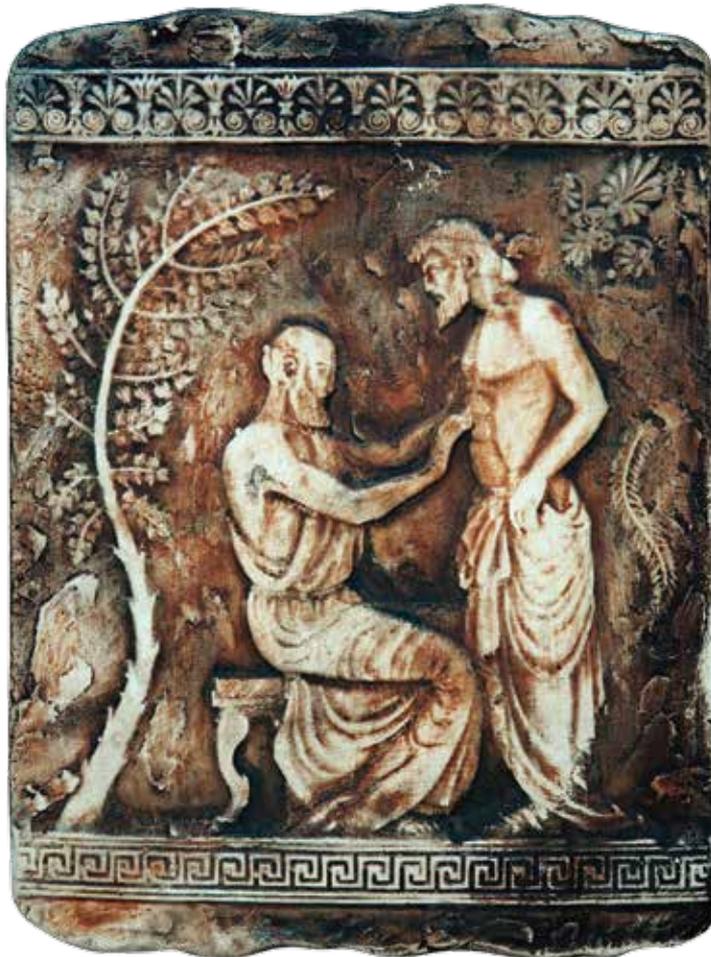


THE SPLEEN: Superfluous organ or immunological wonder?



Hippocrates examining the upper abdomen of a patient. Imagestock

Don K. Nakayama, MD, MBA

Don Nakayama, MD, MBA (AQA, University of California, San Francisco, 1977) is an Adjunct Professor at Florida International University.

The spleen, considered a structural oddity since the time of the Greek physician Aelius Galenus, has long been misunderstood.

For most of medical history its purpose and function was based on folklore. Military surgeons of the 17th century removed spleens that had been eviscerated in battle, as they

believed the organ was not necessary for life.

This raised the question, why was it there?

In the early 1900s, splenectomy for trauma was established dogma; however, by the end of the century everything was done to preserve the integrity of the spleen.

What changed?

A modern understanding of the spleen required the development of two new medical disciplines, hematology and immunology. In the 1940s, its role in sequestration and destruction of blood cells was clarified in hemolytic

diseases and hypersplenism. In the 1950s, its immunological functions were recognized as important in protecting the body against overwhelming bacterial infections. But the traditional view of the spleen as a dispensable organ held until the latter half of the 20th century, when clinicians arrived at a judicious and rational application of splenectomy, saving thousands from iatrogenic infection and death.

Form and function

Part of the mystery of the spleen is that its function was not clear from its anatomy, tucked behind the stomach high in the left upper quadrant. Adjacent to the stomach and pancreas, it is not part of the gastrointestinal tract, and has nothing to do with digestion. Antiquity considered it a gland, but it has no secretions that circulate through the body. Suffused with red cells and white cells, ancient anatomists reasoned that it, and not the bone marrow, was the source of blood.¹

Plump and purple with blood, the organ was thought by ancient anatomists to be the reservoir of anger. One who was “splenic” was hot-tempered and prone to outbursts called “venting one’s spleen.”¹ In Shakespeare’s play “Richard III,” the Duchess of York deplures the intrigues and murders caused by her villainous son. “O preposterous and frantic outrage,” she says to her widowed daughter-in-law Queen Elizabeth, “end thy damned spleen” (II, iv, 67–8).

The spleen’s dark purple hue also suggested that it was the repository of black bile, one of Galen’s four humors. Not having an identifiable route of efflux, like yellow bile from the liver, black bile in the spleen could build with unpredictable effects on mood and behavior. Its release was thought to cause not only anger, but “mirth and pleasure, of lascivious dreams, of imagination and golden age of life.”¹

Folklore faded with objective study of anatomy and histology. Marcello Malpighi, the 17th century father of microscopical anatomy, histology, physiology, and embryology found lymphoid follicles in the white pulp of the spleen.

Injecting splenic vessels with wax, in 1701, the Dutch botanist and anatomist Frederik Ruysch found a complex vascular meshwork that suggested its role as a filter.

In the early 19th century, the removal of senescent red cells from the circulation in red cords of the spleen began to be discerned. However, the German physician Rudolf Virchow resisted the concept of red cell destruction in the spleen, believing that cell death could not be a normal process.¹

What had been an academic exercise among scholars and anatomists in salons and lecture halls acquired clinical

importance when surgeons began to remove the spleen in the late 1800s. Misconceptions arose from lack of knowledge of immunology and hematology—disciplines that were nearly a century away.

Splenectomy

In the 16th and 17th centuries, barber-surgeons removed organs that protruded from battle wounds, the victims surviving without apparent ill effects. A 1743 report of a British dragoon who survived a splenectomy showed that ancient notions of the function of the spleen still held:

The dragoon, tho’ otherwise much wounded, recovered; and I saw him afterwards in good health. He had no stronger inclination for women than before.²

A ruptured spleen from blunt trauma was different from one hanging from a flank wound. It was detected only when bleeding caused physical signs of hemorrhagic shock. The only remedy—if surgeons recognized the problem and operated within hours—was splenectomy. In his 1911 *Textbook of Operative Surgery*, Theodor Kocher made a simple and direct recommendation:

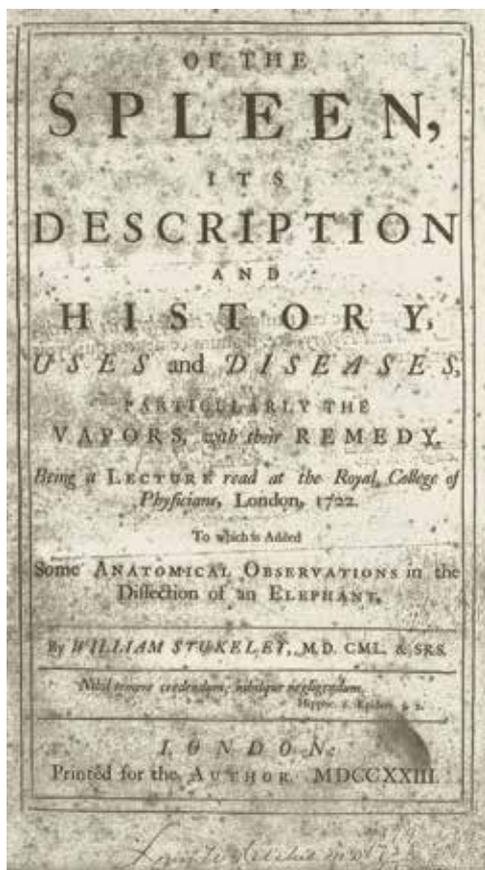
Injuries of the spleen demand excision of the gland. No evil effects follow its removal, while the danger of hemorrhage is effectively stopped.²

The first successful operation for splenic rupture from blunt trauma was December 9, 1892, on a 14-year-old laborer who fell from a scaffold. Recognizing the boy was close to death, the surgeon decided to operate. He removed the spleen, half of which was already lying free in the abdomen. The boy proved sturdy enough to survive his mishap despite a postoperative regimen that included 300 milliliters of saline administered by clysis, digitalis, and frequent small amounts of wine.²

At the time, surgeons knew that an enlarged spleen was associated with some terminal illnesses, and wondered whether its removal might be lifesaving.

Sir T. Spencer Wells, surgeon to Queen Victoria’s household, during an 1862 meeting of the Pathological Society presented:

The spleen could be removed very easily in dogs and other animals; they seemed to remain perfectly well without a spleen, and there certainly could not be more difficulty in removing a large spleen from the human body than a large



Title page from the lecture by Stukeley delivered to the Royal College of Physicians in 1722. Wellcome Library, London

ovarian tumor....[If] I met with a case where the patient was evidently being killed by a large spleen, where all remedies had proved useless...I would certainly be disposed to remove the tumor.²

He got his chance in 1864. His patient was showing slow but certain recovery from splenectomy when she suddenly died five days after surgery, her pulmonary arteries filled with clots at post-mortem. Despite his disappointment, Wells noted that aside from a small amount of pus around the ligatures, they had held and the operation had been a technical success.³

In 1866, Thomas Bryant, of Guy's Hospital in London, performed a splenectomy in an attempt to cure leukemia. Because the spleen filled with white cells in cases of leukemia, he reasoned that the organ must be the source of immature white cells in the circulation. His patient died within an hour of surgery. Undaunted, he persisted and performed another 50 splenectomies for leukemia over the next 20 years, his patients suffering an 88 percent mortality rate.¹

In 1887, Wells got another chance when he performed the first splenectomy for hematological disease. A socially

active woman in her twenties had intermittent episodes of jaundice, abdominal pain, and an enlarging abdominal mass from childhood. After suffering a severe attack, she insisted that a surgeon be called to relieve her of the mass. Wells surmised that the tumor was a uterine fibroid or an ovarian cyst, but upon opening her abdomen he discovered a hugely enlarged spleen. Her uterus and ovaries were normal. His laconic description of delivering the spleen from the abdomen belies the panic that countless surgical residents would later feel, "On attempting to press out the spleen with one hand passed behind it, an accidental rupture was followed by very free bleeding."⁴

Without recourse, he removed the organ and the patient recovered. Not only was she relieved of discomfort from the mass, but remained free from jaundice and "seem[ed] to do better without a spleen than with one."⁴

More advanced planning was involved in the first splenectomy for immune thrombocytopenic purpura (ITP). In 1916 in Prague, medical student Paul Kaznelson made the connection between platelet destruction in the spleen and thrombocytopenia in cases of purpura simplex. Just as splenectomy ameliorated some cases of hemolytic anemia, he surmised that the procedure might correct platelet counts in certain cases of purpura. He convinced his surgery tutor, Hermann Schloffer, to remove the spleen in a 36-year-old woman who had a history consistent with ITP. The operation successfully returned platelet counts to normal, and her lesions resolved.⁵

The occasional cures justified surgery for splenomegaly with hope that removal of the spleen would somehow make the patient better, especially in cases complicated by anemia. In a review of the 739 splenectomies in the literature up until 1905, many were performed for non-specific indications such as hypertrophy (176 of 739, 23.8%), anemia, leukemia, and "pseudoleucaemia," with a mortality of more than 25 percent.⁶

In 1910, William Mayo (AΩA, University of Michigan, 1927, Honorary) was candid in his assessment:

Our knowledge of the function of the spleen has been so vague, and our ability accurately to determine its physical proportions so unreliable, that it has been impossible to recognize diseased conditions until they reached a stage so advanced that splenectomy became a necessary consequence....[Many] of the anemias and associated blood states may ultimately be best treated by operative procedures directed to the spleen and other blood-forming organs.⁷

Over the next two decades, hematology as a discipline

began to mature, and clinical experience accumulated so that clinicians recognized conditions where the procedure was effective. Although the diagnostic terms were archaic, in 1930, pediatrician Thomas B. Cooley, and his surgical consultant Grover C. Penberthy (AQA, University of Michigan, 1949, Alumnus), identified diseases that responded to splenectomy: hemolytic icterus (a term that today includes hereditary spherocytosis), purpura hemorrhagica (immune thrombocytopenic purpura), and erythroblastic anemia (thalassemia major, a disease defined by Cooley that also bears his name). They determined it was ineffective in aplastic anemia, leukemia, and Banti's disease (portal hypertension due to cirrhosis of the liver). In sickle cell anemia, it would relieve pain from sequestration crises and splenic infarction, but had no effect on the underlying pathology.⁸

Splenectomy was an option of last resort in conditions that defied treatment, or lacked a precise diagnosis. Not surprisingly, the results were disappointing. Examples included splenic anemia, "the waste basket diagnosis of pediatric hematology,"⁸ and erthroblastosis fetalis (hemolytic disease of the newborn from Rh incompatibility). Faced with a baby with profound jaundice and anemia, the infant's spleen was removed in desperation. Reading Cooley's and Penberthy's case report, the baby's recovery was due to transfusions received after surgery and gradual clearance of maternal antibodies to fetal red cells. However, they were convinced that splenectomy somehow helped in this case, and speculated that surgery earlier in its course would reverse more aggressive cases.⁸ "[The] vogue for splenectomy in various conditions is undoubtedly increasing," they noted.⁸ For certain diagnoses it worked, and, after all, like the appendix, patients didn't need their spleen.

Post-splenectomy sepsis

Not everyone thought that the spleen was so easily expendable. In 1903, Nicholas Senn, a member of the founding editorial board of *Surgery, Gynecology, and Obstetrics*, was prescient in his caution against unwarranted removal of the spleen:

The spleen has its important functions to perform, and, although in its absence other organs appear to assume its role in the organism and compensate for its loss, we as yet are not warranted in assuming that its removal is a matter of so little consequence that it is not necessary to limit it to cases in which no other alternative is left.⁹

As splenectomy became commonplace in the 20th

century, it often led to post-splenectomy sepsis. Within days, or even years, after splenectomy, patients would develop the sudden onset of a high fever, with vomiting, headache, and confusion. Well and healthy hours before, their condition would rapidly deteriorate despite massive doses of antibiotics. Coma or death often followed in as few as one or two days. Infants appeared to be especially vulnerable.²

The illnesses were generally meningitis, pneumonia, or septicemia and shock. Patients suffered a fulminant course that resisted resuscitation and antibiotic therapy. Involved bacteria were pneumococcus in half of cases, followed by meningococcus, *Escherichia coli*, *Haemophilus influenzae*, staphylococcus, and streptococcus, in decreasing frequency. Some cases involved disseminated intravascular coagulation and adrenal necrosis (Waterhouse-Friderichsen syndrome).²

In 1919, researchers Dudley Morris and Frederick Bullock injected rats that had undergone splenectomy with plague bacillus. Animals that had lost their spleens had a mortality rate of 81 percent, much higher than the 39 percent in controls with a spleen. They warned surgeons that the spleen might be important in human immune defenses:

It is not improbable that the human body deprived of its spleen shows a similar increased susceptibility to infection. Bearing this in mind, some of the fatalities following splenectomy, especially where death was attributed to infection, may find a ready explanation and tend to increase our caution in the removal of this organ.¹⁰

Complete understanding of the problem was hampered by incomplete follow-up of patients. Few reviews followed patients beyond discharge from the hospital.²

In 1952, Indianapolis surgeons Harold King and Harris Schumaker, Jr., made a disturbing finding in their review of about 100 cases at the Indiana University Hospitals. Five infants with hereditary spherocytosis suffered severe bacterial infections two-and-a-half months to three years after surgery—four had meningitis, and two died. Splenectomy had left the infants vulnerable to infection.¹¹

It was a difficult concept, a beneficial operation was putting patients' lives at risk. Most susceptible were those with thalassemia major and hereditary spherocytosis, both uncommon diseases rarely encountered outside of referral centers for hematological disorders. A surgeon might see one or two cases in a lifetime.

The injured spleen

Splenectomy was lifesaving when major ruptures led to large amounts of bleeding and shock. Nineteenth century dogma held that spleens with minor injuries also required splenectomy to prevent later blood loss from delayed rupture, a phenomenon where a hematoma would suddenly bleed freely into the peritoneal cavity when the splenic capsule gave way a few days after the initial insult.¹²

Injuries also occurred during elective surgery. Residents were taught that it was simpler to remove a bleeding spleen than to try to repair it.

Surgeons resisted changing their approach to the injured spleen. Studies by the Johns Hopkins Hospital,¹² and the Children's Hospital in Boston¹⁴ concluded post-splenectomy sepsis was a phenomenon confined to infants and certain hematological disorders. Healthy older children and adults who had their spleen removed due to an injury were not at risk. "Fear of increased infection," J. Alex Haller (AΩA, Johns Hopkins University, 1951) of Hopkins wrote in 1966, "should not interfere with performance of splenectomy."¹³

One year later, Angelo Eraklis, of Boston, came to the same conclusion, "[Splenectomy] may be carried out without fear of increased susceptibility to fatal infection."¹⁴ Published in the *New England Journal of Medicine*, with co-authors Louis Diamond (AΩA, Harvard Medical School, 1951, Alumnus), one of the founders of pediatric hematology, and Robert Gross (the foremost pediatric surgeon of the era), the article carried the weight of authority.

In 1973, Don Singer, of Houston, clarified the issue in an extensive review of all reported cases since Harris and Schumaker's report—2,795 patients with splenectomy, including 688 trauma cases. Patients with blood disorders were more susceptible to severe infections after splenectomy; of those with thalassemia, one-quarter (24.8 percent) developed post-splenectomy sepsis, with an 11 percent mortality. The rates for splenic injuries were much lower, 1.45 percent and 0.58 percent, respectively, more than 50 times the rates of the general population. Older children and adults were not spared, and remained susceptible.¹⁵

Immunological functions

Researchers confirmed the immunological functions of the spleen, finding that tuftsin, a polypeptide produced primarily in the spleen, stimulates maximal phagocytic activity in macrophages and neutrophils.¹⁶ The marginal zone in the white pulp of the spleen was found to be the major site for generation of T cell-independent antibody responses, the immune system's major defense against carbohydrate antigens of bacterial capsules.¹

In 1980, Roger Sherman, the president of the leading organization of trauma surgeons in the U.S., stated, "A major role of the spleen in host defense to infection is no longer controversial."²

Clinicians began to rethink their approach for hematological conditions. They avoided surgery in infants and young children, and in cases where manifestations of the disease were relatively mild. Patients who came to surgery received long-term prophylactic antibiotics directed against the most common organisms implicated in post-splenectomy sepsis, pneumococcus, meningococcus, and *H. influenzae*. Immunizations against the organisms were added as they became available.

A self-healing organ

Surgeons recognized that injured spleens often stopped bleeding without surgical intervention.

In 1962, Marcelo Campos Christo of Brazil reported eight successful partial splenectomies for penetrating and blunt injuries in adult patients.¹⁸ In 1965, surgeons at the Hospital for Sick Children in Toronto reported that among patients undergoing surgery for a ruptured spleen, nearly half (19 of 40, 47.5%) had no active bleeding from the organ at the time of laparotomy. In another 12 patients, they made the clinical diagnosis of splenic injury on the basis of history and examination and were able to avoid surgery. Nearly 60 percent of the patients (31 of 52, 59.6%) with the clinical diagnosis of splenic injury did not require an operation.¹⁷

Not wanting to stray too far from surgical doctrine of total splenectomy for all injuries, the Toronto surgeons concluded that either repair or partial resection for splenic injury would be acceptable approaches to conserve splenic function.¹⁷

In 1971, at a professional meeting, Haller rose from the audience, and portraying the voice of the surgical establishment, made sure there was no misunderstanding:

I think, however, that some physicians may misinterpret the comments in the abstract, which favor conservative management of patients with splenic trauma. For that reason I think you must be careful not to give the impression that you recommend a non-operative approach to the patient with a ruptured spleen....[There] is no good evidence that a healthy child over 2 yr of age has any increased incidence of serious infection after splenectomy.¹⁹

Part of the reluctance to completely embrace a non-operative strategy was the difficulty in making the diagnosis of splenic injury. Symptoms often were vague and

non-specific, especially in a frightened child with other injuries. A left-side rib fracture or a shadow on a plain film of the abdomen might suggest the presence of a ruptured spleen, but required additional signs for assuredness.

Advances in imaging technology provided more precision in diagnosis of splenic injury, first with nuclear scans in the 1970s, then computed tomography (CT) in the 1980s. These two advances allowed surgeons to carefully monitor a stable patient without concern that a significant injury had been missed.

Surgeons in children's hospitals began to test a non-operative strategy. Using nuclear scans Dennis King of Columbus, Ohio, in 1981, reported a successful non-operative approach in 30 patients, and successful repairs in 16 more, an overall salvage rate of two-thirds (46 of 68, 67%).¹⁹

In 1988, Richard Pearl updated the experience at the Hospital for Sick Children where surgeons routinely used nuclear scans and began to apply CT. He reported an overall salvage rate of 95.9 percent (70 of 73), 65 (86.7%) not undergoing laparotomy, and another five undergoing repair or partial splenectomy.²⁰

By the 1990s, the non-operative approach to splenic injury had become standard,²¹ which also worked with liver injuries. New interventions to manage bleeding from the spleen were introduced—selective angiography, and embolization of the splenic artery—avoiding splenectomy for trauma.²²

Today's clinical strategy has immensely changed from splenectomy as a primary therapy to finding a safe and effective approach thereby avoiding removal of the spleen.

Over the centuries, the underlying rationale required new disciplines of medicine, hematology and immunology to correct generations of misconceptions, and misunderstanding of the spleen. Surgical practice has evolved prodigiously to reflect scientific and clinical evidence of the true nature of the spleen.

References

1. Wilkins BS. Historical Review. The spleen. *Br J Haematol.* 2002;117(2): 265–74.
2. Sherman R. Perspectives in Management of Trauma to the Spleen: 1979 Presidential Address, American Association for the Surgery of Trauma. *J Trauma.* 1980;20(1): 1–12.
3. Wells TS. Excision of enlarged spleen, with a case in which the operation was performed. *Med Times Gazette.* 1866;Jan 6: 2–5.
4. Wells TS. Remarks on Splenectomy, with a Report of a successful Case. *Med Chir Trans* 1888;71: 255–63.
5. Stasi R, Newland AC. ITP: a historical perspective. *Br J Haematol.* 2011;153: 437–50.

6. Carstens JH. A short history of splenectomy. New York: A.R. Elliott Publishing Co.; 1905.

7. Mayo WJ. Principles underlying surgery of the spleen: With a report of ten splenectomies. *J Amer Med Assoc.* 1910;54(1): 14–8.

8. Penberthy GC, Cooley TB. Results of splenectomy in childhood. *Ann Surg.* 1935;102(4): 645–55.

9. Senn N. The surgical treatment of traumatic hemorrhage of the spleen. *J Amer Med Assoc.* 1903;41(21): 1241–5.

10. Morris DH, Bullock FD. The importance of the spleen in resistance to infection. *Ann Surg.* 1919;70(5): 513–21.

11. King H, Shumacker HB. Splenic studies. I. Susceptibility to infection after splenectomy performed in infancy. *Ann Surg.* 1952;136(2): 239–42.

12. Evans C. Ductless glands: Rupture of the spleen from external violence. *Trans Pathol Soc London.* 1866;17: 299–301.

13. Haller JA Jr, Jones EL. Effect of Splenectomy on Immunity and Resistance to Major Infections in Early Childhood: Clinical and Experimental Study. *Ann Surg.* 1966;163(6): 902–8.

14. Eraklis AJ, Kevy SV, Diamond LK, Gross RE. Hazard of overwhelming infection after splenectomy in childhood. *N Eng J Med.* 1967;276(22): 1225–9.

15. Singer DB. Postsplenectomy Sepsis. *Perspect Pediatr Pathol.* 1973;1: 285–311.

16. Najjar VA, Nishioka K. 'Tuftsin': a Natural Phagocytosis Stimulating Peptide. *Nature.* 1970;228(5272): 672–3.

17. Upadhyaya P, Simpson JS. Splenic trauma in children. *Surg Gynecol Obstet.* 1968;126(4): 781–90.

18. Christo MC. Segmental resections of the spleen: Report on first eight cases operated on. *Hospital.* 1962 Sep;62: 575–90.

19. King DR, Lobe TE, Haase GM, Boles ET Jr. Selective management of injured spleen. *Surgery.* 1981;90(4): 677–82.

20. Pearl RH, Wesson DE, Spence LJ, et al. Splenic injury: A 5-Year Update With Improved Results and Changing Criteria for Conservative Management. *J Pediatr Surg.* 1989;24(5): 428–31.

21. Bond SJ, Eichelberger MR, Gotschall CS, et al. Nonoperative Management of Blunt Hepatic and Splenic Injury in Children. *Ann Surg.* 1996;223(3): 286–9.

22. Harbrecht BG. Is anything new in adult blunt splenic trauma? *Am J Surg.* 2005;190(2): 273–8.

The author's address is:

Sacred Heart Medical Group, Pediatric Surgery
5147 North Ninth Ave., Suite 318
Pensacola, FL 32504
Email: nakayama.don@gmail.com.