A Brief History of Bone Marrow Transplantation

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UCLA Medical Center
Celgene Corp
Disclosures

Celgene Corp
StemRad
Fusion Pharma
Young people are not interested in history
I'm a historian. Ask me in 10 years and I'll tell you why what happened was inevitable.

Albert Tedlow
Those who cannot remember the past are condemned to repeat it

George Santayana
Those who cannot remember the past are likely to repeat the same experiment, claim success and priority and publish it (if no one is looking)

The doctor formerly known as Bob
Mankind’s greatest discoveries
Hungarian paprika
Bone marrow transplantation?
The thing that has been is the thing that shall be; and the thing that is done is that which shall be done: There is nothing new under the sun

Ecclesiastes
Táin Bó Cúailgne
(The Cattle Raid of Cooley)
ca 500 BCE
Finglin treating Celthem
New Guinea females and bone marrow
Apothecary
Virtutem forma decora

Leonardo da Vinci 1474
Charles-Édouard Brown-Séquard
How far have we come?
LOOK and FEEL BETTER... Now!

Physicians discuss the personal benefits of in-home cell therapy and why everyone needs it.

It was towards the end of 2013 when Dr. Stephen Pfeifer of Fishers took a degree that she no longer needed regular Botox treatments.

WHAT IS COLLEGEN?

Collegen is a transformative treatment that stimulates the human body's natural healing power. Collegen Swiss Cell Therapy triggers the repair and rejuvenation of individual cells. One of its key ingredients is a proprietary Cellular Marine Complex. The complex is extracted from the DNA of deep-sea, pollution-free marine life associated with powerful anti-aging properties. Other ingredients include Peptides E Collagen, which reinforces skin elasticity and Hydro...
World War II

Leo Szilard

Albert Einstein
Einstein to Roosevelt

Albert Einstein  
Old Grove Rd.  
Hassen Point  
Peconic, Long Island  
August 2nd, 1939

Y.D. Roosevelt,  
President of the United States,  
White House  
Washington, D.C.

Sir:

Some recent work by N. Fermi and L. Szilard, which has been communicated to me in manuscript, leads me to expect that the element uranium may be turned into a new and important source of energy in the immediate future. Certain aspects of the situation which has arisen seem to call for watchfulness and, if necessary, quick action on the part of the Administration. I believe therefore that it is my duty to bring to your attention the following facts and recommendations:

In the course of the last four months it has been made probable - through the work of Joliot in France as well as Fermi and Szilard in America - that it may become possible to set up a nuclear chain reaction in a large mass of uranium, by which vast amounts of power and large quantities of new radioactive elements would be generated. Now it appears almost certain that this could be achieved in the immediate future.

This new phenomenon would also lead to the construction of bombs, and it is conceivable - though much less certain - that extremely powerful bombs of a new type may thus be constructed. A single bomb of this type, carried by boat and exploded in a port, might very well destroy the whole port together with some of the surrounding territory. However, such bombs might very well prove to be too heavy for transportation by air.

The United States has only very poor ores of uranium in moderate quantities. There is some good ore in Canada and the former Czecho-Slovakia, while the most important source of uranium is Belgian Congo.

In view of this situation you may think it desirable to have some permanent contact maintained between the Administration and the group of physicists working on chain reactions in America. One possible way of achieving this might be for you to entrust with this task a person who has your confidence and who could perhaps serve in an unofficial capacity. His task might comprise the following:

a) to approach Government Departments, keep them informed of the further development, and put forward recommendations for Government action, giving particular attention to the problem of securing a supply of uranium ore for the United States;

b) to speed up the experimental work, which is at present being carried on within the limits of the budgets of University laboratories, by providing funds, if such funds be required, through his contacts with private persons who are willing to make contributions for this cause, and perhaps also by obtaining the co-operation of industrial laboratories which have the necessary equipment.

I understand that Germany has actually stopped the sale of uranium from the Czecho-Slovakian mines which she has taken over. That she should have taken such early action might perhaps be understood on the ground that the son of the German Under-Secretary of State, von Neusicker, is attached to the Kaiser-Wilhelm-Institut in Berlin where some of the American work on uranium is now being repeated.

Yours very truly,

[Signature]

(Albert Einstein)
Manhattan Project
Tickling the dragons tail
Tickling the dragons tail
PAUL NEWMAN
FAT MAN & LITTLE BOY

The story of the extraordinary people who changed our world.

Dwight Schultz
Bonnie Bedelia
Laura Dehn
John Cusack
Natasha Richardson
Trinity 1945
Fat Man and Little Boy
Hiroshima
Nagasaki
Se non ammazza ingrassa

*What doesn’t kill you will make you fat*
Leukemia in Atomic Bomb Survivors

I. General Observations

By Robert D. Lange, M.D., William C. Moloney, M.D., and Tokuso Yamawaki, M.D.

Leukemogenesis induced by repeated exposures to x-ray and other forms of radiation energy has long been recognized in man and in experimental animals. The explosion of the atomic bombs in Japan exposed two large human populations to single brief but massive doses of ionizing irradiation and subsequently a marked increase in leukemia among survivors was reported. The present study consists of a review of all cases of leukemia referred to the Atomic Bomb Casualty Commission from 1948 to April 1952 together with thirty-nine new cases, bringing the total to seventy-five established cases of leukemia occurring in atomic bomb survivors in Hiroshima and Nagasaki up to January 1, 1953.

Methods and Materials

In the five year period from 1948 through 1952, one hundred and fifty cases of leukemia were investigated by the Atomic Bomb Casualty Commission. Of these, twenty-six cases were excluded because of failure to meet the criteria of adequate clinical and radiation data with blood smears, bone marrow smears, or autopsy material available for study by the authors.

The sources of the leukemia cases were as follows:

1. Patients encountered during routine medical and hematologic surveys of atomic bomb survivors. Ten such cases have been discovered: four during a hematologic survey of nine hundred epilated Hiroshima survivors originally studied in 1947-1948 by Snell, Neel, and Ishibashi, and by Yamasawa in 1949 and six during the medical survey of two thousand five hundred and eighty adult survivors in Hiroshima and Nagasaki.

2. Patients referred to the Atomic Bomb Casualty Commission by local physicians or visited by Commission doctors in Hiroshima and Nagasaki hospitals.

3. Cases discovered through death certificates. Only those cases in which there was adequate clinical and radiation history with blood and bone marrow smears available for study by the authors were included.

In all, one hundred and twenty-four cases of leukemia were studied, seventy-five among exposed and forty-nine in nonexposed individuals. The term “exposed”, as used in this report, is applied to anyone present in the cities of Hiroshima and Nagasaki during the atomic bombings. Exposure is further qualified by the factors of distance from the hypo-
Leukemia in Hiroshima Atomic Bomb Survivors

By Robert Heyssel, A. Bertrand Brill, Lowell A. Woodbury, Edwin T. Nishimura, Tarunendu Ghose, Takashi Hoshino and Mitsuru Yamasaki

A causal relation between radiation and leukemia has been well demonstrated. The reported cases of leukemia in people exposed to radium, thorotrast, occupational x-ray, therapeutic x-ray to the thyroid region in childhood and possibly in utero diagnostic x-ray, have been few in number. Estimates of the increased risk associated with exposure of man to radiation depend heavily upon studies of the survivors of the atomic bombing of Hiroshima and Nagasaki and of patients with ankylosing spondylitis treated with high doses of radiation directed principally to the spinal marrow. Since the earlier reports from Hiroshima and Nagasaki established the increased incidence of leukemia in survivors, the number of cases has increased, and knowledge of population groups upon which to base analyses has improved. For the first time it is now possible to present analyses of incidence based on fixed samples of survivors. The present report summarizes the findings observed in the Hiroshima survivors from 1945 to 1958. A similar report is being prepared on the survivors of the Nagasaki atomic explosion.

Materials and Methods

Immediately following the bombing, and intermittently for two years thereafter, teams of scientists entered Hiroshima to render assistance and to obtain information on the effects of radiation on humans. They, as well as members of the local medical community, were cognizant of the potential significance of hematologic findings resulting from irradiation. With improvement of local conditions and medical facilities, a systematic investigation became possible, and a routine hematologic survey was instituted. Since 1948, scientists of the Atomic Bomb Casualty Commission in cooperation with physicians in the community have made intensive efforts to detect hematologic and other abnormalities in both the exposed and the nonexposed segments of the population. To collect information on patients with hematologic abnormalities before 1950, lists of patients and any available slides and related materials were exchanged by the ABCC and local physicians and continuously reviewed. Since 1950 these efforts have been intensified, so that few if any leukemia cases among survivors remaining in Hiroshima or its immediate environs can have been missed. Even for the first four years after the bombing, the likelihood of missing cases of leukemia is probably small.
Atomic haematologists
Atomic Haematologists

1950 Jacobsen  Shielding spleen of radiated mice prevented death.
Atomic Haematologists

1950 Jacobsen  Shielding spleen of radiated mice prevented death.  Why?
Even an incorrect hypothesis can pay off for smart people.
Evidence for a Humoral Factor (or Factors) Concerned in Recovery from Radiation Injury: A Review*

Leon O. Jacobson

(Division of Biological and Medical Research, Argonne National Laboratory, Department of Medicine and Institute of Radiobiology and Biophysics of the University of Chicago, Chicago, Ill.)

The death of animals exposed to single total-body doses of ionizing radiations in the lethal range is assumed to be due to the failure of functional reconstitution of one or more of the tissues in the body (e.g., the hematopoietic system), and until recently the possibility of a specific approach to the management of the severe injury produced by such an exposure seemed far-fetched.

Prophylactic measures, such as pretreatment with estrogen (33) or cysteine (43), have been used to reduce radiation morbidity and mortality in experimental animals, but, while of great fundamental importance, they are not effective in enhancing recovery when given after the radiation exposure has been sustained. Experiments which may be termed "therapeutic approaches" to the problem have yielded results that have changed this rather discouraging picture to one of restrained optimism; these studies—some of which have been reported previously and others which are herein reported in the open literature for the first time—are briefly reviewed in the paragraphs to follow.

The Effects of Lead-Shielding the Exteriorized Splenic Compared to Shielding Other Tissues-Bone

Lead-shielding of the surgically exteriorized spleen (average weight, 0.1 gm.) of adult mice during exposure to 1,025 r total-body x-radiation markedly enhances survival (77.0 per cent), compared to the same exposure without spleen-shielding (11.1 per cent)

* This investigation was supported (in part) by a research grant from the National Cancer Institute, U.S. Public Health Service, by a grant from the Armour Laboratories, and by an American Cancer Society Institutional Grant.

† These percentage figures vary throughout manuscript, because survival varies from one experiment to another.

Received for publication February 5, 1952.
Erythropoietin

Erslev/Adamson/Goldwasser et al.
1950 Lake Windermere
After talking with many people I am convinced we should try intravenous injection of a normal bone marrow suspension after radiation with the idea of repopulation of the destroyed bone marrow. It should not be too difficult as only a little may be necessary to produce the effect.
The rest is history.....
Atomic Haematologists

1950 Jacobsen  Shielding tibia/spleen of radiated mice prevented death. IP injection of spleen/bone marrow rescued mice.

1952 Lorenz/Congdon/Uphoff  IV injection of spleen/bone marrow rescued mice
Modification of Acute Irradiation Injury in Mice and Guinea-Pigs by Bone Marrow Injections

EGON LORENZ, Ph.D., CHARLES CONGDON, M.D., and DELTA UPHOFF, M.S.

The problem of finding an agent or a method that will protect against the effects of whole-body irradiation has always been an attractive one, but in recent years many more investigators have been bending their efforts in this direction. The agents or methods brought to light by these investigations may be divided into three groups. To the first group belong those which have to be given prior to the irradiation, one of the best known representatives of this group being cysteine (1). The second group consists of agents or procedures that are used during irradiation; the most effective method of this group is the protection of the exteriorized spleen of the mouse by lead, discovered by Jacobson et al. (2). The third group of protective measures are effective when given post-irradiation. Among these are the intraperitoneal transplantation of spleens after irradiation which, as Jacobson (3) has shown, significantly increases survival of irradiated mice, and the injection of bone marrow following doses which are lethal to untreated mice and guinea-pigs, which is the subject of this paper.

The discovery of the beneficial effects of splen shielding against lethal doses of radiation raises the question whether a cellular or a humoral factor or both are involved in protection, since the shielded spleens of mice show abundant hematoipoietic following irradiation. Even the recent data of Jacobson et al. (3), dealing with the protective action of intraperitoneally transplanted spleens after lethal doses of irradiation, have not shown with certainty which factor or factors are involved, although the evidence appears to favor a humoral substance. The fact, however, that the shielded spleen of the mouse shows hematopoiesis makes it tempting to assume that seeding of hematopoietic elements to various organs and tissues from the spleen may play a role in the recovery process.

If this be the case, then seeding with the cellular constituents of bone marrow, as by intravenous injection, should also be effective in hastening recovery. Previous experiments, however, do not seem to bear this reasoning. Rekers and his associates (4, 5) treated dogs with intravenous injections of dog bone marrow after irradiation to 350 r. Only an equivocal improvement in survival rate was obtained. Talbot and Gerstner (6), using stock Sprague-Dawley rats (genetically not homogeneous) obtained an insignificant prolongation of mean survival time in rats injected intravenously with rat bone marrow after irradiation to 800 r. The failure of these experiments to yield any significant increase in survival, in comparison to irradiated control animals, may have been due to several factors, the most important of which may have been injection of non-viable cells and the use of genetically heterologous bone marrow.

The crucial experiment should consist, therefore, in the intravenous injection of homologous bone marrow after a lethal acute dose of radiation, the cell constituents of the bone marrow being kept viable as far as possible. In a preliminary experiment (7), data were presented showing that intravenous or intraperitoneal injections of homologous bone marrow into genetically homogeneous hybrid mice (LAF1) or inbred guinea-pigs (family 2) protected these animals to a considerable degree against a lethal acute dose of radiation. The observations to be recorded here extend the previous data to include several other strains of mice and to protective effects of heterologous bone marrow.
Some Experiences with Irradiation Injury

JOSEPH W. HUBBARD, M.D., and E. DONNELL THOMAS, M.D.

The following is a brief review of recent experiences with the treatment of the marrow injury that follows whole-body irradiation in man. The studies described are essentially those made with colleagues at the Mary Imogene Bassett Hospital, Cooperstown, New York: Dr. Otto Sahler, Radiologist; Dr. Joe Cannon, Pediatrician; Dr. Charles Ashley, Pathologist; Drs. H. L. Locht, Jr., John A. Mannick, Emery Herman, William Greenough, Edward Hager, and Major T. W. Rich, U. S. Air Force, Research Associates. For a starting point this group has used the classical work on marrow replacement and marrow transplantation as extensively explored in irradiated rodents (1). As pilot for its own studies it has used the dog, an animal in which the treatment of post-irradiation marrow injury appears to offer difficulties comparable to those encountered in man (2, 3). The patients observed have been those with leukemia who received whole-body irradiation as part of their therapy. Doses have been 150 to 1,500 r measured in air at midbody position. Exposures have been at 2 to 2.5 meters target-to-source distance, with a pair of symmetrically placed cobalt-60 units, one on either side of the patient at rest in bed. Dose rates have been 30 to 40 r per hour. Administration has been essentially continuous; thus about forty-five hours have been required for an exposure totaling 1,500 r.

Figure 1 shows a dog three months after an exposure of 750 r. The animal is quite well. He received no infusion of marrow but was given fresh blood and antibiotics daily until his own marrow regenerated, about five weeks after exposure. This type of recovery from radiation injury presupposes a long and hazardous period of marrow aplasia and meticulous supportive therapy, for a month at least. The dog is from a series recently studied, with us, by Major T. W. Rich of the U. S. Air Force.

A child receiving an exposure of 1,000 r was isolated and given antibiotics and fresh blood. In the two weeks following irradiation, seven infusions totaling several billion fetal hematopoietic cells were administered. Since no evidence of marrow function appeared in three weeks, several billion fresh adult marrow cells were taken from one of the patient’s relatives and infused on the twenty-third day after irradiation. Evidence of returning marrow function appeared on the thirty-second day, that is, white cells, particularly polymorphonuclear leukocytes, appeared in the circulation at that time. However, immunologic analysis of the erythrocytes...
Chernobyl
Atomic haematologists

1950  Jacobsen  Shielding tibia/spleen of radiated mice prevented death.  IP injection of spleen/bone marrow rescued mice.
1952  Lorenz  IV injection of spleen/bone marrow rescued mice and guinea pigs.
1955  Main & Prehn  Chimeric mice accept donor skin grafts
Atomic haematologists

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Atomic Haematologists

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1954 Uphoff  Secondary disease
Primary and Secondary Diseases (GvHD)
Atomic Haematologists

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1955  Barnes & Loutit  P→F₁ vs. F₁→P
GvHD
Atomic haematologists

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1950s  Snell  Inbred mice
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1959  Thomas twin transplant  leukaemia
Beagles
Autografts of Bone Marrow in Dogs After Lethal Total-Body Radiation

By John A. Mannick, Harry L. Lochte, Jr., Charles A. Ashley, E. Donnell Thomas and Joseph W. Ferrebee

Alpen and Baum have shown that infusions of autologous marrow induce recovery in dogs after exposure of the entire body to 400 or 600 r of 250 kv x-rays. The purpose of this communication is to report that recovery in dogs can be induced promptly by autologous marrow infusion after exposure to x-ray or gamma radiation in dosages up to 1500 r. Both bone marrow and lymphoid tissue are restored. The restoration of the latter tissue is of an order not yet obtained with homologous marrow in this species after similar amounts of irradiation.

Material and Methods

Eight purebred beagle dogs were used as experimental animals, 2 male and 6 female. The dogs were between 5 and 18 months of age and weighed from 6 to 8 Kg. They were caged separately or in pairs in a general animal room and were exposed, because of a transient population of sick dogs, to the same seasonal canine disorders as the group of dogsgrafted with homologous marrow previously reported from this laboratory. Prior to radiation all dogs were dewormed and actively immunized against distemper and hepatitis by attenuated vaccine.

Dogs were kept fasting on the day of irradiation and were fed only ground beef on the evening before in order to insure a minimum of osseous and other calcium-containing material in the gut at the time of irradiation. All animals were given daily intramuscular injections of 400,000 U. of procaine penicillin and 0.5 Gm. streptomycin beginning on the day of irradiation and continuing for at least 7 days thereafter. Other antibiotics, parenteral fluid therapy, fresh blood transfusions and dog hyperimmune serum were used as required.

Baseline determinations of hemoglobin concentration, hematocrit, white blood cell count, differential count, reticulocyte count and platelet count were performed on all animals prior to irradiation and were repeated on the sixth or seventh day after irradiation and thereafter at biweekly intervals until full hematologic recovery had occurred.

Serum samples for filter paper electrophoresis were drawn on four of the eight dogs prior to irradiation and at two weeks following irradiation. Samples were drawn on all dogs at one month and two months following irradiation.

Irradiation was given by two methods:

Method 1.—Dogs were anesthetized with intravenous pentobarbital sodium (25 mg./Kg.) and placed under a standard 250 kvp x-ray therapy machine. Target distance was 100 cm. to midline of the animal. Dose rate was 5 r/min. in air at theoretical midline with filters 0.25 mm. Sn, 0.4 mm. Cu and 1.0 mm. Al, HVL 2.2 mm. Cu, 250 kvp and 10 ma. Animals...
A word about stem cells...
Haematopoietic Stem Cells

Alexandr Maximov

Alexandr Friedenstein
Atomic haematologists

1950s  Snell  Inbred mice.
1958  Mathe’  Vinca NPF accident
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1960  Till & McCullough CFU-S
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1973  HLA-matched unrelated donor transplant  SCID
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1973  HLA-matched unrelated donor transplant  SCID
1977  Thomas 100 leukaemia transplants
One Hundred Patients With Acute Leukemia Treated by Chemotherapy, Total Body Irradiation, and Allogeneic Marrow Transplantation

By E. Donnall Thomas, C. Dean Buckner, Meera Banaji, Reginald A. Clift, Alexander Feer, Nancy Flownoy, Brian W. Goodell, Robert O. Hickman, Kenneth G. Lerner, Paul E. Neiman, George E. Sale, Jean E. Sanders, Jack Singer, Mary Stevens, Rainer Storb, and Paul L. Weiden

One hundred patients, 54 with acute myelogenous leukemia (AML) and 46 with acute lymphoblastic leukemia (ALL), considered to be in the end stages of their disease, after combination chemotherapy were treated by marrow transplantation. All patients were given a marrow graft from an HLA-identical sibling after receiving 1000-rad total body irradiation (TBI). One group of 43 patients was given cyclophosphamide (CY), 60 mg/kg on each of 2 days, 5 and 4 days before TBI. In a second group of 31 patients, additional chemotherapy was given before CY and TBI. In a third group of 19 patients, BCNU was given before CY and TBI. A fourth group of 7 patients received other chemotherapy regimens before TBI. Six patients died 3–17 days after marrow infusion without evidence of engraftment. Ninety-four patients were engrafted and only one patient rejected the graft. Thirteen patients are alive with a marrow graft, on no maintenance antileukemic therapy, and without recurrent leukemia 1–4½ yr after transplantation. Three have chronic graft-versus-host disease (GVHD). Four patients are alive 1½–3½ yr after grafting but have had a relapse of their leukemia. Of 93 evaluable patients, 19 did not develop GVHD and 24 developed very mild GVHD. Fifty patients developed moderate to severe GVHD, and 40 of these were treated with antithymocyte globulin. Interstitial pneumonia occurred in 54 patients and was the primary cause of death in 34. Interstitial pneumonia often occurred in association with GVHD and the most common etiologic agent was cytomegalovirus. A total of 31 patients have had a relapse of leukemia. There was no definite correlation between relapse of leukemia and the presence or absence of GVHD. The relapse rate appeared to be relatively constant over the first 2 yr and was extremely low after that time. Neither survival nor leukemic relapse appeared to be influenced by the type of leukemia nor by the preparative chemotherapy regimen given before TBI. Patients in fair clinical condition at the time of transplantation showed significantly longer survival times than patients in poor condition ($p = 0.001$). This observation, coupled with the observation that some patients may be cured of their disease, indicates that marrow transplantation should now be undertaken earlier in the management of patients with acute leukemia who have an HLA-matched sibling marrow donor.
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1968  SCID and Wiskott-Aldrich transplants
1970s  Buckner, Fliedner Freeze bone marrow
1973  MURD transplant SCID
1977  Thomas 100 leukaemia transplants
1988  UCB transplant  Gluckman, Broxmeyer Fanconi
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1993 HLA-haplotype-matched transplants Henslee-Downey
Some of many pioneers

Don Thomas  George Santos  George Mathe’  Dirk van Bekkum

Mortimer Bortin  Robert Good  Fritz Bach  John Fahey
The Emperor's New Clothes

Based on the story by Hans Christian Andersen

Illustrated by Mike Gordon
There is nothing new under the Sun

Cyclophosphamide
Transplants 1958-1968

Reported Human Bone Marrow Transplants, 1958-1968
Worldwide Transplants 1967-2013

Gratwohl Lancet 2015
11 Transplant Centres Reporting to IBMTR 1968-73

Hungary
460 Transplant Centres Reporting to CIBMTR 2014
Transplants 1968-1978

- SCID
- Aplastic anaemia
- Cancers
Transplants 2013

Aplastic anaemia/SCID

Leukaemia

Lymphoma

Plasma cell myeloma
The 2\textsuperscript{nd} and 3\textsuperscript{rd} Generations

Why Transplant Sometimes Fail

... mainly because the clinical applications were undertaken too soon, most of them before even the minimum of basic knowledge required to bridge the gap between mouse and people had been obtained. Our laboratory is now humans but the problem persists.

van Bekkum and de Vries Radiation Chimeras 1967
The opera is not over until the fat lady sings.
If I have seen further than others, it is by standing upon the shoulders of giants.

(Isaac Newton)
And they will hammer their swords into plowshares…

Isaiah 2:1
Woody Allen, asked whether he’d like to live on in the hearts of people after his death

I would prefer to live on in my apartment.
Cocktails anyone?