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Radiation accidents with multi-organ failure in the United States

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Abstract. Only a small number of radiation accidents in the United States have been severe enough to result in multi-organ failure (MOF). Medical details of selected medical misadministration and criticality cases are reviewed, with an emphasis on pathophysiology. The four criticality cases are particularly relevant for analysis of MOF, since medical treatment was supportive and did not appreciably alter the clinical evolution of radiation injury.

Introduction

Only a small number of radiation accidents in the United States post World War II have been severe enough to result in multi-organ failure (MOF). The cases with radiation-induced MOF are summarised in Table 1. Since 1945, 4 deaths have resulted from criticality accidents, 21 from medical misadministration in the course of radiation therapy or diagnostic procedures, and 1 from a lost source [1]. In addition, three people died of blunt trauma at the SL/1 reactor accident (Idaho National Engineering and Environmental Laboratory, 1961). Details of this accident have been described elsewhere [2]. Medical details of selected medical misadministration and criticality cases are reviewed below, with an emphasis on pathophysiology. The four US criticality cases are particularly relevant for analysis of MOF, since medical treatment was supportive and did not appreciably alter the clinical evolution of radiation injury.

Medical misadministration cases

Therac-25 cases

A series of misadministrations occurred when software errors caused an automated radiation therapy machine to deliver massive overdoses in six cases in the United States and Canada in the period 1985–87. Estimated doses were reported in the range 80–250 Gy. One patient experienced multi-organ injury and died 5 months after exposure. One patient had severe injury to the brain and brain stem, quickly became disoriented, comatose and died 3 weeks after exposure. Three other patients received severe local injury, and one died from radiation-related complications. All patients were aware of the misadministration and most clinical symptoms appeared over a period of weeks [3, 4].

Indiana, PA, iridium-192 incident

An 82-year-old woman was diagnosed with anal cancer and treated with high dose rate brachytherapy at Indiana Regional Cancer Center, Indiana, Pennsylvania, on 16 November 1992. High-intensity ^{192}Ir brachytherapy was begun, but one source was not retracted afterwards and remained in place for 4 days until it dislodged. Hospital staff ignored warning signals, believing that safety equipment was giving a false alarm, and the source was not discovered until it was transferred to a medical incinerator. The patient died 5 days after the exposure [1, 5, 6].

Industrial accelerator malfunction case

Van de Graaff accident involving amputation of forearms and legs, with life-saving bone marrow transplant (1969)

An experienced Van de Graaff accelerator operator at the Gulf Oil Corporation Research Laboratory in Pittsburgh was exposed to intense bremmstrahlung radiation while unscrewing target cooling tubes, unaware that multiple safety interlocks had failed. From film badge readings, the operator was estimated to have received a mean marrow dose of 6 Gy, with approximately 60 Gy to the forearms and 20–30 Gy to the lower legs. The operator underwent a successful bone marrow transplant 9 days post exposure from his identical twin, reversing a severe granulocytopenia and lymphopenia. Nevertheless, the

Table 1. The US experience with multi-organ failure

Accident	Type	Dates	Fatalities
Therac-25 accidents	Radiation therapy misadministration (estimated dose 80–250 Gy)	1985–87	3
Indiana, PA, ^{192}Ir accident	High dose brachytherapy accident	1992	1
Van de Graaff accident	Industrial accelerator malfunction	1969	0
LANL-1	Solid criticality accident	1945	1
LANL-2	Solid criticality accident	1946	1
LANL-3	Liquid criticality accident	1958	1
Wood River Junction	Liquid criticality accident	1964	1

LANL, Los Alamos National Laboratory.

highly exposed forearms and lower legs required sequential amputations. Although confined to a wheelchair thereafter, the operator led an active life until passing away from a heart attack many years later at the same age as his twin brother [7–11].

Criticality cases

Los Alamos plutonium sphere cases

Two criticality events occurred with the same 6.2 kg delta-phase plutonium sphere at Los Alamos National Laboratory (LANL). The first incident occurred on 21 August 1945, when a worker was preparing a critical assembly by stacking tungsten carbide bricks around the plutonium core as a reflector. He moved the final block over the assembly but, noting that this block would make the assembly supercritical, he withdrew it. The brick fell onto the centre of the assembly, resulting in a super-prompt critical state of approximately $6 \times E{+}15$ fissions [12]. The worker sustained an average whole body dose of approximately 5.1 Gy and a dose to the right hand of approximately 100–400 Gy. The patient died of sepsis 28 days post accident.

The second criticality accident occurred in 1946 during an approach to criticality demonstration at which several observers were present. The operator used a screwdriver as a lever to lower a hemispherical beryllium shell reflector into place. While holding the top shell with his left thumb in an opening at the spherical pole, the screwdriver slipped and caused a critical configuration. The fission yield in this accident was estimated at $3 \times E{+}15$ fissions. The operator received an estimated acute whole body dose of approximately 21 Gy, with a dose to the left hand of 150 Gy and somewhat less to the right hand. Seven observers were exposed in the dose range 0.27–3.6 Gy [12]. The operator died 9 days later.

Los Alamos liquid criticality event

On 30 December 1958, during purification and concentration of plutonium, unexpected plutonium-rich solids were washed from two vessels into a single large vessel that contained layered, dilute aqueous and organic solutions. The tank contained approximately 295 l of a caustic stabilised organic emulsion [12]. The added nitric acid wash is believed to have separated the liquid phases. Accident analysis shows that the aqueous layer was initially slightly below delayed critical (approximately 203 mm thick, critical thickness 210 mm). When the stirrer was started, the central portion of the liquid system was thickened, changing system reactivity to super-prompt critical. The excursion yield was approximately $1.5 \times E{+}17$ fissions. Bubble generation was the negative feedback mechanism for terminating the first neutron spike. The system was driven permanently subcritical by mixing of the two layers. This accident resulted in the death of the operator 36 h post accident. The dose to the upper extremity was estimated to be 120 Gy $\pm$ 50%. Two other persons received acute doses of 1.34 Gy and 0.53 Gy, respectively [12].

Wood River Junction case

This liquid process accident occurred on 24 July 1964, at the United Nuclear Fuels Recovery Plant, Wood River Junction, RI. A chemical processing plant [12] was designed to recover highly enriched uranium from scrap material left over from the production of fuel rods. Uranyl nitrate solution U(93) was poured into a carbonate reagent vessel. The critical excursion occurred when nearly all of the uranium had been transferred, resulting in approximately $1.1 \times E{+}17$ fissions. It is probable that the system oscillated, resulting in a series of excursions with total energy release equivalent to $1.3 \times E{+}17$ fissions. The acute dose to the operator was estimated to be 100 Gy. Two supervisory personnel received approximately 1 Gy and 0.6 Gy, respectively. The operator died 49 h post accident.

Clinical course of the criticality cases

Case 1 – Los Alamos plutonium sphere (Haematopoietic Syndrome; Cutaneous Radiation Injury Syndrome; whole body dose approximately 5.1 Gy, dose to right hand 100–400 Gy)

The patient was a 26-year-old male whose past medical history was significant only for Wolff-Parkinson-White Syndrome diagnosed 3 years prior to the incident [13]. On admission to hospital, his vital signs were within normal limits and his only initial complaint was numbness and tingling of both hands. The initial physical examination was also within normal limits.

Within 30 min post accident, the patient's right hand had become diffusely swollen. Emesis began approximately 1½ h post event, and nausea continued intermittently for the next 24 h. The patient experienced subjective improvement but had a mild temperature, gastric distress and weakness during days 3–6. By day 5 the patient experienced a distinct rise in temperature with tachycardia and began to appear increasingly toxic. On day 10 he developed severe stomatitis, a paralytic ileus and diarrhoea. Clinical signs of pericarditis were noted on day 17, and the patient's mental status became irrational. The clinical course is notable for progressive pancytopenia. Figure 1 demonstrates an exponential decrease of lymphocytes during the first 4 days post accident.

Within 36 h post accident, blisters were noted on the volar aspect of the right third finger, and within 24 h thereafter, extensive blistering was noted both on the palmar and volar surfaces of the hand. A decision was made on day 3 to surgically drain the blisters, but by the third week the right hand had progressed to a dry gangrene. Desquamation of the epidermis involved almost all of the skin of the dorsum of the forearm and hand. In addition, epilation was almost complete at the time of death.

On day 28, the patient's temperature had risen to 41.1℃. He had lost a great deal of weight, developed thoracic–abdominal erythema and had signs of sepsis. On day 28 the patient because comatose and died. During the patient's clinical admission, treatment consisted of fluid support, penicillin antibiotic therapy, thiamine and two blood transfusions.

On autopsy, severe skin necrosis was observed as well as overt dry gangrene. The cardiorespiratory system was significant for pericarditis, cardiac hypertrophy,

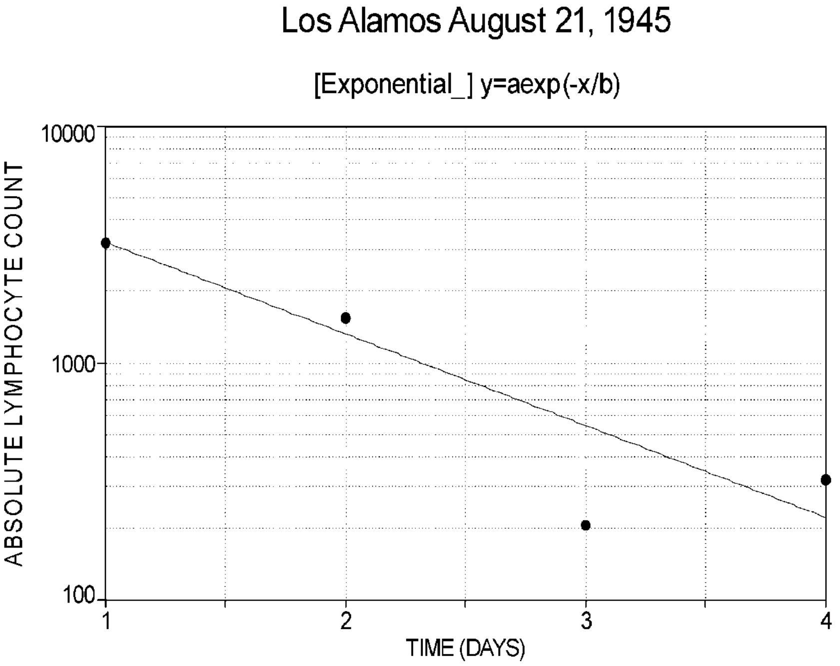

Figure 1. Lymphocyte kinetics in the 1945 Los Alamos National Laboratory LANL-1 criticality accident.

pulmonary oedema and alveolar haemorrhage. The spleen was noted to have no germinal centres, and the mucosa of the large bowel was ulcerated as was the buccal mucosa. The bone marrow was noted to be hypoplastic, and lymph nodes also showed significant lymphocyte depletion. The testes demonstrated significant atrophy with aspermia. A solitary ulcer was noted in the large colon in addition to a right renal infarct.

Case 2 – Los Alamos plutonium sphere (Gastrointestinal Syndrome; Cutaneous Radiation Injury Syndrome; acute dose approximately 21 Gy, dose to the left hand 150 Gy)

The patient was a 32 year-old male, admitted to hospital within 1 h post accident. His medical history was generally unremarkable. His occupational history was significant only for several prior, generally chronic occupational exposures, none exceeding 0.005 Gy in a week. The patient complained of nausea in the hour prior to admission and vomited once in the first hour post accident.

The general condition of the patient was quite good in the first 5 days post accident. On the fifth day there was a precipitous drop in his leukocyte count and his condition began to decline rapidly. The patient rapidly lost weight, became mentally confused on day 7 post event, became comatose, and died quietly on the ninth day.

Medical therapy during the 9-day course was largely symptomatic. Penicillin was given intramuscularly 50 000 U every 3 h beginning on day 5 because of granulocytopenia. Blood transfusions were also given daily after the fifth day. On day 6, fever and tachycardia developed, and on the seventh day the patient developed a severe paralytic ileus. The patient died in cardiovascular shock on the ninth day. At the time of death both hands showed extensive radiation damage.

On autopsy, examination of the skin was remarkable for early vesicle formation in the abdominal skin and marked epidermal damage. The cardiorespiratory system was remarkable for cardiac haemorrhage and myocardial oedema, and the terminal bronchi showed features of aspiration pneumonia. The spleen exhibited no germinal centres, and the mucosa of most of the gastrointestinal tract showed sloughing, most pronounced in the jejunum and ileum. Widespread degenerative changes were noted in the adrenal cortex, and hyaline degeneration in the renal tubular epithelium. Examination of the red bone marrow showed it to be of liquid consistency.

Case 3 – Los Alamos Liquid Criticality Event (Central Nervous System (CNS) Syndrome; dose to the upper extremity 120 Gy $\pm$ 50%)

The patient was a 50-year-old male with no significant past medical history [14]. The clinical course has been divided into four separate phases. Phase 1 (20–30 min post event): immediate physical collapse and mental incapacitation, progressing eventually into semi-consciousness; phase 2 (90 min): signs and symptoms of cardiovascular shock accompanied by severe abdominal pain; phase 3 (28 h): subjective minimal clinical improvement; phase 4 (2 h): rapidly appearing irritability and mania, progressing to coma and death. The clinical course was remarkable for continuing, profound hypotension, tachycardia, and intense dermal and conjunctival hyperaemia. The patient died 35 h post exposure.

On autopsy, examination of the bone marrow was most significant for absence of mitotic activity. The lungs showed pycnotic, degenerating cells in the pleura, degenerating lymphocytes and neutrophils in the sub-pleural connective tissue, and many areas of focal atelectasis interspersed with foci of emphysema. All lymph nodes were markedly atrophic and lymphoid follicles in the spleen were greatly depleted.

Examination of the heart showed acute myocarditis, myocardial oedema, cardiac hypertrophy and a fibrinous pericarditis. Examination of the brain demonstrated cerebral oedema, diffuse vasculitis and cerebral haemorrhage. The gastrointestinal system showed necrosis of the anterior gastric wall parietal cells, acute upper jejunal distention, mitotic suppression throughout the entire gastrointestinal tract and acute jejunal and ileal enteritis.

Case 4 – Wood River Junction (CNS syndrome; approximately 100 Gy)

The patient was a 38-year-old male with a negative medical history. Following the initial criticality excursion [15], the patient appeared stunned, ran from the building and immediately vomited. He also experienced immediate diarrhoea and complained of severe abdominal cramping, headache, thirst and profuse perspiration. His initial vital signs showed borderline blood pressure elevation and tachycardia. Approximately 4 h post accident, the patient experienced transient difficulty in speaking, hypotension and tachycardia. A portable chest radiograph 16 h post admission showed hilar congestion (Figure 2). Physical examination also showed the left hand and forearm to be oedematous as well as left-sided conjunctivitis and periorbital oedema (Figure 3). On day 2 the patient became very disoriented, hypotensive and anuric. The patient died 49 h post accident in cardiovascular shock.

At autopsy, interstitial oedema of the left hand, arm and abdominal wall was noted. Examination of the heart, lungs and abdominal cavity revealed acute pulmonary oedema, bilateral hydrothorax, hydropericardium, abdominal ascites, acute pericarditis, interstitial myocarditis and inflammation of the ascending aorta. Examination of the gastrointestinal tract showed severe subserosal oedema of the stomach and the transverse and descending colon. The bone marrow was noted to be aplastic, and lymph nodes, spleen and thymus were depleted of lymphocytes. The brain showed minimal change, with rare foci of microglial change. The testes showed interstitial oedema and overt necrosis of the spermatogonia.

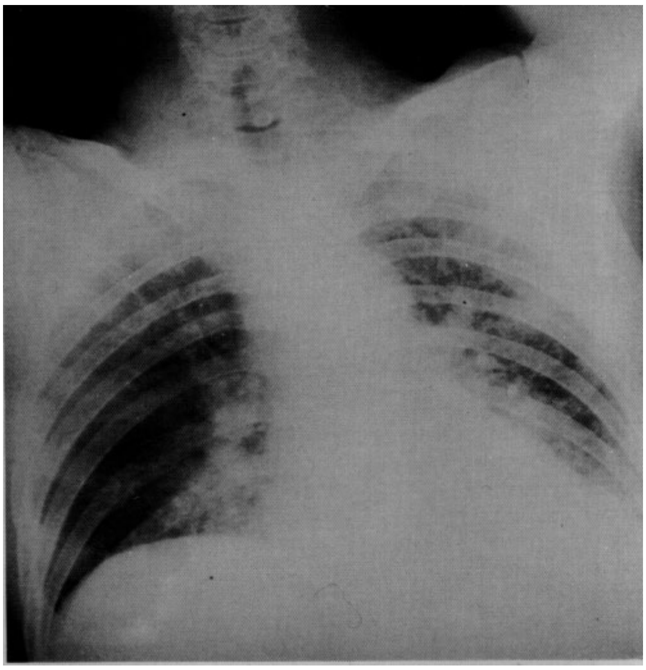

Figure 2. Portable chest radiograph 16 h post event in the Wood River Junction accident. Figure reprinted with permission of the New England Journal of Medicine.

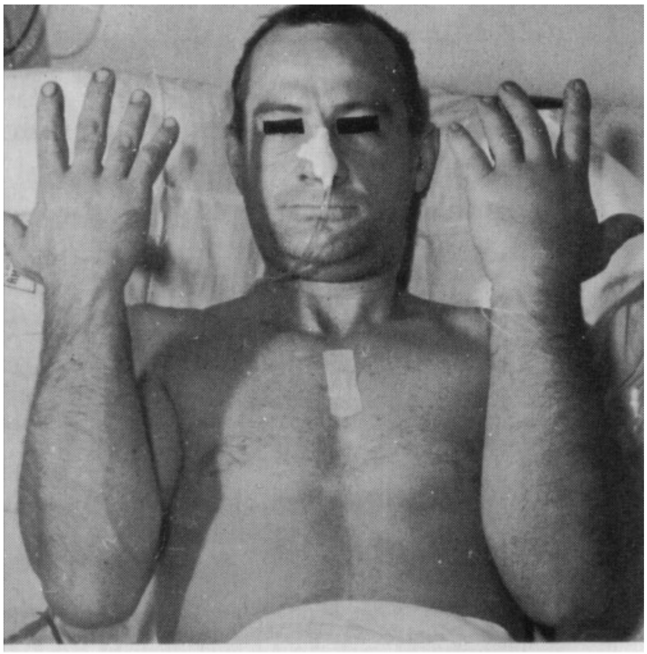

Figure 3. Wood River Junction patient 24 h post accident. Note oedema in the left arm. Figure reprinted with permission of the New England Journal of Medicine.

Early prediction of MOF in severe radiation accidents

It is possible in many cases to predict when MOF will be clinically important. Figure 4 presents data ($N=114$ cases) for the time to emesis post accident [16, 17] as a function of dose. For time to emesis of less than 1 h post accident, the median dose in this cohort is found to be 6.5 Gy (interquartile range 5–11 Gy). Therefore, patients who experience radiation-induced emesis within 1 h after an incident will likely experience MOF. The sensitivity and specificity of emesis as a medical test has been found to approach unity for absorbed dose $D>3$ Gy.

Following either a γ accident or criticality accident with dose greater than a threshold of approximately 1 Gy γ equivalent, lymphocytes decrease from the peripheral blood according to an equation of the form:

$$L(t) = L(0)e^{-Kt} \qquad (1)$$

where $L(0)$ is the lymphocyte count pre accident, $L(t)$ is the lymphocyte count at time t post accident, and the rate constant K has been shown to be a linear function of dose D [18]. Using serial complete blood count (CBC), if $K>1$ (lymphocytes decrease by more than a factor of 1/e in 24 h), then the predicted dose is greater than 8–10 Gy and MOF is likely.

One of the most interesting aspects of the US criticality cases is the high incidence of cardiac pathology (pericarditis, pericardial effusions, myocarditis, etc.) noted at autopsy. Whilst it is often noted that the heart is relatively radioresistant, many of these historic accidents occurred with the source near the thoracic level, likely giving both a non-uniform dose distribution and a relatively high dose to the heart and mediastinum. Radiation-induced heart disease is generally described as a delayed

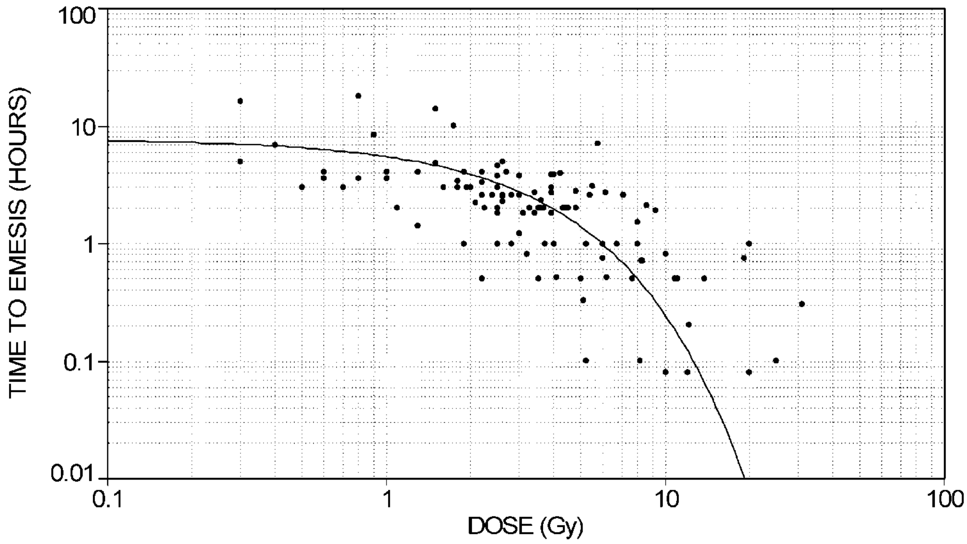

Figure 4. Time to emesis as a function of dose with exponential fit $y=ae^{-x/b}$. From the single exponential fit, the parameters ($\pm$SE) are found to be: a=12.9$\pm$1.2 Gy and b=1.7$\pm$0.2 h; r^2=0.41.

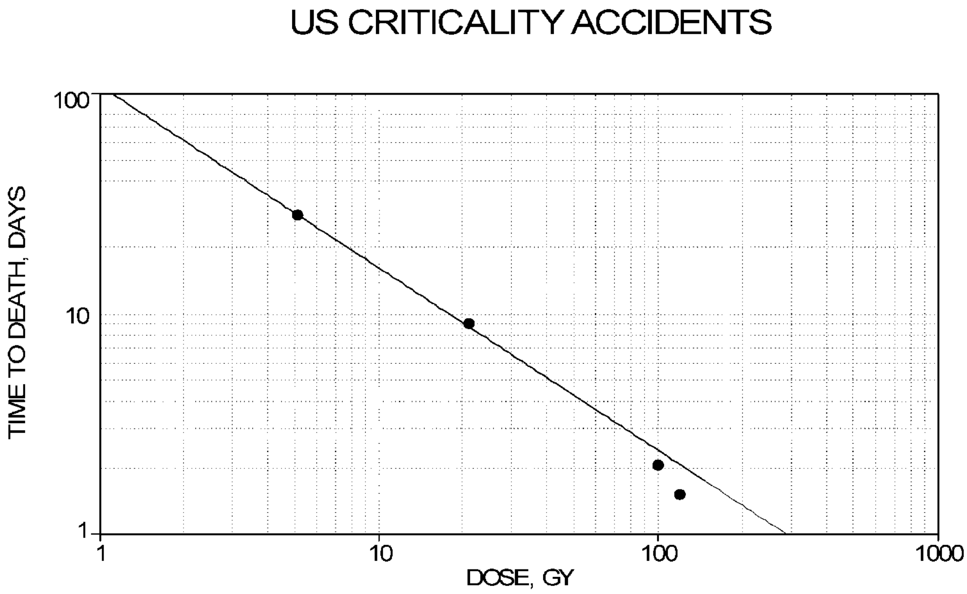

Figure 5. Time to death as a function of dose for the four US criticality accidents. Power function fit: $\ln(y)=a+b\ \ln(x)$; $b=-0.84\pm0.04$; r^2=0.99.

manifestation of therapy, but acute effects both in humans and in animal models have been well described in high dose cases [19–22].

The US criticality cases are historically important since they were fatal radiation accidents and medical treatment did not appreciably alter the clinical course of disease. These cases can therefore serve as useful models of the natural course of acute radiation-induced tissue damage. Figure 5 presents the time to death in these four cases as a function of dose. A power function fit is presented to guide the eye.

Acknowledgment

Figures 2 and 3 are reprinted with permission of the New England Journal of Medicine.

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