

Cancer Research

Hyperthermia (42°) of the Yoshida Sarcoma in the Rat Effect of Hyperglycemia on Blood Flow, pH, and Response to

Stuart K. Calderwood and John A. Dickson

Cancer Res 1980;40:4728-4733.

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Effect of Hyperglycemia on Blood Flow, pH, and Response to Hyperthermia ^{(CANCER RESEARCH 40, 4728–4733, December 1980)
0008-5472/80/0040-0000\$02.00
(42°) of the Yoshida Sarcoma in the Rat¹} **(42[°]) of the Yoshida Sarcoma in the Rat¹
Stuart K. Calderwood and John A. Dickson**

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ABSTRACT

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BISTRACT elsew
Hyperglycemia (blood glucose, >20 mmol/liter) caused a 90 ml (8
TOO% inhibition of blood flow in the solid Yoshida sa **ABSTRACT**

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to 100% inhibition of blood flow in the solid Yoshida sarcoma

of rat feet, as measured by the fractional distribution of 86 Rb (chlor

and **ABSTRACT**

Hyperglycemia (blood glucose, >20 mmol/liter) caused a 9

to 100% inhibition of blood flow in the solid Yoshida sarcom

of rat feet, as measured by the fractional distribution of ^{86}R

and ¹³³Xe clearance Hyperglycemia (blood glucose, $>$ 20 mmol/liter) caused a 90 ml (8 to
to 100% inhibition of blood flow in the solid Yoshida sarcoma
of rat feet, as measured by the fractional distribution of ^{se}Rb
and ¹³³Xe clearance. B remained unaltered. Hyperglycemia abroad flow in the solid Yoshida sarcoma
of rat feet, as measured by the fractional distribution of 86 Rb (chloridand 133Xe clearance. Blood flow through the normal gastrocne-
mius mus or rat ¹³³Xe clearance. Blood flow through the normal gamius muscle was increased by 50%, while liver blow
remained unaltered. Hyperglycemia abrogated the tem
differential (approximately 1°) between the heating t
the tum dus muscle was increased by 50%, while liver blood flow
mained unaltered. Hyperglycemia abrogated the temperature
ferential (approximately 1°) between the heating bath and
is tumor, promoting more uniform tumor heating.
Du

differential (approximately 1°) between the heating bath and
the tumor, promoting more uniform tumor heating bath and
the tumor, promoting more uniform tumor heating.
During the period of reduced blood flow, the pH of the from the tumor. Tumor intracellular pH, measured by partition-
from the tumor, promoting more uniform tumor heating.
extracellular fluid, measured by miniature glass electrode, de-
clined from 7.19 to 6.63 due to decreased ing the period of reduced blood flow, the pH of the tumor
extracellular fluid, measured by miniature glass electrode, de-
clined from 7.19 to 6.63 due to decreased efflux of lactate
from the tumor. Tumor intracellular pH, Extracellular fluid, measured by relationships and the tumor. Tumor intracellular fluid, measured by relationships of dimethyloxazolidinedione increased from 7.21 to 7.36. At a very high blood glucose of In a very high blood glucose concentration (50 mmol.)
At a very high blood glucose concentration (50 mmol/liter),
and dimethyloxazolidinedione across the cell membrane,
treased from 7.21 to 7.36.
At a very high blood gluco From the tumor. Tumor intracellular pH, measured by partition-
inge of dimethyloxazolidinedione across the cell membrane,
increased from 7.21 to 7.36. The concentration (50 mmol/liter), and of
the tumor was isolated from

ing of dimethyloxazolidinedione across the cell membrane,
increased from 7.21 to 7.36. The tumor was isolated from the host, with almost total blockade
of water, chloride, glucose, lactate, and dimethyloxazolidine-
dione my of dimentyloxazonal
increased from 7.21 to 7.36.
At a very high blood glucose concentration (50 mm
the tumor was isolated from the host, with almost total b
of water, chloride, glucose, lactate, and dimethyloxaz
dione e At a very high blood glucose concentration (50 mmol/liter),
at a very high blood glucose concentration (50 mmol/liter),
water, chloride, glucose, lactate, and dimethyloxazolidine-
one exchange between the tumor and the bl At a very high blood glacese concentration (50 mmol/mer), mil of
the tumor was isolated from the host, with almost total blockade 0.3 to
of water, chloride, glucose, lactate, and dimethyloxazolidine-
dione exchange between

enable more vast solated from the flost, which allocated bookade
of water, chloride, glucose, lactate, and dimethyloxazolidine-
dione exchange between the tumor and the blood.
Hyperglycemia therefore represents a convenien dione exchange between the tumor and the blood.
Hyperglycemia therefore represents a convenient means of
isolating the Yoshida sarcoma from the host blood supply to
enable more selective treatment with hyperthermia and pos

INTRODUCTION

bly other modalities. estim
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INTRODUCTION Tu
Temperatures of 41–43° selectively destroy many types of
malignant cells (21, 24). Above 43°, there is increasing damage
to normal tissues, and the use of heat to treat tu m
 Temperatures of 41–43° selectively destroy many types of

malignant cells (21, 24). Above 43°, there is increasing damage

to normal tissues, and the use of heat to treat tumors resistant

to 41–43° (5, 7) depends on Temperatures of 41–43° selectively destroy many types of $\frac{31}{4}$
malignant cells (21, 24). Above 43°, there is increasing damage
to normal tissues, and the use of heat to treat tumors resistant
tio 41–43° (5, 7) depend remperatures of $41-43$ selectively destroy many types of $9H_2$
malignant cells (21, 24). Above 43°, there is increasing damage
to normal tissues, and the use of heat to treat tumors resistant
to 41–43° (5, 7) depends on manyirant cens (21, 24). Above 43 , there is increasing damage
to normal tissues, and the use of heat to treat tumors resistant
tion,
to 41–43° (5, 7) depends on selectively heating the tumor or
the use of a potentiator o to homial issues, and the use of heat to treat tuniors resistant
to 41–43° (5, 7) depends on selectively heating the tumor or
the use of a potentiator of the hyperthermia. Von Ardenne (26)
suggested the use of glucose as the use of a potentiator of the hyperthermia. Von Ardenne (26)
suggested the use of glucose as such a sensitizer. Hypergly-
cemia was envisaged as inducing lactic acidosis in tumors by
exploiting the increased glycolysis suggested the use of glucose as such a sensitizer. Hypergly-

cemia was envisaged as inducing lactic acidosis in tumors by

exploiting the increased glycolysis associated with malignant

cells (29). A decrease in tumor pH celling was envisaged as inducing lactic actubes in tumors by
exploiting the increased glycolysis associated with malignant
cells (29). A decrease in tumor pH to approximately 6.5 would,
according to Von Ardenne's hypothe exploiting the increased glycolysis associated with malignant MCC
cells (29). A decrease in tumor pH to approximately 6.5 would, N. H.
according to Von Ardenne's hypothesis, labilize lysosomal plifiel
membranes; at this de Lens (29). A decrease in tunior pri to approximately 0.5 would,
according to Von Ardenne's hypothesis, labilize lysosomal plifit
membranes; at this decreased pH, heating at 42° would lead hage
to tumor autolysis (26). The actorumy to voir Artenne's hypothesis, habitze rysosomal plifter
membranes; at this decreased pH, heating at 42° would lead hage
to tumor autolysis (26). The present report describes the effect of a
of hyperglycemia on ext membranes, at this decreased porton tumor autolysis (26). The press
of hyperglycemia on extra- and
Yoshida rat sarcoma and present
acts by selectively inhibiting tum
more uniform tumor heating. of hyperglycemia on extra- and intracellular pH in the solid
Yoshida rat sarcoma and presents evidence that hyperglycemia
acts by selectively inhibiting tumor blood flow, thus facilitating
more uniform tumor heating.
MATER

Its by selectively infibiting tumor biood how, thus facilitating tained
pre uniform tumor heating.
ATERIALS AND METHODS bleedit
Tumor System. Details of the history, maintenance, and electro
owth characteristics of the more unnorm tumor neating.
 MATERIALS AND METHODS blee
 Tumor System. Details of the history, maintenance, and elect

growth characteristics of the Yoshida sarcoma are described trode

incis Tumor System. Details of the history, maintenance, and

bwth characteristics of the Yoshida sarcoma are described

This work was supported by the North East of England Council of the Cancer

search Campaion.

ia infirmary, Newcastle upon Tyne, England
elsewhere (8). For this work, the tumor was grown in the
dorsum of the left hind foot of the rats to a volume of 1.0 to 1.5 ia infirmary, Newcastle upon Tyne, England
elsewhere (8). For this work, the tumor was grown in the
dorsum of the left hind foot of the rats to a volume of 1.0 to 1.5
ml (8 to 10 days after implantation). a *Infirmary, Newcastle upon Tyne, England*
elsewhere (8). For this work, the tumor was grown in the
dorsum of the left hind foot of the rats to a volume of 1.0 to 1.5
ml (8 to 10 days after implantation).
Radioisotopes.

remained unaltered. Hyperglycemia abrogated the temperature
differential (approximately 1°) between the heating bath and
the tumor, promoting more uniform tumor heating.
the tumor, promoting more uniform tumor heating.
Du dorsum of the left hind foot of the rats to a volume of 1.0 to 1.5
ml (8 to 10 days after implantation).
Radioisotopes. ${}^{3}H_{2}O$ (specific activity, 5 Ci/ml), Na³⁶Cl
(chlorine, 3 mCi/g), ${}^{86}RbCl$ (rubidium, 2 to dissolved in 0.9% NaCl solution (xenon, 2 to 10 Ci/ml), Na³⁶Cl
(chlorine, 3 mCi/g), ⁸⁶RbCl (rubidium, 2 to 10 Ci/g), ¹³³Xe
dissolved in 0.9% NaCl solution (xenon, 2 to 10 Ci/ml),
2-[³H]deoxyglucose (15 Ci/mol), an divided by the anti-miplant
attorigation salt (chlorine, 3 mCi/g), 86 RbCl (rubidium, 2 to 10 Ci/g), 133 X
dissolved in 0.9% NaCl solution (xenon, 2 to 10 Ci/ml)
2-[³H]deoxyglucose (15 Ci/mol), and L-[U-¹⁴C]lact **Hadioisotopes.** $-$ **H₂O** (specific activity, 5 Ci/mi), Na⁻-Ci

(chlorine, 3 mCi/g), ⁸⁶RbCl (rubidium, 2 to 10 Ci/g), ¹³³Xe

dissolved in 0.9% NaCl solution (xenon, 2 to 10 Ci/ml),

2-[³H]deoxyglucose (15 Ci/mol (chlorine, 3 mCi/g), ^{co}RbCl (rubidium, 2 to 10 Ci/g), ¹³³Xe
dissolved in 0.9% NaCl solution (xenon, 2 to 10 Ci/ml),
2-[³H]deoxyglucose (15 Ci/mol), and L-[U-¹⁴C]lactic acid, so-
dium salt (5 to 20 Ci/mol), were obt 2-[³H]deoxyglucose (15 Ci/mol), and L-[*U*-¹⁴C]lactic
2-[³H]deoxyglucose (15 Ci/mol), and L-[*U*-¹⁴C]lactic
dium salt (5 to 20 Ci/mol), were obtained from The Ra
ial Centre, Amersham, England. 5,5-Dimethyloxa:
¹⁴ I Hyleoxyglacose (15 Ci/Inol), and L-10- Cyacuc acid, so-
im salt (5 to 20 Ci/mol), were obtained from The Radiochem-
al Centre, Amersham, England. 5,5-Dimethyloxazolidine[2-
C-12.4-dione (DMO,² 2 to 10 Ci/mol) was obtai dium sait (5 to 20 Cl/mol), were obtained from The Radiochem
ical Centre, Amersham, England. 5,5-Dimethyloxazolidine[2
¹⁴CJ-2,4-dione (DMO,² 2 to 10 Ci/mol) was obtained from NEP
Chemicals GmbH, Dreichenhain, West Germ

rical Centre, Aliteristann, England. 3,3-Dimetriyioxazonume
1⁴CJ-2,4-dione (DMO,² 2 to 10 Ci/mol) was obtained from NEN
Chemicals GmbH, Dreichenhain, West Germany.
Glucose Determination. Blood glucose was measured by
g Chemicals GmbH, Dreichenhain, West Germany.
Chemicals GmbH, Dreichenhain, West Germany.
Glucose Ostermination. Blood glucose was measured by
glucose oxidase using a blood sugar test combination [Boeh-
ringer Corporation (Glucose Determination. Blood glucose was measured by
glucose oxidase using a blood sugar test combination [Boeh-
ringer Corporation (London) Ltd., Bell Lane, Lewes, E. Sussex,
England]. The blood glucose estimation was car diacese Determination: Dicota glucose was ineasured by
glucose oxidase using a blood sugar test combination [Boeh-
ringer Corporation (London) Ltd., Bell Lane, Lewes, E. Sussex,
England]. The blood glucose estimation was c glucose oxidase dairig a blood sugar test combination poor-
ringer Corporation (London) Ltd., Bell Lane, Lewes, E. Sussex,
England]. The blood glucose estimation was carried out on 0.1
ml of 0.16% uranyl acetate). For tumo miger corporation (Echaen) Etat, Den Earte, Eewes, E. Cussex,
England]. The blood glucose estimation was carried out on 0.1
ml of deproteinized heart blood (0.1 ml of whole blood in 1.0
ml of 0.16% uranyl acetate). For tum Lingiandj. The blood glucose estimation was carried out on 0.1
ml of deproteinized heart blood (0.1 ml of whole blood in 1.0
ml of 0.16% uranyl acetate). For tumor glucose determination,
0.3 to 0.5 g tumor tissue was homog In of deprotentized freart blood (0.1 ml of whole blood in 1.0
ml of 0.16% uranyl acetate). For tumor glucose determination,
0.3 to 0.5 g tumor tissue was homogenized in 2.0 ml distilled
water using a Polytron microhomoge 0.3 to 0.5 o transfer acetate). For tunior glucose determination,
0.3 to 0.5 g tumor tissue was homogenized in 2.0 ml distilled
water using a Polytron microhomogenizer (Northern Media
Supply Ltd., Hull, England) at full sp of the state was nonogenized in 2.0 mi distinct
water using a Polytron microhomogenizer (Northern Media
Supply Ltd., Hull, England) at full speed for 1 min. To 0.5 ml of
this homogenate was added 1.0 ml of 0.16% uranyl ace Supply Ltd., Hull, England) at full speed for 1 min. To 0.5 ml of
this homogenate was added 1.0 ml of 0.16% uranyl acetate
for deproteinization. The solution was vigorously mixed and Supply Eta., Hall, England, at fall speed for
this homogenate was added 1.0 ml of 0.
for deproteinization. The solution was vig
centrifuged at 3000 rpm for 10 min, are
stimated in 0.1 ml of supernatant. Results
mmol glucos **Tumor pH Measurement.** For determination of intracellular deproteinization. The solution was vigorously mixed and intrifuged at 3000 rpm for 10 min, and the glucose was timated in 0.1 ml of supernatant. Results were expr

able more selective treatment with hyperthermia and possi-

y other modalities.

y other modalities.

TRODUCTION

TEMELICION

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 pH (pH,), rats were given an i.p. injection containing 50 μ Ci 3H₂O, 1 μ Ci ³⁶Cl, and 1 μ Ci ¹⁴C]DMO in 1.0 ml 0.9% NaCl solution. Following sacrifice of animals 2 hr after isotope injection. salmated in 0.1 hill of superinatant. Results were expressed as
mmol glucose per liter blood or tumor.
Tumor pH Measurement. For determination of intracellular
pH (pH_i), rats were given an i.p. injection containing 50 Tumor pH Measurement. For determination of intracellular
pH (pH_i), rats were given an i.p. injection containing 50 μ Ci
³H₂O, 1 μ Ci ³⁶Cl, and 1 μ Ci [¹⁴C]DMO in 1.0 ml 0.9% NaCl
solution. Following sacrif Frame primes as determined as described previously (θ H₂O, 1 μ Ci ³⁶Cl, and 1 μ Ci [¹⁴C]DMO in solution. Following sacrifice of animals 2 hration, tissue concentrations of radiochemic determined as described p Tupon), rais were given an i.p. injection containing so μ Ci
 $_2$ O, 1 μ Ci ³⁶Cl, and 1 μ Ci [¹⁴C]DMO in 1.0 ml 0.9% NaCl

lution. Following sacrifice of animals 2 hr after isotope injec-

in, tissue concentrati Capillary glass electrodes (type MI 400) with a 1-mm-diameter (the and a reference microelectrode (type MI 400) with a 1-mm-diameter (tip and a reference microelectrode (type MI 400) with a 1-mm-diameter (tip and a refere

solution. Following sacrifice of animals 2 in after isotope injection, tissue concentrations of radiochemicals and pH_i were
determined as described previously (3).
Tumor extracellular pH (pH_e) was measured by miniatur N. H.). The electrodes were coupled by high-impedance and CHI saturated with AgCI (Microelectrodes, Inc., Londonderry, N. H.). The electrodes were coupled by high-impedance am-
N. H.). The electrodes were coupled by high-i determined as described previously (3).

Tumor extracellular pH (pH_e) was measured by miniature

capillary glass electrodes (type MI 400) with a 1-mm-diameter

tip and a reference microelectrode (type MI 401) filled with capillary glass electrodes (type MI 400) with a 1-mm-diameter
tip and a reference microelectrode (type MI 401) filled with 3
M KCI saturated with AgCI (Microelectrodes, Inc., Londonderry,
N. H.). The electrodes were couple capinary giass electrodes (type wir 400) with a 1-mini-diameter
tip and a reference microelectrode (type MI 401) filled with 3
M KCI saturated with AgCI (Microelectrodes, Inc., Londonderry,
N. H.). The electrodes were coup up and a reference inforcelectrode (type MI 401) filled with 3
M KCI saturated with AgCI (Microelectrodes, Inc., Londonderry,
N. H.). The electrodes were coupled by high-impedance am-
plifier to a digital pH meter (type PH M NOI saturated with Agot (Microelectrodes, Inc., Londonderry, N. H.). The electrodes were coupled by high-impedance amplifier to a digital pH meter (type PHM 63; Radiometer, Copenhagen, Denmark). For anesthesia, the rats N. H.). The electrodes were coupled by high-impedance am-
plifier to a digital pH meter (type PHM 63; Radiometer, Copen-
hagen, Denmark). For anesthesia, the rats were given 0.1 ml
of a 1:5 dilution of Nembutal veterinary plinet to a digital primeter (type Frim 03, hadiometer, Copen-
hagen, Denmark). For anesthesia, the rats were given 0.1 ml
of a 1:5 dilution of Nembutal veterinary i.p. (pentobarbitone
sodium, 60 mg per ml; Abbott Laborato riagent, Denmark). For anesthesia, the rats were given O.1 minor
of a 1:5 dilution of Nembutal veterinary i.p. (pentobarbitone
sodium, 60 mg per ml; Abbott Laboratories, Queenborough,
Kent, England) per 50 g of body weight sodium, 60 mg per ml; Abbott Laboratories, Queenborough, Kent, England) per 50 g of body weight. Narcosis was maintained by additional small doses of the barbiturate as required. The anesthetized rat was immobilized on an socium, ou mg per mi; Abbott Laboratories, Queenborougn,
Kent, England) per 50 g of body weight. Narcosis was main-
tained by additional small doses of the barbiturate as required.
The anesthetized rat was immobilized on a Nent, England) per 50 g or body weight. Narcosis was maintained by additional small doses of the barbiturate as required
The anesthetized rat was immobilized on an electrically insulated board, the distal 1 cm of its tail rained by additional small doses of the barbiturate as required.
The anesthetized rat was immobilized on an electrically insulated board, the distal 1 cm of its tail was amputated, and the
bleeding tail was immersed in a 2 The anesthetized rat was infinded ized on an electrically insulated board, the distal 1 cm of its tail was amputated, and the bleeding tail was immersed in a 250-ml Erlenmeyer flask containing 200 ml 0.9% NaCl solution and incision in the upper surface of the tumor. The electrode was interested to a depth of 3 to 5 mm through a small incision in the upper surface of the tumor. The electrode was a surface of the tumor. The electrode was $\frac{1$ ectrode. For measurement of tumor pH, the glass microelec-
ode was inserted to a depth of 3 to 5 mm through a small
cision in the upper surface of the tumor. The electrode was
² The abbreviations used are: DMO, 5,5-dimet trode was inserted to a depth of 3 to 5 mm
incision in the upper surface of the tumor. The abbreviations used are: DMO, 5,5-dimethyl-2,4-
intracellular pH; pH_e, extracellular pH; i.t., intratumoral.

Tumor System.

growth characteris

This work was supper

Research Campaign.

Received September This work was supported by the North East of England Council of the Cancer
Research Campaign.
Received September 17, 1979; accepted August 20, 1980.

Research Campaign. ² The abbreviations used are: DMO, 5,5-dimethyl-2,4-oxazolidinedione; pH_i,

4728 Received September 17, 1979; accepted August 20, 1980.

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then secured vertically in position and connected to the digital
pH meter, and the system was left to stabilize. When electrode $\begin{aligned} \text{then} \text{ secured vertically in position and connected to the digital} & \text{glucc} \\ \text{pH meter, and the system was left to stabilize. When electrode} & \text{min} \text{ a} \\ \text{stability was achieved, a pH reading with a variation of} < \pm 0.03 & \text{ appri} \end{aligned}$ then secured vertically in position and connected to the digital gluco
pH meter, and the system was left to stabilize. When electrode min a
stability was achieved, a pH reading with a variation of $<\pm 0.03$ appro
unit/hr then secured vertically in position and connected to the digital glucos
pH meter, and the system was left to stabilize. When electrode min a
stability was achieved, a pH reading with a variation of $\lt\pm 0.03$ appro
unit/h then secured vertically in position and connected to the digital gluce
pH meter, and the system was left to stabilize. When electrode min a
stability was achieved, a pH reading with a variation of $<\pm 0.03$ approx
unit/ pH meter, and the system was left to stabilize. When electrode min and continued to increase to a plateau concentration of stability was achieved, a pH reading with a variation of $< \pm 0.03$ approximately 60 mmol/liter b stability was achieved, a pH reading with a variation of $\leq \pm 0.03$ approximit/hr was recorded; this usually required 40 to 60 min. In tration experiments on hyperglycemia, an i.p. injection of 50% glucose porar [6 g/kg unit/hr was achieved; a principle with a variation of ≥ 20.00 and the experiments on hyperglycemia, an i.p. injection of 50% glucose [6 g/kg body weight (11)] was given at this point, or an i.v. infusion of 20% glucos experiments on hyperglycemia, an i.p. injection of 50% glucose
geoperiments on hyperglycemia, an i.p. injection of 50% glucose
if it is point, or an i.v. the the capital was monitored for 4 to 9 hr. At the end of the exper Experiments of tryperty yournal, and the injection of ∞ ∞ gluebes botated in that if β y/kg body weight (11)] was given at this point, or an i.v. the binfusion of 20% glucose was started via the femoral vein an tumor. **Blood Flow Measurement.** Blood flow was determined by 2nd methods, the fractional distribution of ⁸⁶Rb (22) and ¹³³Xe further clearance (2). In the first method, animals were given injections

was examined to ensure that it had been situated in viable of 6 tumor.
 Elood Flow Measurement. Blood flow was determined by 2 ing

methods, the fractional distribution of ⁸⁶Rb (22) and ¹³³Xe furth

clearance (2). I **Blood Flow Measurement.** Blood flow was determined by 2 ing 1
methods, the fractional distribution of 86 Rb (22) and 133 Xe furth
clearance (2). In the first method, animals were given injections pH_e
of 100 μ C in a concentration proportional to the tissue fractional distribution of 86 Rb (22) and 133 Xe furthe clearance (2). In the first method, animals were given injections pH_e dof 100 μ Ci of 88 Rb in 0.1 ml of 0 clearance (2). In the first method, animals were given injections
of 100 μ Ci of ⁸⁶Rb in 0.1 ml of 0.9% NaCl solution into the right
femoral vein. This isotope becomes distributed between tissues
in a concentration pr of 100 μ Ci of ⁸⁶Rb in 0.1 ml of 0.9% NaCl solution into the right
femoral vein. This isotope becomes distributed between tissues
in a concentration proportional to the tissue fraction of the
cardiac output (22). The of 100 μ Ci of ⁸⁶Rb in 0.1 ml of 0.9% NaCl solution into the right could not be measured under infusion conditions because
femoral vein. This isotope becomes distributed between tissues ³H₂O, [¹⁴C]DMO, and ³⁶C in a concentration proportional to the tissue fraction of the cardiac output (22). The rats were sacrificed 40 sec after injection, and blood flow values were calculated by multiplying the cardiac output fraction for the cardiac output (22). The rats were sacrificed 40 sec after chain
injection, and blood flow values were calculated by multiplying ${}^{3}H_{2}$
the cardiac output fraction for the organ by the total cardiac infu
output for a

mjection, and blood now values were calculated by multiplying
the cardiac output fraction for the organ by the total cardiac
output for a pentobarbitone-anesthetized 200-g rat (14).
Xenon clearance was measured after i.t. coupled to a rate of a rate of the crystal by the colar cardiac imputs
output for a pentobarbitone-anesthetized 200-g rat (14). of iso
of ¹³³Xe in 0.05 ml of 0.9% NaCl solution. Tumor radioactivity between
was detected Mapple for a perifold bifore-altestretized 200-y fat (1-7. or 180

Senon clearance was measured after i.t. injection of 50 μCi

of ¹³³Xe in 0.05 ml of 0.9% NaCl solution. Tumor radioactivity betwe

was detected using a was detected using a potassium iodide scintillation crystal jected in
coupled to a ratemeter and chart recorder. The crystal was with the
positioned 1 to 2 cm above the tumor and shielded to avoid tumor a
detection of 1 was detected using a potassium iodide scintillation crystal jecupled to a ratemeter and chart recorder. The crystal was we positioned 1 to 2 cm above the tumor and shielded to avoid tudetection of 1^{33} Xe in the lungs o coupled to a rate
integration of 133 is in the followed a multiexpone
was calculated from the sequation: Exponential function (Chart 4), and
propose the half-time of tumor cle
on:
Blood flow (ml/min) = $\frac{\log_e 2 \times \lambda}{t_{1/2} \text{ (min)}}$

$$
Blood flow (ml/min) = \frac{\log_e 2 \times \lambda}{t_{1/2} (min)} \tag{2}
$$

was calculated from the han-time of turnor clearance $(t_1/2)$ exists
using the equation:
Blood flow (ml/min) = $\frac{\log_e 2 \times \lambda}{t_1/2}$ (min) (2) sing
where λ is the partition coefficient for ¹³³Xe between tumor
cells an $\begin{array}{c} \mathsf{Bloc} \ \mathsf{where} \ \lambda \ \mathsf{is} \ \mathsf{the} \ \mathsf{par} \ \mathsf{cells} \ \mathsf{and} \ \mathsf{blood}. \end{array}$ **Example 3** Blood flow (ml/min) = $\frac{\log_e 2 \times \lambda}{t_{1/2} \text{ (min)}}$ (2) si

nere λ is the partition coefficient for ¹³³Xe between tumor
 Tumor Angiography. The vascular network of 2- to 3-ml

shida sarcomas growing in the

 $t_{1/2}$ (min)
where λ is the partition coefficient for 133 Xe between tumor
cells and blood.
Tumor Anglography. The vascular network of 2- to 3-ml
Yoshida sarcomas growing in the leg muscles of the rats was
demon where λ is the partition coefficient for ^{133}Xe between tumor
cells and blood.
Tumor Angiography. The vascular network of 2- to 3-ml
Yoshida sarcomas growing in the leg muscles of the rats was
demonstrated by X-ra where A is the partition coefficient for the between tunior
cells and blood.
Tumor Angiography. The vascular network of 2- to 3-ml
Yoshida sarcomas growing in the leg muscles of the rats was
demonstrated by X-ray photogr **Tumor Angiography.** The vascular network of 2- to 3-ml
Yoshida sarcomas growing in the leg muscles of the rats was
demonstrated by X-ray photography after injection of contrast
medium at laparotomy into the aorta 1 cm abo Yoshida sarcomas growing in the leg muscles of the rats was
demonstrated by X-ray photography after injection of contrast
medium at laparotomy into the aorta 1 cm above the iliac
bifurcation. Leg tumors were used because l Fosmua sarcomas growing in the leg misscles of the fast was
demonstrated by X-ray photography after injection of contrast
medium at laparotomy into the aorta 1 cm above the iliac
bifurcation. Leg tumors were used because l definoristrated by A-ray photography after injection of contrast
medium at laparotomy into the aorta 1 cm above the iliac
bifurcation. Leg tumors were used because little success was
achieved in demonstrating the arterial medium at laparotomy into the aorta 1 cm above the illac
bifurcation. Leg tumors were used because little success was
achieved in demonstrating the arterial system distal to the ankle
by this technique. Photographs were ta needle. Tumor Hyperthermia. Tumors were taken 18 sec after injection of 8 to 10 ml 45% Hypaque (sodium diatriozate; Winthrop boratories, Surbiton. Surrey, England) through a 21-gauge edle.
Tumor Hyperthermia. Tumors were heated

Laboratories, Surbiton. Surrey, England) through a 21-gauge needle.

Tumor Hyperthermia. Tumors were heated by water bath

immersion. Bath and tumor temperatures were simultaneously

monitored by thermistor probes as descr immersion. Bath and tumor temperatures were simultaneously

RESULTS

to 7 determinations (animals); bars, S.D.
 Effect of Hyperglycemia on Tumor pH. The effect of glucose

administration by i.p. injection or i.v. infusion on blood and

Effect of hyperglycemia on pH at 2.4 i
and 1.5
RESULTS
Effect of Hyperglycemia on Tumor pH. The effect of glucose
administration by i.p. injection or i.v. infusion on blood and
tumor glucose concentrations is shown in Chart 1. The i.p. **RESULTS**
Effect of Hyperglycemia on Tumor pH. The effect of glucose
administration by i.p. injection or i.v. infusion on blood and
tumor glucose concentrations is shown in Chart 1. The i.p.
injection of glucose (6 g/kg) RESULTS

Effect of Hyperglycemia on Tumor pH. The effect of glucose

administration by i.p. injection or i.v. infusion on blood and

tumor glucose concentrations is shown in Chart 1. The i.p.

injection of glucose (6 g/kg) **Effect of Hyperglycemia on Tumor pH.** The effect of glucose
administration by i.p. injection or i.v. infusion on blood and
tumor glucose concentrations is shown in Chart 1. The i.p.
injection of glucose (6 g/kg) caused a Einect of hypergrycemia of Tullion ph. The effect of glucose
administration by i.p. injection or i.v. infusion on blood and
tumor glucose concentrations is shown in Chart 1. The i.p.
injection of glucose (6 g/kg) caused a different for 4 hr after injection of 1.v. initiation of blood and
impection of glucose (6 g/kg) caused a rapid increase in blood
glucose level from a mean of 2.8 to a level greater than 30
maintained for 4 hr after injec injection of glucose (6 g/kg) caused a rapid increase in blood
glucose level from a mean of 2.8 to a level greater than 30
mmol/liter was
maintained for 4 hr after injection, decreasing to control values
by 6 hr. When a h glucose level from a mean of 2.8 to a level greater than 30 maintained for 4 hr after injection, decreasing to control values
by 6 hr. When a higher glucose dose was given by infusion
(Chart 1; total glucose dose over 8 hr, 16 g/kg), the blood
DECEMBER 1980
DECEMBER 1980

Hyperglycemia and Yoshida Sarcoma

qlucose concentration increased rapidly to 33 mmol/liter at 30 Hyperglycemia and Yoshida Sarcoma
glucose concentration increased rapidly to 33 mmol/liter at 30
min and continued to increase to a plateau concentration of Hyperglycemia and Yoshida Sarcoma
glucose concentration increased rapidly to 33 mmol/liter at 30
min and continued to increase to a plateau concentration of
approximately 60 mmol/liter by 4 hr. Tumor glucose concen-Hyperglycemia and Yoshida Sarcoma
glucose concentration increased rapidly to 33 mmol/liter at 30
min and continued to increase to a plateau concentration of
approximately 60 mmol/liter by 4 hr. Tumor glucose concen-
tratio Hyperglycemia and Yoshida Sarcoma
glucose concentration increased rapidly to 33 mmol/liter at 30
min and continued to increase to a plateau concentration of
approximately 60 mmol/liter by 4 hr. Tumor glucose concen-
tratio glucose concentration increased rapidly to 33 mmol/liter at 30
min and continued to increase to a plateau concentration of
approximately 60 mmol/liter by 4 hr. Tumor glucose concen-
tration following both glucose dose sche min and continued to increase to a plateau concentration
min and continued to increase to a plateau concentration
tration following both glucose dose schedules showed a
porary increase, declining again to trace levels by 4 approximately 60 mmol/liter by 4 hr. Tumor glucose concentration following both glucose dose schedules showed a temporary increase, declining again to trace levels by 4 hr, while the blood glucose level remained elevated (

ured by capillary electrode, decreased from 7.19 to a minimum ured by capillary electrode, decreased from 7.19 to a minimum of 6.63 within 4 hr; pH_i, however, showed a slight but not a minimum of 6.63 within 4 hr; pH_i, however, showed a slight but not the blood glucose level remained elevated (Chart 1).
The effect of both glucose regimens on tumor pH is shown
in Table 1. Following i.p. glucose injection, tumor pH_e, meas-
ured by capillary electrode, decreased from 7. The effect of both glucose regimens on tumor pH is shown
in Table 1. Following i.p. glucose injection, tumor pH_e, meas-
ured by capillary electrode, decreased from 7.19 to a minimum
of 6.63 within 4 hr; pH_i, however, in Table 1. Following i.p. glucose injection, tumor pH_e, measured by capillary electrode, decreased from 7.19 to a minimum
of 6.63 within 4 hr; pH_i, however, showed a slight but not
significant ($p > 0.05$) pH increase fur rable 1. Following i.p. glacose injection, tallied pris, measured by capillary electrode, decreased from 7.19 to a minimum
of 6.63 within 4 hr; pH_i, however, showed a slight but not
significant ($\rho > 0.05$) pH incre pHe decreased non-7.19 to a minimum
of 6.63 within 4 hr; pH_i, however, showed a slight but not
significant ($p > 0.05$) pH increase from 7.21 to 7.36. Increas-
ing the blood glucose level by infusion did not produce any
 significant ($p > 0.05$) pH increase from 7.21 to 7.36. Increas-
ing the blood glucose level by infusion did not produce any
further decrease in pH_e compared to the single i.p. injection,
pH_e decreasing from 7.19 to a **Effect of Hyperglycemia on 3H₂O, ³⁶CI, and [¹⁴C]DMO Example between the Tumor and Host.

Effect of Hyperglycemia on 3H₂O, 3⁶CI did not enter the tumor (Chart 2).

Effect of Hyperglycemia on ^{3H}₂O, ³⁶CI, and**

single glucose injection at 6 g/kg. **change between the Tumor and Host. The concentration of** 3H₂O, [¹⁴C]DMO, and ³⁶CI did not enter the tumor (Chart 2).
 Effect of Hyperglycemia on ${}^{3}\text{H}_{2}$ O, ${}^{36}\text{Cl}$, and [¹⁴C]DMO Exchange between the Tum Countries the measured under implied to conditions because
 ${}^{3}H_{2}O$, $[{}^{14}C]DMO$, and ${}^{36}CI$ did not enter the tumor (Chart 2).
 Effect of Hyperglycemia on ${}^{3}H_{2}O$ **,** ${}^{36}CI$ **, and** $[{}^{14}C]DMO$ **Ex-

change bet Effect of Hyperglycemia on** ${}^{3}H_{2}O$ **,** ${}^{36}Cl$ **, and** $[{}^{14}C]DMO$ **Ex-
change between the Tumor and Host.** The concentration of
 ${}^{3}H_{2}O$, $[{}^{14}C]DMO$, and ${}^{36}Cl$ in tumors at the fourth hr of glucose
infusion was 1 change between the Tumor and Host. The concentration of ${}^{3}H_{2}O$, [¹⁴C]DMO, and ${}^{36}Cl$ in tumors at the fourth hr of glucose infusion was 1 to 2% of that in controls (Chart 2a). No inhibition of isotope uptake into ${}^{3}H_{2}O$, [${}^{14}C$]DMO, and ${}^{36}C$ in tumors at the fourth hr of glucose infusion was 1 to 2% of that in controls (Chart 2a). No inhibition of isotope uptake into the normal tissues was observed under these conditio infusion was 1 to 2% of that in controls (Chart 2a). No inhibition
of isotope uptake into the normal tissues was observed under
these conditions. There was also inhibition of isotope exchange
between the tumor and the hos miusion was T to 2×6 of that in controls (chart 2a). No immotion of isotope uptake into the normal tissues was observed under these conditions. There was also inhibition of isotope exchange between the tumor and the or isotope uptake into the homial itssues was observed under
these conditions. There was also inhibition of isotope exchange
between the tumor and the host; this prevented isotopes in-
jected into the tumor from entering t these conditions. There was also immodiate it isotope exchange
between the tumor and the host; this prevented isotopes in-
jected into the tumor from entering the plasma and equilibrating
with the normal tissues (Chart 2b) derively the tumor and the host, this prevented isotopes hi-
jected into the tumor from entering the plasma and equilibrating
with the normal tissues (Chart 2b). Isotopes injected into the
tumor at 2 hr after infusion bega ected into the tumor from entering the plasma and equilibrating
with the normal tissues (Chart 2b). Isotopes injected into the
tumor at 2 hr after infusion began were present in the host
tissues at 4 hr in concentrations o which the homial ussues (Chart 2D). Isotopes hijected into the
tumor at 2 hr after infusion began were present in the host
tissues at 4 hr in concentrations of less than 1% of the tumor
level. Under normal conditions, isot tissues at 4 hr in concentrations of less than 1% of the tumor
level. Under normal conditions, isotopes injected into the tumor
equilibrated freely with the host tissues in 2 hr (Chart 2c).
There was no inhibition of isoto sissues at 4 in in concentrations of less than 1 % of the tumor
level. Under normal conditions, isotopes injected into the tumor
equilibrated freely with the host tissues in 2 hr (Chart 2c).
There was no inhibition of iso

Chart 1. Blood (III) and tumor (II) glucose concentrations after injections of

Chart 1. Blood (III) and tumor (II) glucose concentrations after injections of

glucose (6 g/kg rat i.p.). Another series of animals was infu **Example 1.5 hr. •,blood (III)** and tumor (D) glucose concentrations after injections of glucose (6 g/kg rat i.p.). Another series of animals was infused with 20% glucose at 2.4 ml/hr and also given 0.75-ml i.p. injections Chart 1. Blood (and tumor (2) glucose
glucose (6 g/kg rati.p.). Another series of an
at 2.4 ml/hr and also given 0.75-ml i.p. inje
and 1.5 hr. \bullet , blood glucose levels; O, tumo
to 7 determinations (animals); *bars*, S.D. at 2.4 ml/hr and also given 0.75-ml i.p. injections of 50% glucose at 0, 0.5, 1, and 1.5 hr. \bullet , blood glucose levels; \circ , tumor glucose levels. Points, means of 5

tion

In after i.p. glucose injec-
 6.63 ± 0.21 (17) 7.36 ± 0.14 (12)

In after glucose infusion 6.70 ± 0.10 (8)
 $\frac{a}{b}$ Mean \pm S.D.
 $\frac{b}{c}$ Numbers in parentheses, number of tumors (animals) investigated.

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S. K. Calderwood and J. A. Dickson

S. K. Calderwood and J. A. Dickson
by Yoshida sarcoma slices was measured in vitro after hyper-
glycemia in vivo (Table 2). Differences in uptake of the isotope S. K. Calderwood and J. A. Dickson
by Yoshida sarcoma slices was measured *in vitro* after hyper- the fl
glycemia *in vivo* (Table 2). Differences in uptake of the isotope in
between slices from 6 hyperglycemic animals and S. K. Calderwood and J. A. Dickson
by Yoshida sarcoma slices was measured in vitro after hyper-
glycemia in vivo (Table 2). Differences in uptake of the isotope
between slices from 6 hyperglycemic animals and 6 control
(no S. K. Calderwood and J. A. Dickson
by Yoshida sarcoma slices was measured in vitro after hyper-
glycemia in vivo (Table 2). Differences in uptake of the isotope in the ga
between slices from 6 hyperglycemic animals and 6 c by Yoshida sarcoma slices was measured *in vitro* after hyper-
glycemia *in vivo* (Table 2). Differences in uptake of the isotope In
between slices from 6 hyperglycemic animals and 6 control prese
(normoglycemic) animals w grycenia *in vivo* (rabie 2). Dimerences in update of the isotope
between slices from 6 hyperglycemic animals and 6 control prese
(normoglycemic) animals were not significant even at the 10% flow
level. It was concluded t between slices from 6 hypergly
(normoglycemic) animals were n
level. It was concluded that hyperfect on uptake of ^{se}Rb by Yosi
not interfere with the measuren
⁸⁶Rb transport into the cells.
Following glucose infusion. by the interior animals were not significant even at the 10% flow the the it was concluded that hyperglycemia has no marked levels fect on uptake of ⁸⁶Rb by Yoshida sarcoma cells and should The t interfere with the measu ever. It was concluded that hypergrycemia has no marked level
effect on uptake of ⁸⁶Rb by Yoshida sarcoma cells and should
not interfere with the measurement of blood flow by altering by h
⁸⁶Rb transport into the cells

effect of uptake of the by fosmula sational dells and should
above infusion of the measurement of blood flow by altering b
⁸⁶Rb transport into the cells.
weight, per hr in control tumors to 0.06 ml per g per hr at 1 hr, ⁶⁶Rb transport into the cells.
⁶⁶Rb transport into the cells.
Following glucose infusion, blood flow measured by ⁸⁶Rb re-
uptake decreased progressively from 0.41 mg per g, dry
weight, per hr in control tumors to Following glucose infusion, blood flow measured by 86 Rb recommendate decreased progressively from 0.41 mg per g, dry are st weight, per hr in control tumors to 0.06 ml per g per hr at 1 hr, degre to 0.03 ml per g per Following glucose initiation, blood flow filesatied by Ab Republic update decreased progressively from 0.41 mg per g, dry a weight, per hr in control tumors to 0.06 ml per g per hr at 1 hr, dto 0.03 ml per g per hr at 2 h uptake decreased progressively from 0.41 mg per g, dry are shown in Chart 4. After infusion or injection of glucose, the weight, per hr in control tumors to 0.06 ml per g per hr at 1 hr, degree of blood flow inhibition, a weight, per in in control tantors to 0.00 mi per y per in at 1 iii, degree of
to 0.03 ml per g per hr at 2 hr, and to trace levels by 4 hr was esse
(Chart 3). Tumor blood flow was inhibited for as long as the (Chart 3).
bl Chart 3). Tumor blood flow was inhibited for as long as the (Chart 3). Tumor blood flow was inhibited for as long as the (Chart blood sugar level remained elevated. A single i.p. injection of Impglucose (6 g/kg) also caus blood sugar level remained elevated. A single i.p. injection of lm
glucose (6 g/kg) also caused a marked decrease in tumor was
blood flow from 0.41 to 0.04 ml/g/hr at 1 hr and a minimum anim
of 0.01 ml/g/hr at 2 hr. Tumor glucose (6 g/kg) also caused a marked decrease in tumor
blood flow from 0.41 to 0.04 ml/g/hr at 1 hr and a minimum anima
of 0.01 ml/g/hr at 2 hr. Tumor blood flow remained at a great
decreased level of 0.03 ml/g/hr at 4 h blood flow from 0.41 to 0.04 ml/g/hr at 1 hr and a minimum
of 0.01 ml/g/hr at 2 hr. Tumor blood flow remained at a green
decreased level of 0.03 ml/g/hr at 4 hr, gradually increasing ve
to 50% of control level by 8 hr. Th blood flow from 0.41 to 0.04 ml/g/hr at 1 hr and a minimum
of 0.01 ml/g/hr at 2 hr. Tumor blood flow remained at a greatl
decreased level of 0.03 ml/g/hr at 4 hr, gradually increasing vesse
to 50% of control level by 8 hr

(C) 50

Chart 2. Effect of hyperglycemia on uptake of ${}^{3}H_{2}O$ (m), ${}^{36}Cl$ (D), and [¹⁴C]-
DMO (Ξ) by rat tissues. In a, glucose was given by i.v. infusion, and at 2 hr the
animal was given an i.p. injection of Chart 2. Effect of hyperglycemia on uptake of ${}^{3}H_{2}O$ (\blacksquare), ${}^{36}Cl$ (\blacksquare), and [¹⁴C}-DMO (\blacksquare) by rat tissues. In a, glucose was given by i.v. infusion, and at 2 hr the animal was given an i.p. injection Chart 2. Effect of hyperglycemia on uptake of 4H_2O (\blacksquare), and $[{}^1C$ -DMO (${}^{\square}Q$) by rat tissues. In a, glucose was given on i.p. inpiction of the isotope mixture (50 μ Ci 3H_2O , 1 μ Ci 3C Cl, and 1 animal was given an i.p. injection of the isotope mixture (50 μ Ci ³H₂O, 1 μ Ci ³⁶Cl, and 1 μ Ci [¹C]DMO in 1.0 ml of 0.9% NaCl solution). Infusion was continued for a further 2 hr; then the animal was sacri a further 2 hr; then the animal was sacrificed, and isotope concentrations (cpm/
g tissue, wet weight) were determined as percentage of cpm compared to
normoglycemic controls. P, plasma; D, diaphragm; G, gastrocnemius; L, g tissue, wet weight) were determined as percentage of cpm compared to
normoglycemic controls. P, plasma; D, diaphragm; G, gastrocnemius; L, liver; T,
Yoshida tumor. In b, after 2 hr glucose infusion, the isotope mixture 0.1 μ Ci ∞ Cl, and 0.1 μ Ci ["CJDMO in 0.1 ml 0.9% NaCl solution) was injected into the tumor, and infusion was continued. Results are expressed as percentage of com (cpm/g tissue) compared to activity in the tumor Shipection. In c, results are again communisties accurace 2 in animals in each proper pressure expressed as a percentage in remaining in the tumor. Results are means from 5 experimental and 5 animals in each group. S.D.'s

ntrol animals in each group. S.D.`s were 5 to 10% of mean value in each case.
Table 2
Effect of hyperglycemia on ^{es}Rb uptake by Yoshida sarcoma slices
Tumors were from 6 normoglycemic animals after 4 hr sagittal anesthes Table 2
Effect of hyperglycemia on ^{es}Rb uptake by Yoshida sarcoma slices
Tumors were from 6 normoglycemic animals after 4 hr sagittal anesthesia and
6 hyperglycemic animals anesthetized for 4 hr after an injection of glu Tumors were from 6 normoglycemic animals after 4 hr sagittal anesthesia and 6 hyperglycemic animals anesthetized for 4 hr after an injection of glucose (6 g/ kg i.p.). Immediately upon removal, thin tumor sections (less t Tumors were from 6 normoglycemic animals after 4 hr sagittal anesthesia and
6 hyperglycemic animals anesthetized for 4 hr after an injection of glucose (6 g/
kg i.p.). Immediately upon removal, thin tumor sections (less t

kg i.p.). Immediately upon removal, thin tumor sections (less than 1 cu mm) were
prepared (9). The slices were washed in 5 ml of Waymouth's medium, containing
0.1% albumin, and 100-mg aliquots were weighed into 5-cm Petri prepared (9). The slices were washed in 5 ml of Waymouth's medium, containing 0.1% albumin, and 100-mg aliquots were weighed into 5-cm Petri dishes.
To the tumor slices were added 3 ml of medium containing ^{ase}Rb (2.5 µC removal of tumor from the animal and addition of ⁸⁶Rb to culture medium was less than 45 min. After equilibration (2 hr), slices were washed 3 times in 5 ml of ice-cold phosphate-buffered saline (pH 7.4) (9). Radioactiv ice-cold phosphate-buffered saline (pH 7.4) (9). Radioactivity was expressed as

the flank and in 1.0- to 3.0-ml i.m. tumors in the rat legs.
In the gastrocnemius, blood flow increased by 50% in the

e flank and in 1.0- to 3.0-ml i.m. tumors in the rat legs.
In the gastrocnemius, blood flow increased by 50% in the
esence of hyperglycemia (20 or 50 mmol/liter), while blood the flank and in 1.0- to 3.0-ml i.m. tumors in the rat legs.
In the gastrocnemius, blood flow increased by 50% in the
presence of hyperglycemia (20 or 50 mmol/liter), while blood
flow through the liver was not significantl the flank and in 1.0- to 3.0-ml i.m. tumors in the rat legs.
In the gastrocnemius, blood flow increased by 50% in the
presence of hyperglycemia (20 or 50 mmol/liter), while blood
flow through the liver was not significantl the flank and in 1.0- to 3.0-
In the gastrocnemius, bl
presence of hyperglycemia
flow through the liver was
levels of blood glucose.
The finding of inhibition o The fiank and in 1.0-10 3.0-min.i.i. tuniors in the rat legs.

In the gastrocnemius, blood flow increased by 50% in the

flow through the liver was not significantly altered at these

levels of blood glucose.

The finding

presence or mypergrycenina (20 of 30 inition/liter), while blood
flow through the liver was not significantly altered at these
levels of blood glucose.
The finding of inhibition of blood flow in the Yoshida sarcoma
by hype recorded 4 hr after commencement of the 2 glucose,
are finding of inhibition of blood flow in the Yoshida sarcoma
by hyperglycemia was confirmed using the ¹³³Xe clearance
technique to measure blood flow. Xenon clearance The finding of inhibition of blood flow in the Yoshida sarcoma
by hyperglycemia was confirmed using the ¹³³Xe clearance
technique to measure blood flow. Xenon clearance curves
recorded 4 hr after commencement of the 2 gl by hyperglycemia was confirmed using the ¹³³Xe clearance
technique to measure blood flow. Xenon clearance curves
recorded 4 hr after commencement of the 2 glucose regimens
are shown in Chart 4. After infusion or injectio rechnique to
recorded 4 hr
are shown in (
degree of bloo
was essential
(Chart 3).
Impairment Explorated 4 in alter commencement of the 2 glucose regimens

E shown in Chart 4. After infusion or injection of glucose, the

gree of blood flow inhibition, as indicated by ¹³³Xe clearance,

is essentially similar to th are shown in Chart 4. Alter intusion or injection or glucose, the
degree of blood flow inhibition, as indicated by ¹³³Xe clearance,
was essentially similar to the values obtained by ⁸⁶Rb uptake
(Chart 3).
Impairment of

was essentially similar to the values obtained by ^{se} clearance,
was essentially similar to the values obtained by ^{se}Rb uptake
(Chart 3).
Impairment of the tumor blood supply in hyperglycemic hosts
was also indicated by was essentially similar to the values obtained by Thu uptake
(Chart 3).
Impairment of the tumor blood supply in hyperglycemic hosts
was also indicated by angiography (Fig. 1). In hyperglycemic
animals, the number of demons Umpairment of the tumor blood supply in hypergly
was also indicated by angiography (Fig. 1). In hyp
animals, the number of demonstrable tumor blood v
greatly reduced compared to controls, and the
vessels supplying the norm **Example in the conduct of the parally reduced compared to controls, and the patency of ssels supplying the normal tissues is evident.
Exchange of Labeled Metabol Host during Hyperglycemic animals, the number of demonstrable tumor blood vessels was greatly reduced compared to controls, and the patency of vessels supplying the normal tissues is evident.
Exchange of Labeled Metabolit**

differential effect of the 2 levels of hyperglycemia (achieved by differential effect of the 2 levels of hyperglycemia (achieved by glucose injection or infusion) on exchange of metabolities between the Tumor and Host duri greatly reduced compared to controls, and the patency of
vessels supplying the normal tissues is evident.
Exchange of Labeled Metabolites between the Tumor and
Host during Hyperglycemia. Chart 5 illustrates further the the Tumor and Host. At a blood glucose level of 20 mmol Host during Hyperglycemia. Chart 5 illustrates further the differential effect of the 2 levels of hyperglycemia (achieved by glucose injection or infusion) on exchang riost during hyperglycemia. Chart 3 mustrates further the
differential effect of the 2 levels of hyperglycemia (achieved by
glucose injection or infusion) on exchange of metabolites be-
tween tumor and host. At a blood glu differential effect of the 2 levels of hyperglycemia (achieved by
glucose injection or infusion) on exchange of metabolites be-
tween tumor and host. At a blood glucose level of 20 mmol/
liter, there was an 85% inhibition glucose injection of initiasion) on exchange of inetabolities be-
tween tumor and host. At a blood glucose level of 20 mmol/
liter, there was an 85% inhibition of 2-³H]deoxyglucose uptake
into the tumor. Glucose infusion

Their, there was an 83% inhibition of 2-1 righteoxyglucose uptake
into the tumor. Glucose infusion (blood glucose, 50 mmol/liter)
led to 100% inhibition of 2-deoxyglucose uptake into the tumor.
A similar pattern was found them was lod
hen [¹⁴C]lact
oma in norm
⁰⁻⁵]

o 2 4
Hours after gluce
Chart 3. Effect of hyperglycemia induced by a s
i.v. infusion (@) on Yoshida sarcoma blood flow meas
means of 5 determinations (animals); *bars*, S.D. by a single i.p. injectii
measured by ^{se}Rb up
).
Glucose infusion
gnce not defected)

after 13 Xe injection into tumor
Chart 4. Clearance of 13 Xe after i.t. injection into the Yoshida foot sarcoma,
showing sample chart recordings of 13 Xe clearance of individual tumors 4 hr
after glucose injecti CONGRESS CONDUCTER CONTROL CON

Chart 5. Inhibition of $2\left\{\frac{1}{2}\right\}$ 4 6 8
Chart 5. Inhibition of $2\left\{\frac{3}{2}\right\}$ Hours After Glucose
Yoshida foot tumor after a single i.p. injection of glucose (6 g/kg; blood glucose, at 6
20 mmol/liter (\leftarrow)). Ea Chart 5. Inhibition of 2-[³H]deoxyglucose ([³H]-2-dGlucose) uptake in the
Yoshida foot tumor after a single i.p. injection of glucose [6 g/kg; blood glucose, 50
20 mmol/liter for 4 hr (- - - -)] or after i.v. glucose Yoshida foot tumor after a single i.p. injection of glucose [6 g/kg; blood glucose, at is 20 mmol/liter $(- - 1)$. Each rat received 10 µC isotope infusion [blood glucose, 50 mumol/liter $(- - 1)$]. Each rat received 10 µC is mmol/liter (-----)]. Each rat received 10 μ Ci isotope i.p. in 1 ml 0.9% NaCl solution; each *point* represents tumor activity in an animal sacrificed 30 min after injection. The analog 2-deoxyglucose has transport prop The analog 2-deoxyglucose has transport properties similar to those

it is only slowly metabolized, making it a suitable marker for the stu-

transport (10).

Table 3

Effect of glucose (6 g/kg) on ["Cliactate efflux from

glucose transport (10).

Table 3

Effect of glucose (6 g/kg) on \int_1^1 C diactate efflux from tumors

[¹⁴C diactate (1 µCi in 0.1 ml of 0.9% NaCl solution) was injected into tumors

In after i.p. administration of gluc

2 Fraction of Galucose at a dose of flux from turnors
2 hr after i.p. administration of glucose at a dose of 6 g/kg. Animals were
2 hr after i.p. administration of glucose at a dose of 6 g/kg. Animals were
3 sacrificed Effect of glucose (6 g/kg) on $l^{14}C$] actate efflux from tumors

[¹⁴C]Lactate (1 µCi in 0.1 ml of 0.9% NaCl solution) was injected into tumors

2 hr after i.p. administration of glucose at a dose of 6 g/kg. Animals we ['C]Lactate (1 μ Ci in 0.1 ml of 0.9% NaCl solution) was injected into tumors 2 hr after i.p. administration of glucose at a dose of 6 g/kg . Animals were sacrificed 30 min after the lactate injection, and ¹⁴C activity 2 hr after i.p. administration of
sacrificed 30 min after the lact
the tumor and normal organs. In
min after an i.t. injection of $[1^4C]$,
both as cpm/g, wet weight, and
value being taken as 100%.

 a Mean \pm S.D. of 4 determinations (animals).

Gastrocne 18,926 ± 3,168 18.7 7,916 ± 1,615 2.16 113

mius cin

a Mean ± S.D. of 4 determinations (animals).

were sacrificed 30 min later, the plasma and other organs de

contained 43% of the total radioactivity of the c The circuit of a determinations (animals).

Were sacrificed 30 min later, the plasma and other organs denne (27)

contained 43% of the total radioactivity of the carcass. After concomita

glucose loading of the host at 20 mean ± S.D. or 4 determinations (animas). The contained activity of the carcase into the contained 43% of the total radioactivity of the carcass. After concordinced 43% of the total radioactivity of the carcass. After conc were sacrificed 30 min later, the plasma and other organs denne
contained 43% of the total radioactivity of the carcass. After conco
glucose loading of the host at 20 mmol/liter for 2 hr, only 9.8% cemia
of the activity in glucose loading of the host at 20 mmol/liter for 2 hr, only 9.8% of the activity injected into the sarcoma was recovered in tissues apart from the tumor (illustrated for sample organs in Table 3). After 4 hr infusion (bloo of the activity injected into the sarcoma was recovered in
tissues apart from the tumor (illustrated for sample organs in
Table 3). After 4 hr infusion (blood glucose 50 mmol/liter),
almost 100% of the cpm remained in the In the activity injected into the sationial was recovered in tactic activities

Table 3). After 4 hr infusion (blood glucose 50 mmol/liter), membra

almost 100% of the cpm remained in the tumor at 30 min after Low pH

isot

Tumor Heating at 42°. The decreased tumor blood flow gued, would lack the flexibility needed to pass through narrov caused by hyperglycemia diminished the thermal load neces-
sary for tumor heating and also promoted a more **Effect of Hyperglycemia on the Thermal Load Required for** creas **Tumor Heating at 42°**. The decreased tumor blood flow gued, caused by hyperglycemia diminished the thermal load necescapilli sary for tumor heating and als **Tumor Heating at 42°.** The decreased tumor blood flow g
caused by hyperglycemia diminished the thermal load neces-
sary for tumor heating and also promoted a more uniform tumor T
temperature during heating (Chart 6). In caused by hyperglycemia diminished the thermal load necessary for tumor heating and also promoted a more uniform tumor Titemperature during heating (Chart 6). In normoglycemic rats, in the temperature gradient between the temperature during and also promoted a more dimomrating the temperature during heating (Chart 6). In normoglycemic rats, initiatif the temperature gradient between the water bath at 43° and The tumor was approximately $1.$ the temperature during neating (chart o). In homogrycemic rats, the temperature gradient between the water bath at 43° and The tumor was approximately 1.0° (i.e., tumor 42°) for the first blood 40 min of heating the tumor was approximately 1.0° (i.e., tumor 42°) for the first
40 min of heating. This gradient decreased to 0.7° as the heat contractment was continued to 50 and 60 min. In tumors heated 4 in
the fatter glucose injectio Following glucose infusion for 4 hr, the temperature gradient was continued to 50 and 60 min. In tumors heated 4 in
the after glucose injection at a dose of 6 g/kg, the temperature correlation for 4 mean of approximately 0 between twas commuted to be and be min. in tumors in
the after glucose injection at a dose of 6 g/kg, the tem
gradient was reduced to a mean of approximately (
remained at this level throughout the 60-min heating
Following atier glucose injection at a cose of o g/kg, the temperature crease
adient was reduced to a mean of approximately 0.2° and gluco
mained at this level throughout the 60-min heating period. much
llowing glucose infusion for gradient was reduced to a mean of approximately 0.2 and gradient was reduced to a mean of approximately 0.2 and gradient remained at this level throughout the 60-min heating period. much between tumor and bath was abolish

Chart 6. Temperature gradient between Yoshida sarcoma and water bath (at 43°)in control, normoglycemic animals (•),after a single i.p. glucose injection Chart 6. Temperature gradient between Yoshida sarcoma and water bath (at 43°) in control, normoglycemic animals (\bullet), after a single i.p. glucose injection (at 6 g/kg (\circ), or after i.v. glucose infusion (\Box). Point Chart 6. Temperature gradient between Yoshida sarcoma a
43°) in control, normoglycemic animals (\bullet), after a single i.p.
at 6 g/kg (O), or after i.v. glucose infusion (\Box). Points, mo
numbers in parentheses, number of Chart 6. Temperature gradient between Yoshida sarcoma and water bath (at 43°) in control, normoglycemic animals (\bullet), after a single i.p. glucose injection at 6 g/kg (O), or after i.v. glucose infusion \Box). Points, me

at 6 g/kg (O), or after i.v. glucose infusion (D). Points, means; bars, S.D.;
numbers in parentheses, number of animals in each group.
compared to that of control animals at a mean room air tem-
perature of 25°. Normoglyc numbers in parentheses, number of animals in each group.
compared to that of control animals at a mean room air tem-
perature of 25°. Normoglycemic animals had a rectal temper-
ature of 34.2 ± 1.3° (S.D.) (8 rats), while

DISCUSSION

were sacrificed 30 min later, the plasma and other organs denne (27), who has proposed a hypothesis to account for the contained 43% of the total radioactivity of the carcass. After concomitant fall in tumor blood flow an almost 100% of the cpm remained in the tumor at 30 min after Low pH has been shown to alter erythrocyte membrane struc-
isotope injection.
 Effect of Hyperglycemia on the Thermal Load Required for creased erythrocyte rig The concomitant changes in blood supply and pH_e in the
SCUSSION
The concomitant changes in blood supply and pH_e in the
shida sarcoma after hyperglycemia suggest that the 3 effects glucose imusion had a temperature of 32.5 ± 1.7 (o rats).

DISCUSSION

The concomitant changes in blood supply and pH_e in the

Yoshida sarcoma after hyperglycemia suggest that the 3 effects

are interrelated. The evid DISCUSSION
The concomitant changes in blood supply and pH_e in the
Yoshida sarcoma after hyperglycemia suggest that the 3 effects
are interrelated. The evidence for inhibition of blood flow in the
tumor is strong; both tu **DISCUSSION**
The concomitant changes in blood supply and pH_e in the
Yoshida sarcoma after hyperglycemia suggest that the 3 effects
are interrelated. The evidence for inhibition of blood flow in the
tumor is strong; both The concomitant changes in blood supply and pH_e in the Yoshida sarcoma after hyperglycemia suggest that the 3 effects are interrelated. The evidence for inhibition of blood flow in the tumor is strong; both tumor uptake The concommant changes in blood supply and pri_e in the
Yoshida sarcoma after hyperglycemia suggest that the 3 effects
are interrelated. The evidence for inhibition of blood flow in the
tumor is strong; both tumor uptake are interrelated. The evidence for infinition of blood flow in the
tumor is strong; both tumor uptake and clearance of a wide
range of chemical species was inhibited during hyperglycemia
(Charts 2 and 5; Table 3), and quan finding is strong, both tuntor uptake and clearance of a wide
range of chemical species was inhibited during hyperglycemia
(Charts 2 and 5; Table 3), and quantitation of the inhibition by
different methods (⁸⁶Rb distribu range of chemical species was immoted during hypergrycemia
(Charts 2 and 5; Table 3), and quantitation of the inhibition by
different methods (⁸⁶Rb distribution and ¹³³Xe clearance)
yielded comparable results (Charts 3 conaris 2 and 5, rable 5), and quarmation of the immoltion by
different methods (⁸⁶Rb distribution and ¹³³Xe clearance)
yielded comparable results (Charts 3 and 4). The results con-
firm an earlier finding of Algire & yielded comparable results (Charts 3 and 4). The results confirm an earlier finding of Algire & Legallais (1) who found that hyperglycemia (blood sugar level unspecified) inhibited blood circulation in tumors growing in tr firm an earlier finding of Algire & Legallais (1) who found that hyperglycemia (blood sugar level unspecified) inhibited blood rightly central turbod sugar lever displecified) infinited blood
circulation in tumors growing in transparent chambers im-
planted in mice. In rat tumors, inhibition of blood flow during
hyperglycemia has been reported mor circulation in turities growing in transparent chambers im-
planted in mice. In rat tumors, inhibition of blood flow during
hyperglycemia has been reported more recently by Von Ar-
denne (27), who has proposed a hypothesis planted in nice. in rat tuniors, immotion of blood now during
hyperglycemia has been reported more recently by Von Ar-
denne (27), who has proposed a hypothesis to account for the
concomitant fall in tumor blood flow and p mypergiycemia has been reported more recently by Von Ar-
denne (27), who has proposed a hypothesis to account for the
concomitant fall in tumor blood flow and pH_e (27). Hypergly-
cemia, it is postulated, leads to a stimu define (27), who has proposed a hypothesis to account for the
concomitant fall in tumor blood flow and pH_e (27). Hypergly-
cemia, it is postulated, leads to a stimulation of glycolysis with
lactic acidosis in the tumor; Concollidate fail in tunior blood flow and ph_e (27). Hypergly-
Cemia, it is postulated, leads to a stimulation of glycolysis with
lactic acidosis in the tumor; erythrocytes entering the acidified
tumor would be expected befina, it is postulated, leads to a sumulation of gigcorysis with
lactic acidosis in the tumor; erythrocytes entering the acidified
tumor would be expected to undergo a pH-mediated change in
membrane conformation causing ractic actions in the tunior, erythrocytes entering the actioned
tumor would be expected to undergo a pH-mediated change in
membrane conformation causing a decreased flexibility (27).
Low pH has been shown to alter erythro dinior would be expected to undergo a pri-inediated change in
membrane conformation causing a decreased flexibility (27).
Low pH has been shown to alter erythrocyte membrane struc-
ture (25) and to increase blood viscosity nembrane combiniation causing a decreased nexibility (27).
Low pH has been shown to alter erythrocyte membrane struc-
ture (25) and to increase blood viscosity [attributed to in-
creased erythrocyte rigidity (17)]. Such er Low pH has been shown to alter erythrocyte membrane structure (25) and to increase blood viscosity [attributed to increased erythrocyte rigidity (17)]. Such erythrocytes, it is argued, would lack the flexibility needed to gued, would lack the flexibility needed to pass through narrow capillaries and would physically block the tumor vessels (27).
The theory (27) therefore implicates a decrease in pH as the initiating event, with a resulting eased erythocyte rigitally (17)]. Such erythrocytes, it is aread, would lack the flexibility needed to pass through narrow pillaries and would physically block the tumor vessels (27). The theory (27) therefore implicates a gued, would lack the hexibility heeded to pass through narrow
capillaries and would physically block the tumor vessels (27).
The theory (27) therefore implicates a decrease in pH as the
initiating event, with a resulting i

capinaries and would physically block the tumor vessels (27).
The theory (27) therefore implicates a decrease in pH as the
initiating event, with a resulting inhibition of tumor blood flow.
The present data do not sup initiating event, with a resulting inhibition of tumor blood flow.
The present data do not support this hypothesis. Tumor
blood flow decreased rapidly after glucose injection, and the
curve of blood flow inhibition (Chart minaling event, with a resulting immotion of turnor blood flow.
The present data do not support this hypothesis. Tumor
blood flow decreased rapidly after glucose injection, and the
creased of the blood glucose curve (Chart The present data do not support this hypothesis. Tumor
blood flow decreased rapidly after glucose injection, and the
cirve of blood flow inhibition (Chart 3) was almost a mirror
image of the blood glucose curve (Chart 1); much more slowly and pluty and pluty and pluty in the curve of blood flow inhibition (Chart 3) was almost a mirror image of the blood glucose curve (Chart 1); blood flow decreased as blood glucose increased and flow incre train the 4 hr colour now infinition (chart 3) was almost a mirror
image of the blood glucose curve (Chart 1); blood flow de-
creased as blood glucose increased and flow increased as
glucose decreased. Tumor pH_e declined mage of the blood glucose curve (Chart 1), blood how de-
creased as blood glucose increased and flow increased as
glucose decreased. Tumor pH_e declined progressively but
much more slowly than blood flow, reaching a minim creased as blood glucose increased and now increased as
glucose decreased. Tumor pH, declined progressively but
much more slowly than blood flow, reaching a minimum in 3.5
to 4 hr [detailed in an earlier publication (6)]. glucose decreased. Tumor pric decimed progressively but
much more slowly than blood flow, reaching a minimum in 3.5
to 4 hr [detailed in an earlier publication (6)]. Previous work
also showed that glycolysis (both aerobic between tumor and bath was abolished (Chart 6). also showed that glycolysis (both aerobic and anaerobic) in the
The rectal temperature of hyperglycemic rats anesthetized Yoshida tumor was inhibited by 35 to 60% during hyp

S. K. Calderwood and J. A. Dickson
(26). Within 30 min after glucose injection, however, there was S. *K. Calderwood and J. A. Dickson*
(26). Within 30 min after glucose injection, however, there was woul
a rapid accumulation of lactate in the tumor to 2 to 3 times the resis S. *K. Calderwood and J. A. Dickson*
(26). Within 30 min after glucose injection, however, there was would
a rapid accumulation of lactate in the tumor to 2 to 3 times the resist:
normal level (6). Again, the rapidity of t S. K. Calderwood and J. A. Dickson
(26). Within 30 min after glucose injection, however, there was
a rapid accumulation of lactate in the tumor to 2 to 3 times the
normal level (6). Again, the rapidity of this accumulation S. K. Calderwood and J. A. Dickson
(26). Within 30 min after glucose injection, however, there was would
a rapid accumulation of lactate in the tumor to 2 to 3 times the resist
normal level (6). Again, the rapidity of thi (26). Within 30 min after glucose injection, however, there was would
a rapid accumulation of lactate in the tumor to 2 to 3 times the resist
normal level (6). Again, the rapidity of this accumulation par-
alleled the ele section, while the unit anter gluebols injection, in the events, there was would a rapid accumulation of lactate in the tumor to 2 to 3 times the resisted normal level (6). Again, the rapidity of this accumulation par-
al the initial event, with a subsequent decrease in tumor of blood increase.

flow and was well in advance of the fall in tumor pH_e. The time to vise

sequence of events therefore favors inhibition of blood flow as rates,
 secondary to arrest of lood sugar and the decrease in blood increase
flow and was well in advance of the fall in tumor pH_e. The time to visco
sequence of events therefore favors inhibition of blood flow as rates, is
the but and was went in advance of the ran in tunior phi_e. The time to vis-
sequence of events therefore favors inhibition of blood flow as rates
the initial event, with a subsequent decrease in tumor. The tend
maintenance dequence of events increase favors inhibited to blood now as rates
the initial event, with a subsequent decrease in tumor pH_e micro
secondary to arrest of lactate egress from the tumor. The tend
maintenance of tumor pH_i the initial event, with a subsequent decrease in tumor pH_e
secondary to arrest of lactate egress from the tumor. The
maintenance of tumor pH_i at control levels despite a 0.6-pH
unit fall in pH_e (Table 1) is probably maintenance of tumor pH_i at control levels despite a 0.6-pH
unit fall in pH_e (Table 1) is probably due to intracellular buffering
and active transport of protons out of the cell (20), as well as
the self-limiting effe and active transport of protons out of the cell (20), as well as
the self-limiting effect of hyperglycemia preventing access of 23).
glucose to the cells. initial
intial The report by Gullino *et al.* (15) of a considerabl

the self-limiting effect of hyperglycemia preventing access of 23
the self-limiting effect of hyperglycemia preventing access of 23
glucose to the cells. in
in glucose utilization by the Walker 256 carcinoma, hepatoma po
 different of hyperglycemia preventing access of 25). In glucose to the cells.

The report by Gullino et al. (15) of a considerable increase aggre

in glucose utilization by the Walker 256 carcinoma, hepatoma post-

5123, a The report by Gullino et al. (15) of a considerable increase aggre
in glucose utilization by the Walker 256 carcinoma, hepatoma post-
5123, and fibrosarcoma 4956 rat tumors in the first few hr after blood
hyperglycemia (b Ine report by Guillio et al. (15) or a considerable increase aggre
in glucose utilization by the Walker 256 carcinoma, hepatoma post-c-
5123, and fibrosarcoma 4956 rat tumors in the first few hr after blood
hyperglycemia (if glacose dimension by the walker 250 calculoma, replacing provided by the attention of the first few hr after
byperglycemia (blood glucose, \geq 20 mmol/liter) would seem to
be at variance with the present data. The uti by perglycemia (blood glucose, and diniors in the matrier in after blood
hyperglycemia (blood glucose, and mol/liter) would seem to by g
be at variance with the present data. The utilization did reach brand
a saturation le the divergity of the present data. The utilization did reach branch a saturation level after 6 to 7 hr of hyperglycemia, although no chavalues for tumor blood flow were quoted by the authors (15). tocreased glucose utiliz de at variance with the present data. The difference of discrepancy as asturation level after 6 to 7 hr of hyperglycemia, although no collues for tumor blood flow were quoted by the authors (15). It increased glucose utili values for tumor blood flow were quoted by the authors (15). tocrit
Increased glucose utilization in tumors after hyperglycemia which
would imply that no rapid inhibition of tumor blood flow oc-
proce
curred. The discrepan values for tumor blood now were quoted by the authors (15). toom
Increased glucose utilization in tumors after hyperglycemia whic
would imply that no rapid inhibition of tumor blood flow oc-
procurred. The discrepancy betw would imply that no rapid inhibition of tumor blood flow oc-
would imply that no rapid inhibition of tumor blood flow oc-
curred. The discrepancy between the findings of Gullino et al.
when
and the present study may be due and the present study may be due to differences between C
experimental tumors used in the studies. Moreover, the tumors c
used in the investigations of Gullino *et al.* (15) were grown in
ovarian tissue isolated from the o and the present study may be due to differences between our
experimental tumors used in the studies. Moreover, the tumors cem
used in the investigations of Gullino *et al.* (15) were grown in and
ovarian tissue isolated fr grown by simple s.c. or i.m. implantation as used in the investigations of Gullino *et al.* (15) were grown in a contrain tissue isolated from the other normal tissues and connected to the host blood supply by a single ar stated in the investigations of dumino et al. (15) were grown in and obtained the tumors in the tumors is ovarian tissue isolated from the other normal tissues and con-
nected to the host blood supply by a single artery an ovarian tissue isolated from the other normal tissues and con-
nected to the host blood supply by a single artery and vein. effect
This is a considerably different situation to that of the tumors with s
grown by simple s.c This is a considerably different situation to that of the tumors with
grown by simple s.c. or i.m. implantation as used in the present The
study. In these circumstances, the tumor blood supply is con-
if a g
nected by an a This is a considerably different situation to that of the tumors with subsequent interruption of tumor blood flow.
grown by simple s.c. or i.m. implantation as used in the present The glucose-induced specific inhibition o grown by simple s.c. or i.m. implantation as used in the present
study. In these circumstances, the tumor blood supply is con-
if a g
nected by an agglomeration of tumor-induced new vessels to
and the vascular beds of surr study. In these circumstances, the tumor blood supply is con-
mected by an agglomeration of tumor-induced new vessels to and
the vascular beds of surrounding normal tissues (30). It is rend
conceivable that blood flow in s rected by an aggrome
the vascular beds of
conceivable that bloo
susceptible to disrupt
large artery and vein
to a normal organ.
The effect of gluco: Fractual beas of surfounding fiormal ussues (30). It is reflued
inceivable that blood flow in such tumors might be more The lo
sceptible to disruption than in tumors supplied by a single tumor
ge artery and vein that const susceptible to disruption than in tumors supplied by a single
susceptible to disruption than in tumors supplied by a single
targe artery and vein that constituted the original vasculature
to a normal organ.
The effect of g

between these processes in a tumor and the effect of glucose on tumor pH would thus seem to be complex, depending on rates of glucose influx into the tumor, (actate production and efflux, and buffering power. The balance v The effect of glucose on tumor pH would thus seem to be cemial
complex, depending on rates of glucose influx into the tumor, (Chai
lactate production and efflux, and buffering power. The balance would
between these proces ine enect of glucose of tunior pri would this seem to be complex, depending on rates of glucose influx into the tumor, (Chalactate production and efflux, and buffering power. The balance would between these processes in a Complex, depending on a
lactate production and eff
between these processe
glycemia upon pH_i/pH_e rainhibits tumor blood flow
this inhibition occurs.
The mechanism for th The mechanism for the selective decrease in tumor blood
were these processes in a tumor and the effect of hyper-
would in the selective decrease concentration issue
is inhibition occurs.
The mechanism for the selective dec glycemia upon pH_i/pH_e ratio may hinge on whether the glucose
inhibits tumor blood flow and at what glucose concentration
this inhibition occurs.
The mechanism for the selective decrease in tumor blood
flow at high bloo

giycemia upon phi_i ph_e ratio may impe on whether the glucose
inhibits tumor blood flow and at what glucose concentration tissue
this inhibition occurs.
flow at high blood glucose level is not indicated by the current B Infinitions tumor blood flow and at what glucose concentration
this inhibition occurs.
The mechanism for the selective decrease in tumor blood sensition
flow at high blood glucose level is not indicated by the current
diat The mechanism for the selective decrease in tumor blood
flow at high blood glucose level is not indicated by the current
data. The selective nature of the effect of high blood glucose
levels on tumor blood flow may be attr The mechanism for the selective decrease in tumor blood
flow at high blood glucose level is not indicated by the current
data. The selective nature of the effect of high blood glucose able
levels on tumor blood flow may be and and in the selective nature of the effect of high blood glucose able than all and the selective nature of the effect of high blood glucose able the velasion tumor blood flow may be attributed to the known tissue differ data. The selective nature of the effect of high blood glucose
levels on tumor blood flow may be attributed to the known
differences between the blood supply of normal and malignan
tissues (14, 18). Tumor blood flow in gen variation issue alternated to the known that
differences between the blood supply of normal and malignant Exan
tissues (14, 18). Tumor blood flow in general is more sluggish conce
and less responsive to local and systemic differences between the blood supply of normal and manghant
tissues (14, 18). Tumor blood flow in general is more sluggish
and less responsive to local and systemic control than is blood
flow in normal tissues (14, 18). Th and less responsive to local and systemic control than is blood technique and less responsive to local and systemic control than is blood technique flow in normal tissues (14, 18). The normal and tumor microtion (vascular flow in normal tissues (14, 18). The normal and tumor micro-
flow in normal tissues (14, 18). The normal and tumor micro-
tion of dilated, tortuous capillaries and sinusoids with a primitive,
often discontinuous, wall (12, Fractures of the tumor vessels being composed
of dilated, tortuous capillaries and sinusoids with a primitive,
often discontinuous, wall (12, 30). Periods of stasis, followed
by resumed blood flow, often in the contrary d vascular systems also unter, the tumor vessels being composed
of dilated, tortuous capillaries and sinusoids with a primitive,
often discontinuous, wall (12, 30). Periods of stasis, followed
by resumed blood flow, often i often discontinuous, wall (12, 30). Periods of stasis, followed **ACKNOWLED**
by resumed blood flow, often in the contrary direction, are
features of the tumor microcirculation (13). The major deter-
minants of blood flow in by resumed blood flow, often in the contrary direction, are features of the tumor microcirculation (13). The major determinants of blood flow in tumor capillaries are the physical state of the blood and integrity of the mi of the blood and integrity of the microcirculation (19). While of the blood and integrity of the inforcence

there is no evidence to suggest that hyperglycemia might

change the radius of tumor blood vessels, any such alteration 1. Algire, G. H., and Legallais, F. Y. Vascular reaction

unit fall in pH_e (Table 1) is probably due to intracellular buffering aggregates become significant compared to the shearing and active transport of protons out of the cell (20), as well as forces of blood flow, with a would imply that no rapid inhibition of tumor blood flow oc-
curred. The discrepancy between the findings of Gullino et al.
and the present study may be due to differences between
Qur concept, therefore, envisages an initi would have a drastic effect on blood flow, inasmuch as vessel
resistance is inversely proportional to the fourth power of the would have a drastic effect on blood flow, inasmuch as vessel
resistance is inversely proportional to the fourth power of the
radius (19). A more likely effect of hyperglycemia would be via would have a drastic effect on blood flow, inasmuch as vessel
resistance is inversely proportional to the fourth power of the
radius (19). A more likely effect of hyperglycemia would be via
increased blood viscosity. Blood would have a drastic effect on blood flow, inasmuch as vessel
resistance is inversely proportional to the fourth power of the
radius (19). A more likely effect of hyperglycemia would be via
increased blood viscosity. Blood would have a drastic effect on blood flow, inasmuch as vessel
resistance is inversely proportional to the fourth power of the
radius (19). A more likely effect of hyperglycemia would be via
increased blood viscosity. Blood resistance is inversely proportional to the fourth power of the radius (19). A more likely effect of hyperglycemia would be via increased blood viscosity. Blood flow is inversely proportional to viscosity (19), a property radius (19). A more likely effect of hyperglycemia would be via
increased blood viscosity. Blood flow is inversely proportional
to viscosity (19), a property which, particularly at low shear
rates, is largely due to erythr The favor Record in the favor of the setted to favor and the victorial increased blood viscosity. Blood flow is inversely proportional to viscosity (19), a property which, particularly at low shear rates, is largely due to the classed blood viscosity. Blood how is inversely proportional
to viscosity (19), a property which, particularly at low shear
rates, is largely due to erythrocyte aggregation (23). The tumor
microvasculature, with a larg a low situative (19), a property which, particularly at low sitear
rates, is largely due to erythrocyte aggregation (23). The tumor
microvasculature, with a large resistance to blood flow, would
tend to favor RBC aggregati For a state of blood flow, would
microvasculature, with a large resistance to blood flow, would
tend to favor RBC aggregation (23). In these circumstances,
the chemical forces acting between cells in the formation of
aggre Increase in the range resistance to blood now, would
tend to favor RBC aggregation (23). In these circumstances,
the chemical forces acting between cells in the formation of
aggregates become significant compared to the sh ithe chemical forces acting between cells in the formation of aggregates become significant compared to the shearing forces of blood flow, with a resultant increase in viscosity (19, 23). Increase in blood viscosity has th the chemical forces acting between cells in the formation of
aggregates become significant compared to the shearing
forces of blood flow, with a resultant increase in viscosity (19,
23). Increase in blood viscosity has the aggregates become significant compared to the shearing
forces of blood flow, with a resultant increase in viscosity (19,
23). Increase in blood viscosity has the potential, therefore, to
initiate a vicious circle of furthe blood flow, will a resultant increase in viscosity (19, 23). Increase in blood viscosity has the potential, therefore, to initiate a vicious circle of further slowing of blood flow, more aggregates, and higher viscosity an by glucose may be some alteration in the erythian, underlying this interation in the aggregates, and higher viscosity and thus upset the pre- to post-capillary resistance (23). The primary event precipitating blood flow in aggregates, and higher viscosity and thus upset the pre- to post-capillary resistance (23). The primary event precipitating blood flow inhibition when blood viscosity is rapidly increased by glucose may be some alteration post-capillary resistance (23). The primary event precipitating blood flow inhibition when blood viscosity is rapidly increased
by glucose may be some alteration in the erythrocyte mem-
brane (adhesiveness, fluidity), platelet aggregation, or a
change in the bulk properties of the bloo by glucose may be some alteration in the erythrocyte membrane (adhesiveness, fluidity), platelet aggregation, or a change in the bulk properties of the blood (osmolality, hematocrit) or in the tumor vessels (constriction, by glucose hay be some aneration in the erythrocyte membrane (adhesiveness, fluidity), platelet aggregation, or a change in the bulk properties of the blood (osmolality, hematocrit) or in the tumor vessels (constriction, b tocrit) or in the tumor vessels (constriction, blockage), after Change in the buik properties of the blood (osmolanty, hema-
tocrit) or in the tumor vessels (constriction, blockage), after
which the vicious circle described might be triggered. The
process is reversible, inasmuch as tum docht) of in the tumor vessels (constriction, blockage), after
which the vicious circle described might be triggered. The
process is reversible, inasmuch as tumor blood flow resumes
when normoglycemic conditions are restor which the victous circle described inight be triggered. The
process is reversible, inasmuch as tumor blood flow resumes
when normoglycemic conditions are restored (Charts 1 and 3).
Our concept, therefore, envisages an init When normoglycenic conditions are restored (charts 1 and 3).
Our concept, therefore, envisages an initial effect of hypergly-
cemia on tumor blood flow, and this may encompass afferent
and efferent vessels and/or microvasc but concept, therefore, envisages an initial effect of the
cemia on tumor blood flow, and this may encompass
and efferent vessels and/or microvasculature, with su
effect is a postulated decrease in pH within tumor ca
with mia on tumor blood now, and this may encompass amerent
d efferent vessels and/or microvasculature, with subsequent
fects on tumor pH. In Von Ardenne's hypothesis, the primary
fect is a postulated decrease in pH within tumo effects on tumor pH. In Von Ardenne's hypothesis, the primary
effects on tumor pH. In Von Ardenne's hypothesis, the primary
effect is a postulated decrease in pH within tumor capillaries,
with subsequent interruption of tu

large artery and vein that constituted the original vasculature
to a normal organ.
to a normal organ.
The effect of glucose on tumor pH would thus seem to be
cemia, a reduced thermal load would suffice to heat the tumor
co effect is a postulated decrease in pH within tumor capillaries,
with subsequent interruption of tumor blood flow.
The glucose-induced specific inhibition of tumor blood flow,
if a general finding, has broad potential for t with subsequent interruption of tumor blood flow.
The glucose-induced specific inhibition of tumor blood flow,
if a general finding, has broad potential for the investigation
and treatment of tumors; use of the sugar in th Whit subsequent interruption of tunior blood flow.
The glucose-induced specific inhibition of tumor blood flow,
if a general finding, has broad potential for the investigation
and treatment of tumors; use of the sugar in t The glucose-induced specific infinition of during blood how,
if a general finding, has broad potential for the investigation
and treatment of tumors; use of the sugar in this context is
rendered more attractive since it is It a general intuing, has broad potential for the investigation
and treatment of tumors; use of the sugar in this context is
rendered more attractive since it is a physiological substance.
The low pH_e accompanying hyperg and treatment of tuniors, use of the sugar in this context is
rendered more attractive since it is a physiological substance.
The low pH_e accompanying hyperglycemia may sensitize some
tumors to hyperthermia as proposed b rendered intre attractive since it is a physiological substance.
The low pH_e accompanying hyperglycemia may sensitize some
tumors to hyperthermia as proposed by Von Ardenne (26, 27),
although in the Yoshida sarcoma hyper The low pri_s accompanying hyperglycemia may sensitize some
tumors to hyperthermia as proposed by Von Ardenne (26, 27),
although in the Yoshida sarcoma hyperglycemia caused no
such thermal sensitization (6). In associatio difficult permitterial as proposed by von Ardenne (26, 27),
although in the Yoshida sarcoma hyperglycemia caused no
such thermal sensitization (6). In association with hypergly-
cemia, a reduced thermal load would suffice although in the Toshida sationia hypergycenna caused no
such thermal sensitization (6). In association with hypergly-
cemia, a reduced thermal load would suffice to heat the tumor
(Chart 6), and the selective nature of the Such thermal sensitization (o). In association with hypergly-
cemia, a reduced thermal load would suffice to heat the tumor
(Chart 6), and the selective nature of the blood flow inhibition
would permit normal tissues to b would permit normal tissues to be maintained at nondamaging
temperatures by the cooling influence of the bloodstream. This
would be of special importance in the treatment of malignant
tissues not sensitive to heat damage would permit normal itssues to be maintained at hondamaging
temperatures by the cooling influence of the bloodstream. This
would be of special importance in the treatment of malignant
tissues not sensitive to heat damage a would be of special importance in the treatment of malignant
tissues not sensitive to heat damage at 42° (5, 7) and that
currently require higher temperatures at which the differential
sensitivity between normal and tissues, promoting increased specificity in cancer therapy. the subsurface in the control of the differential currently require higher temperatures at which the differential sensitivity between normal and malignant tissues is lost (4).
Blood flow inhibition by hyperglycemia would, Examples of this applier temperatures at which the dimerential
sensitivity between normal and malignant tissues is lost (4).
Blood flow inhibition by hyperglycemia would, in general, en-
able tumors to be treated or studie sensitivity between normal and malignant tissues is lost (4).
Blood flow inhibition by hyperglycemia would, in general, en-
able tumors to be treated or studied in isolation from the normal
tissues, promoting increased spe Biood now immolitori by hyperglycemia would, in general, en-
able tumors to be treated or studied in isolation from the normal
tissues, promoting increased specificity in cancer therapy.
Examples of this application could able tumors to be treated or studied in isolation from the hormal tissues, promoting increased specificity in cancer therapy.
Examples of this application could be the deposition of high
concentrations of drugs in glucosesupply.

ACKNOWLEDGMENTS

We gratefully acknowledge the expert technical assistance of Robin McCoy **ACKNOWLEDGI**
We gratefully ackr
and John Geggie.

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Fig. 1. Arterial blood supply in normal and Yoshida sarcoma-bearing (arrow) hind legs of untreated rat (a) and after 4 hr hyperglycemia [blood glucose, 5
liter (b)]. The network of vessels supplying the tumor is visualized liter (b)]. The network of vessels supplying the tumor is visualized in a, while only the main arterial trunk is clearly identified in b. Blood vessels were given injections of contrast medium (Hypaque) prior to X-ray phot

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