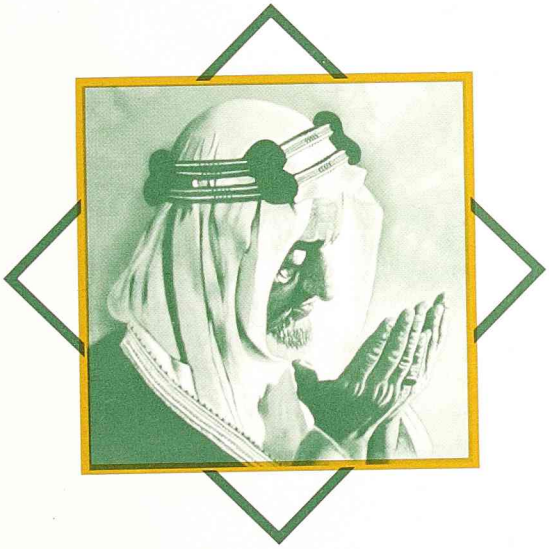
جائزة الملك فيصل العالمية
King Faisal International Prize



THE KING FAISAL MEMORIAL ARTICLES IN MEDICINE AND SCIENCE VIII

THE 2008
KING FAISAL
INTERNATIONAL PRIZE

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THE 2008
KING FAISAL
INTERNATIONAL PRIZE

Custodian of the Two Holy Mosques
King Abd Allah Ibn Abdul Aziz Al-Saud
Patron of the King Faisal Foundation

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INTRODUCTION

The King Faisal Foundation continues the traditions of Arabic and Islamic philanthropy, as they were revitalized in modem times by King Faisal. The life and work of the late King Faisal bin Abd Al-Aziz, son of Saudi Arabia's founder and the Kingdom's third monarch, were commemorated by his eight sons through the establishment of the Foundation in 1976, the year following his death. Of the many philanthropic activities of the Foundation, the inception of King Faisal International Prizes for Medicine in 1981 and for Science in 1982 will be of particular interest to the reader of this book. These prizes were modeled on prizes for Service to Islam, Islamic Studies and Arabic Literature which were established in 1977. At present, the Prize in each of the five categories consists of a certificate summarizing the laureate's work that is hand-written in Diwani calligraphy; a commemorative 24-carat, 200 gram gold medal, uniquely cast for each Prize and bearing the likeness of the late King Faisal; and a cash endowment of SR750,000 (US$200,000). Co-winners in any category share the monetary award. The Prizes are awarded during a ceremony in Riyadh, Saudi Arabia, under the auspices of the Custodian of the Two Holy Mosques, the King of Saudi Arabia.

Nominations for the Prizes are accepted from academic institutions, research centers, professional organizations and other learned circles worldwide. After preselection by expert reviewers, the. Short-listed works are submitted for further, detailed evaluation by carefully selected international referees. Autonomous, international specialist selection committees are then convened at the headquarters of the King Faisal Foundation in Riyadh each year in January to make the final decisions. The selections are based solely on merit, earning the King Faisal International Prize the distinction of being among the most prestigious of international awards to physicians and scientists who have made exceptionally outstanding advances which benefit all of humanity.

(Excerpt from Introduction to 'Articles in Medicine and Science 1"
by H.R.H. Khaled Al Faisal,
Chairman of the Prize Board and
Director General of King Faisal Foundation)

2008 Prize Awards in Medicine and Science

The 2008 awards were presented in March 2008

The Prize for Medicine (Topic: Trauma Management) has been awarded jointly to: Professor Donald D. Trunkey (USA) and Professor Basil A. Pruitt Jr. (USA)

Professor Donald D. Trunkey (USA) is one of the most influential leaders in the field of trauma management. He conceived and validated an organized trauma system for a better outcome of the injured patient; and disseminated this system world-wide. His observations have led to the formation of mobile surgical units, thereby improving significantly the survival of injured patients.

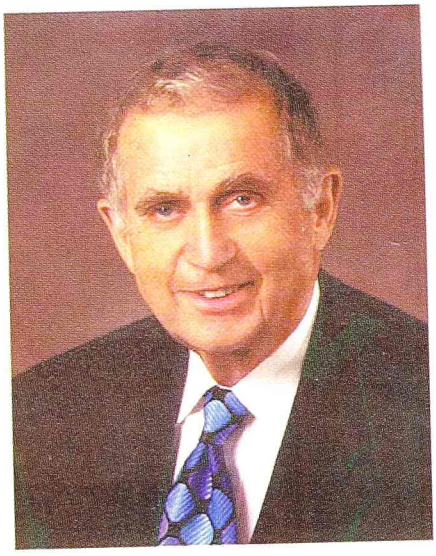
Professor Basil Arthur Pruitt Jr. (USA) is an internationally renowned clinical leader in burn surgery and a distinguished researcher in the science of improving the outcome of serious burn injury. His work, over the past 50 years, has covered the entire spectrum of burn care and has had a significant impact on the improvement of trauma care.

The prize for Science (Topic: Biology) has been awarded to: Professor Rudiger Wehner (Germany)

Professor Wehner is an outstanding neuroethologist whose work revolved around the general question of how a 0.1-milligram brain of a 10-milligram animal solvescomplex computational tasks. He has focused on the extraordinary navigational skills of visually guided desert ants. His work has inspired many international research groups to use this elegant animal model for various conceptual and methodological approaches aiming at the questions of how nervous systems evolved, how they work and how they control behavior

WINNER OF THE 2008
KING FAISAL INTERNATIONAL PRIZE
FOR MEDICINE

Medal: King Faisal International Prize for Medicine



Professor Donald D. Trunkey
Co-Winner of the 2008 King Faisal International Prize for Medicine

Synopsis of Achievements
Professor Donald D. Trunkey

Professor Donald Trunkey is an internationally renowned trauma surgeon, and one of the first surgeons to incorporate the concepts of remaining active on the trauma call schedule. He continues to be a strong advocate for improved trauma care throughout the world.

Raised in farm country in Eastern Washington, Professor Trunkey practiced farm work, mining, hod carrying, carpentry, and building-contracting. He obtained his B.S. and MD degrees from Washington State University. Following his internship, he served for two years as a medical officer in the U.S. military base in Germany, then completed his training in general surgery at the University of California, San Francisco, spent one year in the Organ Preservation Laboratory and another year at Southwestern Medical Center in Dallas, Texas, on a special NIH fellowship in trauma.

After completing his fellowship in Dallas, Professor Trunkey returned to the University of California, San Francisco, where he became intensely involved in the care of trauma patients. He became Chief of the Burn Center at San Francisco General Hospital and also had an extensive interest in elective vascular surgery and non-cardiac thoracic surgery. He established a laboratory to study mechanisms of shock at the cellular level with a special interest in myocardial performance following shock, lung injury, and cellular immune mechanisms following injury. In 1978, he became Chief of Surgery at San Francisco General Hospital and in April 1986, he assumed the Chair at Oregon Health Sciences University Department of Surgery, where he build a strong general surgery residency based on all the primary components of general surgery. His own special interest remains trauma surgery. He authored 67 scientific articles, 24 books and around 200 book chapters and presented many honorary lectures.

In addition to King Faisal International Prize, Trunkey received many other prestigious awards and honors including: Distinguished Service Award of the American College of Surgeon, Washington State University College of Science Distinguished Alumnus Award, Barry Goldwater Service Award, International Society of Surgery Prize, Honorary Membership of the British Association for Accident and Emergency Medicine and Honorary Fellowships of the Royal Colleges of Surgeons of England, Ireland, Edinburgh, Glasgow, South Africa and Brazil, medal of the Royal College of Medicine of England and honorary professorship of the Royal College of Surgeons of Edinburgh..

Lessons Learned from an Academic Trauma Surgeon

Professor Donald D. Trunkey
Professor of Surgery
Department of Surgery
Oregan Health & Science University
Portland, Oregon
USA

Introduction

During my surgical residency at the University of California, San Francisco, I thought that academic medicine would be an attractive career. I analyzed why some of my role models had successful academic careers, and it seemed some of the common threads were the following: All were successful doing clinical surgery; many were able to carry on basic research and to make their research clinically applicable. At least one of the role models I was acquainted with not only did basic research, but also did health services research. This research analyzes deficiencies within various clinical programs and then tries to correct them. It was clear to me that you could integrate all of these into a successful career. However, I did not finalize this until my chief residency, and I went to my professor of surgery, J. Englebert Dunphy, and told him what I wanted to do. He immediately arranged a National Institutes of Health Fellowship with Dr. G. Tom Shires at Southwestern Medical School in Dallas, Texas.

Basic Research

I started the fellowship in July 1971. Although there were requirements for some clinical activity - Parkland Hospital had an enormous clinical load - 90% of my time was spent learning basic research techniques in Dr. Shires' lab and developing my own research interest. In 1964, Dr. Shires, using volume of distribution studies, had shown that following a shock insult, interstitial fluid in an animal model was depleted by as much as 60%, and that the cells took up water and salt and excreted potassium and hydrogen iron. The methodology was criticized, and so he developed a new model based on the Nernst equation. This required placing an

animal in shock, and inserting a microelectrode into a single skeletal muscle cell, and measuring the trans-membrane potential throughout the shock course. At the termination of the shock insult, the animal was sacrificed; electrolytes in the muscle and water content were measured, and using the determined trans-membrane potential, the sodium and chloride inside the cell could be calculated and compared to the extracellular values. It was shown that sodium and chloride did indeed enter the cell during the shock insult. Potassium left the cell and hydrogen increased in the interstitial space. After learning the various techniques, I took the same animal primate model and not only subjected them to the hemorrhagic shock insult, but also resuscitated them for a period up to seven days after the original shock insult. [1] [Fig 1] This set of experiments showed that the animals' membrane potential fell in the shock period from -90 to -60 (-55 was the K+ equilibrium point or cell death) recovered to near -90 over about a 48-hour period, but never quite returned to normal during the seven days. In addition to the transmembrane potential, I also stimulated the nerve to the muscle, which in turn initiated an action potential in the cell that had been penetrated by the microelectrode. During shock, the amplitude of the action potential diminished, and the curve widened. This was predicted to have happened secondary to the change in Na+ and K+ concentrations. The next set of experiments was to repeat the same methodology in the primate model but was subjected to septic shock by injecting live Escherichia coli intravenously. [2] These animals were also resuscitated, and similar results were determined; however, the insult to the cells seemed to be more severe.

I returned to San Francisco in 1972 and extended the research learned in Texas to studies other than sodium chloride and potassium. [3,4,5] I next looked at calcium and magnesium shifts in muscle during both hemorrhagic shock and septic shock insults. These studies showed that there were very profound shifts in calcium and magnesium, but this was in skeletal muscle. What would happen in cardiac muscle? I went to the University of California, Los Angeles to Dr. Glenn Langer's laboratory and learned how to do his perfused myocardial contractility model. This consisted of dissecting the intraventricular septum of a rabbit

and cannulating the anterior descending coronary artery so that the model was perfused and beating. This was mounted in a myograph, and a strain gauge was attached so that contractility could be measured. Plasma from a normal rabbit could then be perfused or plasma from a shock rabbit could be perfused. [6] These studies went on for several years and confirmed precisely what had happened in the primate model. Calcium and magnesium shifts in skeletal muscle and cardiac muscle were very similar. [Fig 2] Most importantly, the experiments showed that the membrane potential in the septal model fell and the action potential broadened, which correlated with a decrease in dP/dt. We showed a direct correlation between the absolute amount of ionized calcium and decrease in myocardial contractility. We took this information to the intensive care unit, where we were the first to show that in patients with myocardial infarct, ionized calcium fell within their serum, but in patients who were septic and had decreased myocardial performance, the ionized calcium was significantly lower, and there were no survivors if the ionized calcium fell below 1.6 meq/l. [7] Replacement of calcium did not help these patients and may have made them worse. This implied the calcium was entering the cells and binding to the mitochondria.

During the time that we were using a primate model to study the effects of shock, we also developed methodology where the extra-vascular lung water could be measured during the experiments and following resuscitation. [8] This was based on a thermal-dye technique. A thermistor was placed at the tip of a Swan-Ganz catheter. Cardiac output was measured with cardiogreen dye and the thermistor. The difference between the two was shown to be an increase in extra-vascular lung water. Multiple animal experiments were then conducted using different resuscitation regimes in order to determine what would be best in human shock. [9,10,11,12] This methodology was soon applied to patients in the intensive care unit, and allowed us to measure the amount of extra-vascular lung water (EVLW) that occurred following resuscitation of patients with hemorrhagic shock and septic shock. The most dramatic increases in EVLW were in severe burn patients who became septic. Also at this time, Dr. Carol Miller was recruited to our laboratories. She had a major interest in immunology, and in

particular, mononuclear white-cell function. Using animal models and patients who were admitted to the burn center, we showed that following a major thermal injury, there were defects in the immune response, which included an increase in T-suppressor cells. There was a concomitant increased release of plasminogen activator substance, which made the patient hypercoagulable. [13,14]

During the last three years at San Francisco General Hospital, we shifted our basic science research to study excitation-secretion coupling in endocrine tissue. We had shown in the myocardium that excitation-contraction coupling had been altered by the shock insult, and we thought the same thing would happen in excitation-secretion coupling, since the cell membrane mechanisms are somewhat similar. Using a tissue culture model of adrenalcortical cells, we exposed the cells to normal plasma and shock plasma. Excitation-secretion coupling was clearly altered. [15] Cell morphology was also altered, but viability was maintained. Most importantly, the cells exposed to control plasma continued to secrete corticosterone (rat cortisol), whereas those cells exposed to shock plasma had a dramatic decrease, and furthermore, there was a drop in cyclic AMP within the cell membranes, and the shocked cells did not respond to ACTH, whereas the control cells did. We also showed that the cells maintained the ability to convert pregnenolone to progesterone and then to corticosterone. We concluded the defect was in the cell membrane and due to three sites: a) inhibition of binding of corticotrophin; b) inhibition of cyclic amp; and c) inhibition of production of pregnenolone from cholesterol.

Clinical Surgery and Clinical Studies

In 1986, I left San Francisco and became Chairman of the Department of Surgery at Oregon Health & Science University. In addition to my clinical and research activities, I now added the burden of being an administrator. I was extremely fortunate from the standpoint of research, since there were two PhD investigators who were very interested in studying cellular oxidative metabolism following a shock insult. Dr. Lena Mela Riker and Dr. Angelo Vlessis were very keen on carrying out more experiments. Using

grant money, we set up a laboratory, and showed in a myocardial cell culture model that free radicals caused a block of pyruvate decarboxylization. [16] This in turn led to a loss of cellular ATP. With pyruvate effectively blocked, the only alternative fuels were either ketones or glutamate. We then developed a guinea pig model where we studied total body metabolism before and after induction of increased granulocyte metabolism. If we stimulated the granulocytes in these animals, they became hypermetabolic and increased oxygen consumption. This was also associated with hydrogen peroxide generation and an increase in lung water. In contrast, if we stimulated the granulocytes but blocked NADPH oxidase, oxygen consumption was normal, and the neutrophils did not damage the lung causing an increase in lung water. We concluded from these studies that during sepsis, total oxygen consumption may increase 25% and is caused by increased white cell oxygen consumption – not eukaryotic cells. [17] In addition to hydrogen peroxide, we were also interested in other oxidants such as super oxide and nitric oxide. These two oxidants can combine to form peroxynitrate. Working with a physical chemist, Dr. Brian A Gilbert, we showed that the catecholamine ring can be oxidized by peroxynitrate, and when we analyzed human plasma and urine in patients who were in septic shock, indeed the catecholamine ring had been oxidized, and this led to the formation of adrenochromes in the patient's urine. [18,19]

Clinical Research

After returning to San Francisco in 1972, I was extremely busy doing clinical surgery, primarily trauma. This included vascular trauma, thoracic trauma, burns, and extremity injuries. The Surgical Service at San Francisco General Hospital was divided into three distinct services. The first was trauma and emergency surgery, which admitted approximately 3200 – 4000 patients per year. We also had an elective surgery patient service that admitted 900 – 1000 patients a year, and a final service, which was the extremity service, which admitted 1600 patients a year. We rotated every third month on the different services. During the time that we were on the Trauma Service, we were taking call every other night. The importance of the clinical surgery was that I could teach

this to the residents and students, as well as take care of patients in the intensive care unit. Much of my clinical research occurred in the intensive care setting. I have already mentioned the measurement of EVLW in patients. I carried out randomized trials in patients with portal hypertension and different surgical techniques to correct hemorrhage from esophageal varices. Our first study was to compare patients (Childs C) who had porta-caval shunts with patients who were treated medically. The overall mortality was 100% for patients treated medically compared to 50% when patients were treated in the surgical arm. We then compared ligation of the varices at the esophagus vs. porta-caval shunt, and then compared porta-caval shunt with mesocaval shunt. Our conclusion was that a side-to-side created shunt or mesocaval shunt had less morbidity and mortality. Our final study was to compare Childs C portal hypertensive patients with sclerotherapy vs. porta-caval shunt. Our initial results were that the two techniques had similar mortalities; approximately 50%; however, at one year, the patients who had been treated with sclerotherapy had required several more treatments, and the survivability had dropped to 35%, whereas those patients treated surgically maintained their viability at one year. This study was published in the New England Journal of Medicine. [20]

Early in my San Francisco experience, we performed two autopsy studies that showed that there were preventable deaths if patients did not reach a trauma center in a timely way or if they did not go to a trauma center. In 1974, we did a third study comparing the outcome of trauma patients in two counties in California. In Orange County, there were no trauma centers, and patients went to the nearest hospital, whereas in San Francisco, all trauma patients went to a single hospital, San Francisco General Hospital. [21] The comparison was relatively dramatic. In Orange County, 33% of the deaths were clearly preventable. Some of these patients arrived alive in an emergency room with a ruptured spleen, were never seen by a surgeon, and died over a 4-6 hour period. This study was subsequently repeated after establishing a trauma system in Orange County and the preventable death rate had dramatically dropped to 3%. Another comparative study was done in the Bay area of San Francisco and examined nine counties. [22] One county (San

Francisco) had a trauma center, whereas the other eight counties did not. Again, the preventable death rate in the eight counties where a trauma center did not exist, was approximately 30-43%. Although this information was used to try to establish more trauma centers in the Bay area, initially it was unsuccessful due to politics and a perceived lack of finances. Ultimately, the entire Bay area now has an integrated trauma system.

In 1980, I became Chairman of the Committee on Trauma for the American College of Surgeons. During this tenure, I continued my interest in health services research and trauma systems. During this tenure, we were able to establish Advanced Trauma Life Support as a consensus-based model of trauma resuscitation. This course was originally developed by an orthopaedic surgeon in Nebraska. Since that time, we have offered this course to 475,561 individuals worldwide. We also developed the National Trauma Data Bank, which is a registry that now has over two million trauma patients registered, which serves as a base for more health services research. We also developed a verification process for hospitals that have been designated as Level I, II, or III hospitals. This verification process is a peer review process that is carried out at the hospital. It entails review of medical records, particularly patients who have died and have been classified as possibly preventable, preventable, or not preventable. We review their peer review process and whether or not they make changes that are appropriate when errors are made.

More recently, I have turned my attention to trauma on a worldwide basis. [23] I have recently completed an inventory of countries that have trauma systems and those that do not. If one examines the work by Murray and Lopez in their Burden of Disease Study, trauma is a worldwide problem, particularly in developing countries. In their study, they divided the world into developed and developing regions, and subcategorized the world into eight distinct economic regions. In 1990, 5 million people worldwide are estimated to have died from intentional and unintentional injuries. The risk of injury death is very strongly influenced by region, age, and sex. If one compares mortality from violent causes, in the European market economies, injuries caused

about 6% of all deaths in 1990 compared with 9-11% in other regions. It is particularly striking and problematic in Sub-Saharan Africa and Latin America, where 12-13% of deaths are related to violence. It is primarily a problem in males, where it accounts for 16-17% of deaths.

In an attempt to quantify the burden of disease and injury of various human populations, Murray and Lopez have used the concept of Disability Adjusted Life Years (DALYs). A DALY is defined as the sum of life years lost due to premature mortality and years lived with disability adjusted for severity. Worldwide, in 1990, road traffic accidents were number nine as a cause of DALYs. In developed regions, traffic accidents were the number four cause of DALYs, and self-inflicted injuries were number nine. In developing regions, road traffic accidents was number nine, war was number 16, violence was number 18, and self-inflicted injuries was number 19. Overall, trauma accounts for 14.5% of the burden in developed regions and 15.2% in developing regions. It is noteworthy that the European economic regions consume 80% of the world's resources for healthcare. The mortality from trauma is almost double in these developing countries compared to developed countries. Some developed countries have trauma systems, and the mortality tends to be less than it is in countries that do not have trauma systems.

This last fall at a meeting in Montreal of the International Surgery Society, I presented two papers related to trauma as a worldwide problem and necessary solutions. [in press] The solutions will not be easy, particularly in developing countries. Nevertheless, the developed countries must continue to develop mature trauma systems and provide resources to do the same in developing regions.

References

1. Trunkey DD, Illner H, Wagner LY, and Shires GT. The effect of hemorrhagic shock on intracellular muscle action potential in the primate. Surg. 1973;74:241-50.
2. Trunkey DD, Illner H, Wagner IY, and Shires GT. The effect of septic shock on skeletal muscle action potential in the primate. Surg. 1979;85:638-43.
3. Trunkey DD, Holcroft JW, and Carpenter MA. Calcium flux during hemorrhagic shock in baboons. J Trauma. 1976;16(8):633-8.
4. Carpenters MA, Trunkey DD, and Holcroft JW. Ionized calcium and magnesium in the baboon: Hemorrhagic shock and resuscitation. Circ Shock. 1978; 5:163-72.
5. Trunkey DD, Carpenter MA, and Holcroft JW. Ionized calcium and magnesium: The effect of septic shock in the baboon. J Trauma. 1978;18:166-72.
6. Raffa J, and Trunkey DD. Myocardial depression in sepsis. J Trauma. 1978;18(9):617-22.
7. Woo P, Carpenter MA and Trunkey DD. Ionized calcium: The effect of septic shock in the human. J Surg Res. 1979;26:605-10.
8. Holcroft JW, and Trunkey DD. Extravascular lung water following hemorrhagic shock in the baboon: Comparison between resuscitation with Ringer's lactate and plasmanate. Ann Surg. 1974; 180(4): 408-17.
9. Holcroft JW, and Trunkey DD. Pulmonary extravasation of albumin during and after hemorrhagic shock in baboons. J Surg Res. 1975;18(2):91-7.
10. Holcroft JW, Trunkey DD, and Lim RC Jr. Further analysis of lung water in baboons resuscitated from hemorrhagic shock. J Surg Res. 1976;20:291-7.
11. Holcroft JW, Trunkey DD, and Carpenter MA. Excessive fluid administration in resuscitating baboons from hemorrhagic shock, and an assessment of the thermodye technique of measuring extravascular lung water. Am J Surg. 1978;135:412-16.
12. Sturm JA, Carpenter MA, Lewis FR, Graziano C, and Trunkey DD: Water and protein movement in the sheep

lung after septic shock: Effect of colloid vs. crystalloid resuscitation. J Surg Res. 1979;26:233-48.
13. Baker CC, Miller CL, Trunkey DD, and Lim RC Jr: Identity of mononuclear cells which compromise the resistance of trauma patients. J Surg Res. 1979;26:478-87.
14. Baker CC, Trunkey DD, and Baker WJ. A simple method of predicting severe sepsis in burn patients. Am J Surg. 1980;139:513-17.
15. Catalano RD, Parameswaran V, Ramachandran J, and Trunkey DD. Mechanisms of adrenocortical depression during Escherichia coli shock. Arch Surg. 1984;119:145-50.
16. Vlessis AA, Bartos D, Muller P, Trunkey DD. Role of reactive O_2 in phagocyte-induced hypermetabolism and pulmonary injury. J Appl Physiol. 1995;78(1):112-1-16.
17. Vlessis AA, Goldman RK, Trunkey DD. New concepts in the pathophysiology of oxygen metabolism during sepsis. Brit J Surg. 1995;82:870-6.
18. Gilbert BA, Winner S, Kurupatti R, Bartos D, Trunkey DD, Slater M. Peroxynitrite-mediated oxidation of epinephrine and 6-nitroepinephrine. Presented at the NW Regional Meeting, American Chemical Society, 1999.
19. Kurupatti R, Slater M, Bartos D, Trunkey DD, Bryant AG. Isolation of epinephrine and its oxidation products from human plasma and urine. Presented at the NW Regional Meeting, American Chemical Society, 1999.
20. Cello JP, Grendell JH, Crass RA, Weber TE, and Trunkey DD. Endoscopy sclerotherapy versus portacaval shunt in patients with severe cirrhosis and acute variceal hemorrhage. Long-term follow-up. NEJM. Jan 1987;316(1):11-15.
21. West JG, Williams MJ, Trunkey DD, Wolferth CC Jr. Trauma Systems. Current Status--Future challenges. JAMA. 1988;259(24):3597-600.
22. Trunkey DD. Bay Area trauma care. SF Med Soc Bulletin. 1982;22-5.
23. Trunkey DD. Trauma in modern society: major challenges and solutions. *Surgeon* (The Royal Colleges of Surgeons of Edinburgh and Ireland) 2005 3: 3; 165-170.

Figure 1.

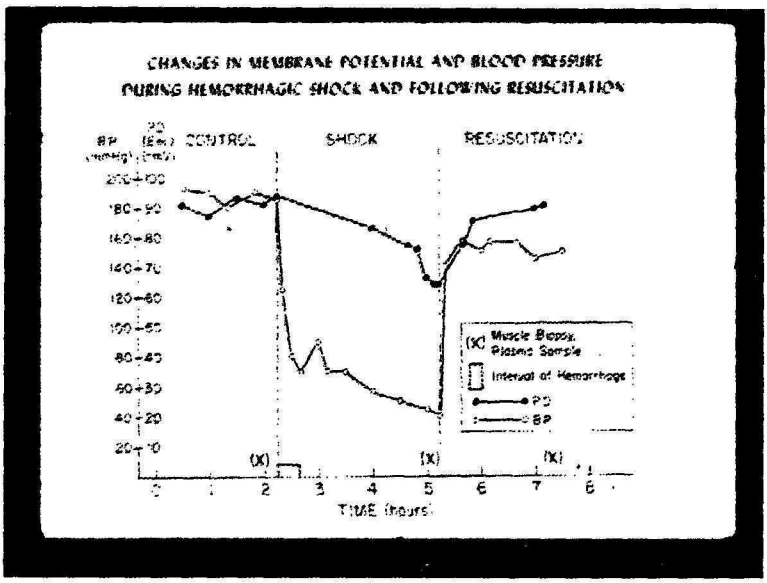


Figure 2.

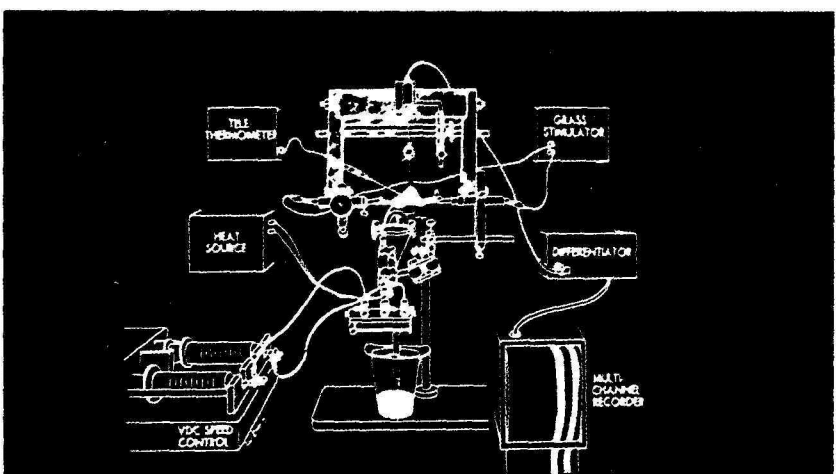


FIG 2. The arterially perfused interventricular septum mounted vertically on a myograph. Developed tension (DT) and dP/dt simultaneously recorded.

Professor Basil A. Pruitt Jr.
Co-Winner of the 2008 King Faisal International Prize for Medicine

Synopsis of Achievements
Professor Basil A. Pruitt Jr.

Professor Basil Pruitt Jr. is a world authority in burn surgery and a distinguished researcher in the science of improving the outcome of serious burn injury. His work, over the past 50 years, has covered the entire spectrum of burn care and has had a significant impact on the improvement of trauma care. He was born in New York in 1930, pursued undergraduate education at Harvard College and Harvard University, and obtained his MD from Tufts University in 1957. After completing his internship in Boston General Hospital and residency in Boston and Brooks General Hospitals, he became fellow of the American College of Surgeons in 1964 and served as a an army surgeon for 35 years, including 27 years as leader the Burn Center of the US Army Institute of Surgical Research in Southern Texas, which was developed by Pruitt into one of the best burn centers in the world. In 1996, he joined the University of Texas where is currently Professor of Surgery at Texas University Medical Center in San Antonio; and the Uniformed Services University of the Health Sciences in Maryland, Consultant at the NIH Surgery, Anesthesia and Trauma Study Section, and member of the American Board of Surgery.

He organized and directed a multi-disciplinary clinical and research program focused on burn care and trauma management, which resulted in improved resuscitation, ventilatory management, wound care and metabolic support regimens that - collectively - significantly increased survival, reduced complications, accelerated convalescence and improved functional recovery. Pruitt mentored a whole generation of burn center directors and surgeons from the US and overseas. He has published 440 research papers, 13 books and around 220 conference abstracts.

In addition to King Faisal International Prize, Professor Pruitt received numerous national and international prizes and awards for his achievements as a clinician, teacher, and researcher. He is president or member or of 40 surgical, medical and scientific societies, Editor-in-Chief for the *Journal of Trauma* since 1995, member of the editorial boards of 13 other journals, and ad hoc reviewer for an additional 26 journals. He has been a visiting professor, honorary lecturer and invited lecturer in more than 200 universities and medical centers worldwide.

Integrated Clinical/Laboratory Research and Improvements in Burn Care

Basil A. Pruitt, Jr., MD, FACS
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During the past five decades, both evolutionary and revolutionary changes in the care of burn patients have reduced the magnitude and duration of organ dysfunction, decreased the incidence of life-threatening complications, and increased survival. In the 1950s and 1960s, the biphasic response of all organ systems to burn injury was characterized and the relationship of organ dysfunction to severity of injury identified. That information led to the development of formulae which could be used to estimate the amount of fluid to be given for resuscitation in the immediate postburn period. The commonly used formulae differed markedly in terms of the amount and composition of the fluids recommended to prevent burn shock and organ failure. That variability, which reflected in part the physiologic resilience of many burn patients, also influenced late occurring complications of fluid management. To optimize fluid resuscitation and develop a regimen which could prevent shock and organ failure and avoid the consequences of excessive volume, the cardiovascular responses to burn injury and fluid therapy were studied in severely burned patients treated at the U.S. Army Institute of Surgical Research Burn Center.

Those studies indicated that in the immediate post-injury period crystalloid fluid had the same resuscitative capacity as did colloid-containing fluid and that prompt restoration of cardiac output and limitation of plasma volume loss were achieved in extensively burned patients in whom fluid was infused at the rate of 2 ml/kg body weight/% body surface area burned (Figure 1).[1] Subsequent clinical studies indicated that crystalloid-based resuscitation supported cardiac output throughout the first ten days post-injury, as did resuscitation that included colloid-containing fluid, but was not associated with a progressive increase in lung water as occurred in patients who received colloid-containing fluid in the first 24 hours (Figure 2). In short, a relative low volume of crystalloid fluid could resuscitate patients with extensive burns, and colloid-containing fluid did not decrease the fluid volume needed in the first 24 hours nor exert a lung protective effect.[2]

Correlative laboratory studies evaluated other potential means of reducing fluid administration to minimize the occurrence of resuscitation-associated pulmonary dysfunction and compartment syndromes. Studies in an animal model of burn injury confirmed that restoration of cardiac output at 6 hours after burn injury was indifferent to the use of colloid-containing fluid, identified the physiologic responses to salt dose and volume dose following burn injury, and defined the limited usefulness of hypertonic salt solution and its long-term consequences in a setting of strikingly elevated evaporative water loss from the surface of the burn wound.[1] Subsequent clinical studies identified long-term retention of the salt load administered during resuscitation emphasizing the need for meticulous fluid management following resuscitation to prevent a "delayed" onset of pulmonary edema. The relative low volume Modified Brooke formula developed on the basis of these studies has reduced the incidence of renal failure to 0.3% in 3,266 recently treated burn patients and has decreased the occurrence of compartment syndromes and pulmonary dysfunction.

The virtual elimination of burn shock and the early survival of patients with extensive burns were associated with the emergence of other complications and organ system pathologies that affected outcome. Clinical reviews indicated that the occurrence of acute upper gastrointestinal tract ulceration as a cause of bleeding or perforation increased in proportion to the extent of the burn. The application of fiberoptic technology permitted the identification of gastritic changes in the mucosa of the stomach and duodenum as early as five hours after burn injury, which could progress to frank ulceration within four days (Figure 3). Progression of the gastritic changes to ulceration was correlated with gastric acid production, and the prophylactic effect of antacid treatment in arresting that progression was documented. Correlative laboratory studies confirmed shock-related redistribution of blood flow within the gastric wall and further clinical studies documented the effectiveness of a histamine H2-receptor antagonist in preventing progression to ulceration and perforation.[3] In a recent eleven year period, only 9 of 3,266 patients (0.3%) evidenced upper-GI bleeding and only one patient required operative intervention for treatment of a perforation.

The prevention of burn shock and control of stress ulcers revealed the importance of associated smoke injury inhalation as the most significant comorbid factor determining burn patient outcome. In the early 1960s, a clinical review of burn patients revealed that the clinical signs of

inhalation injury were either transient or of relatively late onset, which made clinical diagnosis uncertain. Additional clinical studies revealed that the presence of inhalation injury increased mortality above that predicted on the basis of age and burn size by a maximum of 20%. In addition to the inhalation injury per se, 75% of patients with inhalation injury developed pneumonia within the first seven days following injury. Pneumonia is associated with a similar comorbid effect that is independent but additive to that of inhalation injury. Consequently, a burn patient with inhalation injury who develops pneumonia has a maximum 60% increase in mortality above that predicted on the basis of age and burn size.[4]

Once again the application of fiberoptic technology made possible bronchoscopic identification of the chemical tracheobronchitis induced by the inhalation of the irritative products of incomplete combustion with 86% accuracy. The addition of newly developed imaging techniques utilizing radioactive xenon to supplement the bronchoscopic examination identified pulmonary injury in patients who had inhaled a smoke composed of particles of less than 0.05 micron mass median diameter which typically take rest in the terminal bronchi and alveoli where the resulting inflammation can not be visualized bronchoscopically. Together these modalities increased the accuracy of diagnosis of inhalation injury to 93% (Table I).[5]

The problem of inhalation injury was then taken to the laboratory, where an ovine model of inhalation injury was developed in which disturbance of pulmonary function occurred in proportion to the dose of smoke administered.[6] Using a six inert gas technique to describe the matching of air flow and blood flow within the lung, it was found that inhalation injury produced a modest increase in true shunt and was associated with the appearance of a lung compartment of low air flow and high blood flow.[7] Those findings indicating the central importance of airway inflammation and obstruction led to the use of high frequency ventilation, specifically high frequency interrupted flow positive pressure ventilation, to facilitate removal of endobronchial debris and maintain airway patency and minimize ventilation-perfusion mismatching in the lung. The clinical application of high frequency ventilation has significantly decreased the incidence of pneumonia in burn patients with inhalation injury with an accompanying reduction in mortality to the extent that mild inhalation injury no longer has a comorbid effect and the comorbidity of severe inhalation injury has been significantly reduced (Table II).[8] That persistent comorbidity has prompted laboratory studies evaluating the effect of pharmacologic agents on inhalation injury. Both

a platelet-activating factor inhibitor and pentoxifylline when administered following inhalation injury reduce the impairments of pulmonary function, the morphologic changes within the lungs, and the mismatching of air flow and blood flow.[9] Those agents appear to be promising candidates for clinical evaluation as means of reducing further the comorbidity of severe inhalation injury.

The true revolution in burn patient management in the past five decades has occurred in the area of wound care. At the midpoint of the 20th century it was commonplace for patients with extensive burns who were treated by daily cleansing and debridement, with grafting delayed until granulation tissue formed, to develop degeneration of the burn wound, pursue a progressively deteriorating clinical course, and expire in the second or third postburn week with little if any wound healing evident. Autopsy examinations focused on the burn wound revealed that the degenerative wound changes were caused by infecting bacteria, most commonly Pseudomonas aeruginosa organisms. Those bacteria could invade the microvasculature in the area of the burn and then disseminate hematogenously to remote organs and tissues. Such invasive burn wound sepsis was identified as the cause of death in 60% of patients who expired at burn centers in those years. This problem was taken to the laboratory, where a murine model was developed in which the avascular eschar provided a rich pabulum that supported microbial growth and proliferation to precisely mimic the pathogenesis of invasive burn wound infection. It was then demonstrated that effective topical antimicrobial chemotherapy in the form of mafenide acetate burn cream could limit the microbial density within the burn wound and prevent the occurrence of invasive burn wound infection. When brought back to the clinic, topical chemotherapy reduced the occurrence of invasive burn wound infection by 50%.[10] However, the protection it provided was imperfect and infections did occur, typically in patients with massive burns and significant comorbidities. A wound biopsy grading system was then developed to describe the microbial status of the burn wound, differentiate colonization from invasion, and determine the likelihood of hematogenous dissemination and the need for systemic antibiotic therapy.[11]

Control of the bacterial density in the burned tissue with topical chemotherapy made possible surgical excision of the burn injured tissue, with a significantly diminished risk of inducing bacteremia and endotoxemia by excision related wound manipulation.[12] Immediate application of topical chemotherapy and early burn wound excision further reduced the incidence of invasive burn wound sepsis to one-tenth

of its former level. In recent years there has been further reduction of the incidence of burn wound infection, but of those infections which do occur, two-thirds are now caused by opportunistic fungi (Figure 4).[13] Invasive fungal infection which can spread rapidly increases the risk of death equivalent to that of a burn involving an additional 33% of the total body surface area. The emergence of fungal infections has placed increased emphasis on the importance of wound surveillance. Use of the burn wound biopsy techniques developed at the Institute of Surgical Research to document invasive fungal infections at a stage when prompt excision can remove all infected tissue makes it possible for surgical intervention to control the infection and reduce mortality (Figure 5).[14]

The current rarity of invasive burn wound infection and the use of early burn wound excision has generated the new challenge of providing coverage of the excised burn wound in patients with a paucity of donor sites. That void was historically filled by the use of viable cutaneous allografts, but the risk of disease transmission by such material has focused attention on the development of synthetic skin substitutes and the use of culture-derived tissue. Early studies at the Institute of Surgical Research identified a bilaminate structure as being essential for the effective function of a skin substitute.[15] The outer layer of such a membrane is an epidermal analogue which functions as a barrier and the inner layer, a dermal analogue, permits the ingrowth of host tissue to effect biologic union. Collagen-based bilaminate membranes have been developed by others and shown to be as effective as cutaneous xenograft when used to provide temporary closure of excised burn wounds. The ultimate need to replace the epidermal analogue of such membranes with the patients' own skin has led to the use of culture-derived tissues, i.e., cultured autologous keratinocytes and most recently composite tissues. The initial enthusiasm about cultured keratinocytes has been significantly tempered by our finding that the fractional loss of such tissue increased as the extent of burn increased, i.e. persistence of the cultured cells was least in the patients who needed successful engraftment most.[16]

We have at present moved back at the laboratory level to determine the role of low amperage direct current in burn wound care. The results from early studies indicated that low amperage direct current (0.6 $\mu A/cm^2$) can limit the duration and magnitude of the increase in capillary permeability caused by burn injury and can increase blood flow in skin appendages and in the micro vasculature to prevent necrosis in the zone of stasis. The low amperage current also exerts bacterial control comparable to that of topical chemotherapy in a model of invasive burn wound infection. Additionally, the application of current using a silver

impregnated membrane as the anode reduces apoptotic activity in injured tissues, accelerates the remodeling of skin grafts and the closure of mesh graft interstices, and improves skin graft donor site healing.[17] Recent studies indicate that in addition to those effects, low amperage current reduces inflammation, decreases scarring, limits post-graft wound contraction, and decreases the antigenicity of allogeneic dermis (Table III).[18]

Improvements in the metabolic management of severely burned patients have also resulted from integrated clinical and laboratory research. Burn injury is associated with an increase in resting energy expenditure which is proportional to the extent of the burn and reaches levels unequalled in medicine. The cooling effect of evaporative water loss from the burn wound was originally thought to be the cause of postburn hypermetabolism, but studies conducted in a metabolic chamber in which the temperature, humidity, and wind velocity could be controlled identified the fact that thermoregulatory set points are altered in burn patients, who are internally warm and not externally cold.[19] Clinical and laboratory studies described the neurohormonal milieu characterized by early predominance of catabolic hormones and later predominance of anabolic hormones that orchestrated the distribution and utilization of nutrients in injured man (Figure 6). Whole limb plethysmographic studies further identified that the hypermetabolism was wound directed, i.e., blood flow to an unburned leg in a patient was significantly less than blood flow to that patient's contralateral burned leg, but no different than the blood flow to the leg of an unburned patient.[20] That physiologic response speaks for meeting calorie needs and against pharmacologic intervention to reduce metabolic rate and wound blood flow which could impair healing.

Integrated research further defined the differential effects of fat and carbohydrate as calorie sources, the interactions of muscle mass and liver in gluconeogenesis, and the deleterious effect of infection on post-injury metabolic adaptations. Clinical studies have further defined the usefulness of hormonal interventions such as the administration of insulin-like growth factor to increase the efficiency of nutritional support and reduce muscle wasting.[21] Collectively these studies have resulted in the formulation of what can be called "full service" metabolic support. Such a regimen supplies the nutrients required to meet metabolic needs[22], reduces muscle wasting due to inactivity, prevents cold stress by maintaining an environmental temperature of comfort[23], and minimizes the adverse metabolic consequences of sepsis by early diagnosis and treatment of infection. Such metabolic support optimizes wound healing, maintains physical capability, and accelerates convalescence. It must be

emphasized that these improvements in burn care were the result of the collaborative activities of surgeons, internists, pathologists, anesthesiologists, physiologists, biochemists, and microbiologists with whom I have had the privilege of working.

In the aggregate, the elimination of burn shock and early post-injury organ failure, the taming of inhalation injury, the virtual elimination of invasive burn wound sepsis, and the use of physiologically-based metabolic support have essentially doubled the extent of burn associated with a 50% risk of death and facilitated the societal integration of even severely burned patients (Table IV). The past five decades can be viewed as the era of the burn patient who has unequivocally benefitted from broad-based programs of integrated clinical/laboratory research. As is always the case, those improvements have revealed new problems which will yield to future research that will further improve burn patient outcomes.

References

1. Pruitt BA Jr: Advances in fluid therapy and the early care of the burn patient. World J Surg 1978;2:139-150.
2. Goodwin CW, Dorethy J, Lam V and Pruitt BA Jr: Randomized trial of efficacy of crystalloid and colloid resuscitation on hemodynamic response and lung water following thermal injury. Ann Surg 1983; 197:520-531.
3. Pruitt BA Jr and Goodwin CW Jr: Stress ulcer disease in the burn patient. World J Surg 1981;5:209-222.
4. Shirani KZ, Pruitt BA Jr and Mason AD Jr: The influence of inhalation injury and pneumonia on burn mortality. Ann Surg 1987;205:82-87.
5. Agee RN, Long JM III, Hunt JL, Petroff PA, Lull RJ, Mason AD Jr, Pruitt BA Jr: Use of 133Xenon in early diagnosis of inhalation injury. J Trauma 1976;16: 218-224.
6. Shimazu T, Yukioka T, Hubbard GB, Langlinais PC, Mason AD Jr, and Pruitt BA Jr: A dose-responsive model of smoke inhalation injury. Ann Surg 1987;206:89-98.
7. Shimazu T, Yukioka T, Ikeuchi H, Mason AD, Wagner PD, Pruitt BA Jr.: Ventilation-perfusion Alterations after Smoke Inhalation Injury in an Ovine Model. J. Applied Physiology 1996; 81(5):2250-2259.
8. Cioffi WG Jr, Rue LW III, Graves TA, McManus WF, Mason AD Jr, Pruitt BA Jr: Prophylactic use of high-frequency percussive ventilation in patients with inhalation injury. Ann Surg 1991;213:575-582.
9. Ogura H, Cioffi WG, Okerberg CV, Johnson AA, Guzman RF, Mason AD Jr and Pruitt BA Jr: The effects of pentoxifylline on pulmonary function following smoke inhalation. J Surg Res 1994;56:242-250.
10. Pruitt BA Jr, O'Neill JA Jr, Moncrief JA and Lindberg RB: Successful control of burn wound sepsis. J Amer Med Assn 1968;203: 1054-1056.
11. Pruitt BA Jr, Foley FD: The use of biopsies in burn patient care. Surgery 1973;73: 887-897.
12. McManus WF, Mason AD Jr and Pruitt BA Jr: Excision of the burn wound in patients with large burns. Arch Surg 1989;124:718-720.
13. Pruitt BA Jr., McManus AT, Kim SH, and Goodwin CW: Burn Wound Infections: Current Status. World J Surg. 1998; 22:135-144.

14. McManus WF, Goodwin CW Jr and Pruitt BA Jr: Subeschar treatment of burn-wound infection. Arch Surg 1983;118:291-294.
15. Pruitt BA,Jr.:Theevolutionary development of biologic dressings and skin substitutes.J Burn Care Rehab 1997, 18: S2-S5.
16. Rue LW, Cioffi WG, McManus WF, Pruitt BA Jr: Wound Closure and Outcome in Extensively Burned Patients Treated with Cultured Autologous Keratinocytes. J Trauma 1993; 34:662-668.
17. Kirrish BS, Walker HL, Langlinais PC, Johnson AA, and Pruitt BA Jr: Stimulating effect of low voltage on healing of skin grafts on the burned pig. Jordan Medical Journal 1988;22:55-62.
18. Chu C-S, Matylevich NP, McManus AT, Goodwin CW, Pruitt BA Jr.: Accelerated Healing with a Mesh Autograft/Allodermal Composite Skin Graft Treated with Silver Nylon Dressings with and without Direct Current in Rats. J Trauma 2000;49:115-125.
19. Wilmore DW, Aulick LH, Pruitt BA Jr: Metabolism during the hypermetabolic phase of thermal injury. Advances in Surgery 1978;12:193-225.
20. Aulick LH, Wilmore DW, Mason AD Jr, Pruitt BA Jr: Influence of the burn wound on peripheral circulation in thermally injured patients. Am J Physiol 1977;233(4):H520-H526.
21. Cioffi WG, Gore DC, Rue LW III, Carrougher G, Guler H-P, McManus WF and Pruitt BA Jr: Insulin-like growth factor-l lowers protein oxidation in patients with thermal injury. Ann Surg 1994;220:310-319.
22. Carlson DE, Cioffi WG Jr, Mason AD Jr, McManus WF and Pruitt BA Jr: Resting energy expenditure in patients with thermal injuries. Surg Gynecol Obstet 1992;174:270-276.
23. Kelemen JJ, Cioffi WG, Mason AD Jr., Mozingo DW, McManus WF, Pruitt BA Jr.: Effect of Ambient Temperature on Metabolic Rate after Thermal Injury. Ann Surg 1996; 223:406-412.

Fig. 1

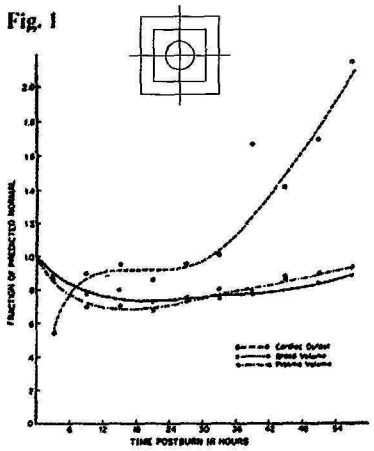

Fig. 2

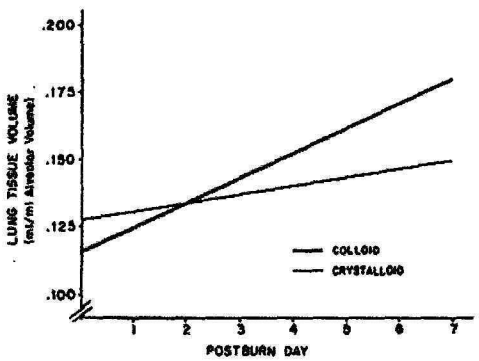

Fig 3

Fig 4

Invasive Burn Wound Infections
1991-2004

Admissions: 3,876

Patients with Invasive Wound Infections

Bacterial			
Gram negative bacilli:	20	25	
Gram positive cocci:	5		90
Fungal			
Aspergillus sp.:	47		
Mucor sp.:	16	65	
Candida sp.:	2		
Incidence		2.3%	
Mortality		55/90 (61%)	

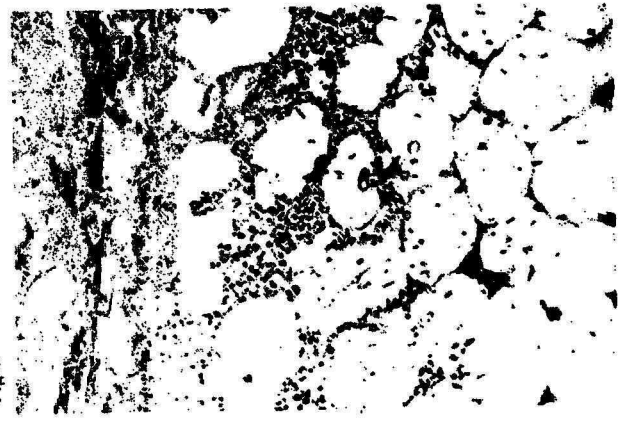

Fig 5

Fig 6

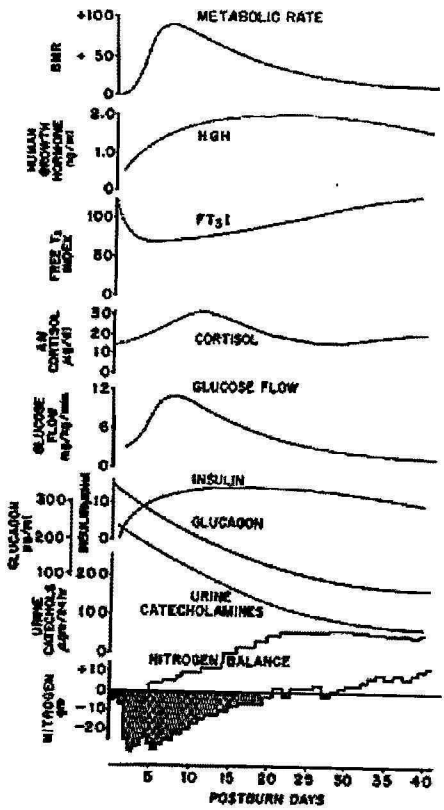

Figure Legend

Figure 1 In ten patients with an average extent of burn of 65% of the total body surface, fluid therapy estimated as 2.0 ml/kg body weight/% total body surface burned rapidly restored cardiac output toward normal. At the same time, blood and plasma volume continued a slow decrease to approximately 30% of predicted normal at 24 hours. In the second 24 hours, plasma volume is restored to essentially normal levels and cardiac output rises to supranormal levels as one of the first manifestations of postburn hypermetabolism.

Figure 2 Colloid-containing resuscitation fluids given in the first 24 hours exerted no protective effect on the lung. Lung tissue volume (a measurement of lung water) increased significantly during the seven day study period in 15 burn patients who received colloid but remained essentially unchanged in the 14 patients who received crystalloid fluid.

Figure 3 Endoscopic examination of the stomach and duodenum commonly reveals focal areas of ischemia and hemorrhagic gastritic change as early as five hours after injury in patients with burns of 35% or more of the total body surface. Note the characteristic "bullseye" lesion at 4 o'clock. Therapy to reduce acid production limits progression to frank mucosal ulceration and prevents the occurrence of life-threatening hemorrhage and perforation.

Figure 4 Invasive burn wound infections: 1991-2004.

Figure 5 Photomicrograph of a burn wound biopsy specimen showing proliferation of fungal elements in the nonviable eschar in the uppermost one quarter of the field. The presence of hyphae with characteristic 45 degree branching in the viable underlying tissue, such as that at 9 o'clock just to the left of the center of the field, confirms the diagnosis of invasive Aspergillus burn wound infection.

Figure 6 The metabolic response to thermal injury is characterized by an early predominance of catabolic hormones and a later predominance of anabolic hormones that sequentially orchestrate initial muscle wasting and later restoration of body mass and convalescence.

Table I
Diagnosis of Inhalation Injury

Diagnostic Technique	Estimate of Accuracy
Bronchoscopy alone	86%
^{133}Xenon scan alone	87%
Bronchoscopy plus ^{133}Xenon scan	93%

Table II
Effects of High-Frequency Percussive Ventilation on Outcomes of 54 Patients with Inhalation Injury

	Predicted Number	Observed Number
Pneumonia	25 (45.8%)	14 (25.9%) *
Mortality	23 (42.6%)	10 (18.5%) *

*$p<0.05$

Table III
Effects of Low Amperage Direct Current on Wound Healing

I. Decreases apoptotic activity in injured tissues

II. Increases blood flow in zone of stasis

   A. Maintains blood flow to hair follicles

   B. Reduces dermal ischemia

III. Accelerates revascularization of wound

IV. Accelerates remodeling of skin grafts

V. Accelerates closure of mesh graft interstices

VI. Improves donor site healing

   A. Decreases time for healing

B. Conserves dermal thickness (increases number of harvests)

VII. Decreases inflammation

VIII. Reduces scarring

IX. Decreases post-grafting wound contracture

X. Promotes engraftment of allogeneic dermis

Table IV
Improvement in Burn Patient Mortality: 1945-2002
U.S. Army Institute of Surgical Research Burn Center

LA_{50}* Age Group	1945-1957	1979-1983	1987-1991	1992-2002
Pediatric (0-14 years)	51%	45%	72%§	71%§
Young adult (15-40 years)	43%	61%	82%†	75%†
			72%‡	65%‡
Older adult (>40 years)	23%	39%	46%#	45%#

§5 years †21 years ‡40 years #60 years

*LA_{50}: Extent of burn, expressed as percentage of total body surface, causing 50% mortality

WINNERS OF THE 2008
KING FAISAL INTERNATIONAL PRIZE
FOR SCIENCE

Medal: King Faisal International Prize for Science

Professor Rudiger Wehner
Winner of the 2008 King Faisal International Prize for Science

Synopsis of Achievements
Professor Rudiger Wehner

Professor Rudiger Wehner is an internationally renowned neuroethologist whose work revolved around the general question of how a 0.1-milligram brain of a 10-milligram animal solves complex computational tasks. He has focused on the extraordinary navigational skills of visually guided desert ants (*Cataglyphis spp.*). His work has inspired many international research groups to use this elegant animal model for various conceptual and methodological approaches aiming at the questions of how nervous systems evolved, how they work and how they control behavior.

Wehner has shown that *Cataglyphis* while roaming over desert terrain for distances of up to 100 metres employs a computational strategy called vector navigation: it measures all angles steered (by employing a neural compass) and all distances covered (by employing a neural odometer) and integrates these measures into a mean vector, which guides it back to its start. One of Webner's major 'landmark' discoveries is how *Cataglyphis* uses the pattern of polarized light in the sky (which humans are unable to see) as a compass to determine walking directions. Wehner and his team have unravelled the computational and neurobiological details of the ant's skylight compass, discovered and studied various mechanism of landmark guidance that complement the animal's vector navigation system and simulated the animal's way of navigation in computer software and implemented it a in robot (Sahabot) that navigates by polarized skylight cues just as Cataglyphis does. In this context, Webner's work more and more attracts the attention of the artificial intelligence and neuroinformatics communities. Furthermore, his finding that the ant's brain is organized in a modular way, with separate sensory-motor systems devoted to different behavioural tasks, has important implications for understanding the general design features of larger brains such as those of birds and mammals. Wehner has recently extended his research to studying the physiological and ecological framework within which the ant's navigational skill has evolved. He found that the spatial and temporal foraging characteristics, a particular mode of respiration and special expression patterns of heat-shock genes allow for an extreme reduction of water loss and the most extreme heat tolerance observed in any terrestrial animal. Furthermore, Wehner performed molecular systematics and phylogeography to uncover the evolutionary history of *Cataglyphis*. Wehbner has published four books, a 330-page Handbook chapter, and 225 scientific publications. His 1000

page Zoology textbook, "THE WEHNER/GEHRING", now in its 7th edition, is widely used and highly valued by colleagues and students alike. Beside King Faisal International Prize, Wehner has received numerous awards and honors.

How Mini Brains Solve Mega Tasks – Lessons from Desert Ants

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This essay is about my forty-year long affiliation, both professional and emotional, with a small desert organism, the ant *Cataglyphis*, which my students and I have been studying at the northern fringe of the Saharan desert as well as in our neurobiological laboratory at the University of Zürich. I shall never forget the hot summer day when I followed an individual forager of *Cataglyphis fortis,* as it dashed and darted about the salt-pan floor of the Chott-el-Djerid in southern Tunisia. It was winding its way in a tortuous search for food, but once it had found a prey item, a dead fly, nearly one hundred metres away from the nest, it returned home as the crow flies, along a straight line to an inconspicuous hole leading to its underground colony, the starting point of its foraging journey [**1, 2**]. How did it find its way? How did the neural cockpit residing in its tiny brain (Figure 1) accomplish this feat of navigation? What sensory cues had been involved, and what had been the computational algorithms applied by the insect navigator in integrating its path? These questions struck me from the very beginning and have been with me ever since. My essay will address some of the most enthralling of these questions. First, however, let me embark on a more general train of thought.

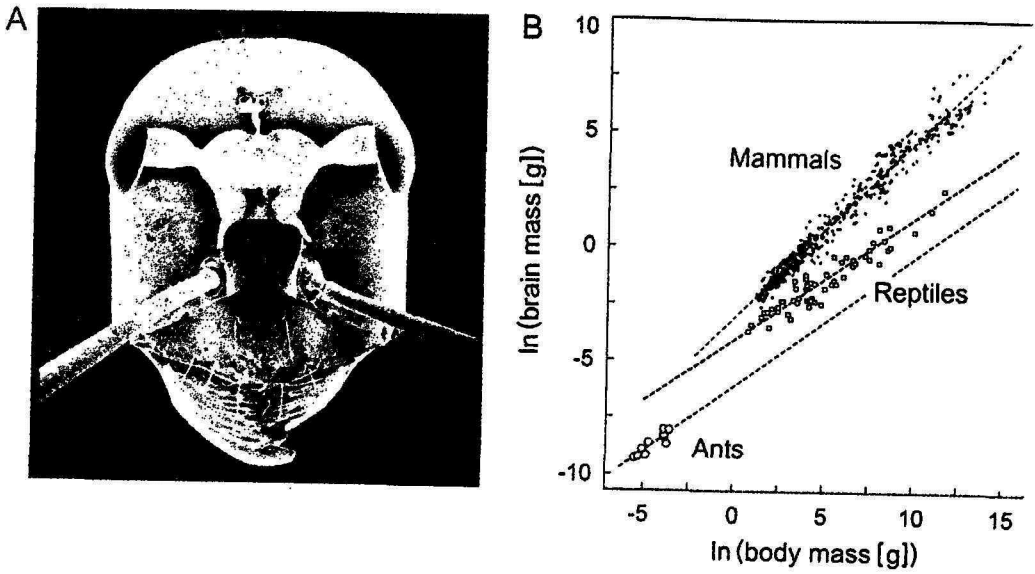

Figure 1. *Cataglyphis bicolor.* **A** Frontal view of the head of a *C. bicolor* worker with brain superimposed (yellow). **B** Brain allometry: brain weight versus body weight (double-logarithmic scale) in terrestrial vertebrates (mammals, reptiles) and ants.

From small to large in the biological world

Live on earth ranges from the minute to the gigantic, from bacteria to higher vertebrates as large as baleen whales, and so do the ways of how this wide range of organisms has become the focus of research in the biological sciences: from molecular analyses to studies of animal behaviour. Bacteria have been the first in which DNA has revealed itself as the material substrate of genetic information [**3**], and primates (e.g., [**4**]) as well as other social mammals such as the ground-living meerkats [**5**] are now model organisms in research on high-level cognitive functions.

Within the vast range of organisms only animals are endowed with fast, elaborate and often extremely sophisticated ways of information processing mediated by nervous systems. Again, the levels of complexity range from mere basiepithelial nerve nets in cnidarians such as polyps and jelly fish [**6**] to massive brains in cephalopods [**7**] and vertebrates [**8**]. And it is also here, in the realm of the biological computers, that the focus of research spans a wide range of conceptual and methodological approaches: from the molecular and cellular to the neurophysiological and behavioural. In small nerve nets consisting of, say, no more than about 30 nerve cells as is the case in the crustacean stomatogastric ganglion, a neural circuitry programmed for nothing but coordinating the chewing movements of the lobster's stomach, the workings of individual

nerve cells, synapses, neurotransmitters, and molecular receptors are in the limelight of current research [**9**], while the complex behaviours mediated by large brains render organismal systems approaches and detailed behavioural analyses absolutely necessary. For example, in trying to unravel how the brains of sea turtles [**10**] or migratory birds [**11**] enable their owners to steer proper courses over thousands of kilometres, state-of-the-art techniques such as behavioural molecular mapping of avian brains [**12**] or satellite based telemetry of freely moving animals [**13**], to mention just two, have to be included into the experimental tool bag.

Within this range from small to large, from simple to complex, insects hold a somewhat middle position. Their brains are small enough to be amenable to neurophysiological analyses, but their behaviours are complex enough to be of interest even to the cognitive scientist. This middle position reflects itself in discussions now going on for more than hundred years about whether insects - especially social insects such as wasps, ants, and bees - are mere "reflex machines" [**14**] capable of nothing but strictly stereotyped modes of behaviour performed "with mathematical precision" [**15**] and occasionally dubbed "sphecism" (derived from the Latin name for the digger wasp, *Sphex*; [**16**]), or whether higher "psychological functions" [**17**], some degrees of "intelligence" [**18-20**] or even "cognitive" capacities [**21**] have to be assigned at least to the most-highly advanced insect species. Even though all of these arguments are, of course, profoundly semantic, the debate about the insect's prerational intelligence highlights an important point: insect behaviour is characterized by rigid, stereotyped, automaton-like performances strictly prewired in the insect nervous system as well as by experience-based contextual adaptability, flexibility, learning and memory. The question is how this flexibility riding on rigidly preordained modes of behaviour comes about – or, in neurobiological terms - what the structure and dynamics of the insect's neural toolkit look like.

A unique model organism: *Cataglyphis*

Spatial navigation is a useful topic to investigate the kind of question raised above. In trying to do so I return to the extraordinary, awe-inspiring navigational capabilities of the desert ants mentioned in the beginning. These elegant, long-legged, extremely speedy *Cataglyphis* ants (Figure 2), the racehorses of the insect world, inhabit the sand-dune and gravel-plain deserts of North Africa [**22**] and Southwest Asia including Saudi Arabia [**23**]. They explore these harsh and food-

impoverished environments individually, not by following scent trails as the much more numerous seed-collecting harvester ants do, but by performing path integration. At our field station in Maharès (Tunisia) we have dissected the ant's behaviour in detail and have unravelled the decisive steps in the ant's path

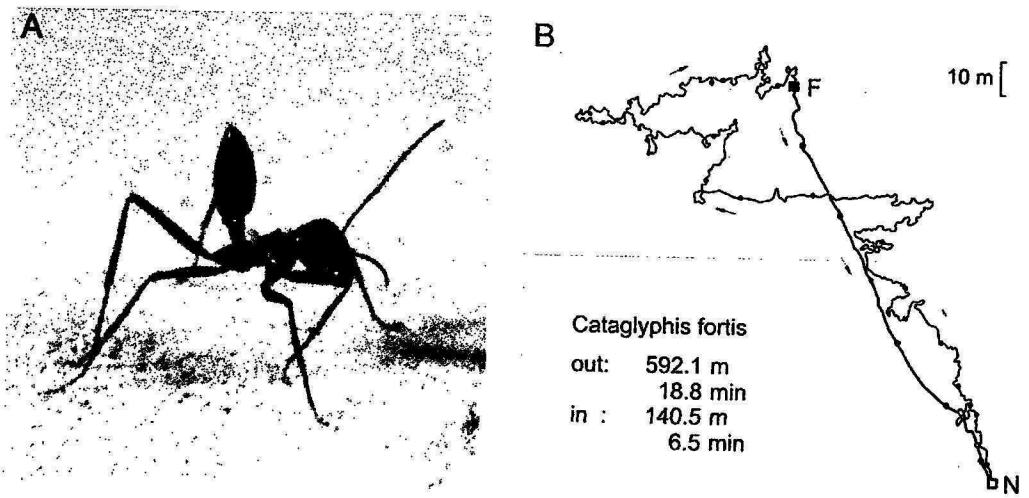

Figure 2. A *Cataglyphis bicolor* in full alert. The gaster is held in an upright position to reduce overheating as well as the moment of inertia during turning movements. **B** Outbound (black) and inbound (red) run of a forager, *Cataglyphis fortis*. N, position of nest; F, place where the ant had found a food item, a dead fly.

integration system: the skylight compass and the proprioceptive odometer as well as the vector-summation and vector-subtraction scheme, by which the ants finally integrate the angular (compass-mediated) and linear (odometer-mediated) components of their movements into a path-integration vector. Hence, path integration turns out to be "vector navigation" [**1**].

Cataglyphis is a unique model organism, because in these desert ants fine-grain behavioural analyses can be experimentally combined with anatomical and physiological studies of the animal's nervous system. The brain itself is tiny not only by absolute standards (0.1 mg) but also in relation to body size: it is smaller than the brain of any terrestrial vertebrate species, had this vertebrate the body mass of an ant [**24**] (Figure 1B). How comes that such a mini brain can accomplish mega tasks, e.g., computations as complex as those involved in vector navigation?

The polarization compass – reading skylight patterns

The *Cataglyphis* compass is a case in point. It relies on an optical phenomenon in the sky that we humans are unable to see, the pattern of polarized light [**25-28**]. This is a complex pattern varying with the position of the sun (Figure 3). However, rather than depending on the complete knowledge of these patterns, the ants apply a robust shortcut strategy by referring only to some global pattern features.

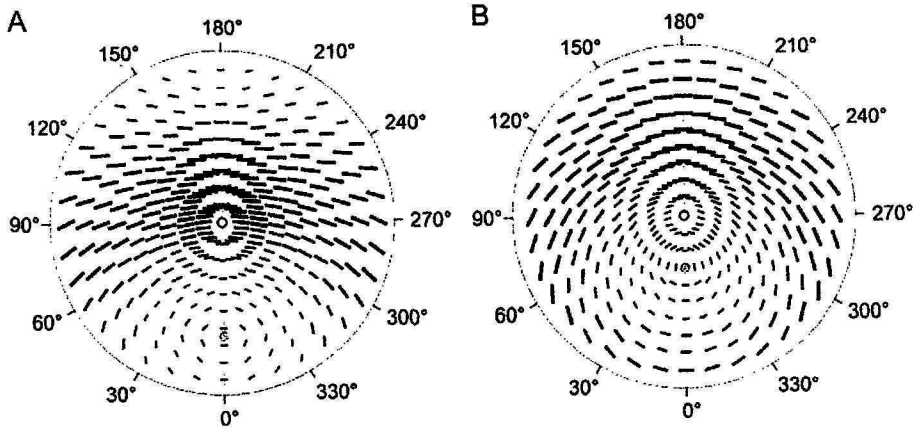

Figure 3. The pattern of polarized light in the sky. The orientation and size of the blue bars depict the angle and degree of polarization, respectively. Yellow disc, sun at elevations of 25° (**A**) and 60° (**B**) above the horizon; open circle, zenith.

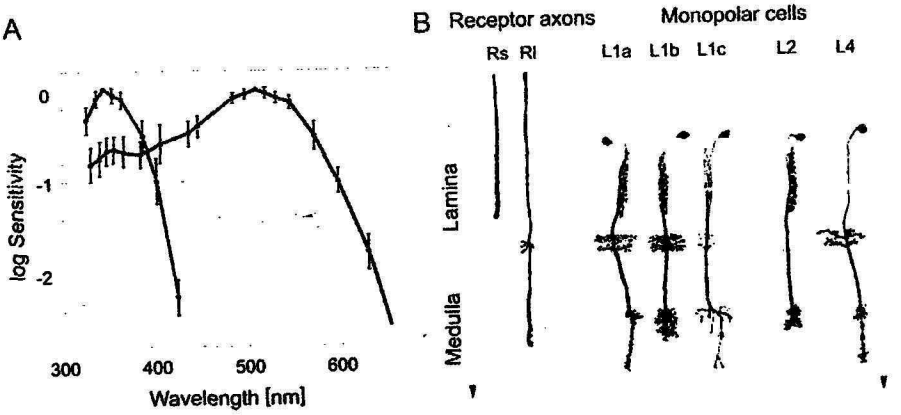

Figure 4. A Spectral sensitivity functions of the ultraviolet and green receptors of *Cataglyphis bicolor* as deduced from intracellular electrophysiological recordings. **B** Receptor axons (green and pink) and interneurons (black) of the lamina.

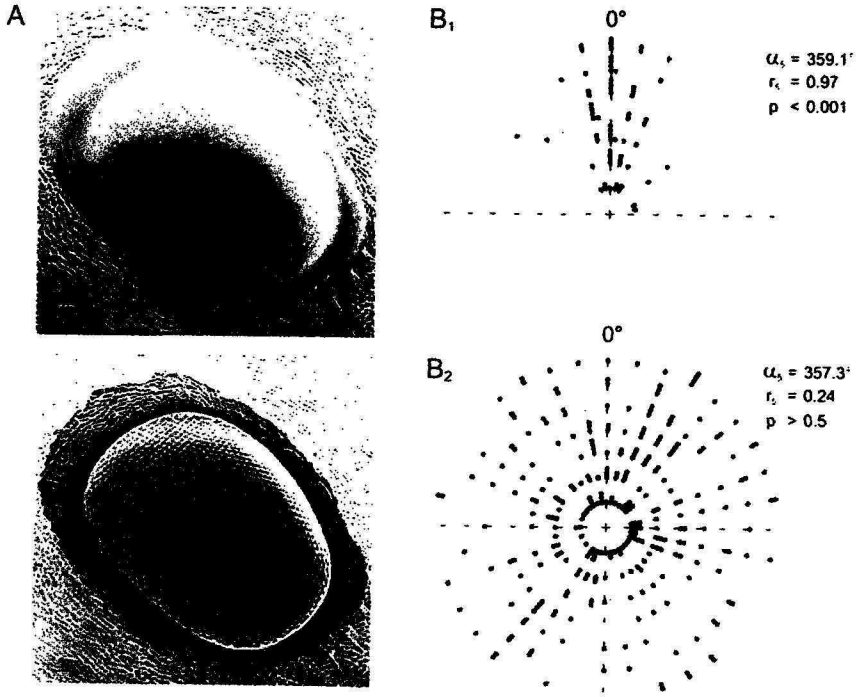

Figure 5. A Transparent sheet applied to the compound eye of a *Cataglyphis bicolor* worker (above) and removed from the eye (below), so that the behaviour of the same animal could be tested in a post-experimental control. The optical transmission characteristics of the eye cover allow only particular spectral wavelengths to reach the ant's photoreceptors. **B** Directional choices of ants, which due to proper eye covers could see only the short-wavelength (ultraviolet, $\mathbf{B_1}$) or long-wavelength (green, $\mathbf{B_2}$) part of the skylight spectrum. The homeward direction is denoted by 0°. As the ant's directional choices show, the skylight compass works only in the ultraviolet range of the spectrum. Only in this case are the ants oriented in their home direction.

Specialised photoreceptors located at the uppermost dorsal rim of the eye and sensitive to ultraviolet as well as polarized light pick up the information from the sky (Figures 4 and 5). A neural circuit underlying these receptors ensures that the polarization compass becomes insensitive to fluctuations of ambient light intensity as they occur during the course of the day. The intensity-invariant information is then channelled into a set of large, wide-field integrator neurons (Figure 6), which span the width of the entire brain and combine information form the left and right eye [**29**] (reviews [**30, 31**]). Finally, an array of compass neurons [**32, 33**] reads the outputs of the integrators and tells the animal in which direction

it is running (relative to the solar or anti-solar azimuth, the zero point of the polarization compass).

This wide-field, low-pass neural solution of a complex visual problem is smart, as it helps to attenuate more or less random response variations caused by atmospheric disturbances, but it has snags. Large, non-random disturbances in the skylight patterns caused, e.g., by varying distributions of clouds, lead to variations in the integrator response profiles, and, hence might result in navigational errors. These errors caused by systematic experimental variations of the ant's view of the sky enabled us to unravel the ant's compass strategy [**34**]. As a result, *Cataglyphis* exploits only the

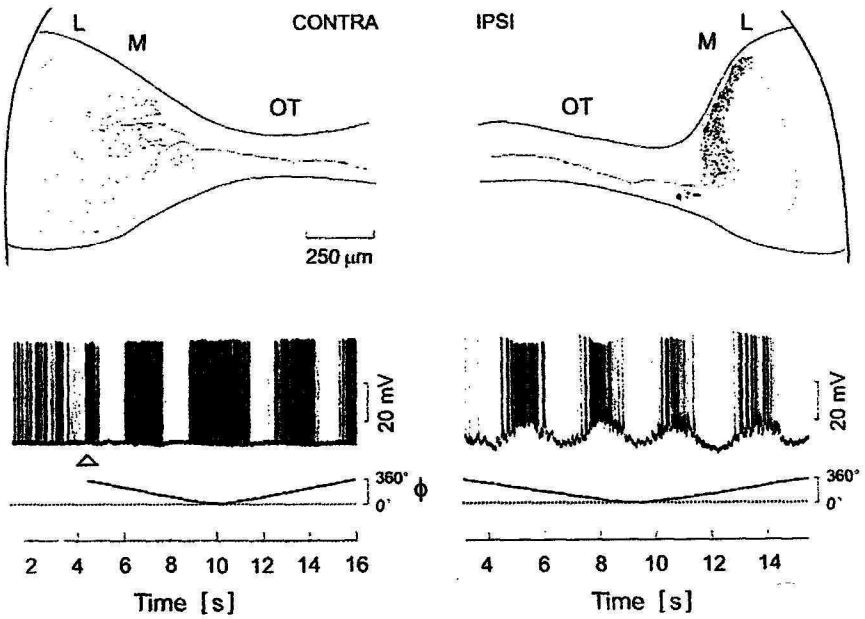

Figure 6. Polarization-sensitive integrator neuron of *Gryllus campestris*. Right: input side, left: output side. L, lamina; M, medulla; OT, optic tract. Below: intracellular recordings from the input (right) and output (left) part of the neuron as the angle of polarization rotates through 360°. Every 180° the neuron fires maximally.

relatively simple geometrical rules that characterize the global skylight pattern. It disregards the local details of these patterns. In general terms, this tells us that we should never underestimate the functional economy of nervous systems.

The odometer – stepping on stilts and stumps

The ant's odometer represents another economic solution to a long-standing problem in neuroethology. Our high-speed cinematographic studies, which showed that *Cataglyphis* ants when foraging at a given ambient temperature maintain a constant stride length, prepared the ground for a rather straightforward hypothesis: in gauging distances travelled the ants could just count the number of steps necessary to cover a particular distance. And, in principle, this is what they actually do. Animals, in which micro-surgery had been used to lengthen or shorten their legs, and which consequently walked on stilts or stumps, unambiguously showed that *Cataglyphis* assesses distance travelled by employing a stride integrator [**35**]. Stilters and stumpers in which leg length had been increased or decreased just before the animals started their homebound runs, overshot or undershot their goal, respectively, and did so by the amount exactly predicted by the experimentally altered lengths of their strides (Figure 7). We currently work on the question of how stride length is monitored by the ants' sensory and nervous system. Whatever the mechanisms are, mechanoreceptive (proprioceptive) inputs from the legs and leg joints are certainly involved.

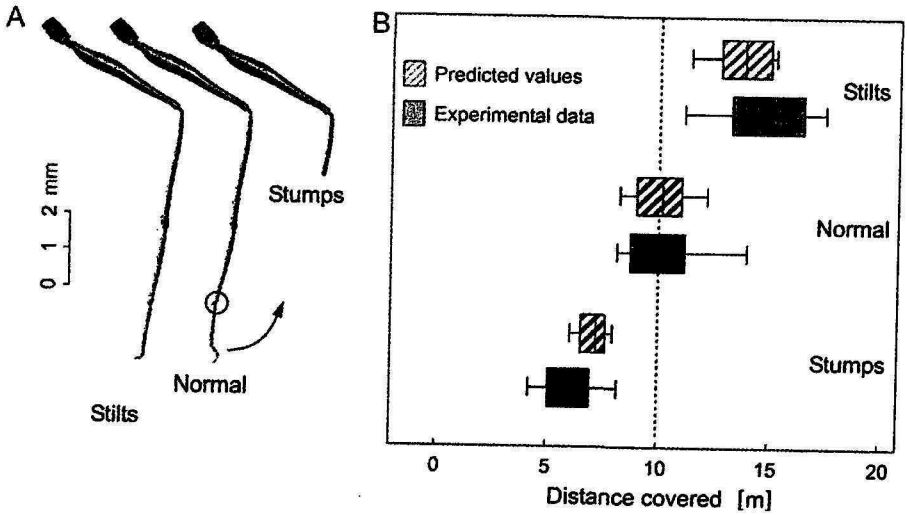

Figure 7. Stumpers and stilters in *Cataglyphis fortis*. Shortening or lengthening the ant's legs (**A**) – the latter by gluing fine bristles to the tibiae and tarsi – decreases or increases the ant's stride length, respectively. As a consequence, the stilters overshoot the training distance (10m), while the stumpers undershoot it (**B**, filled box plots) by the amounts predicted from the altered stride lengths (hatched box plots).

Within the path integrator, odometer information is used only if compass information is available simultaneously. If the latter is missing, e.g.,

when the animal has no access to the compass-relevant skylight cues, odometer output is discarded and the integrator is shut off [**36, 37**]. Hence, the integrator represents a mathematical "and-gate" in becoming active only if both the odometer and the compass circuit deliver proper information.

Landmark guidance – the mnemonic ant

When *Cataglyphis* forages within the vast and essentially featureless terrain of the Saharan salt pans, path integration is the only means of acquiring positional information. However, any path-integration mechanism is by necessity prone to cumulative errors: the longer the journey, the larger the overall errors [**38, 39**] (Figure 8A). To compensate for these errors *Cataglyphis* employs an efficient search strategy by performing a system of loops of ever-increasing size around the point at which the path integrator had been reset to zero, i.e., where the goal is to be expected [**2, 40-42**]. As the ant's looping system expands the more, the farther the animal has originally ventured out form the nest (Figure 8B), one could say, that, in mathematical terms, the search density profile is adapted to the target probability function.

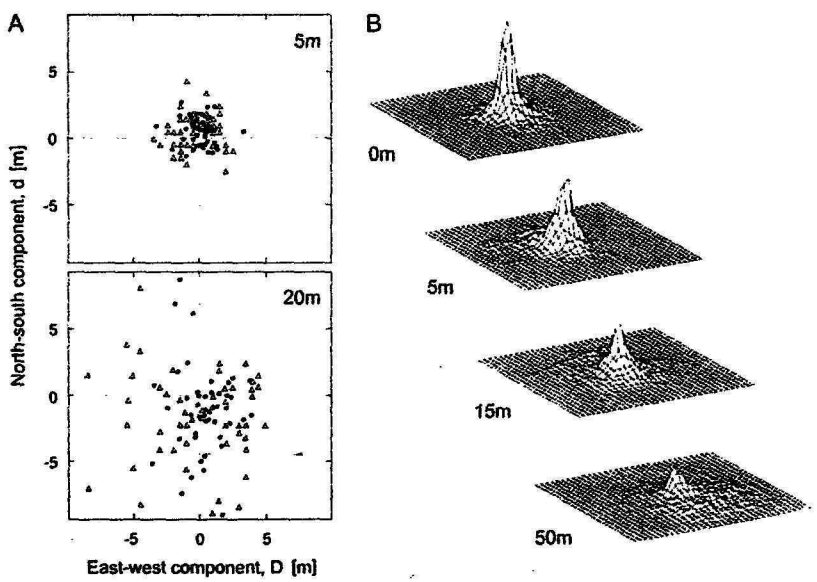

Figure 8. A Error accumulation in path integration. The signatures depict where the ants, *Cataglyphis fortis*, start to search for the nest after they have returned from a short (5m) or long (20m) foraging trip. **B** The search density profile is the wider, the larger the distance is from which the ants have returned (0 - 50m).

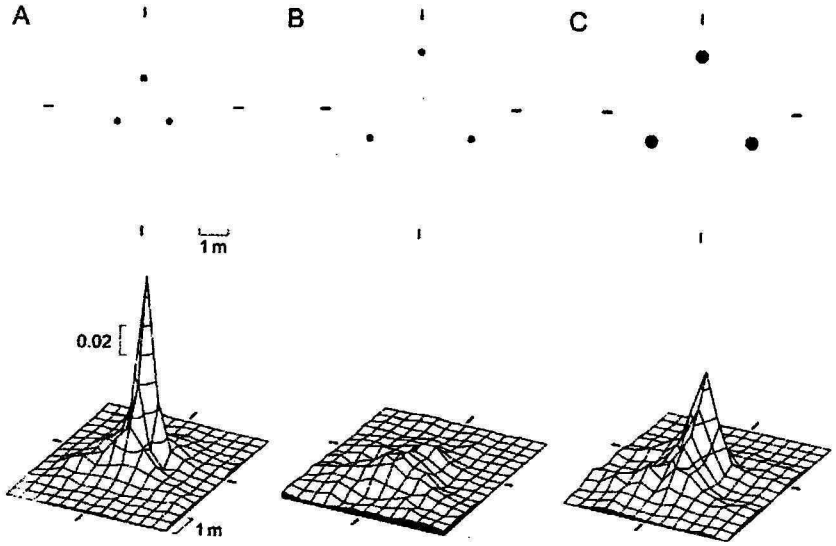

Figure 9. Landmark-based matching-to-memory strategy. The ants have been trained to the centre of an array of three cylindrical landmarks (black dots as shown in left upper panel) and tested under the three landmark configurations A, B and C. The lower panels depict the ants' search density profiles (red). **A** Control test (landmarks as in training). **B, C** Critical tests with the landmarks presented at double training distance (**B**) or presented at double training distance and simultaneously increased to double training size (**C**). In **C** the retinal image of the landmark array as seen from the goal coincides with that of the training situation (**A**), but in **B** it does not.

However, in most cases desert habitats are not completely devoid of landmarks, be they stones, tussocks of grass, or small shrubs. Whenever such landmark information is available, *Cataglyphis* makes intensive use of it [**43-45;** for wood ants see **46**] (Figure 9). It employs some kind of image matching algorithm by comparing a retinotopically stored image with the current image and trying to reduce the mismatch between the two. When the mismatch has become zero, the ant has reached its goal [**46-48**] (Figure 10A). We have incorporated such an algorithm into a robot, dubbed "Sahabot", which localized a landmark-defined goal just as the ants did (Figure 10B).

Furthermore, *Cataglyphis* can follow fixed routes by learning landmarks distributed along the "visual corridors" defined by these routes. It can learn different routes for its inbound and outbound journey, and different inbound and outbound routes as well. It does so by acquiring amazing memory stores, remembering simultaneously several sequences of

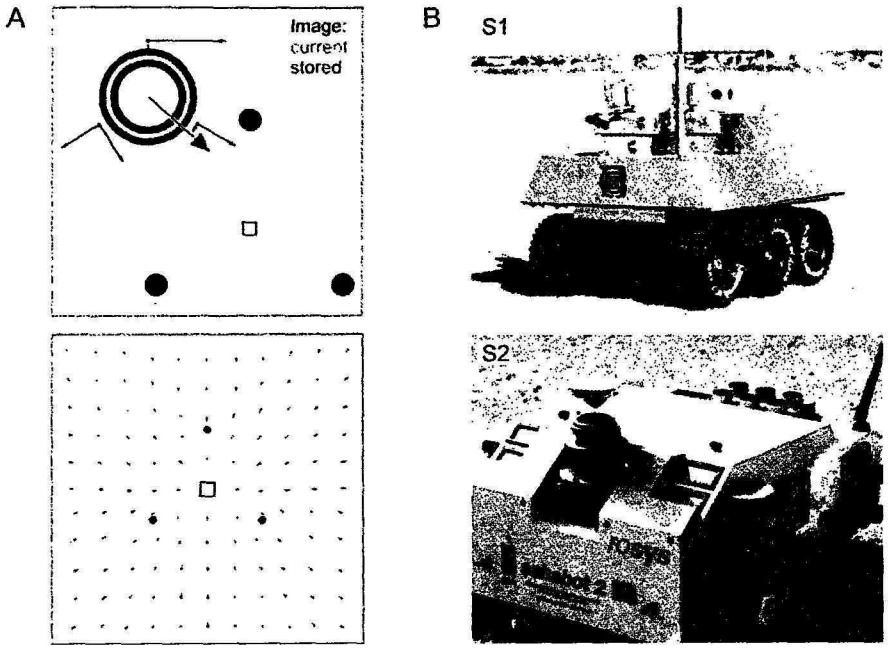

Figure 10. A Image matching algorithm. While navigating, the ants try to match their stored (training) image of the landmark array (inner annulus, pink) with the one perceived at the ants' current position (outer annulus, green). The landmark array is the same as in Figure 9. The algorithm based on the black radial and tangential arrows predicts in what direction (orange arrow) the ants should move in order to get a better match of their current and stored images. **B** Autonomous agents (robots "Sahabot 1 and 2") designed to steer their courses according to the polarization patterns in the sky (S1) and to an array of three cylindrical landmarks (algorithm outlined in Figure A). In S2 a conical mirror is used to project the images of the landmark arrays onto a digital 360° CCD camera. For details of algorithms see [**47**].

landmarks, like pearls on a mental string. The still unanswered question is whether there are really distinct pearls, visual views of places, connected by site-based (local) vectors [**49, 50**], or whether the animals monitor and store visual flow fields of the landmark scenes passing across the ant's wide-angle compound eyes as the animal moves along these routes. The amount of landmark information an individual ant can pick up, remember, and store for extended periods of time is absolutely amazing, really enthralling. Furthermore, *Cataglyphis* can even assess the uncertainty inherent in localising a goal that has been approached

from different distances, and adjust its path-integration vector accordingly [**51, 52**]

In spite of its extensive use of landmark information, *Cataglyphis* does not behave like a cartographer acquiring a graph-like representation of the distribution of landmarks in its foraging terrain. Rather it behaves like a mnemonist storing several landmark-based routes potentially over the entire time of its foraging life [**53**]. It follows path-integration vectors and landmark-based routes, but does not use this landmark information to define positions within a geocentred grid or some other graph-like representation [**30**]. Following procedures rather than computing spatial positions is the insect's way of navigation.

The general lessons *Cataglyphis* has told us are at least twofold. First, the ant's navigational machinery is programmed to solve particular problems encountered by the animal during its foraging lifetime. Certainly, natural selection has not allowed a miniscule brain to provide space and energy for computational and storage capacities, for first-principle approaches, that are not of immediate use to the navigator, particularly because in energetic terms the brain is by far the most costly organ of any animal [**54**]. Second, the particular navigational modules used by *Cataglyphis* (e.g., the skylight compass, the proprioceptive odometer, the path integrator, the image-matching device, the search generator) are interlinked only loosely and do not feed their information into some kind of central processing unit. Seen in this light – and returning to the discussion entertained in the beginning of this essay - *Cataglyphis* does not "think" in any way we humans think of thinking.

Acknowledgments. I would not have been able to tell the story outlined in this essay had I not got the chance to cooperate over now forty years of research with dozens of wonderful, highly motivated and skilful graduate students. Wherever they are now in the world – many hold university positions in various countries – it is also here that I would like to express my sincere thanks to them. We had great times together, out in the Arabian sands and thereafter in our Zürich laboratories. In the beginning, it was a risky endeavour to focus my major research activities on what was then a peculiar organism inhabiting the harsh environment of the Saharan desert and being hitherto unknown to the community of neuroethologists. All the more do I feel extremely honoured that my life-long work centred on the sensory and computational capabilities of this remarkable insect has been recognized to such an extent that the King Faisal Foundation rewarded me its prestigious International Prize for Science.

References: [1] Wehner, R. (1982): *Neujahrsbl. Naturf. Ges. Zürich* 184, 1-132. [2] Wehner, R., Wehner, S. (1990): *Ethol. Ecol. Evol.* 2, 27-48. [3] Avery, O.T., Mac Leod, C.M., Mc Carty, M. (1944): *Exp. Med.* 79, 137-158. [4] Schaik, C. van (2004): *Among Orangutans. Cambridge, Mass.: Harvard University Press.* [5] Manser, M. B., Seyfarth, R.M., Cheney, D.L. (2002): *Trends Cogn. Sci.* 6, 55-57. [6] Schmidt-Rhaesa, A. (2007): The Evolution of Organ Systems. *Oxford: Oxford University Press.* [7] Young, J.Z. (1971): The Anatomy of the Nervous System of Octopus vulgaris. *Oxford: Clarendon.* [8] Striedter, G.F. (2005): Principles of Brain Evolution. *Sutherland, Mass.: Sinauer.* [9] Marder, E., Bucher, D. (2007): *Annu. Rev. Physiol.* 69, 291-316. [10] Lohmann, K. J. (2007): *Curr. Biol.* 17, 102-104. [11] Berthold, P., Gwinner, E., Sonnenschein, E., eds. (2003): Avian Migration. *Berlin, New York: Springer.* [12] Liedvogel, M., Feenders, G., Wada, K., Troje, N.F., Jarvis, E.D., Mouritsen, H. (2007): *Europ. J. Neurosci.* 25, 1166-1173. [13] Weimerskirch, H., Wilson, R.P. (2000): *Nature* 406, 955-956. [14] Bethe, A. (1898): *Arch. Ges. Physiol.* 70, 15-100. [15] Fabre, J.H. (1882): Souvenirs Entomologiques. 2nd Serie. *Paris: Delagrave.* [16] Hofstadter, D.R. (1982): *Scient. Amer.* 247/3, 18-31. [17] Wasmann, E. (1899): *Zoologica* 26, 1-133. [18] Lubbock, J. (1889): On the Senses, Instincts, and Intelligence of Animals with Special Reference to Insects. *London: Paul, Trench.* [19] Emery, C. (1893): *Biol. Zbl.* 13, 151-155. [20] Forel, A. (1922): Mensch und Ameise. *Wien: Rikola.* [21] Menzel, R., Giurfa, M., Gerber, B., Hellstern, F. (2001): in Roth, G., Wullimann, M.F., eds., Brain, Evolution and Cognition, pp. 333-366. *New York: Wiley.* [22] Wehner, R., Wehner, S., Agosti, D. (1994): *Senckenbergiana biol.* 74, 163-191. [23] Collingwood, C.A., Agosti, D. (1996): in Krupp, F., Mahnert, V., eds., Fauna of Saudia Arabia, Vol. 15, pp. 300-385. *Riyadh: National Commission for Wildlife Conservation and Development.* [24] Wehner, R., Fukushi, T., Isler, K. (2007): *Brain Behav. Evol.* 69, 220-228. [25] Wehner, R. (1994): *Fortschr. Zool.* 39, 103-143. [26] Wehner, R., Müller, M. (1985): *Nature* 315, 228-229. [27] Wehner, R. (2003): *Naturwiss. Rdsch.* 56, 134-140. [28] Wehner, R. (1998): *Spektrum Wiss.* 98/11, 56-67. [29] Petzold, J. (2001): *Ph.D. thesis, University of Zürich.* [30] Wehner, R. (2003): *J. Comp. Physiol A* 189, 579-588. [31] Wehner, R., Labhart, T. (2006): in Warrant, E., Nilsson, D.E., eds., Invertebrate Vision, pp. 291-348, *Cambridge, UK: Cambridge University Press.* [32] Hartmann, G., Wehner, R. (1995): *Biol. Cybern.* 73, 483-497. [33] Heinze, S., Homberg, U. (2007): *Science* 315, 995-997. [34] Wehner, R., Müller, M. (2006): *Proc. Natl. Acad. Sci. USA* 103, 12575-12579. [35] Wittlinger, M., Wehner, R., Wolf, H. (2006): *Science* 312, 1965-1967. [36] Sommer, S., Wehner, R. (2005): *Naturwissenschaften* 92, 468-471. [37] Ronacher, B., Westwig, E.,

Wehner, R. (2006): *J. Exp. Biol.* 209, 3336-3343. [**38**] Wehner, R., Wehner, S. (1986): *Minitore Zool. Ital., N.S.* 20, 309-331. [**39**] Merkle, T., Knaden, M., Wehner, R. (2006): *J. Exp. Biol.* 209, 3545-3549. [**40**] Wehner, R. (1992): in Papi, F., ed., Animal Homing, pp. 45-144. *London: Chapman and Hall.* [**41**] Wehner, R., Srinivasan, M.V. (1981): *J. Comp. Physiol.* 142, 325-338. [**42**] Müller, M., Wehner, R. (1994): *J. Comp. Physiol. A* 175, 525-530. [**43**] Wehner, R., Räber, F. (1979): *Experientia* 35, 1569-1571. [**44**] Möller, R. (2001): *J. Theor. Biol.* 210, 33-45. [**45**] Wehner, R. Michel, B., Antonsen, P. (1996): *J. Exp. Biol.* 199, 129-140. [**46**] Graham, P., Collett, T.S. (2002): *J. Exp. Biol.* 205, 2499-2509. [**47**] Lambrinos, D., Möller, R., Labhart, T., Pfeifer, R., Wehner, R. (2000): *Autonom. Syst.* 30, 39-64. [**48**] Möller, R., Lambrinos, D., Roggendorf, T., Pfeifer, R., Wehner, R. (2001): in Webb, B., Consi, T.R., eds., Biorobotics, pp. 37-66. *Menlo Park: MIT Press.* [**49**] Bisch, S, Wehner, R. (1998): *Proc. Neurobiol. Conf. Goettingen* 26, 417. [**50**] Collett, M., Collett, T.S., Bisch, S., Wehner, R. (1996): *Nature* 394, 269-272. [**51**] Müller, M., Wehner, R. (1988): *Proc. Natl. Acad. Sci. USA* 85, 5287-5290. [**52**] Wolf, H., Wehner, R. (2005): *J. Exp. Biol.* 208, 4223-4230. [**53**] Sommer, S., von Beeren, D., Wehner, R. (2008) *Proc. Natl. Acad. Sci. USA* 105, 317-322. [**54**] Laughlin, S.B. (2004): in Gazzaniga, M.S., ed., The Cognitive Neurosciences, III, pp. 187-196. *Cambridge, Mass.: MIT Press.*

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