Circulatory and Renal Effects Following Transfusion of Human Blood and its Components to Dogs

By Hadley L. Conn, Jr., M.D., John C. Wood, M.D. and John C. Rose, M.D.

With the Technical Assistance of Phyllis Bach

The cardiovascular effects of the transfusion of human blood and of some of its components were studied in dogs. Human blood, hemoglobin, globin and red cell stroma produced significant circulatory depression. The reaction to stromal materials was considered to represent a combination of peripheral pooling and myocardial depression. The reactions to human hemoglobin and globin indicated primary vasoconstriction as the initial abnormality. The reaction to human blood, apparently, was a combination of the reactions to stroma and hemoglobin, with an anaphylactoid response after second blood transfusions.

During studies on the pathogenesis and the mechanisms responsible for producing the acute anuria syndrome it was found that transfusion of human blood to dogs under appropriate circumstances may lead to acute renal injury. Severe hypotension commonly accompanies or may follow the transfusions. These findings stimulated our interest in the nature of the cardiovascular abnormalities present and the component or components of the blood etiologically responsible. The present study was undertaken with the idea of answering, in part, these questions. Measurements of pressure and blood flow in various parts of the cardiovascular system and measurements of renal function were made in dogs subjected to transfusions of human blood or one of its component parts.

Experimental and Analytical Procedures

Mongrel dogs, weighing 16 to 25 Kg., were anesthetized by intravenous administration of 25 to 30 mg./Kg. of pentobarbitol sodium. Small supplemental doses of anesthetic, sufficient to keep the animal lightly anesthetized, were given. Venous catheters were introduced, under fluoroscopic guidance, into the left renal vein, the main pulmonary artery and the right atrium. Access to arterial blood was gained through a percutaneous needle puncture of the femoral artery or through a polyethylene catheter introduced into this vessel and advanced until the tip lay above the opening of the renal arteries. An indwelling catheter was placed in the bladder and an endotracheal tube was inserted.

Mean pulmonary arterial and right atrial pressures were measured by water manometers. Systemic arterial pressure was measured by a mercury manometer and by a Lilly capacitance manometer, the latter being used also to record pulse pressure and wave contour. In some experiments so-called “pulmonary capillary” pressure was obtained by “wedging” the catheter previously introduced into the pulmonary artery. Electrocardiograms were recorded on a Sanborn direct writing electrocardiograph and heart rates were obtained from these records. Arterial, renal, venous and mixed venous blood oxygen content were determined after the method of Van Slyke and Plaxen. Cardiac output was determined by the Fick oxygen procedure. Glomerular filtration was determined as the creatinine clearance. Renal blood flow was measured by the whole blood para-amino-hippurate (PAH) Fick and nitrous oxide (N₂O) methods described elsewhere. Renal PAH extraction, renal oxygen consumption, renal arteriography, examination of urine, and post-mortem examination of the kidneys were also carried out as described elsewhere. Absorption spectral analyses of the urinary proteins were made. Pulmonary, renal, and total peripheral vascular resistances were calculated from the simple ratio of mean pressure divided by blood flow, and the experimental compared with control values. Stroke volume and filtration fraction were also calculated from the appropriate original data.

These measurements were made initially during a control period and repeated on one or more occa-
sions during this period (up to four hours) after the transfusion of blood or blood product. Measurements were usually also repeated again two days later.

Measurements were made in connection with the following experimental procedures: (1) a first transfusion of whole human blood (7.5 ml./Kg.) was given to seven dogs; (2) a transfusion of human hemoglobin solution (0.5 Gm./Kg.) was given to six dogs, prepared as described by Pennell; (3) a transfusion of modified human globin solution (0.7 Gm./Kg.) was given to four dogs, prepared as described by Strumia and Pennell; (4) three dogs were given successive transfusions of human serum (50 ml.), followed by citric acid and sodium citrate in the amount contained as anticoagulant in 100 ml. of blood and finally human red cell stroma in the amount contained in 100 ml. of whole blood. Red cell stroma was prepared by repeated dilutions of whole blood with cold 0.1 per cent NaCl, centrifugation and redilution of the sediment; (5) a transfusion into two dogs of both the "solubilized" and the "non-solubilized" fractions of red cell stroma, prepared by the addition to stromal sediment of sufficient detergent (Antara, iso-octyl-phenoxypoly-ethoxy-ethanol) to make a final concentration of 0.1 per cent and (6) a second transfusion of human blood (2.5 ml./Kg.) was given to three dogs, two to three weeks after the initial transfusion. A second infusion of human hemoglobin solution (0.5 Gm./Kg.) was similarly timed and given to two dogs.

The early effects of first transfusions of human blood and hemoglobin were also studied in two dogs during the application of the controlled left ventricular output technic, described by Rose. Left ventricular stroke volume and output were controlled. Systemic pressure and pulse wave contour, pulmonary arterial pressure, and pulse wave contour, venous pressure and an electrocardiogram were recorded.

Results

Human Blood: First Transfusions. The mean of the results produced by human blood transfusion into seven dogs is shown in table 1, column 3. During, and for periods of up to one hour after the transfusions of human blood, moderate to severe hypotension was present. Systemic arterial pressure fell to a mean of 46 per cent and pulmonary arterial pressure to 65 per cent of control. This was associated with a fall in cardiac output to a mean of 36 per cent of control. Reduced cardiac output in turn was the result of a decrease in stroke volume to

| Table 1.—Circulatory and Renal Effects Produced in the Dog by the Intravenous Administration of Human Blood, Human Hemoglobin and Modified Human Globin |
|------------------|------------------|------------------|------------------|------------------|
|                  | C                | II               | III              | C                | I                | II               | III              | C                | I                | II               | III              |
| Q                 | 152              | 135              | 158              | 125              | 121              | 125              | 49               | 73              | 135              | 154              | 25               | 25               |
| MMAP              | 12               | 10               | 12               | 13               | 14               | 13               | 8.5              | 5.4             | 13               | 12               | 5                | 7                |
| Fp                | 0.5C             | 0.5C             | 0.5C             | 0.5C             | 0.5C             | 0.5C             | 0.5C             | 0.5C            | 0.5C             | 0.5C             | 0.5C             | 0.5C             |
| MABP              | 150              | 150              | 126              | 126              | 126              | 126              | 126              | 126             | 126              | 126              | 126              | 126              |
| Sg                | 1.8               | 1.8               | 1.8               | 1.8               | 1.8               | 1.8               | 1.8               | 1.8               | 1.8               | 1.8               | 1.8               | 1.8               |
| Hk                | 140              | 140              | 140              | 140              | 140              | 140              | 140              | 140               | 140              | 140              | 140              | 140              |
| BV                | 18               | 15               | 15               | 18               | 12               | 12               | 12               | 12               | 12               | 12               | 12               | 12               |
| MMAP              | 0.1              | 0.1              | 0.1              | 0.1              | 0.1              | 0.1              | 0.1              | 0.1              | 0.1              | 0.1              | 0.1              | 0.1              |
| MMPW              | —                 | —                 | —                 | —                 | 2.5              | 2.5              | 2.5              | 4               | 1.5              | 2.8              | 2.8              | 2.8              |
| GFR               | 29               | 58               | 58               | 55               | 32               | 50               | 57               | 30              | 30               | 70               | 70               | 70               |
| Ra                | 2.3               | 1.96              | 1.96              | 1.96              | 1.96              | 1.96              | 1.96              | 1.96               | 1.96              | 1.96              | 1.96              | 1.96              |
| Rp               | 0.74              | 0.61               | 0.72              | 0.72              | 0.66              | 0.70              | 0.75              | 0.71           | 0.72              | 0.72              | 0.72              | 0.72              |
| Renal QO2         | 8.9               | 5.1               | 6.3               | 6.1               | 4.6              | 5.5              | 4.4              | 7.4               | 7.0              | 7.0              | 7.0              | 7.0              |
| Vp                | 19.5              | 19.8              | 19.8              | 19.8              | 19.8              | 19.8              | 19.8              | 19.8              | 18.3             | 18.3             | 18.3             | 18.3             |
| Vp/KO2            | 2.5               | 2.5               | 2.5               | 2.5               | 2.5               | 2.5               | 2.5               | 2.5               | 2.5               | 2.5               | 2.5               | 2.5               |
| Vp/KO2            | 15.5              | 11.21              | 15.0              | 14.1              | 3.5               | 2.4               | 2.4               | 2.4               | 2.4               | 2.4               | 2.4               | 2.4               |
| Vp/SG              | 18.0              | 18.8              | 17.2              | 17.0              | 7.6               | 7.6               | 7.6               | 7.6               | 7.6               | 7.6               | 7.6               | 7.6               |

H. Hb. = Human Hemoglobin (0.5 Gm./Kg.)
M. H. Gl. = Modified Human Globin (0.7 Gm./Kg.)
Hb. Bl. A = First Transfusion of Human Blood (2.5 ml./Kg.)
Hb. Bl. B = Second Transfusion of Human Blood (2.5 ml./Kg.)
Q = cardiac output ml./min./Kg.
MMAP = mean pulmonary arterial pressure, mm. Hg
Fp = mean pulmonary resistance
MABP = mean systemic arterial pressure, mm. Hg
Sg = mean peripheral resistance
BV = heart rate
SV = stroke volume ml.

* = decrease statistically significant at 5 per cent level, † = increase statistically significant at 5 per cent level.

MPWP = mean pulmonary 'wedge' pressure mm. Hg
RBF = renal blood flow ml./100 Gm. of kidney/min.
GFR = glomerular filtration rate ml./100 Gm./mm.
Ra = mean renal resistance
Rp = mean renal resistance
Rp/RO2 = whole blood extraction percentage for PAH
Renal QO2 = renal oxygen consumption cc./100 gm./min.
ApoO2 = arterial oxygen content, vol. per cent
VeO2 = venous oxygen content, vol. per cent
VpO2 = mixed venous blood oxygen content, vol. per cent
VeO2 = venous oxygen content, vol. per cent
C = control
I, II, and III represent the periods 0–1, 1–4, and 48–120 hours after transfusion, respectively.
30 per cent of control. A slight fall in mean right atrial pressure, accompanied the reduction in stroke volume. Renal blood flow was reduced to 43 per cent of control. All vascular resistances were significantly increased. Electrocardiographically, inversion or a diphasic appearance of the T waves was noted together with abnormalities of pulse pressure and wave contour.

Measurements during the 1 to 4 hour period showed that all pressures tended to return toward normal, mainly as a result of further increase in vascular resistance. However, stroke volume, cardiac output, and renal blood flow, all somewhat increased to an average of about 50 to 60 per cent normal at this time. Mean right atrial and "pulmonary capillary" pressures were now above the control level. Renal studies showed a continued, though lessened, ischemic pattern and after the initial hypotensive anuric period, the urine contained large amounts of hemoglobin.

When the dogs were restudied 2 to 5 days later, all measurements were essentially the same as the control measurements except that traces of hemoglobin were still found in the urine and, unaccountably, glomerular filtration rates were significantly increased. No marked renal lesions were found at postmortem examination.

**Human Hemoglobin.** The means of the results produced by transfusion of human hemoglobin into six dogs are shown in table 1, column 1. Transfusions of human hemoglobin produced no hypotension as did those of human blood. Rather, the mean result was a slight increase in systemic and pulmonary arterial pressures. However, as with human blood transfusions, cardiac output and, concomitantly, renal blood flow fell to 50 and 49 per cent of their respective control values. These changes were associated with a simultaneous reduction in stroke volume to 62 per cent of the controls. Again, all vascular resistances were significantly increased. In similar fashion to the post shock period after human blood administration, the mean right atrial pressures were found slightly elevated. Abnormalities of the T waves were sometimes also observed, following the hemoglobin transfusions.

The renal abnormalities were limited to the circulatory effects, reduced renal blood flow, glomerular filtration and increased vascular resistance, affecting both afferent and efferent arterioles, also to the occurrence of large amounts of hemoglobin in the urine. No cardiovascular or renal abnormalities were detected when measurements were repeated after 48 hours. No appreciable renal changes were observed on histologic examination.

In two dogs an identical transfusion dose of hemoglobin was given two weeks after the first and the measurements repeated. No significant differences in the response were found.

**Human Globin.** The means of the results produced by transfusion of modified human globin into four dogs are shown in table 1, column 2. The acute effects of globin infusions were qualitatively like those of hemoglobin infusions except for the urinary excretion of globin rather than hemoglobin. Quantitatively the cardiovascular and renal disturbances were somewhat less severe, their magnitude averaging about 70 to 90 per cent of those resulting from hemoglobin. Again, the major abnormalities appeared to be a deficit in cardiac output due mainly to significant decreases in stroke volume and increased peripheral resistance. And again, these acute effects persisted at least up to four hours after the transfusions, but had, except for the persistence of slight proteinuria, disappeared after 48 hours. Minimal parenchymatous swelling and degeneration of tubular epithelium were noted on histologic examination of the kidneys.

**Human Serum, Anticoagulant and Red Cell Stroma.** The infusion of fresh human serum and "two-week old" human serum, containing lyzed platelets and white blood cells, produced no demonstrable acute cardiovascular changes in two dogs. Neither did infusions, containing sodium citrate and citric acid in the amount contained in 100 ml. of whole "bank" blood. The transfusion of red cell stroma produced an initial severe hypotension just as did transfusions of blood; systemic blood pressure fell to 45 per cent of control and remained low, 30 to 90 minutes. The cardiovascular abnormalities paralleled, in a rather exact qualitative and quantitative fashion, those occurring
during the first hour after whole blood transfusions. A distinct difference, however, was noted in the ensuing two-hour period. With stromal transfusions, the cardiovascular changes regressed to the point that all pressure-flow-resistance measurements and calculations were within 20 per cent of normal or control. When the dogs were restudied two to three days later, all abnormalities had completely disappeared.

The addition of 1 ml. of a 5 per cent solution of Antara to 50 ml. of stroma suspended in physiologic saline and subsequent incubation of the mixture for 2 to 10 hours resulted in the "solubilization" of a considerable fraction of the sediment. This procedure apparently significantly altered the stromal substance, since both the 'solubilized' fraction and the remaining "non-solubilized" sediments were subsequently transfused into two dogs without discernible effects on cardiac output, heart rate, stroke volume, intravascular pressures or vascular resistances.

**Human Blood: Second Transfusion.** The means of the results of the appropriately timed, second transfusions of human blood into three dogs are shown in table 1, column 4. Qualitatively, the pattern of results was essentially like that seen after a first transfusion of human blood. A great difference was found quantitatively, however, in that the cardiovascular depression was much more severe and prolonged. Severe hypotension, with mean systemic pressure of 35 to 40 mm. Hg, persisted in studies continued up to three hours after beginning the transfusions. Mean pulmonary arterial and right atrial pressures initially also fell to subnormal values. Systemic shock was associated with a very sharp decline in cardiac output, less than 20 per cent of control, resulting in a fall in stroke volume to below 20 per cent of the control. Bradycardia, a somewhat atypical feature of shock, was observed in the first hour and no marked increase in heart rate was observed at any time. A similar effect was observed in some dogs given a first transfusion of blood.

One or more hours after the transfusion, mean pulmonary arterial pressure and calculated pulmonary resistance became amazingly increased, but the systemic hypotension persisted despite calculated mean increase in total peripheral resistance to 2.3 times that of the control. Abnormalities of the T waves were regularly observed as were evidences of pulsus alternans.

Renal studies indicated that, along with the decrease in cardiac output, renal blood flow decreased to very low levels (10 per cent of the controls). The animals were completely anuric throughout these acute studies. Yet, surprisingly enough, PAH extraction was 80 to 100 per cent of control up to one hour and a half after the onset of shock. The oxygen content of renal venous blood averaged only about 3 volume per cent and that of mixed venous blood only about 8 volume per cent, while arterial oxygen saturation and content remained essentially the same as in control values. As a result, body and renal pO₂ (estimated from oxygen content of the appropriate venous blood and assuming tissue-plasma O₂ diffusion equilibrium, and pH 7.4) were very low. Body and renal oxygen consumption were reduced to about 75 and 50 per cent of controls, respectively. The A-V (or A-R) O₂ differences across the kidneys averaged 10.7 volume per cent or about 7 times the normal.

One of the three dogs given a second transfusion was sacrificed at the end of the acute study. The outstanding pathologic finding was the contracted, firm, rigorous state of the cardiac muscle and the small chamber size. An increased amount of blood appeared to be pooled in the venous channels, particularly those of the portal system. A second dog died within 12 hours and the main pathologic findings were those of pulmonary edema and early, patchy pneumonitis. The third dog survived to be studied three days later. At that time, anuria, renal ischemia (renal blood flow of 100 ml./100 Gm./min.) and other findings were recorded, similar to those described elsewhere, resulting from second transfusions. The pathologic lesions in the kidneys resembled those described as occurring in "mismatched transfusion nephrosis."

**Renal Arteriographic Studies after Human Blood and Hemoglobin Transfusions.** Intrarenal distribution of blood flow, as judged from renal
arteriography, was normal in all dogs studied 3 to 5 hours after infusions of human blood and human hemoglobin. Thus, no evidence was adduced to indicate activation of intrarenal vascular “Trueta shunts” by either of these substances.

Cardiovascular Responses to Human Blood and Human Hemoglobin during a Period of Fixed Left Ventricular Output. In order to make some separation of primary central (myocardial) effects from peripheral vascular effects, the response to human blood and human hemoglobin was studied during a period when left ventricular output was fixed at about 125 ml./Kg./min. and stroke volume at about 20 ml. per beat, by use of the mechanical pump. During the first few minutes after hemoglobin transfusions, at a time when experimental artefacts are thought negligible, a marked peripheral constriction was present. Mean systemic arterial pressure increased to as much as about 210 per cent of control. A slight rise in pulmonary arterial pressure was the only other appreciable effect. During the early period after human blood transfusions, mean arterial pressure was only 65 to 70 per cent of control, the T waves of the electrocardiogram were more inverted and the pulmonary arterial pulse wave showed alternans, with mean pressure slightly decreased. A fall in volume in the artificial reservoir replacing the left atrium was also observed, the result of peripheral pooling caused by the transfusion.

DISCUSSION

In making an evaluation of these results it seems proper to note that maintenance of the same structure of the human blood and blood components administered as that which existed in the native state has not been demonstrated, although protein "denaturation" has been assumed small in amount and degree. Contamination of the prepared materials with small amounts of other blood components or extraneous substances has not been excluded. Human blood products, consisting mainly of heterologous proteins, were transfused into dogs. Furthermore, the dogs were not in a normal and, most likely not in a completely steady state throughout the experiments. Pentobarbital sodium, for example, is known to reduce cardiac output significantly. Because the experiments were carried out in a manner, designed to have control and experimental measurements made under otherwise essentially the same conditions, we believe the significant changes recorded can be attributed to the transfused materials.

The results indicate that human blood, red cell stroma, hemoglobin and globin all produced a significant circulatory and renal response when transfused into dogs. Other blood components had no observed acute effects. The abnormalities recorded were all temporary except those, occurring after an appropriately timed second transfusion of human blood, where the subsequent development of renal injury was correlated with prolongation of severe renal ischemia and hypoxia.

Reduced cardiac output, due to decreased stroke volume, and renal ischemia, presumably due to deficient cardiac output, were physiologic disturbances produced by all agents. However, the total circulatory response pattern was not the same for all agents. The results of both hemoglobin and globin transfusions to the intact dogs showed a response characterized by diminished cardiac output and increased peripheral constriction with a resultant normal systemic pressure, but gave no answer concerning which defect was primary. The occurrence of a marked increase in mean systemic pressure following hemoglobin infusions to open-chest dogs, having a normal, fixed left ventricular output, strongly suggests that hemoglobin causes peripheral vasoconstriction. Diminished cardiac function is a secondary or compensatory phenomenon. A similar response presumably accounts for the renal ischemia which accompanies transfusion of human hemoglobin to man. The provocative principle responsible for vasoconstriction has not been demonstrated, although the similarity of results of the hemoglobin and globin experiments in intact animals would apparently implicate the globin fraction. Unfortunately, a contrary conclusion might be drawn for man, since globin administration has been reported to produce no change in renal blood flow.

The response to stromal materials, the early
response to first blood transfusion and the predominating response to second blood transfusions were not like the responses to hemoglobin and globin, but were characterized by "shock level" blood pressures with modest to moderate increases in peripheral resistance, failing to compensate for greatly reduced cardiac output. The associated, slightly reduced venous pressures in the intact preparations and the moderate decline in systemic pressure, coupled with a likely significant increase in peripheral volume in the open-chest, fixed and normal output preparations transfused with blood, indicate that peripheral dilatation and apparently some pooling occurred initially. The concomitant occurrence of a very low cardiac output in the intact preparations, pulsat alternans and electrocardiographic abnormalities in both types of preparations indicate that a marked myocardial depression was likewise produced. Since the stromal and blood reactions were similar and no other blood component caused such a reaction, the shock syndrome is attributed to the action of stromal materials. Furthermore, a protein or protein-complex in the stroma seems responsible, since addition of the "protein solubilizing" detergent Antara caused stroma to lose its noxious circulatory actions. After first transfusions, the response was much like a temporary "foreign protein" reactions; after appropriately timed second transfusions of blood, the more severe response appeared much like that of an immune reaction with anaphylactic or anaphylactoid shock. Yet in both instances, acute cardiac failure and peripheral dilatation with pooling seemed to combine to produce the net effect, the difference in total cardiovascular effect being apparently only quantitative and not qualitative.

Hypotension disappeared in an hour or less in the intact animals given a first blood transfusion. The subsequent response, for periods up to four hours, mimicked the responses to hemoglobin. Since the transfused human blood underwent rapid hemolysis with liberation of appreciable amounts of free hemoglobin into the circulation, the effects of transfused blood on the circulation during the 1 to 4-hour period were probably really those of liberated hemoglobin. With a repeat transfusion, the continued presence of severe hypotension was of sufficient duration to obscure the less profound hemoglobin effect during the period of study. Thus the total circulatory effects of the administration of human blood to the dog seemed to represent the sum of the physiologic responses, produced by red cell stroma and by hemoglobin.

Data have been published which support the contention that in some states of shock, particularly hemorrhagic shock, the renal A-R oxygen difference is little changed, with resulting appreciable decreases in calculated renal oxygen consumption. This situation did not hold in the hypotensive states studied here. A most extreme example was seen after repeated whole blood transfusion. An average A-R difference of 10.7 volume per cent, or seven times the normal was found. These results are more consonant with the belief that renal arterio-venous differences can increase to the extent of maintaining renal oxygen consumption in the range of two thirds or more of normal.

**Summary**

Human blood, human hemoglobin, human modified globin, human red cell stroma, human serum, with and without platelet and white cell materials, and citrate anticoagulant were transfused into dogs.

Whole blood, hemoglobin, globin and stroma produced a significant circulatory depression which was temporary and not followed by renal injury, except after repeated transfusions of whole blood.

The pattern of acute circulatory depression included marked reductions in cardiac output and stroke volume, renal ischemia and increased calculated vascular resistances.

The response to red cell stroma somewhat resembled "foreign protein" shock with the physiologic events being interpreted as compatible with combined acute peripheral dilatation and pooling and acute myocardial depression. A detergent (Antara) prevented this response. The response to hemoglobin (or globin) appeared to be mainly one of primary peripheral vasoconstriction, with subsequent compensatory decline in cardiac output. The
response to human blood appeared to represent a combination of these effects.

The action of apparently similar mechanisms, after appropriately timed second whole blood transfusion, induced anaphylactoid shock with severe physiologic disturbances. These included large increases in the total body and renal arteriovenous oxygen content differences and marked decreases in calculated $P_O_2$ in kidney and other body tissues.

**Summary in Interlingua**

Esseva executate in canes transfusiones de sanguine human, hemoglobina human, modificate globina human, stroma erythrocytic human, sero human con e sin materiales plaçettal e leucocytic, e anticoagulante citrate. Sanguine integre, hemoglobina, globina, e stroma produciva un significative depression circulatori que esseva temporari e non sequite per lesion renal, excepte post repetite transfusiones de sanguine integre.

Le configuration de acute depression circulatori includeva marcate reductiones del volumines per pulso e per minuta del corde, ischemia renal, e augmentos del (calculate) resistentias vascular.

Le reaction a stroma erythrocytic esseva non dissimile a choc per proteina exogene. Le resultante effectos physiologic esseva interpretabilo como conforme a acute dilatation e stagnation peripheric combinate con acute depression myocardial. Un detergent (Antara) preveniva iste responsa. Le reaction a hemoglobina (o globina) pareva esser principally un primari vasoconstriction peripheric con subsequente reduction compensatori del rendimento cardiac. Le reaction a sanguine human pareva representar un combination de iste effectos.

Post appropriemente intervallate secunde transfusiones de sanguine integre, le action de apparentemente simile mechanismos induceva choc anaphylactoide con sever disturbance physiologic. Istos includeva grande augmentos in le differentias arterio-venose de contento oxygenic in renes e corpore total e marcate reductiones del calculate $P_O_2$ in le teixitos del renes e altere organos del corpore.

**References**


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