Kane et al. (11)

| Reciprocal IRA CF titer | Reciprocal CF titer |
|-------------------------|---------------------|
| 8          | 16  | 32  | 64  |
| ≥ 640      | 0   | 1   | 4   | 3   |
| 320        | 0   | 1   | 8   | 6   | 3   |
| 160        | 0   | 2   | 14  | 11  | 2   |
| 80         | 0   | 10  | 23  | 11  | 0   |
| 40         | 0   | 9   | 9   | 5   | 0   |
| 20         | 4   | 4   | 2   | 0   | 0   |
| 10         | 0   | 0   | 0   | 0   | 0   |
| < 10       | 89  | 1   | 1   | 0   | 0   |

### TABLE 8
Laboratory Data on 3 Recipients of Blood from Cytomegaloviruric Donors from Kane et al. (11)

| Recipient | Age/sex | Time         | Virus culture | Reciprocal CMV antibody titer |
|-----------|---------|--------------|---------------|-------------------------------|
|           |         |              | Blood | Urine | CF<sup>a</sup> | IHA<sup>b</sup> | IHA-IgM<sup>c</sup> |
| 025R      | 61-F    | Pretransfusion | —<sup>d</sup> | —     | 32     | 320    | <8   |
|           |         | 9 weeks later | 0     | 0     | 32     | 640    | 32   |
|           |         | 16 weeks later| 0     | 0     | 32     | 1280   | 64   |
| 162R      | 48-M    | Pretransfusion| —     | —     | 16     | 80     | <8   |
|           |         | 13 weeks later| —     | —     | 32     | 320    | QNS  |
| 198R      | 38-M    | Pretransfusion| —     | —     | QNS    | 40     | QNS  |
|           |         | 14 weeks later| 0     | +     | 128    | 320    | 8    |

<sup>a</sup> Complement fixation.  
<sup>b</sup> Indirect hemagglutination.  
<sup>c</sup> IHA antibody titer of serum fraction containing IgM.  
+ , CMV isolated; 0, CMV not isolated; —, not performed.
contrast to the report of Diosi et al. (5) who identified two asymptomatic donors with CMV viremia out of 35 tested. This may well have been a chance observation, but Diosi's methods were sufficiently different from those reported in the other studies that this factor could be responsible for the disparate results. In order to test this hypothesis, we obtained blood and urine samples from 120 donors and attempted to isolate CMV by closely following the procedures described in Diosi's paper. The protocol involved culturing the leukocytes in suspension for 72 hr prior to inoculating them onto cultures of human fetal fibroblast cell cultures. In addition, we cultured three aliquots of cells from each donor in Diosi's medium which contained 10 μg/ml dexamethasone, 10 μg/ml azathioprine, and 2% antilymphocyte serum, respectively, for 72 hr and then inoculated the treated leukocytes onto human fetal tonsil cell cultures. The rationale for doing this was that drug treatment might unmask latent CMV resident in the leukocytes of the donors. Of 120 donors, 71 (59%) had CMV IHA antibody titers of 1:10 or greater, but no CMV was isolated from the untreated or drug-treated leukocytes of any donor. Three antibody-positive donors (2.5%) were excreting CMV in their urine at the time of donation. Recipients of the blood from these donors were not followed. In short, our data support the contention that methodologic differences are not responsible for the failure of numerous investigators to isolate CMV from the leukocytes of normal donors.

Although specifically charged with discussing the blood donor, we want to present some data on a group of open-heart patients who were prospectively followed for evidence of CMV infection. The number of open heart surgeries performed in Kansas City in 1972 was 827. This figure increased to 1199 in 1973 and climbed to 1289 in 1974; however, the average number of units used per case has declined from a figure of six in 1973 to four in 1974, and is about three units per case this year. Two units of fresh blood are made available for each surgery, but actual transfusion of units less than 2-days-old occurs only 15% of the time. Most of the blood transfused in heart surgery is 3- to 8-days-old, and approximately 18% of the transfused units are over 10 days old. Table 9 shows the results of our first study on open-heart patients which was done in Hospital A. The 35 patients in this study received an average of 5.8 units of blood. Throat, urine, and blood samples were collected for virus isolation and serology prior to surgery and at 6 and 12 weeks after surgery. Clinical data were obtained from the patient's cardiologist or his family physician. Three of 35 patients (9%) showed serologic evidence of CMV infection both by IHA and CF tests. Although CMV was isolated from the urine of one of these three patients at 12 week follow-up, no virus isolations were made from any other specimens. No illnesses at-

| Serologic Status | Number of patients | Percentage |
|------------------|--------------------|------------|
| Negative, no change in antibody titer | 2 | 6 |
| Pre-existing antibodies, no change in titer | 30 | 86 |
| Conversion | 1 | 3 |
| Pre-existing antibodies, fourfold or greater rise in antibody titer | 2 | 6 |
| Totals | 35 | 100 |

*Negative means a serum antibody titer of < 1:8 by CF or < 1:10 by IHA.
*Pre-existing antibodies mean a serum antibody of ≥ 1:8 by CF or ≥ 1:10 by IHA.
*Conversion means a change in titer from < 1:8 to ≥ 1:16 by CF or < 1:10 to ≥ 1:20 by IHA.
tributable to CMV were seen in any of the three patients experiencing CMV infection.

Our second study of open-heart patients, still in progress at Hospital B, has the same design as the one previously described. Table 10 displays the preliminary results of this study. Twenty patients have been followed, and none has shown evidence of CMV infection. An average of 2.5 units of blood was used for each case.

To evaluate the relative risk of CMV infection after transfusion with antibody-positive and antibody-negative blood, we have been studying the recipients of one and two unit transfusions (where both donors are either antibody positive or antibody negative). The data accumulated to date are presented in Table 11. The number of patients followed is small, and therefore no conclusions can be drawn. Only 1 of 32 recipients has shown evidence of CMV infection. The patient, who had a presurgical CMV CF titer of 64, received two CMV antibody-positive units during hysterecomy and showed a fourfold rise and viruria at 12 weeks follow-up. No disease was seen in this patient.

In summary, transfusion-associated cytomegalovirus disease is not an obvious problem in this community, at least in terms of adult transfusions. Two factors which are responsible for the apparent absence of disease and the low frequency of CMV infections are excellent surgeons who use very little blood in their operative procedures and the high quality of the blood donor base in the Kansas City metropolitan area.

**TABLE 10**
Serologic Response of Open Heart Patients to CMV as Monitored by CF and IHA Tests, Hospital B

| Serologic Status                          | Number of patients | Percentage |
|------------------------------------------|--------------------|------------|
| Negative,* no change in antibody titer   | 5                  | 25         |
| Pre-existing antibodies,* no change in   | 15                 | 75         |
| titer                                     |                    |            |
| Conversion †                             | 0                  | 0          |
| Pre-existing antibodies, fourfold or     | 0                  | 0          |
| greater rise in antibody titer           |                    |            |
| Totals                                   | 20                 | 100        |

* Negative means a serum antibody titer of < 1:8 by CF or < 1:10 by IHA.
† Pre-existing antibodies mean a serum antibody of ≥ 1:8 by CF or ≥ 1:10 by IHA.
‡ Conversion means a change in titer from < 1:8 to ≥ 1:16 by CF or < 1:10 to ≥ 1:20 by IHA.

**TABLE 11**
Serologic Response to CMV of Single and Double Unit Transfusion Recipients

| Number of recipients | Percentage | Pretransfusion antibody status | Antibody status of donor blood | Conversions or fourfold rises | No change in antibody status |
|----------------------|------------|-------------------------------|--------------------------------|------------------------------|------------------------------|
| 17                   | 53         | Positive*                     | Positive                       | 1‡                           | 18                           |
| 11                   | 34         | Positive                      | Negative*                      | 0                            | 11                           |
| 3                    | 9          | Negative                      | Positive                       | 0                            | 3                            |
| 1                    | 3          | Negative                      | Negative                       | 0                            | 1                            |
| Totals               | 32         | 100                           |                                | 1                            | 31                           |

* Positive is defined as a serum antibody of ≥ 1:8 by CF or ≥ 1:10 by IHA.
* Positive is defined as an antibody titer of ≥ 1:8 by CF and ≥ 1:10 by IHA.
‡ CMV was isolated from the recipient's urine at 8 weeks follow-up.
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