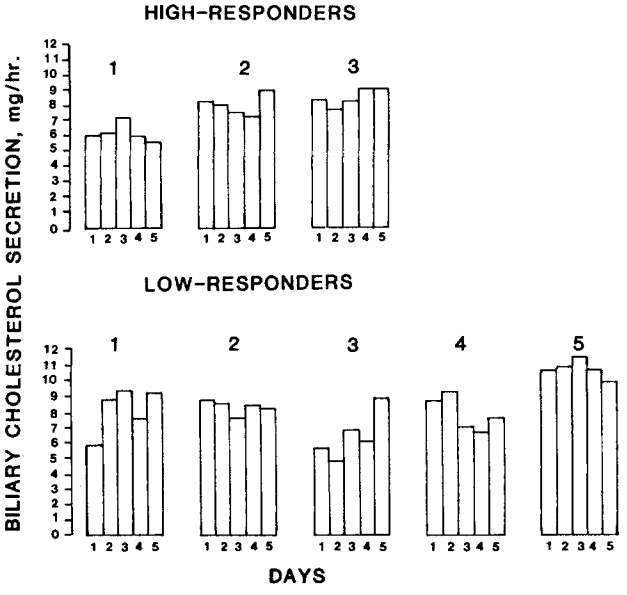

Biliary cholesterol secretion (mg/h) for days 1–5 in each of the 3 high- and 5 low-responding rhesus monkeys measured by the isotope ratio method.

feeding was distributed similarly in the various exchangeable cholesterol pools in the body of both groups of monkeys[10]. Possibly then the failure on the part of the cholesterol-fed high-responders to increase proportionately the excretion of neutral steroids in feces to compensate for the greater absorption of cholesterol might be related to the number or affinity of hepatic lipoprotein receptors which might determine the ability of the animal to cope with the burden of the excess absorbed cholesterol. The excess absorbed cholesterol might cause a greater 'down regulation' of the hepatic lipoprotein receptors because of a higher accumulation of cholesterol in the liver cells in the high-responders than in the low-responders. Studies are currently underway to answer these questions.

Schwartz et al.[6] have shown that free cholesterol on HDL appear more rapidly as biliary cholesterol than that from any other cholesterol containing lipoproteins. In the earlier study[5] in which it was shown that HDL-cholesterol concentration decreased in the high-responders but not in the low-responders upon feeding cholesterol, the free and esterified cholesterol concentrations in HDL were not determined. It is possible, then, that though the HDL-total cholesterol concentraiton decreased in the cholesterol-fed high-responders, the HDL still contained enough free cholesterol to provide for biliary secretion. It may also be possible that other cholesterol carrying lipoproteins provided enough cholesterol for secretion into bile so as to maintain the rate of secretion of biliary cholesterol. Further, newly synthesized cholesterol in the liver may also contribute to the biliary cholesterol secretion. Further studies are needed to address these questions.

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Changes in plasma enzyme concentrations in response to blood substitution with perfluorocarbon emulsion in the conscious rat[1]

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Summary. The effects of near total blood replacement with the proprietary perfluorocarbon (PFC)-based emulsion, Fluosol-DA 20%, on plasma concentrations of 2 enzymes, lactate dehydrogeanse (LDH) and alkaline phosphatase (ALP), have been examined in conscious, chronically catheterized rats. A pronounced fall in both plasma LDH ($p < 0.05$) an ALP ($p < 0.01$) occurred in response to exchange-transfusion. However, at 6 h following blood replacement, plasma concentrations of both enzymes had risen to values significantly greater than those measured immediately before perfusion. The observed changes in plasma LDH and ALP after blood replacement with Fluosol-DA indicated alterations in normal functioning of tissues from which these enzymes originate.
Key words. Blood replacement; perfluorocarbon emulsion; Fluosol-DA; lactate dehydrogenase; alkaline phosphatase; rats.

Totally synthetic, oxygen-carrying blood substitutes are likely to play an increasingly important part in medical science. The availability of such substitutes would have very profound clinical implications and solve a number of problems associated with conventional transfusion[3–5]. Previous work has shown that emulsified perfluorocarbons (PFC) may have value as substitutes for red blood cells and the effects of transfusion with such materials have been examined in a number of mammalian species[5–7]. Moreover, one proprietary preparation, Fluosol-DA 20% – an emulsion containing perfluorodecalin and perfluorotripropylamine and manufactured by the Green Cross Corporation, Japan – has already been tested in preliminary clinical trials in Japan, Canada and the USA with generally encouraging results[8–11].

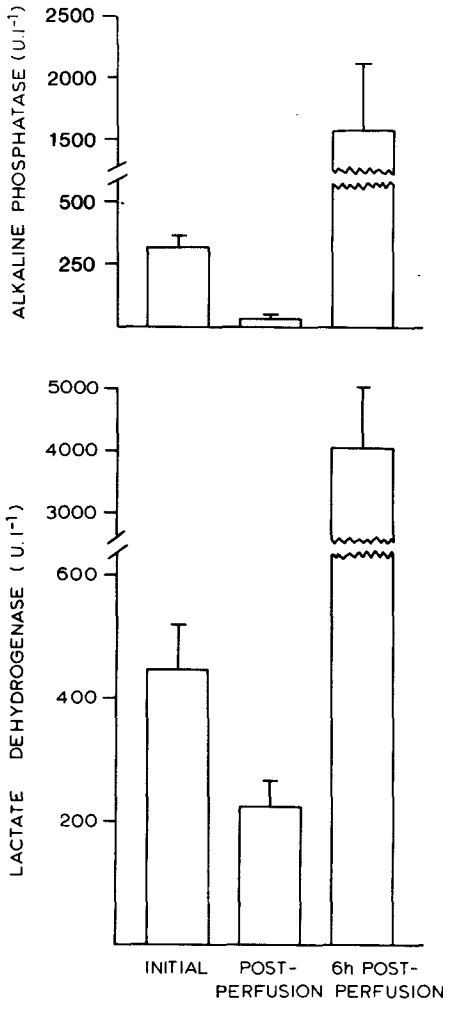
Using a method for continuous, isovolaemic, exchange-transfusion of conscious rats, it has been possible to analyse in detail some of the acute physiological responses to blood replacement with Fluosol-DA[12–14]. This work was an important advance over previous similar studies in which the perfusion procedure was performed on anaesthetised animals[3,15–17] and demonstrated that near-total blood replacement with Fluosol-DA could be achieved in conscious rats with no immediate disruption of normal cardiovascular and respiratory functions.

A clearer understanding of the body's responses to varying de-

grees of blood replacement with PFC-based preparations is an essential pre-requisite to their eventual wider acceptance as components of potential blood substitutes and other therapeutic materials. However, such evaluation involves detailed analysis of the homeostatic responses to emulsified PFC in different animal models together with studies on the longer-term consequences of their use. Thus, the experiments described in this paper were undertaken to test the hypothesis that severe blood replacement with Fluosol-DA in rats can cause disturbances to the normal functioning of major organs, as reflected by changes in plasma enzyme concentrations, and that such changes can contribute to the disruption of homeostasis which eventually follows extreme perfusion with this emulsion[14]. A preliminary account of some of these results has already been published[18].

Materials and methods. Care of animals and experimental procedures. A total of 37 mature female Sprague-Dawley/OLA rats (250–330 g b.wt) were used in these experiments. Animals were maintained in the laboratory animal house on a standard diet (Dixons FFG/M food concentrate pellets; Dixon's, Ware) ad libitum with free access to food and water at all times. Prior to experimentation, animals were allocated randomly into one of 4 experimental groups as follows:

Group I (n = 8): Unoperated controls
Group II (n = 5): Equithesin anaesthesia
Group III (n = 8): Sham-operated
Group IV (n = 16): Catheterization and perfusion with Fluosol-DA



Changes in mean plasma alkaline phosphatase and lactate dehydrogenase concentrations in response to blood replacement with Fluosol-DA 20% in rats. Vertical bars represent SE of each mean value (n = 5–11).

In group IV animals, indwelling femoral arterial and venous catheters were inserted under Equithesin anaesthesia (2 ml·kg^{-1} i.p.) as described in detail previously[12,13]. Food was withheld for 24 h prior to surgery. Sham-operated animals (group III) were treated in an identical manner to those in group IV except that blood vessels were exposed but not catheterized; inguinal skin flaps were closed using cotton sutures. Animals in group II received only 2 ml·kg^{-1} Equithesin by i.p. injection and were then allowed to recover. All animals in groups II–IV were allowed at least 24 h for recovery from anaesthesia and surgery. Continuous, isovolaemic, exchange-transfusion using freshly prepared and pre-warmed (circa 37 °C) Fluosol-DA 20% (table 1) was performed on conscious, chronically catheterized animals (group IV) which were contained individually within specially constructed, transparent, gas-tight chambers fabricated from conventional laboratory animal cages[12,13]. The oxygen tension inside each chamber was maintained at 80–90% throughout the experiments used an Electrodyne IMI 3700 Oxygen controller connected to an oxygen-sensitive probe (Becton Dickinson, Wembley) and flowmeter assembly. Mean arterial blood pressure and heart rate were measured by means of a Bell and Howell type 4-422-001 pressure transducer connected to the arterial catheter. Readings were taken from an Ormed M19 chart recorder every 10 min during blood substitution and thereafter at intermittent intervals until the death of the animal. Respiration rate was monitored by direct observation.

Sampling and analytical procedures. Blood samples were removed from animals in groups I–III by cardiac puncture under light ether anaesthesia. For group IV animals, the arterial effluent was collected and separated serially into 1 ml fractions using an LKB Ultrorac II fraction collector. At 6 h after perfusion, a 1.0–1.5 ml sample of intravascular fluid was removed from the arterial catheter and this was replaced with an equal volume of pre-warmed (37 °C) Fluosol-DA. Samples of blood or arterial effluent collected from all groups of animals were placed into plastic tubes containing either heparin or ethylene diamine tetra-acetic acid (EDTA) as anticoagulant (Sarstedt, Leicester). Haematocrit (packed cell volume %) and 'fluorocrit'[19] were measured using an automatic Hawksley 1500 microhaematocrit centrifuge (Hawksley, Lancing). The remainder of each sample was then centrifuged at 2500 rpm for 30 min at 4 °C and the plasma or supernatant removed and stored at −20 °C.

Plasma total LDH (EC 1.1.1.27) was measured by means of a standard ultraviolet absorption method using pyruvate as a substrate[20]. ALP (EC 3.1.31) was measured by colorimetric assay based on the conversion of *p*-nitrophenylphosphate to *p*-nitrophenol[20]. Both enzymes were determined by optimized tests with all reagents obtained from Boehringer, Mannheim (LDH test kit 124893; ALP test kit 123584).

Statistical analyses. Statistical analyses were made according to the methods of Snedecor and Cochran[21]; means and standard errors (SE) have been used throughout and statistical significance between mean values was assessed using either a conventional Student's t-test or paired t-test accordingly. A probability of $p < 0.05$ was considered significant.

Results and discussion. Mean plasma LDH and ALP concentrations in the 4 groups of experimental animals before exchange-transfusion are given in table 2. Values for unoperated control animals were similar to those reported previously for adult rats[22,23] and cats[24] using identical assay methods. The mean LDH concentration measured in animals receiving only Equithesin (group II) was not significantly different to that found in controls. However, plasma LDH concentrations in both sham-operated (group III) and catheterized (group IV) animals were significantly higher ($p < 0.05$ and $p < 0.01$ respectively) than that found in the control group (table 2). In contrast, mean ALP concentrations in each group of animals were not significantly different (table 2).

Continuous, isovolaemic exchange-transfusion with Fluosol-DA at 1 ml·min^{-1} for 40 min (group IV) reduced the mean

Table 1. Composition of Fluosol-DA 20% (w/v %)

Perfluorodecalin	14.0*
Perfluorotripropylamine	6.0*
Pluronic F-68	2.7†
Yolk phospholipids	0.4†
Glycerol	0.8
NaCl	0.6
KCl	0.034
$MgCl_2$	0.02
$CaCl_2$	0.028
$NaHCO_3$	0.21
Glucose	0.18
Hydroxyethylstarch	3.0+

*Gas-carrying emulsion; †emulsifying agents; +oncotic pressure.

Table 2. Plasma LDH and ALP concentrations in experimental animals before exchange-transfusion[a]

Experimental group	LDH (I.U.·l^{-1})	ALP (I.U.·l^{-1})
I	176 ± 34 (8)	231 ± 34 (8)
II	152 ± 27 (5)	N.D.
III	350 ± 73* (8)	N.D.
IV	447 ± 73** (11)	316 ± 57 (5)

[a]Values are mean ± SEM with number of animals in parentheses; *$p < 0.05$; **$p < 0.001$ compared to control (group I) mean values; N.D., not determined.

haematocrit from 35.8 ± 1.4% to 1.7 ± 0.2% ($p < 0.001$; table 3); no further significant change in this haematocrit occurred during the subsequent post-perfusion period as reflected by the value recorded at +6 h. The quantity of Fluosol-DA in the circulation showed a progressive rise during perfusion to reach a mean fluorocrit value of circa 17–18% (table 3).

Heart rate and respiration rate remained stable during blood replacement; however, at 6 h post-perfusion, heart rate was significantly lower ($p < 0.01$) and respiration rate significantly higher ($p < 0.01$) than the corresponding initial mean values (table 3). Continuous exchange-transfusion was also accompanied by a small but significant ($p < 0.01$) fall in mean arterial blood pressure and this was followed by a further fall up to 6 h post-perfusion ($p < 0.001$; table 3).

A fall in both total plasma LDH and ALP concentrations occurred during blood substitution with mean values for each enzyme at the end of perfusion being 225 ± 43 I.U.l^{-1} and 32 ± 14 I.U.l^{-1} respectively; these values represented between 10–50% of the corresponding initial mean concentrations (fig.). This fall in LDH and ALP contrasted sharply with the pronounced increases in circulating levels of both enzymes which occurred during the subsequent recovery period: LDH concentration at 6 h post-perfusion was over 9 times higher than that measured immediately prior to blood replacement while ALP had risen 5-fold during the same time period (fig.).

Of the 16 rats exchange-transfused with Fluosol-DA in these experiments, 7 (44%) survived for 12 h or more after perfusion with the longest survivors staying alive for almost 36 h; the overall mean survival time post-perfusion was 13 ± 2 h.

The results of these experiments show that near total blood replacement with Fluosol-DA in chronically catheterized rats is followed by pronounced changes in intravascular fluid LDH and ALP concentrations. These results are consistent with the hypothesis that severe blood substitution with Fluosol in rats causes disruption of the normal functioning of major organs leading eventually to irreversible deterioration of homeostatic control.

The fall in circulating enzyme concentrations during exchange-transfusion was an expected consequence of the progressive dilution of the blood with Fluosol-DA: these responses were in accord with changes in blood cells and plasma proteins seen previously during blood replacement with this emulsion in rats[12–14]. However, it should be emphasised that the fall in LDH during perfusion was accentuated by the increased plasma concentration of this enzyme immediately before perfusion. The present finding of an increase in LDH in sham-operated and catheterized animals confirms previous reports that circulating levels of this enzyme are elevated following tissue damage: even a small leakage of LDH from tissue damaged during surgery would lead to a substantial increase in blood concentrations[20]. However, it is noteworthy that, in contrast to the observed changes in LDH, plasma ALP was unaffected by surgery. In this regard, studies on changes in urinary enzymes in response to administration on nephrotoxic compounds in rats have shown that ALP is a much less sensitive index of tissue damage than other enzymes, notably LDH[25]. Furthermore, enzymes such as ALP, which are associated with membrane borders, leak from cells much less readily than enzymes (for example LDH) that are found in the cytoplasmic supernatant[20].

Previous work on the effects of PFC emulsions on circulating enzymes has produced conflicting results. Thus, Naito and Yokoyama[26] reported that administration of 40–80 ml·kg^{-1} Fluosol-DA to adult rats did not alter plasma LDH activity as measured after 1.5 h. However, it is difficult to analyse the extent to which Fluosol itself may have affected LDH in these experiments since the animals also breathed 3% carbon monoxide (CO); CO is known to be a potent stimulus to LDH release into the circulation[27,28]. In contrast, Lutz and Metzenauer[22] observed a transient elevation in serum ALP at 12.5 h following intravascular injection of 4.4 g·kg^{-1} Fluosol-DA stem emulsion in rats. More recently, Ohyanagi and others[29] showed that plasma ALP was elevated only slightly in Jehovah's Witness patients when measured 1 month after receiving 500–1500 ml infusions of Fluosol-DA.

It is most likely that the increases in circulating LDH and ALP post-perfusion were due to leakage of enzymes or cell deterioration which occurred in response to tissue ischaemia, direct cytotoxic effect of Fluosol itself or a combination of both. In the former case, increased activity of lysosomal enzymes leading to cell lysis is a consequence of shock-induced tissue ischaemia to which the liver, heart and kidneys are particularly susceptible[30]. However, it is probable that the severity of any tissue ischaemia occurring after perfusion would have been offset to some extent by animals breathing supplementary oxygen which raises the femoral arterial PaO_2 to > 500 mm·Hg [Lowe and McNaughton, unpublished observations]. Furthermore, it must be emphasised that normobaric oxygen therapy is much less effective than hyperbaric oxygen in reducing tissue damage caused by

Table 3. Haematological, cardiovascular and respiratory changes in response to exchange-transfusion with Fluosol-DA 20%[a]

	Initial	Post-perfusion[b]	6 h after perfusion
Haematocrit (%)	35.8 ± 1.4 (16)	1.7 ± 0.2 (14)**	1.5 ± 0.3 (12)**
Fluorocrit (%)	—	16.0 ± 0.5 (13)	18.3 ± 1.1 (12)
Blood pressure (kPa)	13.4 ± 0.3 (16)	12.2 ± 0.4 (16)†	10.3 ± 0.3 (8)**
Heart rate (beats·min^{-1})	383.0 ± 9.0 (16)	400.0 ± 11.0 (15)	339.0 ± 7.0 (8)*
Respiration rate (breaths·min^{-1})	89.0 ± 2.0 (16)	96.0 ± 3.0 (15)	108.0 ± 5.0 (12)*

[a]Values are mean ± SEM with number of observations in parentheses. [b]Post-perfusion: measurements taken immediately following 40 min exchange-transfusion. †$p < 0.05$; *$p < 0.01$; **$p < 0.001$ compared to initial mean value.

infarction[31]. The possibility that tissue ischaemia could have contributed to cell breakdown and enzyme release post-perfusion is in conflict with the proposed use for PFC emulsions in reducing the severity of infarcts arising from myocardial and cerebral ischemia[32-35].

In support of the second suggestion, evidence from recent in vitro studies has revealed direct cytotoxic effect of Fluosol emulsions although the active agent(s) has not been identified. Thus, Fluosol-43 (FC-43) promoted LDH release into the incubation medium when cultured with murine macrophages[36] while a methanol-soluble extract of Fluosol-DA 20% was able to stimulate histamine release from rat peritoneal mast cells in vitro[37,38]. In addition, culture experiments have shown toxic effects of Fluosol-DA upon human embryonic fibroblast cells[39]. In view of these reports of adverse effects of Fluosol emulsions on cell functions in vitro, the possibility that comparable deleterious effects occurred in perfused animals cannot be excluded.

It is important to emphasise that while the observed changes in plasma enzymes following exchange-transfusion may have been caused directly or indirectly by Fluosol-DA itself, it is possible that other factors – notably exposure of perfused animals to increased ambient oxygen tensions – may also have been responsible. In this regard it has been shown previously that although rats are susceptible to oxygen toxicity[40], this does not, in the short-term at least, appear to be an important factor affecting animals almost totally transfused with emulsified PFC[41]. Further work is necessary to clarify this point and in particular, determine the effects of hyperoxia with and without PFC emulsion on circulating enzymes and other blood constituents in rats and other species. Moreover, the extent to which cellular functions may be altered in the presence of proprietary or modified PFC emulsions should be studied both in vivo and in vitro.

In conclusion, the present experiments have shown that severe blood substitution with Fluosol-DA in rats is followed by marked increases in plasma ALP and LDH concentrations and that these changes are a prelude to the eventual death of perfused animals. While it is important to emphasise that these studies represented an extreme situation in which near-total blood replacement was performed, the results are nevertheless in sharp contrast with previous similar work in which it was reported that rats could survive indefinitely following complete perfusion with emulsified PFC[3,4,42].

1 The Fluosol-DA emulsion used in these experiments was kindly donated by Dr T. Suyama of the Green Cross Corporation, Osaka, Japan.

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