Dependability in Medicine and Neurology

Using Engineering and Management Principles for Better Patient Care

Nikhil Balakrishnan

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Nikhil Balakrishnan
Department of Neurology
Wake Forest University School of Medicine
Winston-Salem, NC, USA

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For Leah

Preface

Dependability is a concept that is well established in engineering and management. Expressed quite simply, a system is dependable if its performance can be justifiably trusted by the user. It is the basis for the world of airplanes, nuclear power, railway, and industrial automation, among others. This book explores the engineering, management, and regulatory principles behind dependability. It helps to understand the salient principles behind dependable systems to inspire their application in day-to-day healthcare.

This book was born of the extraordinary generosity and kindness of Dr. Pascal Traverse at Airbus Industrie, Dr. Ying C. Yeh at the Boeing Company, and Jamie Lambert at Wake Forest University. Their kind guidance helped me understand and explore the world of dependability. Dr. Traverse and Dr. Yeh encouraged me to pursue this work as an interdisciplinary undertaking so that the matter may be understood from several different perspectives and applied to the world of medicine. I am immensely grateful to Reliance Industries Limited (RIL), Mumbai, India, and BB&T (Branch Banking and Trust Corporation), Winston-Salem, USA, for sharing their ideas with me.

This book seeks to introduce physicians to engineering and management ideas well established in the industry. Medical education traditionally does not include contemporary management and engineering ideas. The hope is to inspire a generation of physicians who can think like the great engineers and managers of the iconic companies featured in this book to deliver *dependable healthcare*.

Gratitude is owed to many remarkable individuals who helped the long journey which led to this book. I am immensely grateful to Bryan Arkwright for lending me support during the crucial stages of this work. The roots of this journey began in 1993 at Medical College Kottayam where some very committed faculty dedicated themselves to making a physician out of a reluctant medical student. I enjoyed medical school due to the kindness of Dr. K. S. Raju, Dr. Rajsekharan Pillai, Dr. Alice George, Dr. Remani George, Dr. Sumadevi Balachandran, Dr. Agnesamma Jacob, Dr. S. Vaidyanathan, Dr. L. Rajam, Dr. R. V. Jayakumar & Mrs. Jayakumar, Dr. R. N. Sharma, Dr. A. Vimala, Dr. B. Kanakambaran, and

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I am deeply grateful to Mr. Richard Lansing, Mr. Michael Koy, Mr. Andy Kwan and Ms. Deepthi Vasudevan from Springer for guiding this project. I am also indebted to the Project Manager Mr. Jeffin Thomas Varghese and the entire editorial staff at SPi Global for making this work possible.

I hope the reader will find a wealth of new information and inspiration to apply the methods discussed herein to patient care. I also hope this work will inspire new applications in other medical specialties which will hopefully change healthcare for the better.

This work is dedicated to the memory of my late friend and guide Mr. Monichan Madathil.

Winston-Salem, NC, USA Nikhil Balakrishnan
October 1, 2014

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Chapter 1
The Principles of Dependability

Abstract This chapter presents definitions and important multi-domain concepts involved in the design and operation of dependable systems. It presents the dependability tree and describes the means to attain dependability. It presents the ideas of fault detection, fault tolerance, fault handling, and fault removal which form the basis of all dependable systems. It surveys common safety paradigms across multiple industries from a standards and regulatory perspective. It introduces the concept of defense in depth as the means of attaining safety and dependability.

Definition of Dependability

An important concept in industry and engineering is *dependability* [1]. At an intuitive level, we use the word "dependable" to refer to a product or service which we take for granted. Therefore, from our understanding, a dependable service is always available, trustworthy, reliable, and most importantly, safe. The world of airplanes, high-speed trains, telephones, and highly networked and sophisticated computers managing vital services like the power grid and traffic systems are common examples of *dependable* systems. These systems are special because errors can have catastrophic consequences with the potential for severe injuries and loss of life. By application of rigorous, disciplined, engineering and management methods, industries such as aerospace, high-speed rail, and to a great extent, nuclear power have attained extremely safe operating characteristics. An unsafe event is extremely rare with probabilities of serious accidents being less than one in one billion. This book explores the ideas behind dependable systems and businesses and applies them to healthcare delivery by *using a wide range of case examples from the field of neurology in particular*.

Let us now explore more rigorous definitions of the concept, its standards, and regulatory framework. In computer science parlance, *dependability* can be defined as "a system property that integrates such attributes as reliability, availability, safety, security, survivability, and maintainability [1]." Standards of performance and dependability vary widely between different industries. The most rigorous definitions and standards of dependability were developed for the aerospace industry with digital fly-by wire (DFBW) being one of the most exacting applications. In other domains such as medicine, such standards are not well-defined, neither are the

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methods which contribute to dependability in widespread application. The principles behind dependability are both technological and human, the successful integration of which creates iconic businesses and products.

A Brief History of Evolution of Dependable Systems

The delivery of correct, reliable systems has been a concern since time immemorial. Mathematicians and statisticians working with computing engines struggled with this concept. In 1834, Dr. Dionysius Lardner wrote in the Edinburgh Review "the most certain and effectual check upon errors which arise in the process of computation, is to cause the same computations to be made by separate and independent computers; and this check is rendered still more decisive if they make their computations by different methods [1]."

Systems have a tendency to generate errors and service failure. Dependable systems must constantly overcome these challenges and have a method for keeping errors and faults in check. The earliest challenges with dependability were encountered with the advent of the electronic age. Early electronic components and circuits were unreliable. Since component-wise reliability was poor, the problem became one of how to deliver dependable performance with systems with unreliable components? The solution lay in *redundancy*. The field developed enormously with the digital age and development of information theory by Claude Shannon. At the heart of most of these methods, redundancy is incorporated to detect and correct errors. This can take the form of triple redundant voting architectures developed by John von Neumann [1] or error correcting codes in digital communications where a message of k bits is encoded using N bits (where $N > k$) to provide for error detection and correction. *Dependable systems detect errors; isolate them followed by masking errors so that service delivery is not disrupted*. The theory of redundancy to mask individual component failures was developed by W. H. Pierce in the early 1960s. The field was further developed by the pioneering work of Prof. Algirdas Avizienis with the development of *fault tolerant* systems. This section is based on a review paper by Avizienis et al. [1]. Overview concepts will be discussed here, the interested reader will find a wealth of further information in [1].

The Dependability Tree

The *dependability tree* is a useful concept for understanding the nature of dependability. The dependability tree studies the subject from the viewpoint of threats to, attributes of and means by which dependability is attained. While the original application of this is in computing, these concepts can be borrowed and applied widely and other processes can be understood in the same manner with potential advantages to dependability. Let us start with some definitions. For a computer

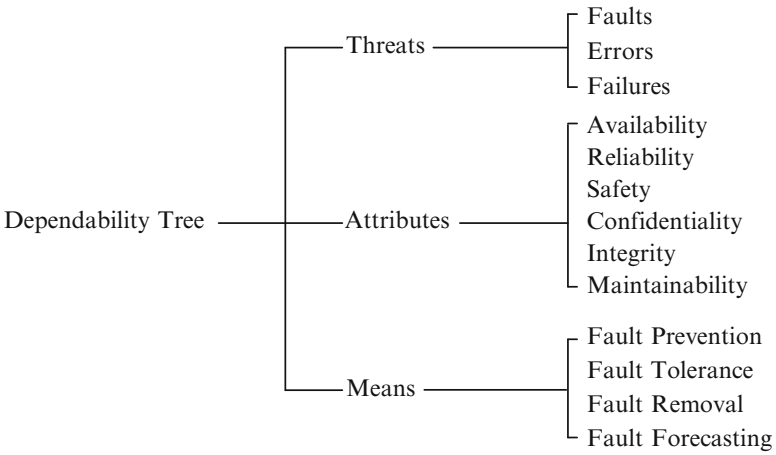

Fig. 1.1 Dependability tree. Adapted from [1]

system, dependability is the ability to deliver service that can be justifiably trusted by the user [1]. From the dependability tree in Fig. 1.1, *the main threats to dependability are faults, errors, and failures. An error is that part of a system state that may result in subsequent failure. Errors may be manifest or maybe latent. A failure happens when an error alters service. A fault is the cause of an error. Therefore faults can lead to errors which lead to failures. The ways in which a system can fail are its failure modes* [1].

Toy Example 1: Consider a commonly encountered situation where a patient with atrial fibrillation and mechanical heart valve is on a stable dose of warfarin for many years for stroke prevention. He maintains therapeutic INR for stroke prevention. At a subsequent hospitalization, a physician enters the wrong dose of warfarin or adds a medicine (for example an antiepileptic such as carbamazepine) that interacts with warfarin and increases its hepatic metabolism. This reduces the therapeutic effect of warfarin leading to a subtherapeutic INR which leads to an embolic stroke. In this example, the wrong dose entered or the drug interaction is the initiating "fault." This led to an altered coagulation system state with reduced therapeutic effect which represents the "error." The subtherapeutic anticoagulation ("error") leads to a "failure" of the service of stroke prevention provided by warfarin.

Let us explore the meaning of attributes of dependability further. The *availability* of a service is the readiness for correct service. *Reliability* refers to continuous delivery of correct service or time to failure. In the computer science literature this is also defined as "probability of failure free operation of a computer program in a specified environment for a specified period of time" [2, 3]. *Safety* is the absence of catastrophic consequences of failures on the user or environment. *Confidentiality* is the absence of unauthorized disclosure of information. *Integrity* is the absence of improper system state alterations. *Maintainability* is the ability to undergo repairs and modifications. The emphasis on the different attributes varies from industry to

industry and the intended service provided by the system. A system is expected to have dependability requirements imposed on it. A system's reactions to faults, whether internal or external is important and is a measure of the robustness of the system.

Applying this concept to healthcare, our goal is to borrow from planes, trains, and computers to create a dependable medical practice, whether in the form of a clinic or a hospital. From a patient or user's perspective, the services provided by the hospital or practice must be reliably trustworthy. Services must be readily available, of high quality. Diagnosis must be accurate, treatment must be safe without errors and at a minimum of side effects. To this we borrow and add one more requirement, frequently overlooked in healthcare but a core component of all industrial projects—costs must be optimum and transparent. Therefore, dependable healthcare, emulating the world of like products and services in engineering provided by our dependable institution must provide service that can be reliably trusted by the user in terms of diagnostic accuracy, optimum treatment, and costs.

Approach to Dependability

From the "means" arm of the dependability tree in Fig. 1.1, the design of a dependable system involves four important aspects [1]:

1. **Fault prevention**: refers to the application of design and operating principles that prevent the occurrence of faults.
2. **Fault tolerance**: refers to the ability of the system to deliver correct service in the presence of faults.
3. **Fault removal**: refers to reducing the number and severity of faults.
4. **Fault forecasting**: refers to predicting and addressing present and foreseeable faults and their consequences.

Fault Prevention

Fault prevention is concerned with primary prevention—incorporating methodologies and technologies in design and operations which prevent the introduction of faults [2]. At the design level, this involves quality control measures involved in design and manufacturing. On a day-to-day basis, this involves safe operating practices including rigorous training, adherence to standards, operating protocols, and maintenance guidelines. For the toy example above, fault prevention can be instituted in design where the electronic medical record would generate multiple severe warnings when the interacting drugs are prescribed warning the physician to potential dangers. At the human level, fault prevention includes rigorous training, familiarity with antiepileptics, or verification of dose and interactions

with a pharmacist so that safer alternatives can be selected. Finally, fault prevention could also involve close monitoring of INR if the physician chooses to use medications that interact with warfarin.

Fault Tolerance

Fault tolerance refers to the ability to deliver correct service in the presence of active faults in the system [1]. *The aim of fault tolerance is to prevent undesirable events, especially catastrophic failure in the presence of faults affecting individual parts of a system* [1, 2]. In other words, a single failure of a system or a combination of failures should not lead to service failure, especially catastrophic failure. A latent fault is a fault that is present in the system but has not resulted in errors. These represent a vulnerability of the system. Once errors occur due to these vulnerabilities, a latent fault becomes active [2].

Fault tolerant systems integrate fault masking with practical techniques for error detection, fault diagnosis, and system recovery [1]. *Masking refers to the dynamic correction of errors which enables the system to continue to deliver correct service in the face of system faults*. While the following discussion is borrowed from the computer science and engineering literature, the aim is to introduce the concepts for broader application. As introduced earlier, the basis of all fault tolerance is appropriate use of redundancy to mask faults, errors, and continued delivery of correct service [1]. Diversity in design is believed to be the "best protection against uncertainty" [2]. Fault tolerance is frequently implemented by error detection and subsequent system recovery [1]. Every fault tolerant system design involves implementation of the following principles [1, 2]:

Error detection: Error detection is the first step in the prevention of system failure. All fault tolerant systems must have a means for error detection. For the toy example above, careful monitoring of the INR to monitor for drug interactions would have detected the error in anticoagulation and prevented the hazardous failure (stroke).

System recovery: It is the transformation of a system from a state which contains one or more errors and possibly faults into a state without detected errors and faults that can be activated again [1]. The process of recovery involves *error handling* and *fault handling*.

1. **Error handling**: The goal of error handling is to eliminate errors from the system state. This can be done in three ways [1, 2].
    - **Rollback**: This is a state transformation where the system is returned back to a saved state that existed prior to error detection, the saved state being called a checkpoint. For the toy example above, this would involve discontinuing the carbamazepine and resuming the last known effective dose of warfarin.
    - **Compensation**: Refers to a situation where the erroneous state contains enough redundancy to enable elimination of errors. This can happen without explicit concomitant error detection and correction in *fault masking*. However

simple masking without correcting the underlying errors and faults can conceal a progressive and eventually catastrophic loss of protective redundancy. Therefore most practical implementations of masking generally involve error detection and fault handling [1, 2]. For the toy example above, let us assume that the patient has an INR checked a few days later (but before the stroke) which is found to be subtherapeutic. Let us also assume the patient continues to be on carbamazepine for seizure prophylaxis. The physician immediately institutes adjunct treatment with low molecular weight heparin injections (example enoxaparin or fondaparinux) which restores anticoagulation and corrects the error in the anticoagulation state. This would be an example of masking where redundancies in drugs that work on the coagulation cascade are used to deliver the service of anticoagulation and prevent service failure (in this instance stroke).

- **Rollforward**: Where a state without detected errors is the new state [1].

2. **Fault handling**: Prevents located faults from being activated again. It involves four steps:

   - **Fault diagnosis**: The faulty components are identified, isolated, and the effects contained for system repair. This identifies the root cause(s) of the error(s) [1]. In the toy example, this would involve identifying responsible drug interaction (or wrong dose) as the fault that led to the error which led to the stroke.
   - **Fault isolation**: Involves physical or logical exclusion of the faulty components from further participation in service delivery. The diagnosed fault becomes dormant [1]. For the example above, this would imply a decision not to rely on the warfarin pathway for delivering dependable anticoagulation. Errors in systems must be contained within predetermined boundaries. This is enabled by modular design of systems and the ability to isolate a faulty system to prevent it from propagating errors. Failure to do so leads to cascading failure with far reaching consequences as discussed in toy example 1. In that example, a fault in warfarin led to the error in the state of anticoagulation which led to the development of a clot in the left atrium (cardiovascular system) which migrated to the brain causing a stroke (central nervous system).
   - **System reconfiguration**: This involves finding ways to work around faults by removing affected systems from operation and incorporating alternate means to deliver service. For the toy example above, the physician can explore alternative methods, including low molecular weight heparins or direct thrombin inhibitors for service delivery. Alternate options include switching to an antiepileptic such as levetiracetam (Keppra) which is renally metabolized and therefore free from interactions with warfarin.
   - **System reinitialization**: This step checks, updates, and records the new configuration and updates system records [1]. For the toy example above, the new state maybe resuming prior dose of warfarin, discontinuing carbamazepine, temporary use of low molecular weight heparins, and instituting levetiracetam for seizure prophylaxis.

Fault handling is typically followed by corrective maintenance that removes the faults isolated by fault handling. This may take diverse forms including equipment replacement or repair [1]. Dependable systems that are designed to fail only in specific modes and only up to an acceptable extent are called fail-controlled systems [1]. A system whose failures are to a great extent minor is called a fail-safe system [1].

Fault tolerance can be studied from both software and hardware perspectives. One of the most common methods used for fault tolerance is to perform multiple computations in multiple different channels either sequentially or concurrently [1, 2]. (See reference to Dr. Lardner in Section "A Brief History of Evolution of Dependable Systems"). Multi-version fault tolerance techniques are a commonly used method to deliver fault tolerance. This method is based on the use of two or more versions of software usually executed in parallel. The idea behind this approach is that different versions of software will use different components and algorithms. Since failures usually result from a certain combination of system states and input data, it is believed that different versions would fail under different circumstances [2, 4]. Therefore, a given input pattern which could provoke failure in one system may not do so in the other enabling delivery of service. This can be performed in different ways and two widely used architectures are presented here.

1. One commonly implemented method for multi-version fault techniques is *N-version programming*. In this technique multiple versions perform computations in parallel and the outputs are compared by voting as shown in Fig. 1.2 [2]. Similar architectures are exploited in hardware. Triple modular redundancy (TMR) is a commonly used fault tolerance architecture with applications in diverse industries ranging from aerospace to industrial automation. This is the architecture used in the Boeing 777 primary flight computer (PFC) system and will be discussed further in Chap. 6. The output from the three modules is compared by the voter. The system is capable of discarding error from one module by performing majority voting of the individual outputs. The fault masking capabilities of the system fail when an error occurs in two or more modules such that a majority vote is no longer valid. The system is additionally susceptible to voter failure [2]. This can be circumvented to some extent by triplicating the voting system so that individual voter failures can be masked by the same process. Additional protections are made in the design and manufacturing process such

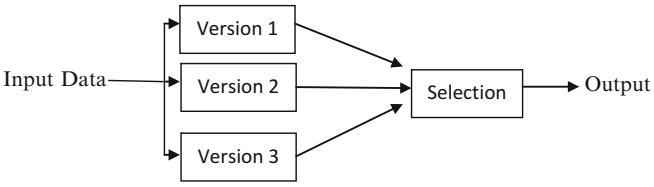

Fig. 1.2 *N-version* Programming model

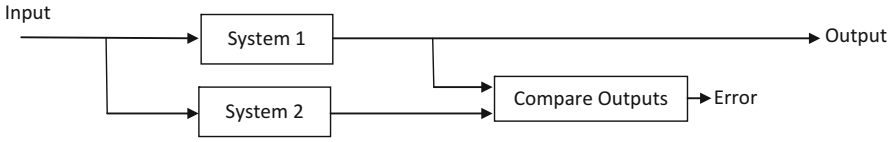

Fig. 1.3 Active redundancy using duplication by comparison

that the voter has a much greater degree of reliability than the rest of the system to prevent system failure.

2. In duplication by comparison shown in Fig. 1.3, errors are detected by comparing the outputs of the two modules. If the outputs disagree by more than a predetermined threshold, an error condition is raised followed by diagnosis and restoration of the system to error free operation. The two systems are designed by two different teams working independently and manufactured by different manufacturers to avoid any common software and hardware vulnerabilities. This architecture is also used widely and will be discussed further in the Airbus fly-by wire system.

Fault Removal

Fault removal is performed both during the development phase of a system life cycle and during its operational life [1]. In this section we expand the lexicon further by introducing two commonly encountered terms—validation and verification. System validation refers to confirming that the system being designed meets the user's requirements, needs, and uses. In other words, we are creating the system that the user wants [1]. System verification refers to whether the outputs of the system conform to the specifications [2]. In other words, verification tests whether the system has been designed correctly to meet the requirements placed on it.

As an example, consider that an aircraft manufacturer wants to develop a new model of airplane which can carry 200 passengers for a distance of 5,000 miles and wants a dependable engine with specified downtimes for maintenance. The engine manufacturer comes up with an initial design which would deliver x lbs. of thrust, y kg/seat mile of fuel economy, etc. System validation involves checking that such an engine meets the customer's intended uses and specifications. The hope of the validation process is to identify early in the process if x lbs. of thrust are sufficient for the application or whether the design should be changed to deliver additional z lbs. of thrust before expensive investments in manufacturing the engine are made. System verification would test the engine that is being designed and manufactured to see if it will deliver the required x lbs. of thrust and required fuel economy under diverse operating conditions.

System validation and verification are recursive processes which are extremely important for delivering dependability. This is best done throughout the design process instead of creating a product and then performing expensive re-engineering to meet customer expectations. Fault removal occurs throughout

the life cycle of a system [1]. In the development phase fault removal consists of three steps: verification, diagnosis, and correction. System verification continuously determines whether the system meets design properties which are termed verification conditions. If the system does not meet the desired properties, the next step is to diagnose the faults which prevented the verification conditions from being met. Fault identification is followed by necessary corrections. The verification process is again repeated to check that the preceding fault removal did not cause any unintended consequences. In software parlance, fault prevention and fault removal are termed fault avoidance. Fault removal during the operational life of a system is termed corrective or preventive maintenance. Corrective maintenance is performed to remove faults that have produced error(s) and have been diagnosed. Preventive maintenance aims to uncover and remove faults before they cause errors during normal operation [1].

Fault Forecasting

Fault forecasting involves evaluating system behavior for the occurrence and activation of faults. This is used to prevent faults in future. This involves two steps—qualitative evaluation and quantitative evaluation. Qualitative evaluation aims to identify, classify, and rank the different ways in which a system can fail, termed failure modes. It identifies the event combinations (component failures or environmental conditions) that lead to system failures [1]. Methods for qualitative evaluation include failure modes and effects analysis (FMEA) and others which will be studied in subsequent chapters. Quantitative methods evaluate probability measures of how attributes of dependability are satisfied thus providing a measure of dependability of a system [1]. Methods such as fault tree analysis (FTA) and reliability block diagrams (RBD) which can be both qualitative and quantitative are explored in detail in subsequent chapters [1].

Failure Intensity and Lifecycle of Dependable Systems

The life cycle of most typical dependable systems is characterized by alternate periods of correct and incorrect service delivery. A useful index of this principle is failure intensity—which is the number of failures per unit of time. Typically, failure intensity decreases as more common faults are discovered and corrected (period termed reliability growth), then stabilizes (stable reliability) followed by a period of decreased reliability followed by repetition of the cycle. This is usually pictured as a "bathtub," see Fig. 1.4.

Important measures of reliability, especially in engineering are mean time between failures (MTBF), mean time to failure (MTTF), and mean time to repair (MTTR) [3]. These are connected by the expression:

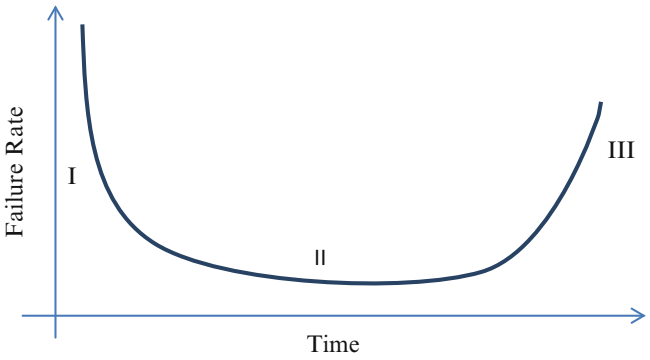

Fig. 1.4 The reliability curve also called "bathtub curve" represents the failure rate of a system vs. time. There are three regions in this curve. Region I constitutes a time of high failure rates when a component is initially manufactured. As design flaws and manufacturing processes are corrected, the failure rate drops in Region II to a flat constant failure rate. Finally as the component ages and starts wearing out in Region III, the failure rate again increases

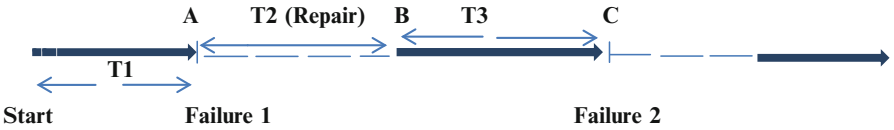

Fig. 1.5 In this figure, *solid lines* represent normal system function and *dashed line* represents failure. A system starts operation and performs without failure till point A. The time interval T1 is defined as the time to first failure or reliability. The *dashed line* represents the time when the system is not available with consequent service failure. It undergoes repair during this time (*T*2), starts functioning again at point B before failing at time C (*T*3) before the cycle repeats itself. The time *T*2 is the time to repair followed by time to failure. Therefore, the time interval between A and C which represents the time between failures can be seen to be the time to repair (*T*2) + time to failure (*T*3). Over repeated cycles, mean times can be used to compute the mean time between failures in Eq. (1.1)

$$\text{MTBF} = \text{MTTF} + \text{MTTR} \tag{1.1}$$

This is illustrated in Fig. 1.5. MTTF is a measure of how long a system is expected to deliver correct service before failure occurs. MTTR is a measure of how easy or difficult it is to repair a system after a failure occurs. In computer controlled systems, advances in software engineering have reduced the number of deterministic design faults. More difficult to control are latent faults in software and hardware which are state dependent and activated by a particular set of input data and operating conditions [2]. These are highly unpredictable since a system crash is triggered by a specific set of input data which exposes a unique, hidden vulnerability in software and hardware resulting in service failure which may not have been foreseen during system development and testing. Therefore, a latent fault in software and hardware becomes activated when the system state and triggering input

sequences come together. Therefore, for many systems, MTTF is dependent on the operating environment. As introduced earlier, this is mitigated in dependable systems by incorporating redundant systems using different hardware and software which very likely have a very different set of state and input vulnerabilities and therefore do not crash under the same circumstances.

The same is applicable to medical knowledge as well. Medical education is verified and validated by rigorous curricula and board certification examinations. However, all knowledge is imperfect and there are regions of vulnerability in each individual's understanding of health and disease. A hidden, unique vulnerability in a physician or healthcare worker's knowledge is challenged by a rare, unique clinical circumstance leading to errors in diagnosis and treatment. As in the systems engineering example, redundancy can be used to deliver dependability. The knowledge redundancy is delivered using teamwork, second opinions, and concurrent opinions so that one individual's unique knowledge vulnerability in a certain clinical situation is masked by another's strength leading to fault prevention, fault masking, and correct service delivery despite individual failure.

Connected Systems and Failure

Most products and services are made of component systems which in turn are made of subsystems in a hierarchical relationship. Systems communicate with one another across system boundaries. In many failures, a fault in one system leads to an error which is propagated across system boundaries to affect many systems leading to profound effects remote from the initial source. At the interface between System 1 and System 2, an error in System 1 is a fault in System 2. By the time the initial error is detected and corrected, the downstream effects are only too well established and emerge as the major problem. Such error cascades are quite common and can have far reaching, sometimes catastrophic consequences. The failure cascade described in Fig. 1.6 is frequently encountered in clinical practice due to the lack of a disciplined approach to system safety and dependability. The following case example is illustrative:

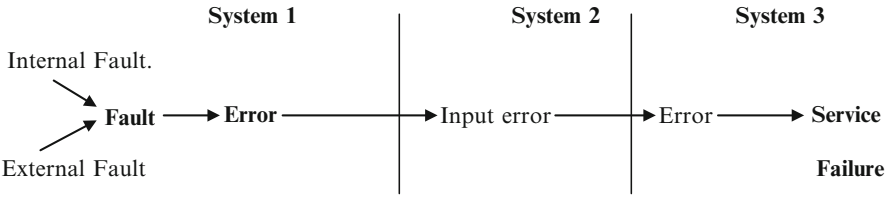

Fig. 1.6 The relation between fault, errors, and failure. A fault in System 1 leads to errors in System 1 which is propagated to System 2. At the interface, the error in System 1 is a fault in System 2 which can lead to a corresponding error. This finally results in failure of service in System 3

Case Example 1

G.S. is a 70-year-old male, s/p pacemaker placement, on anticoagulation with a prior biopsy proven diagnosis of polymyositis. He had been treated with varying doses of prednisone with poor response to treatment. Patient himself provided a limited history but it appears his muscle disease started fairly abruptly after undergoing coronary artery bypass grafting (CABG). Weakness was rapidly progressive leading to difficulty with ambulation in short order. Over the past few years he developed dysphagia. It was not clear if symptoms were related to statin exposure. A review of his biopsy did not show rimmed vacuoles concerning for inclusion body myositis (IBM), however this might have been due to sampling error. He denied any family history of muscular dystrophy. On examination, he had moderate bifacial weakness being unable to whistle. Extraocular movements were otherwise normal. He had severe weakness and wasting of pectoralis major and scapular muscles. Scapular winging was present bilaterally. There was relative preservation of the deltoids bilaterally which were 3+/5. There was severe wasting of the biceps and triceps bilaterally. The wrist extensors were 4/4 bilaterally, the wrist flexors were similar. Patient was unable to make a fist bilaterally with the weakness of flexor pollicis longus (FPL) and deep finger flexors. Hand intrinsics were normal. In the lower extremities hip flexors, knee extensors showed only trace strength. Foot dorsiflexors were 3+/5, plantar flexors were 4/5. At the time of his initial visit, he was on prednisone 10 mg/day for many years.

The main diagnostic concerns after his initial visit were whether he had a muscular dystrophy like facioscapulohumeral dystrophy (FSHD) vs. IBM vs. a severe form of polymyositis or necrotizing myopathy. The latter is potentially treatable. A gene test was sent for FSHD which was normal. Acid maltase screening was normal. Patient was requested to return for a repeat EMG followed by muscle biopsy to better diagnose his condition. The EMG was required to identify a muscle which would yield useful answers on biopsy. Given the rapid onset and progression, if the biopsy showed polymyositis or necrotizing myopathy then treatment in the form of intravenous immunoglobulin (IVIG), pulse methylprednisolone, and Rituximab could be contemplated. If it showed an untreatable condition like IBM, then prednisone could be tapered and discontinued. This plan was complicated by certain social circumstances. He lived 6 h away out of state and required two live-in caregivers to assist him. Anticoagulation would need to be reversed for biopsy. Given his severe weakness, anticoagulation, and need for EMG, it was felt an inpatient approach could synchronize all the steps involved. This was coordinated with his primary care physician. A surgical consultant was briefed on the matter for the biopsy. However, due to pressing personal matters, he was unable to make it for the original appointment.

Three months later, the patient decided he wanted to come to the hospital and get the biopsy. He arrived accompanied by two caregivers on a Monday without prior notice. An EMG could not be obtained the same day. It was planned for

Tuesday morning with biopsy soon thereafter in the afternoon. The surgery service was unable to perform the biopsy at short notice; they required it to be in the operating room given his pacemaker. This could not happen till Friday. Mr. G.S. could not afford to pay his caregivers who themselves could not stay till the end of the week and had to leave by Tuesday evening. In short, the poor man spent 2 days in a hospital, spent thousands of dollars of his own money and nothing was achieved to benefit him. An optimistic, cheerful man by nature, he returned home a deeply disappointed and saddened man. When the author called him to apologize and make amends in any way possible, he said he would never return to the author's care ever again. He was right, the author's services could not be "justifiably trusted" by him.

Applying Dependability Principles to Case Example 1

Let us analyze this failure applying only the principles that have been described thus far. The objective is to deliver dependable service to the patient. As discussed in Section "Approach to Dependability," there needs to be a system for fault prevention, fault tolerance, fault removal, and fault forecasting. The above clinical presentation was not cast in a dependability framework.

1. **Fault prevention**:
   - The author saw his role in isolation. The surgical staff would need to deal with the process of obtaining the biopsy. A thorough discussion with the surgeon to discuss the potential complexity of this case (severe weakness, hard-to-find muscle, stakes involved, social circumstances involved, and the pacemaker) could have prevented this failure sequence from happening. There was a complete lack of planning and teamwork.
2. **Fault tolerance**:
   - None of the steps for fault tolerance were ever employed. While the initiating event was the patient presenting himself without prior notice, this is no excuse. The services required should have been capable of mitigating (masking) this unexpected circumstance and getting the biopsy. There was no rigorous method for error detection and fault tolerance. There was a cascade of failure of service leading to a complete inability to help the patient.

In subsequent chapters, we will explore improvisations instituted from this and similar failures to prevent unreliable service delivery. The above section introduced the principles governing the design and operation of dependable systems. In the next section, we will review safety standards and practices in critical industries, hoping to borrow systems which can be adapted to healthcare delivery.

Review of Dependability Across Multiple Domains

In this section safety systems and regulatory framework across different industries (domains) will be reviewed. This discussion is based on critical embedded systems in a wide spectrum of application domains. CG2E (Club des Grandes Entreprises de l'Embarque) is an initiative launched in 2007 by major companies to integrate performance standards and safety across multiple industries. While the emphasis is on embedded systems which play a major role in most intelligent systems, there are surprising commonalities behind reliability principles across domains which have broad application. Aviation, Space, Automobile, Nuclear, and Railway are the major industries associated with this initiative. The development of critical safety systems is tightly governed by standards which originate within the industry and respective government regulatory agencies. This section will briefly review the salient features and commonalities of the space, automobile, nuclear, industrial automation, and railway industries [6–8].

All the industries discussed here have *categories of safety called safety integrity levels* (*SIL*). The definitions and specifics differ between them based on their respective domains; however the basic principles are similar. *Safety*, *consequently reliability is viewed as a spectrum*, *from events which have minor consequences to those with severe or catastrophic consequences where massive damage and loss of lives is likely*. *Such a classification of safety helps with budgeting and resource allocation for system development*. *Consequently greater reliability*, *redundancy*, *fault tolerance*, *operations performance, and failure mitigation systems can be invested in systems with critical consequences than for systems with minimal impact on overall functioning*. Industrial and regulatory standards govern the development process that must be complied with for safe operation and certification. The systems corresponding to the different safety categories need to meet specific "developmental assurance levels." Development assurance level (DAL) is "a measure of the rigor applied to the development process to limit to a level acceptable for safety the likelihood of errors occurring during the development process of functions and items that have an adverse safety effect" [9]. F-DAL which stands for function DAL is the "intended behavior of a product regardless of the implementation" [9]. DAL applied to items (which refers to component hardware or software with well-defined system boundaries and interfaces) is I-DAL. Therefore, safety categorization in all these industries involves three tightly interconnected aspects—the failure condition category, a quantitative safety requirement and a corresponding DAL. DAL is assigned depending on severity classification of failure conditions, *the more severe the failure condition classification*, *the greater the DAL necessary to mitigate failure effects* [7].

The following is from ARP 4754 for the aviation industry [5] which will be seen in different forms in different industries (Table 1.1).

In aviation, the determination of failure condition classification data is obtained by analyzing prior accident, failure data, regulatory guidance, previous design experience, and consulting with flight crews [7]. Once the failure condition class

Table 1.1 The relationship between severity of failure condition, safety requirements, and DAL [5]

Failure condition class	Quantitative safety requirement (failure rate/hour)	Development assurance level
Catastrophic	Probability $< 10^{-9}$	A
Hazardous	Probability $< 10^{-7}$	B
Major	Probability $< 10^{-5}$	C
Minor	None	D
No safety effect	None	E

For each safety category, there is a corresponding DAL ranging from A (most demanding) to E (least demanding). Therefore, a system whose failure results in catastrophic consequences should have a failure probability of less than one in one billion per hour and all systems connected with it should have the highest development standards corresponding to DAL A

and quantitative safety requirements are determined, the DAL is allocated to the development process of the system and its individual items. DAL A is the most demanding, DAL E the least. F-DAL and I-DAL is a top-down process. The top level functions are then divided into subfunctions and F-DALs assigned. The subsystems are then decomposed into component items and I-DALs are assigned [7]. The I-DAL assignment follows the F-DAL process [7]. Redundancy can be used to reduce the DAL required, in other words DAL A requirements can be met with redundant parts at DAL B if it can be demonstrated that only *multiple independent* failures can cause severe or catastrophic failure [7]. It is extremely important to prove independence to prevent vulnerability from common errors which can cause failure of more than one system simultaneously. The equivalent to DAL in healthcare would be human factors (experience, expertise, domain knowledge and skills of healthcare workers involved in the care of a particular medical condition), system level support (nursing support, type of environment–ICU, monitored bed etc.), laboratory and technology support. Based on the paradigm developed in table 1, complex medical conditions with the most severe failure consequences (example sepsis, myocardial infarction, coma) should receive the highest DAL the institution has to offer (DAL A: most skilled physicians, nurses, ICU care). Conversely, failure conditions without safety consequences (example chronic headaches, body aches) should receive the lowest DAL.

Railway

For the railway domain, the European reference standards are the CENELEC reference system (EN 50126 and EN50129 and the IEC 61508) [6]. The CENELEC standards recommend the depth of analysis undertaken be based on the SIL associated with the system or equipment, similar to the aeronautics discussion

Table 1.2 Tolerable hazard risk/hour and SIL for the railway domain

Tolerable hazard risk (THR), band/hour	SIL
10^{-9} to 10^{-8}	4 (System which can cause multiple fatalities)
10^{-8} to 10^{-7}	3 (System which can cause a single fatality)
10^{-7} to 10^{-6}	2 (System which can cause serious wounds)
10^{-6} to 10^{-5}	1 (Systems which can cause light wounds)

above [6]. CENELEC EN 50126 is dedicated to railway system analysis [6]. It establishes a method for specification and demonstration of reliability, availability, maintainability, and safety (RAMS) [14]. CENELEC EN 50129 is dedicated to demonstrating safety of equipment [6]; it provides guidance on the safety of electronic equipment involved with signaling and safety [8]. CENELEC EN 50128 provides guidance on software used in railway applications. The CENELEC standards provide the methodology to avoid systematic or random faults in railway applications.

Safety and reliability evaluation starts with the dangerous event that if not mitigated will lead to an undesirable accident or a near (quasi) accident [7]. *For each accident or quasi accident, a system to reduce the risk to prevent it from happening is required*. EN 50129 defines the SIL linked to a probabilistic risk estimate called tolerable hazard risk (THR) [7]. The THR is determined for each function which in turn determines the SIL of the corresponding systems, all subsystems, hardware, and software components associated with it. Based on this top-down decomposition, SIL is assigned to all the hardware and software [8]. A system with no impact on safety is said to be "non SIL." There are four levels of SIL (Table 1.2).

The corresponding software safety integrity level is called SSIL. From the dangerous event, THR can be linked to system function. From system, it is allocated to subsystems down to the failure rates of the individual components [7].

The CENELEC standard mandates four documents. The Safety Assurance Plan (SAP) defines the methodology for delivering safety. The Preliminary Hazard Analysis (PHA) is a systematic, comprehensive examination of the undesirable event to identify and classify risk [6]. Hazard log is a list of all undesirable events. Safety log is the evidence that a system is safe for a given application in a specified environment. In SIL 3 and 4 categories, the railway domain works on the "fail stop" design principle [6–8] which is unique among other domains. The system stops the train in case of failures affecting critical systems to ensure safety. This exploits an advantage that ground-based transportation systems have—that of having a rest state which is reachable in a fast controlled manner [8]—a high-speed train traveling at 300 km/h. can be bought to a stop in 1 min 30 s in 3 km. For SSIL 1 and 2 categories, the design process for software is less constrained given the relatively more limited potential for damage. For such applications, commercial off the shelf (COTS) components is allowed.

Space

The European standards for space systems (ECSS or European Cooperation for space standardization) are briefly discussed here from [6–8]. The ECSS-Q30 and 40 deal with dependability and safety, respectively. ECSS-Q80 deals with software product assurance. ECSS Q30 and 40 define the categories resulting from potential failures of the space system. The ECSS categorizes them into Category 1—catastrophic with the most severe safety effects (loss of life, etc.), Category 2—critical which combines critical safety effects (injuries) and severe mission loss effects. Category 3—major and Category 4—minor have only effects on mission performance without safety effect [6, 7]. These categories are different in the sense that no quantitative measures as in other cases are defined. The ECSS standards impose a minimum on the number of independent faults and failure combinations which could lead to catastrophic failure. No combination of two independent faults should lead to catastrophic failure. System functions are initially allocated to different criticality categories [6, 7]. Function decomposition and category allocation proceeds as earlier in a top-down manner following the same rules—a component is assigned to a category based on the severity of consequences of failure [6, 7]. This therefore lays constraints on the design and architecture of the system. ECSS rules also state process safety requirements adapted to system category.

Automobile

Hazard analysis and risk assessment in the automotive domain is governed by ISO 26262. The first step is the identification of vehicle level hazards—injuries to people that can be triggered by failures or malfunction of vehicle systems [7]. The next step is the identification of hazardous events which is a combination of a hazard and an operational situation with the potential to lead to an accident if it is not controlled promptly. For example, loss of braking function leading to accident if the operator is unable to reduce speed using downshifting gears quickly. ISO26262 assigns an automotive safety integrity level (ASIL) which is based on determining three parameters with respect to a hazardous event: the exposure "E," controllability "C," and severity "S." "E" refers to likelihood of exposure of a vehicle to an operational condition which may lead to a hazardous event in the presence of a system failure [6]. For example, the proportion of time a vehicle is driven in wet icy conditions with failure of the antilock braking system. "C" refers to the ability of the person driving the automobile to react in a timely manner to avoid harm when a hazardous event occurs (for the example above, this may involve regaining control after skidding of the car with braking when the antilock mechanism fails in icy conditions). "S" is the estimation of harm caused to person (s) when the hazardous event is not controlled quickly. Based on these, four ASILs are defined with ASIL D being the most demanding regarding mitigation of risk and

ASIL A being the least demanding. Events without impact on safety are categorized as quality management (QM). ASILs are used in ISO 26262 for specifying risk mitigation measures for the development of a system and its hardware and software components. For ASIL A, verifying requirements with test cases is all that is necessary; for ASIL D more rigorous testing based on environmental conditions, fault injection, past field experience are mandatory. A safety goal is defined for each hazardous event; safety goals inherit the same ASIL of their corresponding hazardous event. The ASILs of the safety goals are applied in a top-down manner during system development. Each subsystem inherits the ASIL of the parent system it is derived from [6, 7]. In the design of systems, sufficient independence between systems to prevent common cause failures has to be demonstrated.

ISO 26262 also requires independence (confirmation measures) of the personnel involved in safety assessment from design and development. It specifies the need for a certain minimum level of independence from people in charge of development and releasing a product for production [10]. The level of independence also relates to the ASIL level, the higher the ASIL, the greater the independence requirement [10]. The confirmation measures involve safety reviews, safety audit to verify the development process, and finally a safety assessment to evaluate that the safety case has been made confirming to the ASIL categories. This can be achieved within the same company by creating separate reporting lines for safety engineers.

Nuclear

The main reference documents for this domain are IEC 61226 and IEC 61838 and safety standards published by the International Atomic Energy Agency (IAEA). In this domain, the term *safety refers to prevention of accidents* [6]. A nuclear plant is viewed at two levels, the nuclear plant itself and the instrumentation and control technologies (I&C) that control its operation and function [12]. Safety analysis therefore is performed separately of both systems [6, 12, 13]. An initial safety analysis of the reactor is performed before functions performed by the I&C systems. IEC 61226 classifies a nuclear facility into categories A, B, C, and nonclassified. Different initiating events which can trigger accidents are analyzed early in the design for development of mitigation and supporting functions. Generally, the design and operation of nuclear reactors is governed by internationally agreed deterministic design standards and defense in depth strategies which are discussed further [7, 11, 12].

The main parameters for the classification scheme are the type of reactor, initiating events, plant states and accident conditions, acceptable limits on radiation, major functions needed to mitigate consequences of initiating events, and their supporting functions [7]. Cumulative prior experience with a reactor of a particular design is important [6, 7] since there are few changes to reactor design itself over time. A functional analysis based on severity of consequences of initiating events, their relative frequencies is used for classification of mitigation and supporting

functions [7]. The root causes of initiating events are identified by techniques such as FMEA, FTA, and prior experience (FMEA and FTA are discussed in Chap. 2).

Both deterministic and probabilistic safety assessment (PSA) methods are used in plant design review [7]. These are performed during the original plant design and revised periodically during the life of the plant. Design basis accident analysis is a deterministic technique analyzing the response of a plant to different accident scenarios [11]. This is an important aspect of the safety analysis that is reviewed by the US Nuclear Regulatory Commission (USNRC) and is an important factor in the initial licensing process [11]. In design-based accident analysis, a predefined set of transient events are imposed on simulations of the plant. Assuming defined failures, the plant systems must be shown to be effective in mitigating failure consequences within accepted criteria [11]. For the example of a postulated pipe rupture scenario, the deterministic safety analysis process considers the following systems—size of the rupture, the systems and components affected, initial conditions at the time of rupture in important systems such as power, pressures, and temperatures; response of the active and passive safety systems such as sensing of the event by instrumentation systems, fault isolation by actuation of valves and subsequent opening of feed water system valves. All of these model the physical behavior of the affected systems and calculate the response of the plant. The most important net parameter of interest is how well the I&C and backup systems control the temperature and pressures in the cooling system and in the reactor core; whether in the end the multiple physical barriers that contain radionuclides were breached [11]. Probabilistic techniques such as probabilistic risk assessment are used to assess the effects of initiating effects on system safety or reliability. Probabilistic methods assess physical faults, human factors, and contributing effects which have a high degree of uncertainty [11]. This analysis typically uses fault trees or less often equivalent methods such as Reliability Block Diagrams (RBD) and Markov analysis (MA) (see Chap. 2) [11].

The USNRC has a quantitative safety goal that the probability of reactor core damage shall not exceed 10^{-5}/reactor year. Based on probabilistic methods (such as FTA/RBD discussed in Chap. 2), the most important ways in which the system can fail (called failure modes, see Chap. 2) are identified and mitigation/prevention systems with redundancy are designed to prevent the occurrence of the adverse event(s) [11]. As will be discussed in the section on fault trees in Chap. 2, the use of FTA was heavily pioneered by the nuclear industry since it is such a powerful tool for discovering weaknesses in design, engineering trade-offs, and assessing relative risks [11]. FTAs also help model to what extent an unknown input can affect the safety or reliability of a system [11]. In cases where probabilities of events are not available, a qualitative assessment based on judgment of experts is performed. This is sought in formal and informal processes where experts weigh in on available evidence and make their best judgments [11].

Defense in Depth

The most important method of preventing accidents in a nuclear power plant and mitigating consequences of accidents is the concept of "defense in depth." This is applied ubiquitously to all activities related to a nuclear power plant—whether it be organizational, design related, different power levels or various shutdown states [12]. The idea is to ensure that safety related activities are subject to independent layers of provisions, so that if a failure occurs, it will be detected and compensated by appropriate measures. Application of defense in depth in design and operation throughout the design and operation of a plant provides protection against accidents resulting from equipment and human factors. When applied to the design of a plant, the idea is to provide several layers of defense (inherent features, equipment, and procedures) aimed at preventing harmful effects of radiation on people, the environment, and ensuring adequate mitigation of consequences of undesired events that may occur [12]. The independent effectiveness of each layer of defense is an essential element of nuclear safety, its main idea is to prevent the failure of one level from causing failure of other levels [12]. Three important terms in the nuclear glossary are postulated initiating events (PIE), anticipated operational occurrences and design basis accidents. A postulated initiating event is an event identified at the design stage as being capable of causing deviation from normal operation potentially leading to accident conditions. PIE may happen due to equipment failures, operator errors, or natural events. An anticipated operational occurrence is an operational process deviating from normal operation which is expected to occur at least once during the operating lifetime of a nuclear facility, which is prevented from escalating to accident conditions by the rigorous implementation of safety systems. Examples of anticipated operational occurrences include loss of electrical power, equipment malfunction, and human error. Design basis accidents are accident conditions against which the nuclear power plant is protected by meeting design standards which mitigate damage to fuel and release of radioactive material within authorized limits. There are five levels of defense [12]:

First level: *The first level of defense is to prevent deviations from normal operation and failure of items important to safety* [12]. This sets standards on plant location, design, maintenance, operations, human factors in accordance with quality management and proven engineering practices. This is achieved by setting high standards on materials, components, plant construction and commissioning. This step also performs a detailed analysis of operations and maintenance and incorporates design features that facilitate design of a safer, easier-to-maintain plant. Safety-related technologies are also incorporated at this level [12]. Therefore the first level of defense deals with prevention of abnormal operation and failures [12].

Second level: *The second level of defense detects and controls deviations from normal operational states to prevent anticipated operational occurrences at the plant from escalating to accident conditions* [12]. This is to protect against PIEs which are likely to occur over the operating lifetime of a nuclear plant, despite care to protect against their occurrence [12]. This is achieved by specific protection

systems whose effectiveness is confirmed through safety analysis, establishment of safe operating procedures to prevent initiating events or to minimize their consequences if they occur [12]. These systems have the additional responsibility that they have to return the plant to a safe state [12]. Therefore, the second level deals with the control of abnormal operation and detection of failures [12].

Third level: *The third level protects against the escalation of certain anticipated occurrences or PIE which might not be controlled at the preceding levels and an accident could develop* [12]. Such accidents are expected to occur in the lifetime of a plant despite best efforts to prevent them. This leads to the requirement that safety systems and procedures can prevent damage to the reactor core or prevent significant off-site release of radiation and return the plant to a safe state [12]. Therefore, the third level deals with the control of accidents within the design basis [12].

Fourth level: The fourth level mitigates the consequences of accidents that results from failure of the third level of defense in depth [12]. The most important objective of this level is to ensure confinement, ensuring that release of radioactive material is as low as possible [12]. Therefore the fourth level deals with control of severe plant conditions, preventing accident progression and mitigation of the consequences of severe accidents [12].

Fifth level: The fifth and final level mitigates the radiation consequences of release of radioactive material that results from accident conditions which are not contained by the first four levels of defense. This requires the provision of an adequately equipped emergency control center, emergency plans and procedures for on-site and off-site emergency response [12].

These layers of defense are meant to be independent barriers; care is taken in design and operation to avoid common mode failure (see Chap. 2), to prevent a failure in one level from cascading to the next level of defense. Physical barriers act in conjunction with safety systems to confine radiation to specified areas and prevent leakage [12]. Defense in depth is expected to prevent to the extent possible: challenges to the integrity of physical barriers, failure of one or more barriers, failure of a barrier at a certain level from causing failure of a higher level barrier and harmful consequences of errors in operation and maintenance [12]. The concepts of diversity, redundancy, physical separation, and functional independence need to be applied to achieve necessary reliability [12].

A nuclear plant is expected to operate safely in a limited category of plant categories or states, primarily based on the frequency of their occurrence and potential consequences [7, 12]. Each event in a category is assigned to a maximum allowed release of radiation category governed by international standards [7]. The design of a plant is expected to establish a set of operational limits and conditions for safe operation of a nuclear plant [12]. Exceeding these limits on radiation is considered unacceptable. Plant states typically cover:

- Normal operation
- Anticipated operational occurrences, expected to occur over the lifetime of a plant

Table 1.3 Plant condition categories in France

Plant condition category	Frequency (order of magnitude/year)
PCC1: Operational transient	Permanent of frequent
PCC2: Anticipated operational occurrences	10^{-2} to 1
PCC3: Infrequent accidents	10^{-4} to 10^{-2}
PCC4: Limiting accidents	Less than 10^{-4}

Adapted from [7]

Table 1.4 Defense in depth from the nuclear industry with common medical examples occurring in day-to-day medicine

First level	*Prevent deviation* from normal design, operation, and human performance protocols – Medical example: Hand washing, Sterile precautions with central line insertion
Second level	*Detect and control* deviation from normal operation which can escalate to accident conditions. (These are expected to occur) – Medical example: Detect harmful drug interactions, control drug side effects
Third level	*Protect against escalation* of anticipated occurrences or postulated initiating events (PIE). Prevent damage to reactor core – Medical example: BiPAP for respiratory weakness after myasthenia gravis patient received IV Magnesium
Fourth level	*Mitigate effects of faults* which exceed first, second, and third level containment abilities. Example SCRAM (safety control rod axe man) graphite rods to prevent meltdown – Medical example: ICU monitoring and intubation for myasthenia gravis patient who decompensated with IV Magnesium
Fifth level	*Mitigate consequences of release of radiation* not contained by steps 1–4 – Disaster management team/response/protocols – Command and communication system

- Design basis accidents
- Design extension conditions, including accidents with degradation of the reactor core

Plant condition categories (PCC) which govern nuclear power plants in France are shown in Table 1.3.

Defense in depth with applications to common medical conditions are shown in Table 1.4.

Frequently occurring plant states are expected to have minimal or minor effect on safety and radiation release. Plant states with serious consequences shall have only very low frequency of occurrence [12]. Reactor design involves systems to protect against "cliff edge effect." This happens when a small change in an input parameter causes an abrupt large transition in plant conditions leading to an abnormal, unsafe state [12]. Defense in depth is expected to protect against the cliff edge effect [12].

The most important technical design constraints involve four fundamental safety functions in any reactor [12].

- Control of reactivity.
- Removal of heat from reactor and fuel store.
- Confinement of radioactive material, protecting against radiation, controlled planned radioactive releases, and limiting accidental radiation release. The design of the plant itself should minimize radiation exposure to workers and the public [12].

The design of the plant is expected to apply a systematic approach to identifying a comprehensive set of PIE such that all events with the potential for serious consequences and all foreseeable events with a significant frequency of occurrence are anticipated and mitigated in the design [12]. These are identified on the basis of engineering judgment and combination of deterministic and probabilistic assessment [12]. PIEs include all foreseeable failures of structures, systems, plant components, human errors, operating errors, and failures from internal and external hazards across a diversity of plant operating states [12]. Preventive and protective measures for PIEs are to be implemented in design [12].

The nuclear industry understands dependability and safety to be combination of engineering and management principles [12]. *The plant operator is expected to implement a management system for ensuring all safety requirements in the design are met and implemented at all stages of the project* [12]. The plant operator is also required to establish a formal engineering and management system for ensuring continued safety of the plant design throughout the lifetime of a nuclear plant [12]. The International Nuclear Safety Advisory group has suggested that the plant operator should establish a formal process to maintain the integrity of design of the plant throughout its operating lifetime [12]. This group is tasked with the responsibility of ensuring safety in design modifications, implementing new technology, research findings, and incorporating past operating experience [12].

The design and operation of I&C systems is considered separate from the reactor itself and is governed by safety guidelines [13]. These are classified into two types, those vital to safety and those not involved in safety [13]. I&C systems vital to safety are those concerned with the reactor protection system, reactor control systems, systems to monitor and control normal reactor cooling, systems to monitor and control emergency power supplies and containment and isolation systems. Typical I&C primary functions include protection functions, control functions, monitoring, and display and testing functions. Protection functions provide defense against failures in other plant systems. These are required to be designed to automatically initiate operation of safety systems, including reactor shutdown under certain circumstances to ensure design limits are not exceeded due to anticipated operational occurrences [13]. Protection systems also need to detect design basis accidents and initiate systems to limit consequences of these accidents [13]. Control systems refer to all systems that control plant parameters; these ensure the plant is kept within its operating envelope and process variables

are maintained within limits assumed in the safety analysis of the plant [13]. Failures in the control system necessitate action by the protection system [13]. These can mitigate the effects of PIEs or transients. Monitoring and display functions (information systems) present the current state of the plant to the operators and allow immediate action against transients and maintain the plant within a safe operating envelope by monitoring plant status in a control room [13]. Testing functions provide assurance on availability of stand-by systems and assurance that these have not been degraded by failure [13]. I&C systems sense the onset of challenge from a PIE and initiate actions as necessary to meet desired safety functions to ensure that safety limits are not exceeded [13]. The requirements for design require that where prompt and reliable action is needed in response to a PIE, provision should be made to initiate the necessary safety system actions automatically to prevent progression to a more severe condition [13]. Most importantly, design requirements for reliability ensure that I&C systems critical for safety have at least a minimal redundancy [13]. The safety features required to cope with a PIE needs to be determined; these need to include alternate "success paths" through which safety functions could be achieved [13]. A single failure should be assumed in the system and its consequences determined [13]. Compliance with independence within safety systems to prevent propagation of failures must be confirmed [13]. The analysis must demonstrate that redundant defense systems should not have single points of vulnerability [13]. Despite the single failure, the safety functions of I&C systems should still be completely performed [13]. Diversity enhances redundancy by providing additional defense against failures affecting more than one system simultaneously. This is based on monitoring different parameters, different logic/algorithms, different actuation technologies for providing multiple ways of detecting and responding to a significant event. Diversity is achieved by different methods—human, design, software, functional, signal, equipment, and manufacturer diversity [13]. Diversity should be present in design and implemented throughout the life of the plant [13]. This may need to be extended to components of systems or subsystems to ensure true diversity. For example, two manufacturers using the same operating system and processors have a susceptibility to the same errors (termed common mode errors—see Chap. 2) and do not constitute adequate diversity [13].

The concept of set points is important for the design and operation of nuclear plants. This concept can be applied to medicine. For any given monitored variable, a safety limit is established on the basis of safety criteria. This limit is that value beyond which unacceptable safety consequences occur [13]. The analysis limit is a value calculated from the safety analysis such that if mitigation systems act when this value is reached, the safety limit will not be reached [13]. The nominal set point is the value at which the trip function is set (i.e., the value at which safety systems are triggered), the margin between nominal set point and analysis limit should be such that mitigation is completed before the safety limit is reached. The allowable limit is a limit beyond the nominal set point to account for random uncertainties in instrument calibration, instrument drift, etc. This band therefore represents the

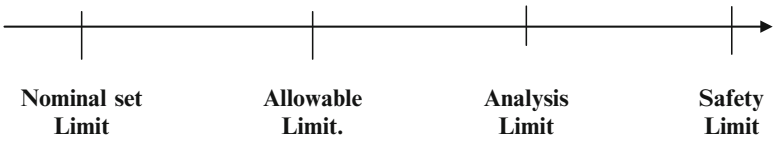

Fig. 1.7 Set points in nuclear safety. Further details on I&C systems may be found in [6–8, 13]

statistical error in measurements of plant parameters [13]. These can be represented on a continuum as in Fig. 1.7 [13]:

Industrial Automation

This extends the discussion of industrial automation to domains not discussed in preceding sections such as metals, cement, oil and gas, and manufacturing. These industries apply standards IEC61511 for continuous and batch processes and IEC62061 for manufacturing industries. These standards assess the electric, electronic, and programmable electronic systems contributing to risk reduction [6]. They are both derived from IEC61508. The standard addresses incorrect hardware or software specifications, omissions in the safety specification, random and systematic hardware failure mechanisms, software errors, common cause failures, human error, and environmental conditions [6]. The standards act on five domains—avoiding and eliminating introduction of systematic faults during specification, development, and test phases; requirements to guarantee fault tolerance and conforming to targeted failure probability rates [6]. The standards also address software integrity [6]. IEC 61508 addresses safety over the entire product lifecycle. For each stage in the product lifecycle, the standards include sets of requirements and mandatory or recommended methods, techniques, and practices to achieve requirements and objectives [6].

Common Framework for Multi-domain Safety

From the description above, what lessons can be learnt and what can be applied ubiquitously? What broad steps need to be applied for safety in sectors such as healthcare and finance where such standards are not common practice or for any new initiative?

Safety in all cases is defined in relation to risk [6]; to a great extent the common theme in all the above domains is that *safety is freedom from unacceptable risk* [6]. Safety requirements are developed by combining hazard assessment and risk analysis techniques [6]. In all domains, safety starts with analysis of consequences of system failure, starting with those functions with critical or hazardous consequences to those with no effect on safety leading to corresponding SIL/DALs [12].

Each system is associated with the worst case consequences of its failure [10]. Based on these, systems to mitigate risk and conforming to defined limits on failure probabilities are developed [6]. Fault tolerance is mandatory for critical functions. Demonstrating compliance with safety standards is essential for certification [6]. In civil aviation, ARP 4761 presents information on safety analysis methods needed for conducting safety assessment. The safety toolkit includes methods like FTA, dependence diagrams (DD), MA, failure modes and effects analysis (FMEA), Common cause analysis (composed of common mode analysis (CMA), zonal safety analysis (ZSA), particular risks analysis (PRA)) which are discussed in Chap. 2. These tools are also used extensively in the nuclear industry [6, 10]. All standards agree on basic principles and on the necessity to isolate different safety systems to prevent fault propagation between systems to prevent common failures.

In sectors which do not have such sophisticated safety mechanisms, there is an increasing trend towards quantification. This takes different forms—such as evidence-based medicine in healthcare and quantitative risk models in the financial sector. It is hoped that these methods will reduce human errors and decrease the need for human judgment since performance can be guaranteed through quantitative methods. It is therefore surprising that the safest industries—nuclear and civil aviation place such a great degree of importance on expert engineering judgment, extensive use of qualitative methods such as FTA/DD, FMEA, and CCA for delivering dependability.

Organization of the Book

This book surveys different domains where "dependability" is an essential requirement. Dependability in any domain is a blend of engineering principles with management techniques, human factors, and regulatory standards. The chapters which address these principles are shown in Fig. 1.8. The essential framework for

Engineering/Systems Principles	**Management Principles**
Chapter 1: Principles of Dependability. Chapter 2: System safety assessment. Chapter 3: Fault Tree Analysis Chapter 4: Failure modes and effects analysis. Chapter 5: Machine Learning principles Chapter 6: Byzantine Generals problem.	Chapter 7: Defining Processes. Chapter 8: Toyota Production System Chapter 9: Reliance Implementation System for a Kaizen project Chapter 10: Knowledge and Culture
Human Systems.	**Regulation**
Chapter 8: Toyota Production System. Chapter 10: Knowledge and Culture.	Chapter 1: Principles of Dependability. Chapter 2: System safety assessment

Fig. 1.8 Dependability as an interaction between engineering/systems principles, management principles, human systems and regulation discussed in this book. The relevant chapters which study a particular aspect in greater detail are as shown above

delivering dependability is surprisingly common across different domains. This book aims to survey important principles behind dependability.

The format of each chapter is to introduce the industrial principle involved with industrial examples to reinforce the concept. The principle is then extended to the world of medicine and conceptually reinforced with a toy example. A toy example is one which is ubiquitously encountered without a specific referable instance which serves to illustrate the principle being introduced. Subsequently, specific case examples from personal experience are presented which apply the principle being discussed.

Chapter 2 discusses the common principles behind dependable systems. These principles are common to planes, trains, nuclear reactors, oil refining where the consequences of failure can be devastating. This chapter introduces the reader to the key methods used for evaluating a system for safety. The proposed design is evaluated using Preliminary System Safety Assessment (PSSA). The process is iterative, concerns identified during the PSSA lead to design changes which are evaluated again using PSSA. Finally, the completed design is evaluated for safety compliance in a manner called system safety assessment. This chapter provides a conceptual overview of 3 extremely useful methods used for system safety: functional hazard assessment (FHA), FTA, and FMEA. Since there is a trend for increasing quantization in medicine, these principles are presented from both a qualitative and quantitative perspective. Basic ideas behind probability and Bayesian analysis are presented. To make the subject matter self-contained, the appendix presents more detailed mathematical fundamentals of reliability which can be skipped by the less mathematically inclined readers. *It should be noted that Chaps. 1 and 2 are quite difficult on initial reading. The medical reader is encouraged to initially skim the contents of these chapters, jump to a detailed presentation from a medical perspective in the relevant chapters and return frequently to these chapters to deepen his understanding.*

Chapter 3 expands the principles behind FTA. Following a quick review of the principles introduced in Chap. 2, medical case examples are presented. FTA is a powerful, graphical, deductive reasoning technique which is used by many industries such as aerospace, nuclear industries for safety analysis, and investigating the root cause(s) of accidents. The method lends itself well for disciplined problem solving in medicine. The cases selected as examples were undiagnosed cases which were verifiably diagnosed by performing a detailed FTA.

Chapter 4 presents the principles behind failure modes and effects analysis (FMEA). FMEA is a method for forward thinking, it helps the investigator explore the different ways in which a system can fail and the consequences of failure. It helps understand the effects of a single component failure on the entire system. This helps design prevention and mitigation strategies. This chapter introduces a useful failure classification model and its applications. FMEA provides a useful framework for analyzing adverse events and side effects. FMEA principles for steroid therapy (including oral prednisone and pulse methylprednisolone), IVIG are presented. Several case examples of successful application of these principles to challenging problems in autoimmune neurology are presented.

Chapter 5 presents some ideas from the artificial intelligence or Machine Learning literature. The reader is introduced to data distillation, how to convert voluminous medical data into useful decision making nodes followed by data visualization. This enables focused problem solving, evaluating candidate solutions and making probabilistic connections between nodes to arrive at a diagnosis and differential diagnosis. Simple graph theory principles are introduced and applied to medical problem solving. Several case examples of rare, undiagnosed cases solved using this technique are presented.

Chapter 6 presents the principles behind making decisions from misleading and erroneous data. In computer science, this is frequently referred to as the byzantine generals problem. One of the most demanding applications of this principle is in DFBW used in new generation commercial aircraft. The architecture behind Airbus and Boeing fly-by wire is studied and presented. These present a useful framework for medical decision making. Subsequently, several medical case examples are presented which were successfully analyzed using these principles in the face of misleading, erroneous information.

While the first six chapters are oriented towards engineering principles, starting with Chap. 7 the emphasis shifts towards management. In Chap. 7, the benefits of a process driven approach which form the basis of all manufacturing are introduced. The traditional V model from systems engineering is introduced. Subsequently, corresponding patient care V model is developed. More contemporary ideas in product development such as continuous engineering, platform approach are discussed. Medical applications of more integrated approaches in industry such as Amyotrophic Lateral Sclerosis (ALS) clinics are discussed. The principles of Product Lifecycle Management (PLM) and its corresponding medical extension Disease Lifecycle Management (DLM) are developed. Several case examples of advantages of DLM over piecemeal approaches to chronic conditions are presented. The principles behind six sigma, checklists are presented with medical applications.

Chapter 8 presents the principles behind the Toyota Production System (TPS). The ideas of W Edwards Deming, Taiichi Ohno are explored in detail. Many of the ideas presented in this chapter have been encountered in different forms in different chapters, therefore this chapter reinforces the concepts and presents additional case examples. Root cause analysis is explored further since it lies at the heart of almost all diagnostic endeavors. FTA (Chap. 3), graphical methods (Chap. 5), byzantine generals problem (Chap. 6) introduced in prior chapters are different methods for implementing root cause analysis.

Chapter 9 studies some ideas from Reliance Industries Limited (RIL) which can yield great benefits in terms of costs and quality in medical problem solving. RIL is one of the foremost global champions in megaproject implementation. Two powerful ideas from RIL's project implementation armamentarium—Reliance microplanning and backwards integration are presented. Subsequently these ideas are used for developing a CIDP treatment method which includes Dr. Deming's Plan-Do-Study-Act cycles for continuous process improvement. Several cases of successful treatment of CIDP are presented. This chapter borrows from ideas presented in many different chapters for successful project implementation. It

presents the reader with a framework to design a performance improvement (*kaizen*) project of his or her own.

Chapter 10 studies the philosophical principles behind successful companies. Branch Banking & Trust (BB&T) Corporation is studied as an example of dependable finance. While the prior chapters studied tools to deliver dependability, this chapter explores abstract principles which generate such ideas and create legendary, enduring companies and businesses. It studies how BB&T weathered a downturn in the world financial markets and what are the factors that helped its survival. The answer surprisingly does not lie in sophisticated computer code or complex algorithms, but lies in its employees rooted in deep company philosophical values. The chapter studies methods to develop employees over time into a powerful asset delivering dependability when quite the opposite has been the trend in western economies. It presents knowledge as the true wealth of organizations and explores ideas to synergize different competencies into complex, innovative services.

This book is not meant to be a rigid toolkit. On the other hand, it hopes to present a perspective which is never taught in medical schools—that of engineering and management. The hope is to inspire a wealth of new applications based on these principles. The case examples presented here are largely drawn from the author's daily work of neuromuscular medicine. However, the hope is these principles will be understood to be common to many different areas in medicine, just as they are in industry. This is why the book is challenging in some areas, it hopes to present a sufficient depth for the reader to develop a dependable method of his or her own.

Philosophical Perspectives

In western philosophy, the pursuit of knowledge as a unifying thought in science, philosophy, and religion started with a young Jewish heretic Baruch Spinoza in the Netherlands in the seventeenth century. An unprejudiced inquiry into the harmony, relationships between observable things, and a search for deeper cause and effect started with Spinoza. He was born on November 24, 1632 in Amsterdam, The Netherlands and died on February 21, 1677 at The Hague in The Netherlands. He was excommunicated for heresy on July 27, 1656. Most of his life he lived in solitude in Rhynsburg, near Leyden. His most celebrated book *The Ethics* was published shortly after his death in 1677 [14, 15]. Metaphysics is the study of things to their ultimate significance. Spinoza's metaphysics is to study matters to their essential substance [14].

Spinoza's teachings emphasize improvement of the intellect. The only permanent happiness is the pursuit of knowledge and the joy of understanding [14]. Only knowledge is power and freedom. Spinoza distinguishes between four types of knowledge [14]:

1. The first is hearsay knowledge or declarative knowledge. These include knowledge of one's birthday which is "*known*" to be true from statement and reinforcement from trustworthy sources.
2. The second, superior form of knowledge is knowledge gained from experience. The knowledge from clinical trials falls into this category.
3. The third is knowledge derived from reasoning—an example cited by Will Durant in [14] is that since the sun appears just as large despite distance, it must therefore be large.
4. The highest form of knowledge is mathematical knowledge which is derived from deduction.

There are three pivotal things in Spinoza's philosophy: *substance*, *attribute and mode*. Attribute is what the intellect perceives of an object. Attributes are descriptive in nature, an object may have a certain color, temperature, or texture. It is what is immediately apparent to the senses. Mode is any individual object or event that reality assumes. In Spinoza's world, people, objects, and thoughts are modes. Substance is what lies beneath; it refers to the reality that lies beneath the modes.

Spinoza's substance, attribute, and mode framework is very useful in medicine. The entire patient interview involves description of symptoms. For example, "my feet are tingling, they are on fire and it is like a thousand bugs crawling all over them" is a frequently heard symptom in the neuromuscular clinic. These represent powerful descriptions of an underlying process, therefore these are attributes. These descriptions are usually heard in the context of an underlying "neuropathy." Neuropathy therefore constitutes the "mode." The cause of the neuropathy itself maybe nerve inflammation as in Guillain-Barré Syndrome, therefore this constitutes the underlying substance. This distinction is of great significance since a mode almost never constitutes a diagnosis; it is merely an intermediate point which consolidates attributes. A common cause of medical error is to misinterpret modes such as "neuropathy," "ataxia" as a diagnosis in itself failing to explore the underlying substance. Similarly, MRI images, CT scans, EMG/EEG reports also constitute modes, they do not represent the substance since the underlying substance producing the specific imaging or electrical features maybe diverse. Chapters 3, 5, and 6 explore graphical analysis of clinical problems along similar principles. Spinoza's philosophy encourages a deeper exploration into the substance which lies at the heart of medical diagnosis.

Down the centuries, this framework has found immense application in engineering and management. The reader will notice that the existential need for pursuit of knowledge and deeper understanding as a goal in itself is an often repeated theme of many great minds in subsequent chapters. It will be encountered in the teachings of W Edwards Deming, Taiichi Ohno, Ikujiro Nonaka, and Hirotaka Takeuchi in Chap. 8 [16]. It forms an important aspect of the core values of BB&T which will be explored in Chap. 10. Therefore, in a sense, the world of dependable airplanes, nuclear power, high-speed trains, and cellular phones are inspired by the teachings of the great philosopher.

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Chapter 2
An Overview of System Safety Assessment

Abstract This chapter provides an introduction to the steps involved in creating dependable systems. This starts with a description of functional hazard assessment (FHA). The steps involved in preliminary system safety assessment (PSSA) and system safety assessment (SSA) are reviewed. The chapter introduces fault tree analysis (FTA) and failure modes and effects analysis (FMEA) as important tools in the safety assessment process. This chapter also introduces the basics of probability theory which can guide quantitative assessment. The concepts behind common cause analysis are introduced. To make the book self-contained, more detailed mathematical concepts are presented in the appendices which can be skipped by less mathematically inclined readers.

Introduction

Chapter 1 described the properties of dependable systems. This chapter introduces systematic methods used in the design and development of dependable systems. Industries such as nuclear, aviation, railways, and their regulatory agencies have over the years developed standards, analytical techniques for safety assessment with interdisciplinary applications which will be introduced in this chapter. These are the methods which are used in system design when a new product or service is conceived.

This chapter borrows heavily from the aerospace industry which has amongst the most rigorous standards. An important guiding document for safety in development of new aircraft is ARP 4761 [1]. *The methods employed are qualitative*, *quantitative, or both*. These include functional hazard assessment (FHA), failure modes and effects analysis (FMEA), fault tree analysis (FTA), dependence diagrams (DD), Markov analysis (MA), and common cause analysis (CCA) (which is composed of zonal safety analysis (ZSA), particular risks analysis (PRA), and common mode analysis (CMA)).

The development process is iterative in nature with system safety being an inherent part of the process. The process begins with concept design and derives an initial set of safety requirements for it. During design development, changes are made to it and the modified design must be reassessed to meet safety objectives. This may create new design requirements. These in turn necessitate further design

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changes. The safety assessment process ends with verification that the design meets safety requirements and regulatory standards [1]. The safety assessment process begins with FHA, preliminary system safety assessment (PSSA), and system safety assessment (SSA). These techniques are applied iteratively. Once FHA is performed, PSSA is performed to evaluate the proposed design or system architecture. The SSA is performed to evaluate whether the final design meets requirements.

The subject matter in this chapter can be initially challenging. The reader is encouraged to skim the contents at first glance and proceed to subsequent chapters which elaborate on the concepts described here in a medical framework and return frequently to reinforce concepts.

Functional Hazard Assessment

FHA is performed at the beginning of system development. Its main objective is to "identify and classify failure conditions associated with the system by their severity" [1]. The identification of these failure conditions is vital to establish the safety objectives. This is usually performed at two levels, for the example of the aircraft industry—at the completed aircraft level and at the individual system level [1].

The aircraft level FHA identifies failure conditions of the aircraft. The system level FHA is an iterative qualitative assessment which identifies the effects of single and combined system failures on aircraft function. The results of the aircraft and system level FHA are the starting point for the generation of safety requirements. Based on this data, fault trees, FMEA can be performed for the identified failure conditions which are studied later.

ARP 4761 provides guidelines on how an FHA should be conducted. Since this is an iterative process, it is performed in broad categories with increasing resolution as the analysis proceeds to finer and finer subsystems. A recommended manner to accomplish this is to list all the performance requirements based on design characteristics. Once the high-level requirements have been identified, the failure conditions associated with them are identified. This is then used to generate lower level requirements. This process is then applied iteratively till the design is complete. An illustrative example for aircraft is as shown below:

Aircraft function	Failure condition
1. To control aircraft trajectory	Loss of aircraft control
	Loss of pitch control (partial control loss)
	Runaway of one control surface

These failure conditions are further broken down in a systematic manner through FHA performed at the system level. FHA therefore is a top-down process; it proceeds from the broad to more specific functions and their failures. The following steps are involved [1]:

Determine and Characterize Inputs at Product Level or System Level

For an aircraft this involves specification of top level functions such as passenger load, thrust, lift, customer requirements, etc. For an automobile, this involves description of the type of vehicle (sedan, minivan, etc.), performance requirements such as horsepower, torque, braking, steering; control systems, transmission, safety systems. For individual systems such as braking, system level approach involves looking at subsystems such as hydraulics, interface with electronic control systems such as antilock braking system (ABS), power brakes, and so on.

FHA Process

Once the inputs (as above) have been identified, the following steps are then applied.

- Identify all the functions with the level under study [1]. These include functions provided by the system and all the other systems interlinked to the system under study.
- Identify and describe failure conditions associated with these functions, considering single and multiple failures under different conditions [1]. Examples include "loss of hydraulics" under "normal weather" or "ice/snow storm" conditions.
- Determine the effects of the failure conditions.
- Classify failure condition effects. This is shown in Chap. 1, Table 1.1. Common classification systems in use across several domains (aviation, railway) are catastrophic (e.g., loss of engines), severe, major, hazardous, minor, and no safety effect (e.g., loss of in-flight entertainment system). Based on failure condition classification, allowable probability limits of occurrence and required developmental assurance levels (DAL) are assigned as described in Chap. 1.
- Assignment of requirements to the failure conditions at the next lower level of analysis. Why is this failure catastrophic or why is it only minor? Identify supporting materials for failure condition effect classification. This can be from simulations, prior experience with similar aircraft, etc.
- Identify methods used to verify compliance with failure condition requirements.

A careful examination of the above method shows that a good FHA is a collaborative, multidisciplinary effort requiring great domain knowledge and insight requiring great qualitative effort. The FHA leads to the PSSA.

FHA in Neurological Diagnosis and Treatment

FHA is a very useful method for analyzing and mitigating morbidity from medical illness, especially neurological illness. In cases where the underlying disease is not directly treatable, FHA is a systematic method for identifying the morbidity from the untreatable illness. The underlying disease causes loss of normal function or permits gain of abnormal function both of which cause significant distress to the patient. Examples of loss of function include weakness, poor balance, difficulty swallowing, and difficulty speaking, etc. Examples of gain of function include severe pain from neuropathy, painful myositis, etc. The failure classification helps quantify the clinical significance of the change in function. Painful neuropathy, through distressing and leading to a poor quality of life would not be expected to shorten life expectancy or cause significant problems with mobility. Therefore this can be classified as minor. Difficulty swallowing on the other hand can lead to progressive weight loss and aspiration which can be fatal. Therefore this failure condition can be classified as major or catastrophic. This helps direct resources and plan treatment costs appropriately. The following case examples are illustrative.

Case Example 1

J.C.C. is a 75-year-old avid saxophone player. He noticed insidious onset of loss of dexterity in his left hand while playing the saxophone for the last several months. He denied any abnormal posturing or pain in the left upper extremity while playing the saxophone. He reported that he was unable to seamlessly move between octaves and was unable to initiate fine movements with his fingers for precise playing of certain rhythms. He denied any pain, numbness, or weakness in the left upper extremity. He had not noticed any loss of dexterity with less challenging tasks such as manipulating a fork and knife while eating. He denied any symptoms in his right upper extremity.

He reported sleep problems with a tendency to sleep walk and sustained a fracture in his right little finger approximately a year ago while possibly acting out his dreams during sleep. He denied any significant changes in smell. He denied any falls. He also denied any visual hallucinations or memory loss. He had noticed some twitching, which may actually resemble a tremor in the left upper extremity, but this was very infrequent. He denied any memory problems or cognitive

difficulties and remained actively involved in the stock market with surprisingly good returns. However he reported severe depression for the last several years.

On examination, mental status and cranial nerve examination were normal save decreased blink rate and facial expression. He had significant diffuse bradykinesia. He had normal 5/5 strength in his bilateral upper extremities without evidence of fasciculations or atrophy. He also had reduced ability to tap his fingers on the left side when compared to the right. Examination of motor tone revealed left upper extremity cogwheel rigidity, exacerbated by exercising his right upper extremity. He had normal tone in the right upper and bilateral lower extremities. Gait examination revealed a festinant gait without retropulsion. There was no evidence of apraxia. Based on this history, physical examination, a diagnosis of Parkinson's disease was made. FHA of J.C.C. reveals the following:

Normal function	Failure condition
1. Fine motor control of fingers of left hand	1. Partial loss of fine motor function of left hand
2. Speed and rhythm of movement	2. Partial slowing of movement in all limbs
3. Normal mood and cheer	3. Severely depressed mood and cheer
4. Normal sleep	4. REM behavior disorder

The FHA can guide therapy. In J.C.C.'s case, treatment of depression with citalopram and REM behavior disorder with clonazepam had the greatest impact on his life. He did not tolerate levodopa well and had a modest response to pramipexole which enabled him to continue his hobby for several more years.

Case Example 2

S.C. is a 61 y/o male who developed bilateral shoulder pain, soreness 5–6 weeks ago. Subsequently he developed shortness of breath, especially when lying down. Symptoms are worst during the night when he wakes severely dyspneic after 3–4 h of sleep. Most routine activities during the day are well tolerated; however he would get severely short of breath with minor exertion. He denied any changes in his vision, any difficulty chewing or swallowing. He also denied any weakness elsewhere or any changes in sensation or bladder function. He denied any antecedent vaccinations, flu-like illnesses or tick bites. He was evaluated by his pulmonologist who noticed high diaphragms on a chest X-ray that was performed as part of routine evaluation. On examination, he had normal mental status, cranial nerves, extremity strength, sensation, and mildly brisk symmetric reflexes with downgoing toes. He was severely orthopneic with paradoxical movements of the diaphragm and observed to need accessory muscles of respiration like the sternocleidomastoid. NCS/EMG showed normal nerve conduction studies and fibrillations and positive sharp waves in the diaphragm with a complete absence of any recruitable motor

units. Based on his clinical, radiographic, and EMG findings he was diagnosed with bilateral diaphragmatic palsy, likely as a consequence of idiopathic brachial neuritis (Parsonage Turner syndrome) because of prodromal shoulder pain. MRI Cervical Spine, spinal fluid studies were normal and an empirical trial of intravenous immunoglobulin (IVIG) and prednisone did not yield any benefit. CT Chest and neck excluded any mass lesions infiltrating the phrenic nerves. FHA helped mitigate his diaphragmatic failure condition.

Normal function	Failure condition
1. Ventilatory function during daytime	1. Partial loss of ventilatory function during daytime (especially exertion)
2. Ventilatory function during nighttime	2. Severe loss of ventilatory function at night time

Based on the results of overnight pulse oximetry, he was started on night time BiPAP with adequate restoration of quality of life. Further pharmacotherapy with repeat IVIG, prolonged steroid therapy or other immunosuppression was not performed.

Case Example 3

D.B.S. is a 60 y/o male presenting with numbness, tingling, and painful paresthesias involving his toes for the last several months. Symptoms started in the right lower extremity, experienced most towards the great toe followed by involvement of the left lower extremity 6 months later. Symptoms are worse when wearing tight shoes, standing and walking for prolonged periods. Feet would feel hot or experience a pressure like discomfort. He denied any urinary, bowel disturbances. He also denied dry eyes and dry mouth. He experienced back trauma in the 1990s which was monitored nonoperatively. Symptoms are not experienced at rest, especially at night. He felt mild involvement of the hands at the time of his appointment. He denied any neck pain. He had an extensive evaluation through his primary care physician which excluded diabetes mellitus and vitamin deficiency. Physical examination revealed normal strength and reflexes down to the ankles. Sensory examination revealed normal joint position sense, mild loss of distal pinprick sensation involving the feet. A nerve conduction study revealed mild demyelinating features suggestive of distal acquired demyelinating symmetrical (DADS) variant of chronic inflammatory demyelinating polyneuropathy (CIDP). Blood work revealed a faint IgM Lambda spike. Follow-up testing revealed very high titers of anti-myelin-associated glycoprotein (anti-MAG) antibodies which frequently causes such a presentation. Therapeutic approaches to the anti-MAG syndrome are very challenging ranging from IVIG, plasmapheresis, steroids, and rituximab [2]. FHA yields the following:

Normal function	Failure condition
1. Normal perception in feet	1. Partial loss of normal sensation in the feet 1.1 Partial loss of skin sensation in the feet
2. Absence of abnormal sensation like tingling, pain involving feet	2. Moderate pain and tingling involving feet
3. Normal serum protein profile in blood	3. Abnormal IgM Lambda spike on serum immunofixation

Since the therapeutic choices are so varied and so expensive, FHA is very useful in guiding therapy.

Given the mild failure conditions observed on FHA, immunotherapy for CIDP was deferred. The patient experienced very little clinical progression despite abnormal test results over 2 years. At the end of 2 years he was placed on Gabapentin 300 mg once to twice daily for symptomatic relief of moderate pain and tingling involving the feet.

Preliminary System Safety Assessment

PSSA is a systematic examination of the proposed system architecture to examine how failures can lead to the functional hazards identified by the FHA and how safety requirements can be met [1]. The PSSA addresses each failure condition identified by the FHA in qualitative or quantitative terms [1]. It involves the use of tools such as FTA, DD, and MA to identify possible faults. The use of these is discussed later. The identification of hardware and software faults and their possible contributions to various failure conditions identified in the FHA provides the data for deriving the appropriate DAL for individual systems. The process is iterative being performed at the aircraft level (for the case of airplanes) followed by individual system levels. The process involves the following steps [1, 3]:

Inputs to PSSA

Aircraft level FHA, System level FHA.

PSSA Process

The PSSA is a top-down process which determines how system failures can lead to the functional impairments or failures identified by the FHA. The following steps are involved in performing a PSSA for the example of aircraft [1]:

1. *Identify and list aircraft and system level safety level requirements*:
   This is derived from the FHA and preliminary CCA (common cause analysis, discussed in detail below in Section "Common Cause Analysis (CMA, ZSA, and PRA)") processes which create the initial safety requirements for the systems. This information is combined with the knowledge of system architecture and performance features. The inputs to this step therefore include the failure conditions from FHA and CCA, system architecture description, description of system equipment, system interfaces with other systems and preliminary CCA (described in Section "Common Cause Analysis (CMA, ZSA, and PRA)") [1].
2. *Determine if the design can be expected to meet identified safety requirements and objectives*
   In this step, each identified severe-major/hazardous and catastrophic failure condition is evaluated in detail. Each of these is analyzed using FTA (discussed in detail below in Section "Fault Tree Analysis") or a similar method to show how item failures either singly or in combination lead to system or at a higher level aircraft failure. This analysis is both qualitative and quantitative. This step demonstrates that all the qualitative and quantitative objectives associated with the failure conditions can be met by the design under consideration. Maintenance intervals for discovery of hidden (latent) failures are also identified in this step. Based on the component systems and their failure consequences identified in the fault trees, the corresponding development assurance level and budgets are developed. All requirements for independence of systems made in the FTA are verified in this step. This step is frequently performed at an early stage in the design, therefore the inputs are based on preliminary domain knowledge, experience with similar designs and judgment available at the time [1].
3. *Derive safety requirements for the design of lower level systems*
   The safety requirements identified at the system level by the preceding steps are then allocated to the items or components making up a system. This involves both hardware and software and is both qualitative and quantitative. It also involves specifications for installation of systems and subsystems (aspects such as segregation, separation of systems, protection from mechanical damage, etc.). Safety allocations include DAL for hardware and software, maintenance intervals and associated "Not to Exceed" times [1].

The PSSA process should be well-documented since this step is frequently revisited during the development process and the reasons for specific design architectures may need to be understood from different perspectives and requirements at different stages of the project.

Fault Tree Analysis

FTA is very powerful, graphical deductive reasoning tool which can identify undesired failure and help the investigator identify their root causes. The technique was developed extensively by the nuclear and aerospace industries and can be

viewed as a systematic method for acquiring information about a system. References [4] and [5] provide a wealth of information about this technique. An introduction to the basic theory of fault trees, including some of the rules of probability theory, Boolean algebra is presented here to introduce the reader to this technique. Medical examples will be presented in Chap. 3.

There are two major methods for performing analysis—inductive and deductive analysis. Inductive analysis involves reasoning from individual cases to a general conclusion [4]. In this method, a particular fault is considered and we attempt to ascertain the effect of that fault or condition on system operation. Examples of this include a fuel pump malfunction and its effects on power output of an engine. Or the effect of failure of an organ and its effect on body function such as renal failure and its consequences on urine output. FMEA, failure modes effects and criticality analysis (FMECA) are some commonly used inductive methods which will be discussed further.

Deductive reasoning method constitutes reasoning from the general to the specific. In this method, we observe that the system has failed in a particular way and we attempt to determine what components failed and in what manner that led to system failure. This is also called "Sherlock Holmesian" thought since the legendary detective had to start with a crime and based on the clues and evidence available reconstruct the events that led to the crime [4]. This mode of analysis is well suited for the investigation of accidents and similar untoward events. FTA is an example of deductive reasoning. Therefore, it lends itself well to medical diagnosis. Inductive reasoning helps tell the investigator what system states can occur, deductive reasoning tells how a particular system state, especially a failure state can occur [4].

A fault tree is a graphical analytic technique composed of the various parallel and sequential combinations of events that will result in the undesired event of system failure. *The method is both qualitative and quantitative*. The undesired event is called the "top event" of a fault tree. Constructing a fault tree requires deep knowledge and insight into the event being investigated since the investigator develops the tree based on knowledge of systems and their connections. The faults can be component hardware failures, software failures, or human failures. *The tree itself represents the logical interrelationships between basic events which can cause the top event of system failure*. It is not an exhaustive enumeration of possibilities, but an exploration of the more likely events which can cause the top event.

The building blocks of a fault tree are primary events, intermediate events, and top events. The building blocks are described here, the symbols are shown in Fig. 2.1. The list is not exhaustive, only the most commonly used events and logic gates are discussed here.

The Primary Events

The primary events of a fault tree are those events which are not further developed. These include the following [4]:

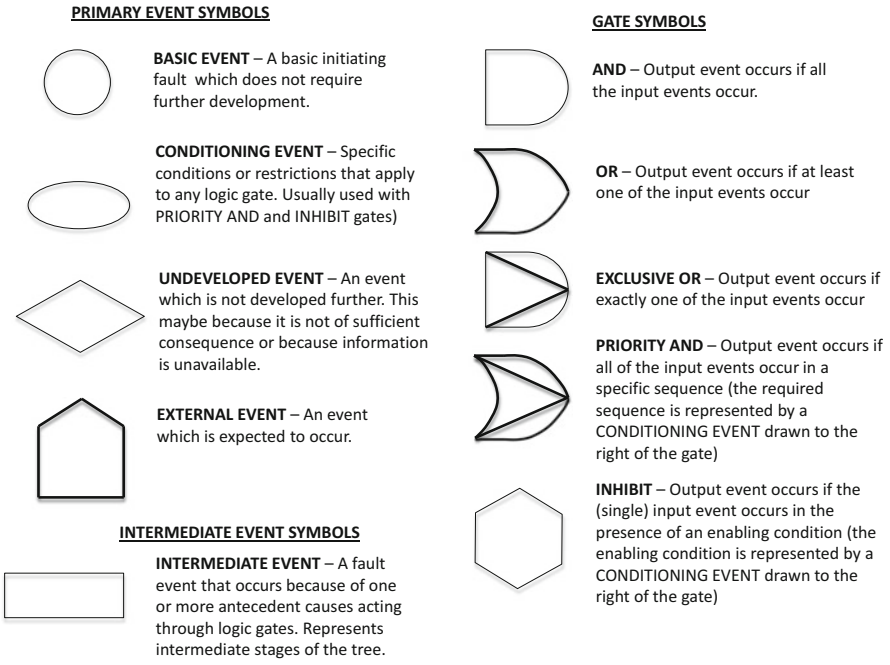

Fig. 2.1 Symbols used in the construction of fault trees, from [4]

1. **Basic event**: This is a basic initiating fault which does not require further development. Examples include fuel valve blocked, microprocessor failure, etc. for top events of engine failure or computer failure. It is represented by a circle.
   (a) **Medical example**: Subtherapeutic INR (basic event) led to thrombus which led to stroke.
2. **Conditioning event**: Specific conditions or restrictions that apply to the logic gates. It is represented by an oval. Used with "Priority AND" and "INHIBIT" gates.
3. **Undeveloped events**: An event which is not developed further, either because developing it further is not relevant for the problem being analyzed or because more information is not available. It is represented by a diamond.
   (a) **Medical example**: A finding uncovered but not relevant to current analysis. Osteoporosis on Chest CT done for lung cancer. Therefore not explored further.
4. **External event**: is an event which is normally expected to occur. For aviation example this includes events such as "icing." These events are not in themselves faults, these events can occur normally. It is represented by the house symbol.

Note that basic events are supposed to be independent in many system safety assumptions which may not be true in the real world.

Intermediate Event Symbols

Intermediate event: a fault event that happens because of one or more primary events acting through logic gates. It is represented by the rectangle symbol.

(a) **Medical example**: Intermediate event: Blood loss (basic event) led to hypotension (Intermediate event) which led to shock liver.

Logic Gates Used in Fault Trees

1. **Boolean "OR" gate**: Output occurs if at least one of the input events occurs.
   (a) **Medical example**: Spinal cord disease OR muscle disease led to weakness.
2. **Boolean "AND" gate**: For this gate, the output occurs if all the inputs are true. The output event occurs if and only if all the input events occur.
   (a) **Medical example**: Right ureter blockage AND left ureter blockage led to kidney failure.
3. **The Inhibit gate**: represented by a hexagon is a special case of the AND gate. The output can be caused by a single input, but a qualifying condition must be present for the output to happen. The conditional input discussed under primary events is the qualifying condition that must be present for the output to happen. Examples include input chemical reagents (input) going to completion (output) in the presence of a catalyst [4].
   (a) **Medical example of Inhibit gate**: (a) Diaphragm weakness from myasthenia gravis in the presence of moderate COPD led to ventilatory failure. Either could not do it alone for a patient with moderate myasthenia gravis and COPD. (b) Stable Congestive Heart Failure (CHF) patient developed hypokalemia (conditioning event) which led to ventricular arrhythmia.

Less frequently used logic gates are the Exclusive OR and Priority AND gates. In an Exclusive OR gate, the output occurs only if one of the inputs occur. When more than one of the inputs happens, the output is zero.

Fault Tree Component Fault Categories

In FTA, faults are classified into three categories—primary, secondary, and command. A primary fault occurs in an environment for which the component is designed. For example, a concrete beam in a building failing under the weight of a load which is less than what the beam is designed for. A secondary failure is a component or system failure in an environment which it is not designed for [4]. For the example above, this

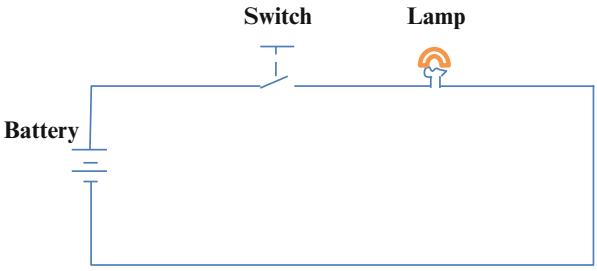

Fig. 2.2 Simple system to illustrate failure effects, modes, and mechanisms. The battery provides the energy for operation of a lamp controlled through a switch

Table 2.1 Failure modes, effects, and mechanisms involved for the example of Fig. 2.2

Failure effect	Failure mode	Mechanism
Switch fails	– Contacts broken	– Mechanical damage
	– High-contact resistance	– Corrosion of contacts
Lamp fails to light	– Lamp filament broken	– Material defect, excess voltage
	– Lamp glass broken	– Mechanical shock
	– Loose contact with socket	– Human error, socket defects
	– Socket contacts damaged	– Human error, socket defects
Low voltage from battery	– Leakage of electrolyte	– Defective casing
	– Contacts broken	– Mechanical shock
Open circuit	– Wire broken	– Mechanical shock, human error
	– Wire burnt	– Short circuit, excessive current

involves the beam failing under a weight more than what it was designed for [4]. A command failure is the proper operation of a component at the wrong time or place.

Failure effects, failure modes, and failure mechanisms are important concepts in analyzing the relationships between events. Consider Fig. 2.2 which shows a simple circuit controlling operation of a lamp based on an illustrative example in [4].

Failure effects understands failures based on their importance—what are the consequences or effects of failure on the system [4]. Failure modes helps describe the specific manner in which failure occurs. Failure mechanisms helps identify the cause(s) of the failure modes [4]. For the example of Fig. 2.2, this is shown in Table 2.1. For example, the failure effect of low voltage from battery can occur due to the failure mode of leakage of electrolyte from battery. Defects in casing of the battery or mechanical shock are the failure mechanisms which can cause leakage of electrolyte from battery.

Lamp System Failure Analysis

The middle column, "system failure modes" constitutes the "top event" that the system analyst has to explore. In fault tree methodology, one of these is selected and the immediate preceding causes of this in column 3 are explored. These immediate

causes will constitute the top events for the subsystem being examined which will then be used to extend the analysis to the chosen subsystems to form the next layer of the fault tree [4]. Consider the toy example of left middle cerebral artery occlusion leading to ischemic stroke. For this example, failure effect is global aphasia (a failure effect which will be classified as severe), failure mode is thrombotic occlusion of the left middle cerebral artery. Failure mechanism could be left carotid atherosclerosis, cardiac embolism, traumatic dissection, vasculitis, and other rare causes of stroke. Working backwards from failure modes to failure mechanisms allows for rigorous examination of the causes of thrombotic stroke.

The system analyst first defines his system and establishes boundaries. He then selects a particular system failure mode as the "*top event*" for further analysis. The system analyst then determines the "immediate, necessary, and sufficient" causes for the occurrence of this top event. These are not the basic causes, but the immediate causes of mechanisms of this event. Once the immediate, necessary, and sufficient causes of the global top event are determined, these in turn are considered the subtop events and the analyst proceeds onto determine the immediate, necessary, and sufficient causes of these. The analysis proceeds by switching back and forth between failure mechanisms and failure modes i.e., the "mechanism" for a system are the modes for the subsystem. Thinking in immediate, *necessary, and sufficient steps is an extremely important principle called the* "*Think Small*" *rule. This proceeds till the desired limit of resolution is reached* [4].

The construction of fault trees follows some basic rules [1, 4, 5]. These are:

1. *State the undesired top level event in a clear, concise statement*. This should be clarified precisely as to what it is and when it occurs.
2. *Develop the upper and intermediate tiers of the fault tree*; determine the intermediate failures and combinations which are immediate, necessary, and sufficient to cause the top level events and interconnect them by the appropriate logic symbols [1, 4]. Extend each fault event to the next lower level. At each level of tree construction, particular attention is paid to the following:
   - Can any single failures cause the event to happen?
   - Are multiple failure combinations necessary for the event to happen?
3. *Develop each fault tree event through more detailed levels of system design till the limit of resolution is reached and a root cause*(*s*) *is established*. Root cause analysis is explored further as a management method in Chap. 8.
4. Evaluate the fault tree in qualitative and/or quantitative terms. Fault trees are qualitative by nature of their construction. Establish probability of failure for individual components; evaluate ability of the system to meet safety margins. If safety objectives are unmet, redesign the system and reiterate the process.

Two other procedural rules are complete the Gate rule and No-Gate-to-Gate rule. The complete the Gate rule states that all inputs to a particular gate should be completely defined before further analysis of any of the inputs is undertaken. The No-Gate-to-Gate rule states that gate inputs should be well defined gate events and the outputs of individual gates should not be connected to other gates. *Once the root*

cause(s) are identified, the investigator must be able to reconstruct the top event by traversing up the tree. As discussed in the appendices, the idea behind the analysis is to identify the "minimal cut set." A "minimal cut set is the smallest combination of component failures, which, if they occur will cause the top event to happen" [1]. It follows by logical extension (see appendices for details) that if a single system failure can cause the top event to happen, then the design is not a fault tolerant system. It also helps understand why there is protection in redundancy (assuming independent failures). Consider a design made of two systems A and B, each with probability of failure of 1/1,000. Let us assume that our first design can fail if system A OR system B fails. Therefore, the probability of the undesired top event happening remains of the order of 1/1,000. Now let us assume systems A and B are used in a redundant manner and both must fail for the undesired top event to occur. Now the probability of failure becomes 1/1,000 × 1/1,000 or 1 in 1,000,000.

Basic ideas from probability are discussed in the following section. Appendices 1 and 2 contain further information on FTA and a closely related structure called DD, their construction and analysis using probability theory and Boolean algebra. The information in the appendices is useful for more mathematically inclined readers and can be safely skipped for understanding the use of FTA methodology for medical diagnosis used in the rest of this book.

Probability Basics

We explore some basic probability theory which has ubiquitous application in decision making. This section looks at a few basic rules from probability theory necessary for understanding fault trees and analyzing them. $P(\mathrm{A})$ is a real number between 0 and 1 which denotes the probability of event A happening. Similarly $P(\mathrm{B})$ is the probability of event B happening. A number closer to 1 denotes a higher probability; numbers closer to 0 denote low probabilities. $P(\mathrm{A}\cup\mathrm{B})$ is the probability of event A or event B happening. $P(\mathrm{A}\cap\mathrm{B})$ is the joint probability of events A and B happening [6].

1. $P(\mathrm{A}\cup\mathrm{B}) = P(\mathrm{A}) + P(\mathrm{B}) - P(\mathrm{A}\cap\mathrm{B})$. This operation happens at the OR gate of the fault tree.
2. $P(\mathrm{A}\cap\mathrm{B}) = P(\mathrm{A}) \cdot P(\mathrm{B}|\mathrm{A})$. This operation happens at the AND gate of the fault tree.

$P(\mathrm{B}|\mathrm{A})$ denotes the probability of event B happening provided we know A has happened. For example, assume a box has ten pairs of socks, of which five pairs are white, three are red, and two are blue. The collection of all socks: white, blue, and red is called the universal set which denotes all possible outcomes. $P(\text{white socks}) = 5/10$, $P(\text{red socks}) = 3/10$ and $P(\text{blue socks}) = 2/10$. However, if we know that a colored sock was drawn from the box, we have restricted our possibilities to 5 since there are three red and two blue socks in the box which are colored. If we have this information, then the probability that a drawn pair of socks is red is

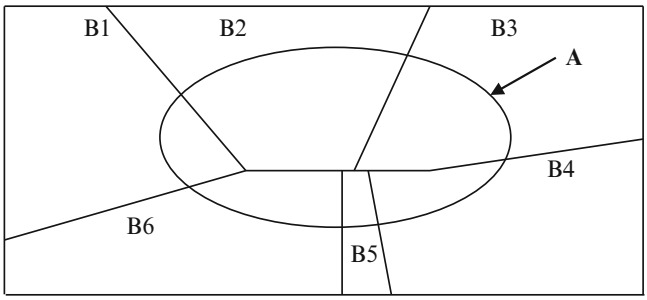

Fig. 2.3 Bayes theorem. The *rectangle* represents the universal set—all possible events. It is partitioned into different regions. Given the occurrence of event A, we are interested in knowing the probability that it originated from a particular region. In the context of reliability, let B1, B2, . . . , B6 represent six different manufacturers of a particular component. Let A represent all defective components. If we have a particular defective component, what is the probability that it was manufactured by manufacturer B1? Bayes analysis helps estimate such probabilities [4]

P(Red Socks|Colored Socks) = 3/5. Similarly P(Blue Socks|Colored Socks) = 2/5 instead of 3/10 or 2/10 if we did not have this information.

If A and B are independent events, where the occurrence of one does not influence the occurrence of the other, $P(\mathrm{A} \cap \mathrm{B}) = P(\mathrm{A}) \cdot P(\mathrm{B})$. An important probabilistic method is Bayes theorem where we are interested in calculating the posterior probabilities of an event. This is a powerful method which forms the heart of many algorithms in artificial intelligence and machine learning [6].

Let the universal set (rectangle in Fig. 2.3) be partitioned into six different regions. B1 + B2. . .B6 = Universal set. Let this be denoted by Bi where i assumes values between 1 and 6 to denote each of the six regions. There is no overlap between the partitions. For the example above, this can be expressed as:

$$\Omega = \sum_{i=1}^{6} \mathrm{B}i \tag{2.1}$$

(In Eq. (2.1) the symbol $\sum$ denotes addition i.e., B1 + B2 + B3 + B4 + B5 + B6.)

The event A can occur as part of the partitions of the universal set as the different regions of overlap of A and individual Bi's demonstrate. We are interested in finding a particular Bi, given the event A has happened [4]. This can be done using Bayes rule:

$$P\left(\mathrm{B}i \middle| \mathrm{A}\right) = \frac{P(\mathrm{B}i \cap \mathrm{A})}{P(\mathrm{A})} \tag{2.2}$$

The event A can occur as part of many different partitions of the universal set. In the example in Fig. 2.3, the total probability of a defective component is the sum of individual probabilities of defectives made by different manufacturers. Therefore

$P(\mathrm{A}) = \sum_{i=1}^{6} P(\mathrm{B}i)P(\mathrm{A}|\mathrm{B}i)$. Assume we are interested in knowing $P(\mathrm{B2|A})$ or in other words the probability of a defective part made by manufacturer # 2. This is called the posterior probability [4]. Substituting the relevant terms, the corresponding posterior probability becomes:

$$P(\mathrm{B2}|\mathrm{A}) = \frac{P(\mathrm{A}|\mathrm{B2})P(\mathrm{B2})}{\sum_{i=1}^{6} P(\mathrm{B}i)P(\mathrm{A}|\mathrm{B}i)} \tag{2.3}$$

Toy Medical Example

To illustrate medical application of Bayes rule, consider the following example. Let the universal set be the set of patients with the following conditions: B1: CHF, B2: COPD (chronic bronchitis and emphysema), B3: Bronchial Asthma, B4: Pulmonary Embolism, B5: myasthenia gravis, and B6: Muscular Dystrophies. Let the region A denote the patients within this universal set who are short of breath. We are interested in knowing what is the probability that a patient with shortness of breath has a particular diagnosis—such as myasthenia gravis.

To make the example illustrative, let the numbers be as follows:

Total number of patients, the universal set: 100.

B1: CHF patients: 30. 30 % of whom are short of breath: 9 patients. Therefore, probability of shortness of breath given that the patient has CHF is given by $P(\mathrm{A|B1}) = 0.3$. $P(\mathrm{B1}) = 30/100 = 0.3$

B2: COPD patients: 30. 50 % of whom are short of breath: 15 patients. Therefore $P(\mathrm{A|B2}) = 0.5$.
$P(\mathrm{B2}) = 30/100 = 0.3$

B3: Bronchial Asthma patients: 20. 20 % of whom are short of breath: 4 patients. Therefore $P(\mathrm{A|B3}) = 0.2$. $P(\mathrm{B3}) = 0.2$

B4: Pulmonary Embolism: 5 patients. 60 % of whom are short of breath: 3 patients. Therefore $P(\mathrm{A|B4}) = 0.6$. $P(\mathrm{B4}) = 0.05$

B5: Myasthenia gravis: 5 patients. 80 % of whom are short of breath: 4 patients. Therefore $P(\mathrm{A|B5}) = 0.80$. $P(\mathrm{B5}) = 0.05$

B6: Muscular Dystrophy: 10 patients. 40 % of whom are short of breath: 4 patients. Therefore $P(\mathrm{A|B6}) = 0.40$. $P(\mathrm{B6}) = 0.1$

We are interested in determining what is the probability of myasthenia gravis given that a patient is short of breath. In other words, we would like to know $P(\mathrm{B5|A})$? By application of Bayes rule from Eq. (2.3):

$$P(\mathrm{B5}|\mathrm{A}) = \frac{P(\mathrm{A}|\mathrm{B5})P(\mathrm{B5})}{\sum_{i=1}^{6} P(\mathrm{B}i)P(\mathrm{A}|\mathrm{B}i)}$$

$$= \frac{(0.80) \times (0.05)}{0.3 \times 0.3 + 0.3 \times 0.5 + 0.2 \times 0.2 + 0.6 \times 0.05 + 0.80 \times 0.05 + 0.4 \times 0.1}$$

$$= \frac{0.04}{0.39} = 0.102 \text{ or approximately } 10\ \%$$

This shows that even though most patients with myasthenia gravis are short of breath (as high as 80 % in the above hypothetical example), since myasthenia is a rare disease in the population when compared with more common causes like COPD and CHF in this example, the overall posterior probability that a patient with shortness of breath has myasthenia gravis is low.

Failure Modes and Effect Analysis

FMEA is a powerful inductive analysis method. FMEA is a method of identifying the failure modes of a system or a piece-part and determining the effects on the next higher level of design [1]. It can be performed at any level within the system (function, black box, piece-part, etc.) [1]. An FMEA can be qualitative or quantitative. FMEA plays an important role in systems safety analysis and supports deductive techniques such as FTA, DD, or MA. FMEA is performed at a given level by analyzing the different ways in which a system may fail. The effect of each failure mode at a given level and the next higher level is determined. FMEA provides answers to the "*What happens if*?" question [4]. The process involves assuming a certain state of function of a component or system, determining the different manners in which it can fail and determining the effect of that component on the rest of the system. The method is illustrated through the example in Fig. 2.4 [1, 4].

The power supply system can fail in many different ways with varying degrees of impact on the system to provide electrical power to the motor. Assume that the generator is the primary power supply with the battery being the backup. A switching mechanism can switch between the generator and backup battery if the generator fails. The battery can provide limited power (for a few hours) till the generator can be restored online. Table 2.2 shows the failure modes of this system.

Table 2.2 lists the components, failure modes of each component, individual probabilities of those happening, and effects on electric motor functioning—classified as minor (motor functions at reasonable but suboptimal level), major (decreased safety margin or motor power output at less than 50 %), severe (severely decreased safety margin or motor output less than 20 %), and critical (motor is completely unable to function). If the switching mechanism fails due to contacts being broken, then the motor fails in a critical manner since power supply to it is completely

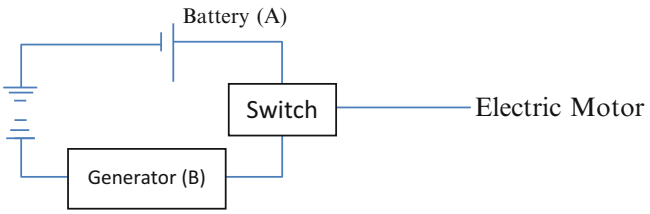

Fig. 2.4 A diesel generator (B) or battery provides electric power for operating a motor selected through a switch. The failure modes of the system are as shown in Table 2.2

Table 2.2 FMEA of power supply system in Fig. 2.4

Component	Failure mode	Probability	Effects on motor
Battery	Low voltage	1×10^{-3}	Major
	Short circuit	1×10^{-6}	Critical
	Fluctuating voltage	1×10^{-2}	Minor
Diesel generator	Engine failure	1×10^{-4}	Severe
	Alternator failure	1×10^{-8}	Severe
	Fluctuating voltage	1×10^{-2}	Minor
Switch	Stuck in generator	1×10^{-6}	Major
	Contacts broken	5×10^{-3}	Critical

disrupted. If it fails in generator mode, the system loses redundancy completely and is unable to switch to battery mode if the generator fails for any reason. In this situation, as long as the generator works, the electric motor continues to work. This failure decreases the safety margin of the system and is therefore classified as major. The moment the generator fails, the electric motor stops since it is unable to switch. This is therefore a latent failure which is classified for this example as a major failure but is not critical. It also has a low probability—1×10^{-6} of occurrence. If the engine of the generator or its alternator fails, the effect on the system is severe since the backup power source—the battery has a capability of providing function only for a few hours. Similarly if the battery fails in short circuit mode and is the sole power source when the generator is down, it causes critical failure. If it fails in low voltage mode, it can cause major effects on motor functioning, but some function would still be provided. Fluctuating voltage can cause fluctuations in motor performance but without failure of service or motor damage, therefore it is classified as minor.

Table 2.2 provides invaluable information on the failure modes and helps identify the components and the respective failure modes with "critical" and "noncritical" effects. The table can be expanded to include numerous other failure modes of the system including "vibration," "engine overheating" with their respective effects on the motor and other interacting systems. In the example above, vibration may cause a slight increase in wear and tear; therefore its effect might be classified as mild. Overheating of the engine compartment may be classified as "major." The quantitative probability information provided by this table can be used for assessing failure probabilities—for example assuming independent failures, the system has a

$5 \times 10^{-3} + 1 \times 10^{-6}$ risk of critical failure. This can be approximated to 5×10^{-3} since the contribution of the 10^{-6} term is negligible. Adding up the failure modes listed as "Severe," we see that the corresponding probability is $1 \times 10^{-4} + 1 \times 10^{-8}$ (engine failure, alternator failure) which can be approximated to 1×10^{-4} (or 1 in 10,000) since the contribution of the other term is negligible.

Analyzing this system, we see that the probability of critical failure is too high, in other words there is a 5 in 1,000 chance of the system failing due to the switch's contacts being broken so that the motor will not work. The net result of the FMEA is it helps allocate resources appropriately. Designers therefore need to invest research and development into designing a better switch with a lower failure probability rate, especially one which will not fail in contacts broken mode. Investments for protecting against fluctuating battery voltage do not make the system safer since their effect on the electric motor is "minor" and the estimated probability of occurrence is also low.

Based on the above toy example, we can now look at the more formal methods for performing an FMEA [1]. The three major steps involved in FMEA are preparation, analysis, and documentation [1].

FMEA Preparation

The first step towards performing a FMEA is determining the customer's requirements, obtaining system documentation, and understanding the operation of the system [1]. The analyst obtains safety-related information, data on failure rates, and information on different failure modes. Functional drawings of the systems of interest, knowledge of probability of failure rates, data from prior experience with similar systems are important. It is important to identify the failure detection mechanism for each component since in many systems it can be latent [1]. Failure detection methods include error monitors, self-test algorithms, and periodic maintenance checks [1].

FMEA Analysis

It is important to determine the objectives and level of resolution of the FMEA. One method which is helpful is to divide the system into functional blocks. Once this is achieved, for each functional block, internal functions and interactions with all connected systems should be analyzed carefully. The next step is to postulate failure modes for each functional block. This requires great insight into the functional block being studied to ask the "*what if*?" questions. Failure effects should be classified based on severity and damage potential with attention dedicated to the most critical. For the example in Fig. 2.4 and Table 2.2, failure of the switch in contacts broken mode is the most critical weakness in the system. Other failure modes with less impact on functionality are explored progressively—those

classified as severe, major, minor, and so on. For each failure mode and failure effect category, the analyst considers the method of failure detection [1]. It is important for the analyst to document his thought process, the assumptions being made, the justification for each failure mode, justification behind the assigned failure rates and rationale for assigning a failure mode to the particular failure effect category. Maintaining the necessary documentation explaining the analysis is very important for later review or independent verification. Quantitative analysis can then be performed from available reliability data based on past experience. The above is applicable for analyzing the effect of the failure mode on the functional block itself and on the next higher level of function.

The next level of resolution in performing an FMEA is to look at each individual component of a functional block called piece-part FMEA. The first step in this process is to create a list of all components (parts list) to be analyzed, followed by their respective failure modes [1]. This can be a challenging task for complex components like integrated circuits consisting of thousands of individual components. Further steps in a piece-part FMEA proceed similar to the functional FMEA, including assessing the impact of failure on the next higher level of function, methods involved in fault detection, and documenting assumptions and rationale behind and analysis. In general, all possible ways that the component can fail to perform its functions must be considered for inclusion in the list of component failure modes. There are certain failure modes which are common across a diverse array of components and must be considered. These include short and open circuit, inoperative mode, intermittent operation, false settings, miscalibration, mechanical wear and tear, loose contacts or loose assembly and fracture, etc. For complex digital devices, computer simulations of different components needs to be performed [1].

FMEA Documentation

The capstone of FMEA preparation and analysis is the FMEA documentation. The recommended report for an FMEA includes [1]:

1. An introductory statement containing a statement about the purpose and objective of the FMEA.
2. Description of how the analysis was performed—listing of assumptions made, description of the analytic methods used, software simulations performed, and limitations of the FMEA.
3. A complete listing of results of the FMEA, including component identification. This is performed in a tabular form as shown in Tables 2.1 and 2.2.
4. Appendices that include drawings or schematic diagrams, any failure mode distributions for lower level components defined during analysis [1].
5. A list of failure rates and their sources used for performing the FMEA.

A related topic is FMECA. In this analysis, criticality of the failure is analyzed in greater detail and controls or mitigating systems are described for limiting the

likelihood of such failures. It is frequently used as a part of SSA. The four aspects of this approach are: (1) fault identification (identifies the possible hazardous condition), (2) effects of fault (explains why this is a problem), (3) projected compensation or control (what has been done to mitigate the effect of failure and control the condition), and (4) summary of findings (whether the situation being analyzed is mitigated or whether further steps should be taken) [4].

One of the most important aspects to realize is that FMEA is a qualitative technique. Therefore it requires great domain expertise and insight. For highly complex systems involving multiple functional blocks (software, engineering, mechanical system, etc.), it is very difficult for a single analyst to possess adequate domain expertise across the spectrum of disciplines involved in the FMEA. In these circumstances, it is very important for a team approach where each set of experts analyzes their relevant systems with excellent interdisciplinary understanding and collaboration between teams to synergize the FMEA [4].

Fault Hazard Analysis (FHA) is a related extension of FMEA which is useful for projects spanning different organizations with one acting as the integrator. This technique is useful for detecting faults that cross organizational interfaces. A typical FHA involves the following columns, the first five of which are used in FMEA [4].

Column 1: Component identification
Column 2: Failure probability
Column 3: Failure modes. (Identify all possible failure modes)
Column 4: Percent failures by mode
Column 5: Effects of failure
Column 6: Identification of upstream component that could initiate the fault being analyzed
Column 7: Factors that could contribute to secondary failures
Column 8: Remarks

Failure modes and effects summary (FMES) is a grouping of single failure modes which produce the same effect [1]. For the toy example in Fig. 2.4, engine failure, alternator failure both cause severe failure effects on electric motor function and would be classified similarly. FMEA is a very powerful tool which helps with treatment planning. While this chapter provides a systematic introduction to the theory of FMEA, medical case examples encountered in clinic will be presented in a subsequent chapter.

Common Cause Analysis (CMA, ZSA, and PRA)

CCA which refers to CMA, ZSA, and PRA is discussed briefly here. These methods look for the numerous common causes which can frustrate the assumption of independence between system failures thereby compromising system safety [1].

Common Mode Analysis

CMA is a qualitative analysis tool used to evaluate a design, especially to understand the integration of component systems. It can be carried out at all levels of design. They are performed to verify that logical AND events in a fault tree are truly independent. Errors in design, manufacturing, maintenance, installation of system components which can defeat safety in redundancy should be carefully analyzed [1]. For example, components with identical hardware and/or software are susceptible to generic faults which could cause abnormalities in multiple systems [1]. For example, suppose systems A AND B need to fail for the top event to happen. Suppose a component of both systems is made by the same manufacturer with a software design error which can cause critical loss of function of both systems under certain circumstances. This creates a common vulnerability in both systems; therefore the assumption of independent failures of systems A and B is no longer valid. A common cause can trigger a simultaneous critical failure of both systems frustrating redundancy in design. When performing CMA, wherever required redundancy is compromised, the analyst must justify the rationale for accepting or rejecting the compromise [1]. The following common mode errors are considered in most analysis [1]: software development errors, hardware development errors, manufacturing/installation/maintenance errors, environmental factors (temperature, vibration, humidity, etc.), calibration errors, etc. [1].

Similar to FMEA, the method is qualitative, often interdisciplinary requiring expertise across multiple domains. The analyst therefore needs to understand the system from design to installation and preventive maintenance [1]. This includes knowledge of design, equipment and component characteristics, maintenance and testing tasks, installation crew practices and procedures, and system specifications (software and hardware). The analysis is performed by examining common susceptibilities from the viewpoint of the common safeguards employed to minimize the risks of common mode faults. These include diversity and dissimilarity in design and manufacturing, testing and preventive maintenance, design quality levels, and training of personnel [1].

The analysis itself proceeds along the following ways: For each hazardous event or catastrophic event in FHA and PSSA, the analyst evaluates each AND event in the FTA (or dependence diagram—see appendices) and verifies the independence principle hold true. The analyst then documents that CMA requirements have been satisfied. A subsequent analysis evaluates CMA events not derivable from FTA/DD methods such as generic failures, environmental effects, physical installation, etc. [1]. Once common mode vulnerabilities are identified, solutions are proposed and design changes are implemented. The entire FTA/DD/CMA process is then iterated till the final design is finalized. The documentation proceeds in a manner similar to FMEA.

Zonal Safety Analysis

ZSA examines physical installation considerations of system hardware which can impair independence between systems. For example, if two critical computer systems A and B are placed in close physical proximity to one another, then an event such as computer A catching fire can cause failure of computer B by their close physical proximity. ZSA examines the influence of physical proximity of such systems which can weaken independence between system failures. In the design of products, especially complex systems such as aircraft, ZSA should be performed early in the design before structural modifications will need to be made at an advanced stage in product development. The conclusions of ZSA will provide inputs to the SSA. Commercial fly-by wire airplanes mitigate this risk by placing computer systems in different areas of the plane so that a limited fire or explosion will not disable all vital systems. Further details can be found in [1].

Medical Example

ZSA examples abound in medicine. The following are frequently encountered and to a great extent preventable. Examples include pneumothorax from subclavian central line placement, brachial plexus injury from stretching during surgical positioning leading to upper extremity weakness; sciatic nerve injury from hip surgery, peroneal nerve injury from knee surgery, and femoral nerve injury during pelvic procedures. Performing ZSA can help prevent and mitigate these from happening and once they happen, channel investigation and treatment in the right direction.

Particular Risks Analysis

This refers to those events which while being outside of the systems and components being analyzed will violate failure independence of systems and cause system failure. This includes events such as fire, hail, lightning strikes, radiation, explosions, etc. Each such identified risk should be the subject of a study examining the cascade of effects associated with the event. Please see [1] for further details. *Medical examples*: Common medical examples include Raynaud's phenomenon and cold exposure, worsening of myasthenia gravis in the summer and with intercurrent infection such as the flu.

Case Example

L.H. is a 69 y/o female with ocular myasthenia gravis. Since symptoms remained isolated to the eyes for over 3 years, the risk of systemic involvement was considered

low. Patient was treated with low-dose Prednisone monotherapy ranging between 5 and 7.5 mg/day. Symptoms remained stable for 2 years before a bad seasonal flu triggered considerable worsening of ptosis, diplopia, and morbidity from ocular myasthenia gravis. The worsening of symptoms due to seasonal flu required over 6 weeks of moderate dose prednisone ranging from 20 to 30 mg to treat.

The main challenge in CCA is to define the analysis perimeter [7]. The data guiding this analysis originates from practical in-service experience and are transformed in envelope cases by aviation safety agencies. CCA has an enormous impact on structural architecture, therefore it must be performed at an early stage in the design to avoid extremely expensive late design changes.

These methods of analysis integrate into the *system safety assessment or SSA*. An SSA is a systematic, thorough evaluation of the implemented system to demonstrate that safety requirements are all met [1]. As discussed earlier, the difference between the PSSA and SSA is that while PSSA is a method to evaluate the proposed design or architecture and derive safety requirements, the SSA is verification that the implemented design meets both qualitative and quantitative requirements as defined in the FHA and PSSA [1]. The SSA integrates all the analysis (FTA/DD, FMEA, FMECA, CMA, ZSA, and PRA) described above qualitatively and quantitatively to verify the safety of the overall system and cover all the safety concerns identified in the PSSA. Therefore, typically this includes the following information [1]:

- System description
- Failure conditions (FHA, PSSA)
- Failure condition classification (FHA, PSSA)
- Qualitative analysis for failure conditions (FTA, DD, FMES)
- Quantitative analysis of failure conditions (FTA, DD, MA, FMES, etc.)
- Common cause analysis
- Safety-related tasks and their intervals (FTA, DD, FMES, MA)
- DAL for hardware and software (PSSA)
- Verification that safety requirements from the PSSA are incorporated into design and/or testing
- The results of nonanalytic verification process (test, demonstration, inspection)

The above sections provide a tutorial overview of the rigorous safety techniques involved in safety borrowed from the aerospace and nuclear industries. The methods discussed can be adapted based on requirements and have broad application. These can be applied to the successful operation of a coffee shop, designing an automobile or to healthcare. It is extremely important to realize that safety is analyzed from both micro and macro perspectives, not only should the individual ball bearing in an aircraft landing gear be analyzed but its ripple effect on higher systems has to be simulated and predicted as well [7].

Case Example: SSA of Pulse IV Methylprednisolone Treatment

Immunosuppression is an unfortunate but necessary part of the practice of neuromuscular medicine. There are numerous methods for performing immunosuppression, oral daily prednisone has been the most widely used and traditional method for the treatment of a variety of diseases in autoimmune neurology and rheumatology. Daily prednisone has a plethora of side effects and for diseases with very long time courses such as CIDP where a high dose maybe necessary over months, they may seem unacceptable. Based on a review of the literature, an attempt was made to switch from daily oral prednisone to pulse IV Methylprednisolone where a high dose of methylprednisolone (between 500 and 1,000 mg) is given IV every few weeks without daily oral steroids [8]. Before instituting this practice, an SSA was conducted. The basis for the SSA was literature review detailing past safety-related side effects from the published literature [8, 9], prior personal and institutional experience. The following major considerations were identified: drug administration syndrome consisting of insomnia, heartburn, sweating, flushing, erythema; weight gain, cushingoid features; glucose intolerance/steroid induced diabetes mellitus, muscle cramps, joint pains, and hypertension [8, 9]. Other listed side effects including lymphoma are rare and not included in the current analysis since this is meant for initial proof of principle. Considering IV Methylprednisolone as a system, the following analysis was used:

1. **Function definition**: IV Methylprednisolone for treatment of inflammatory neuropathy.
2. **Functional hazard assessment** (**FHA**):

   2A. Loss of effective immunosuppression. (Drug being ineffective)
   2B. Major adverse side effects

3. **FTA of failure conditions identified in FHA**: In this step, we will construct fault trees for each functional failure condition identified in (2)

   3.1: **FTA for failure condition 2A**

      3.1.1. **Top event**: Loss of effective immunosuppression.
      3.1.2. *Immediate*, *necessary*, *sufficient causes* for loss of effective immunosuppression include: drug intrinsically ineffective for the condition OR inadequate intensity of current regimen.
      3.1.3. Expanding the tree further: drug intrinsically ineffective for the condition is a basic event and will not be explored further.
      3.1.4. Expanding inadequate intensity of current regimen further, this can happen if dose administered is too low OR the dosing frequency is too infrequent. Further corrective action can be planned based on which of these is the major consideration.

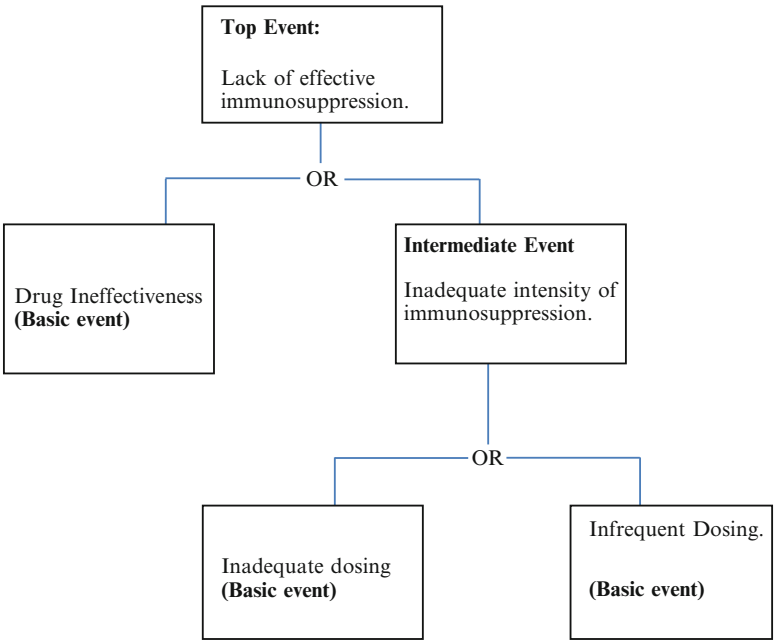

Fig. 2.5 FTA for the top event of lack of effective immunosuppression with IV Methylprednisolone therapy for planned treatment of CIDP

The FTA for the above analysis is shown in Fig. 2.5. For the sake of simplicity, *these trees are constructed with the logical operators inserted in English instead of their mathematical symbols*.

3.2: **FMEA for Lack of Therapeutic Efficiency**: Based on this FHA and FTA, failure modes in terms of therapeutic failure can be identified with relevant consequences and severity classification and mitigation. For the case of CIDP, where there is malfunction of nerves, the following failure modes require consideration. *A*: *Loss of sensory function leading to numbness*, *loss of proprioception*: Numbness by itself is disturbing and can lead to inadvertent physical injury. Based on past experience with similar conditions in related patient populations (example: inherited neuropathies such as Charcot Marie Tooth where there is numbness without pain), patients adapt well to it without safety ramifications. Therefore this is a failure mode with minor ramifications. *B*: *Abnormal sensory function with consequent pain*, *paresthesias*: This failure mode is the most perceived and the most distressing to patients, greatly affecting quality of life. However, this has very limited safety effect and to varying extents can be managed with analgesic medications with wide safety margins, low costs despite the underlying disease itself being poorly controlled. Therefore this is classified as minor, despite being the most obvious manifestation of treatment failure

C: *Loss of motor function in upper extremities*: This can adversely impair all aspects of life—such as eating, reading, and lead to the need for continuous supportive care. Therefore this is classified as major. *D*: *Loss of motor function in lower extremities*: This is another obvious source of morbidity and further injury from falls. *D1*: *Loss of mobility due to lack of strength* where the legs buckle when the patient attempts to stand. Therefore this failure mode is effective only when patient is standing and does not impair sitting and lying down. *D2*: *Loss of mobility due to loss of lack of proprioception* (*lack of balance*): in this mode, a patient has the strength to stand and support his weight, but given lack of knowledge of where the feet are, there is a tendency to fall easily. To some extent, patients compensate with vision to know where their feet are and a cane or walker can help secure balance and prevent falls. Therefore, this failure mode is most limiting in poor light, uneven ground and not operative when sitting and less restrictive on even floors. This failure mode originates in the sensory system but manifests in impairing motor function.

Since progression of motor failure can lead to irreversible loss of function, the discovery of motor failure mode should trigger immediate corrective action in terms of aggressive immunosuppressive therapy.

Based on this, the following FMEA report can be constructed. As described earlier, the following aspects are included in the FMEA documentation.

(a) **Introductory statement** containing a statement about the purpose and objective of the FMEA: The objective of this FMEA is to describe the failure conditions, failure severity, exacerbating conditions, and mitigation strategies associated with failure of treatment with IV Methylprednisolone therapy.

(b) **Description of how the analysis was performed**: This analysis was performed based on a review of the literature detailing the experience of other investigators with the use of IV Methylprednisolone [8, 9] for CIDP and other autoimmune diseases. Failure modes from prior experience with similar conditions such as Charcot Marie Tooth, diabetic neuropathy, and idiopathic neuropathies were also incorporated into the analysis based on assumed similarities.

Assumptions: (1) The treatment trial will be limited, therefore only clinical concerns relevant to a time frame of 8–12 weeks of treatment are being considered.

Limitations of the FMEA include lack of rigorous quantitative data due to limited prior experience; limiting analysis to more immediate and frequently encountered failure modes and not incorporating long-term consequences of immunosuppression such as malignancy.

Table 2.3 FMEA report for loss of therapeutic efficiency of IV Methylprednisolone therapy for CIDP

Function name	Failure mode	Failure environment (lying, sitting, standing)	Failure severity	Mitigation strategies	Comments
Sensory function	Numbness	All phases	Minor	Avoid hot, sharp surfaces, frequent examination of hands, legs, feet	Patient education for mitigating injuries
Sensory function/ motor function	Loss of proprioception	Standing, walking on uneven ground, evening and night. Unsafe driving	*Major*	Avoid uneven surfaces, poor light. Cane, walker for improved balance. Gait Training	Emphasize and develop adaptation strategies
Sensory function	Pain, paresthesias: burning, cold, electric shocks	Resting, lying down. Sometimes better with ambulation	Minor	*Initial and mild pain*: Gabapentin, Pregabalin, Duloxetine, Nortriptyline. *Moderate pain*: Tramadol. *Severe pain*: Opioids	Consider drug combinations. Consider increasing immunosuppression
Motor function	Loss of function in hands	All phases	*Major/ hazardous*	Occupational therapy, Nursing Home, Home health aides	*Increase immunosuppression*
Motor function	Loss of strength and function in legs	Weight bearing phase, standing, walking	*Major*	Physical therapy, occupational therapy	*Increase immunosuppression*

As seen in column 4, the PSSA process shows three failure modes with major consequences and two with minor consequences

(c) **A complete listing of results of the FMEA**: Detailed in Table 2.3.
(d) **Appendices**: Expanded list of side effects, including those not analyzed in this FMEA associated with pulse methylprednisolone therapy are listed in the appendices [8, 9]. (Not shown for this example.)

FMEA header information: see 3.2a, 3.2b, 3.2c, and 3.2.d.

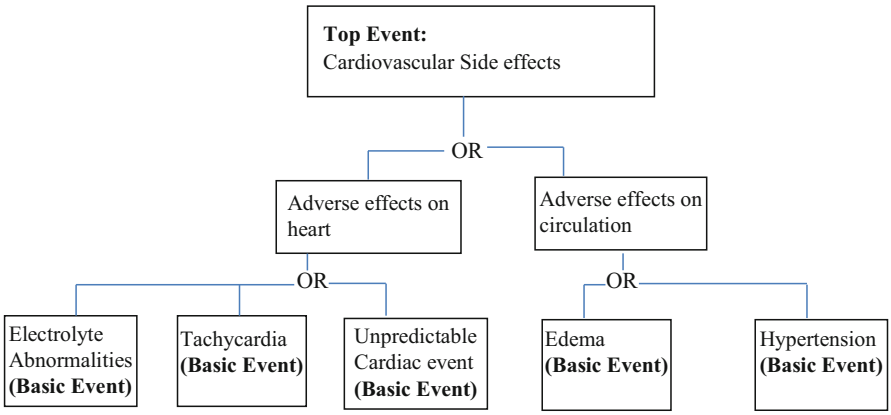

Fig. 2.6 FTA for the top event of cardiac side effects with IV Methylprednisolone therapy for planned treatment of CIDP

3.3. **FTA for failure condition 2B**: An FTA needs to be constructed for each major adverse effect. Cardiovascular and endocrine (blood glucose) adverse effects are explored here since these are the major anticipated adverse effects expected in the short term.

3.3.1. **Top event**: Cardiovascular adverse effects
3.3.2. **Immediate**, **necessary**, **sufficient** causes of the top event include: adverse effects on heart OR adverse effects on circulation.
3.3.3. **Expanding**: adverse effects on heart include tachycardia OR electrolyte changes OR unpredictable effects. Adverse effects on circulation include edema from salt and water retention OR hypertension. These will not be explored further since this is the desired depth of resolution of the fault tree.

The corresponding fault tree is shown in Fig. 2.6.

3.4. FTA for adverse effects on blood glucose.

3.4.1. **Top event**: Blood glucose abnormalities
3.4.2. **Immediate**, **necessary**, **sufficient** causes of the top event include: impaired glucose tolerance OR development of diabetes mellitus.
3.4.3. **Expanding**: impaired glucose tolerance will not be explored further. Same with diabetes mellitus, the severity of diabetes mellitus can be mild, moderate, or severe based on random blood glucose readings or HBA1c. For the purposes of IV Methylprednisolone we define this as the depth of resolution of our fault tree.

The corresponding fault tree is shown in Fig. 2.7.

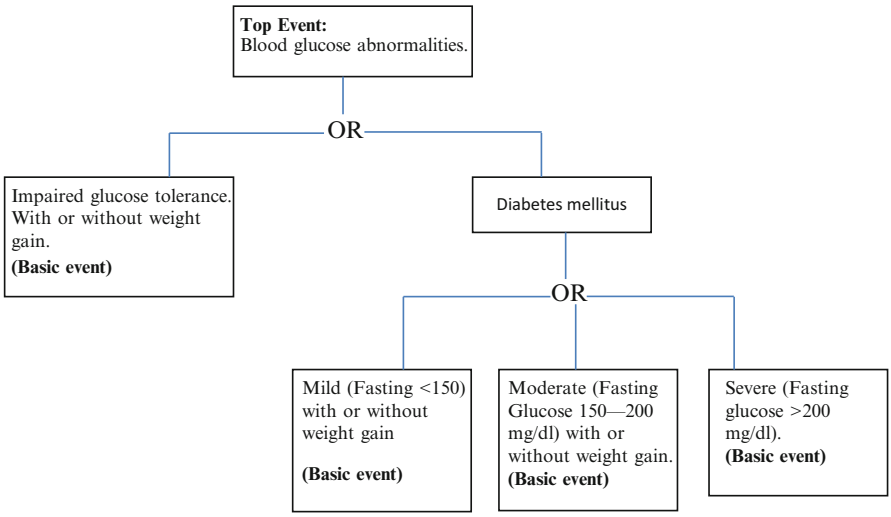

Fig. 2.7 FTA for the top event of blood glucose abnormalities with IV Methylprednisolone therapy for planned treatment of CIDP

3.5. FMEA for adverse side effects of IV Methylprednisolone therapy

Following the methods introduced in Section "FMEA for Lack of Therapeutic Efficiency", FMEA can be performed as follows.

(a) **Introductory statement** containing a statement about the purpose and objective of the FMEA: The objective of this FMEA is to describe the cardiovascular and endocrine adverse side effects, failure severity, exacerbating conditions, and mitigation strategies associated with adverse side effects of IV Methylprednisolone therapy.

(b) **Description of how the analysis was performed**: This analysis was performed based on a review of the literature detailing the experience of other investigators with the use of IV Methylprednisolone [8, 9] for CIDP and other autoimmune diseases. Failure modes from prior experience with steroid use in conditions such as myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosis (SLE) were also incorporated into the analysis based on assumed similarities.

Assumptions: (1) The treatment trial will be limited, therefore only clinical concerns relevant to a time frame of 8–12 weeks of treatment are being considered.

Limitations of the FMEA include lack of rigorous quantitative data; limiting analysis to more immediate and frequently encountered failure modes, and not incorporating long-term consequences of immunosuppression such as malignancy, osteoporosis, aseptic necrosis of the hip, etc.

Table 2.4 FMEA report for cardiovascular and abnormal blood glucose adverse side effects of IV Methylprednisolone therapy for CIDP

Function name	Failure mode	Failure environment (obesity, prior diabetes, hypertension, CHF)	Failure severity	Mitigation strategies	Comments
Cardiovascular	Tachycardia	All populations	Minor	Monitor pulse rate	Patient education for mitigating anxiety
Cardiovascular	Electrolyte abnormalities/ hypokalemia	All populations	Minor (generally)	Monitor electrolytes, especially in combination with diuretics	Monitor closely
			Major in prior CHF		
Cardiovascular	Decompensated CHF	CHF patients	*Major*	Monitor cardiac status, weight gain, edema, dyspnea, orthopnea	Avoid therapy in high-risk populations
			Catastrophic		
Cardiovascular	Edema	CHF patients, prior edema	*Major*	Restrict salt, monitor weight daily	None
Cardiovascular	Hypertension	All populations	Minor (generally)	Restrict salt. Check blood pressure daily. Provide prescriptions for anti-hypertensives. See Chap. 9 for defense in depth	*If experiencing symptoms such as headache, shortness of breath, chest pains go to ER*
			Major in crisis		
Endocrine	Impaired glucose tolerance	Obese patients, prior borderline diabetes cases	Minor	Monitor glucose. Reduce added sugar and calories. Monitor weight	Rarely needs addition of Metformin
Endocrine	Mild diabetes mellitus	Obese patients, prior borderline patients	Minor	Monitor glucose. Reduce added sugar and calories. Monitor weight	Add metformin
Endocrine	Moderate diabetes mellitus	Obese patients, prior mild diabetes	Minor	As above, add Glipizide or sliding scale insulin	Request primary care assistance
Endocrine	Severe diabetes mellitus	Obese patients, prior poorly controlled diabetics	*Major*	As above	Request endocrine consult and partnership

As seen in column 4, the PSSA process shows one failure mode with potentially catastrophic consequence, three failure modes with major consequence in special populations with the rest of the failure modes being minor

(c) **A complete listing of results of the FMEA**: This is shown in Table. 2.4.
(d) **Appendices**: *Expanded list of side effects, including those not analyzed in this FMEA associated with pulse methylprednisolone therapy are listed in the prednisone FMEA in Chap. 4* [8, 9].

FMEA header information: see 3.5a, 3.5b, 3.5c, and 3.5d.

The advantage of performing an FMEA is it provides us the ability to identify potentially high-risk situations with major failure consequences, direct prevention and mitigation strategies appropriately. This approach was adopted in the use of pulse methylprednisolone for treatment of CIDP patients discussed in Chap. 9.

Regulatory Perspective

The above sections described the SSA process. These methods are adopted by companies in product development. They are also used heavily in demonstrating compliance with safety in regulatory filings with agencies such as the United States Federal Aviation Authority (FAA). Table 2.5 demonstrates the failure conditions and corresponding regulatory requirements required by the US FAA. Consider columns 2 and 5 from the table. Column 2 describes a system whose failure has no safety consequences. Examples include malfunction of the in-flight entertainment system. Such an event has no restriction on how frequently it can occur, systems concerned with it may be built to the lowest DAL (Level E). Regulatory compliance can be demonstrated by performing a FHA and design review. Column 5 deals with a system with severe safety consequences which can result in hull loss and multiple fatalities. Examples include Primary Flight Computers (PFC). Consequently, regulatory filings mandate demonstrating that the average probability of failure per flight hour of such a system be less than one in ten billion with FHA, FMEA data used in a detailed FTA to show that the event is extremely remote. The corresponding system also has the highest DAL—Level A.

Appendices

To make this introduction of FTA self-contained, the following sections look at further theoretical aspects of fault trees. These are useful to understand the principles behind software and computer-based FTA packages.

Table 2.5 United States Federal Aviation Administration: AC 25.1309 regulatory requirements for demonstrating safety of airplane systems

Harmonized 25.1309 Requirements and Compliance Summary					
Effect on airplane	No effect on operational capabilities or safety	Slight reduction in functional capabilities or safety margins	Significant reduction in functional capabilities or safety margins	Large reduction in functional capabilities or safety margins	Normally with hull loss
Effect on occupants excluding flight crew	Inconvenience	Physical discomfort	Physical distress, possibly including injuries	Serious or fatal injury to a small number of passengers or cabin crew	Multiple fatalities
Effect on flight crew	No effect on flight crew	Slight increase in workload	Physical discomfort or a significant increase in workload	Physical distress or excessive workload impairs ability to perform tasks	Fatalities or incapacitation
Classification of failure conditions	No safety effect	Minor	Major	Hazardous	Catastrophic
DO-178B S/W and DO-254 H/W Levels	Level E	Level D	Level C	Level B	Level A
Allowable qualitative probability	No probability requirement	Probable	Remote	Extremely remote	Extremely Improbable
Allowable quantitative probability	10^{-3}	10^{-5}	10^{-7}	10^{-9}	
	Average probability per flight hour (or per flight if less than 1 h) on the order of:				
System Compliance Method: (common cause hazards not conductive to numerical analysis, such as foreign object collision, human error, etc. may be analyzed primarily by design review)	*FHA & Design Review*: Design, functional separation, and implementation reviewed to ensure failures will only produce no safety effect	*FHA & Design Review*: Design, functional separation, and implementation reviewed to ensure failures will only produce minor effect	*FHA, Design Review & FMEA Review*: Failure modes and effects analysis reviewed to ensure that failure effects of components involved in the function and failure rates are appropriate for major category	*FHA, Design Review and Fault Tree Analysis (FTA)*: FMEA & FHA data combined in detailed FTA to validate that the system probability of hazard is extremely remote	*FHA, Design Review, and FTA*: FMEA and FHA data combined in detailed FTA to validate that the system probability of hazard is extremely Improbable

(continued)

Table 2.5 (continued)

Harmonized 25.1309 Requirements and Compliance Summary		
Effect category validation	All functional hazards should have a multidisciplinary review by experts representing the engineering and operational areas. Where functions are the same as previous airplanes, past experience should be reviewed. Other conditions should be evaluated in lab and simulation tests. Failures affecting handling qualities will be evaluated in piloted simulation and/or flight test	Specific failures may be evaluated by piloted simulation as necessary

Conditions with increasing impact on safety are listed from left to right. The corresponding allowable probability of failure, DAL, compliance methods for demonstrating safety are described in the rows at the bottom of the table. Courtesy: Dr. Ying C Yeh, unpublished work, Boeing Company

Appendix 1: Evaluating Fault Trees—Failure Sequences, Probability Basics, and Boolean Algebra

Sometimes, system failures must occur in a specific sequence for the top event to happen. As a medical example consider the clinical situation of fracture of the femur (Failure A) which leads to nerve damage (Failure B) followed by damage to the blood vessels from bone fragments (Failure C) followed by blood loss (Failure D) followed by shock (Failure E) followed by fat embolism syndrome (Failure F) followed by altered mental status (Failure G) and then death (top event). The top event of death in this medical example happened because of events happening in that sequence. This is shown in Fig. 2.8.

The following sections explore probabilistic analysis and simplification of fault trees. Fault trees are analyzed using Boolean algebra and probability theory. A few basic concepts applicable to fault trees are presented here. Important rules of Boolean algebra and important probability theory basics applicable to fault trees and mathematical understanding of reliability are discussed in the next two sections.

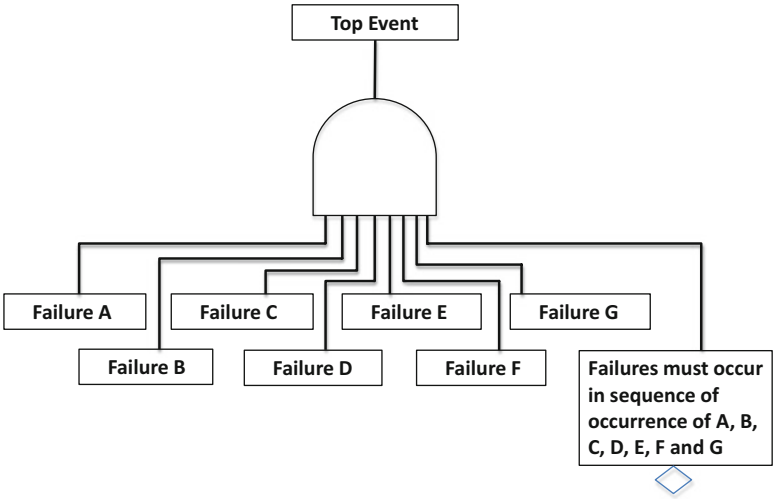

Fig. 2.8 Example of a specific sequence of failures causing the top event. The failures must occur in sequence and they are represented as inputs to an AND gate from left to right with the failure sequence condition represented on the far right as an undeveloped event (with a *diamond* symbol). In general there are $n!$ sequences (n factorial, represented by the symbol! refers to $n \cdot (n-1) \cdot (n-2) \ldots 1$, for example $3! = 3 \cdot 2 \cdot 1 = 6$) in which n systems can fail, therefore a restriction to k possible failure sequences reduces the probabilities by $k/n!$

Important Probability Distributions Used in Fault Trees

For FTA and in reliability theory, a few probability distributions are of great importance. These include the binomial and a special case of the binomial—Poisson. This leads to the exponential distribution which is frequently used to model failure. Some important aspects are presented here, a full discussion of the mathematical concepts is presented in [4].

Consider the example of an experiment which involves tossing a coin "three" times. Let the probability of getting a heads on any one trial be p. Therefore the probability of getting tails is $(1-p)$. The following outcomes are possible (H denotes Heads, T denotes Tails): HHH, HHT, HTH, HTT, THH, THT, TTH, and TTT (eight possible outcomes). HHT, HTH, THH are unique sequences where two heads occur in three trials. Similarly TTH, THT, and HTT are unique sequences where one heads and two tails occur in three trials. 3 heads or 0 heads occur in 1 out of 8 ways each. If we are interested in the case of getting two heads in three trials, the probability of getting two heads is p^2 and one tails is $(1-p)$ for one such sequence. This can be expressed as $p^2(1-p)$ However, there are three such sequences. Therefore the total probability is $3(p^2(1-p)))$. For the general case of n trials for a random variable x, with probability of success p in one trial, the probability of k successes is given by the *Binomial distribution*. This is given by the formula expressed as [6]:

$$b(k;n,p) = \binom{n}{k} p^k (1-p)^{n-k} \tag{2.4}$$

where $\binom{n}{k}$ denotes the number of ways of choosing k out of n items and is given by$\frac{n!}{(n-k)!\,k!}$ [6]. The average number of successes, expressed as λ, is n multiplied by p or np. If the individual probability of success is very low, the number of trials n is very large, the binomial can be approximated by the Poisson distribution which is given by:

$$p(x;\lambda) = \frac{\lambda^x \mathrm{e}^{-\lambda}}{x!} \quad \text{for} \quad x = 0, 1, 2, \ldots \tag{2.5}$$

In Eq. (2.5), e is the natural logarithm with an approximate value of 2.71828 to the first five places of decimal. The Poisson distribution lends itself well to modeling problems in reliability and component failures. If we have a "failure rate" or an "occurrence rate" where α failures occur per unit of time θ, we can determine probabilities of x failures in time t. The new average number of failures λ is given by $\alpha t/\theta$. For example, a light bulb manufacturer reports four light bulbs in a lot will fail every 100 h. If we are interested in determining what is the probability of six failures in 400 h of operation, we calculate λ as $\frac{4\times 400}{100} = 16$. Substituting this value into Eq. (2.5)

$$p(6;16) = \frac{16^6 e^{-16}}{6!} = 0.0026 \tag{2.6}$$

The special case of 0 failures is reliability. The *reliability* of a system $R(t)$ is defined as the probability of continuous successful operation for a time t. Therefore:

$$R(t) = P(0 \text{ failures in time } t).$$

Expressing λ by $\alpha t/\theta$, $x = 0$ in Eq. (2.5), we get:

$$p(x;\lambda) = \frac{\frac{\alpha t^0}{\theta} e^{-\frac{\alpha t}{\theta}}}{0!} \tag{2.7}$$

The first term $\alpha t^0/\theta$ is 1 since it is raised to the power of 0. The denominator 0! is 1. Therefore the above expression for reliability simplifies to:

$$R(t) = e^{-\frac{\alpha t}{\theta}} \tag{2.8}$$

If we use the symbol μ to represent $\frac{\alpha}{\theta}$, Eq. (2.5) is expressed as:

$$R(t) = e^{-\mu t} \tag{2.9}$$

If $R(t)$ is the probability of failure-free operation to time t, then $1 - R(t)$ is the probability of *at least* one failure in time t. In other words, reliability is the probability that the system will perform its specified functions for the specified time t. $F(t)$ represents the cumulative probability of failure in time t. From Eq. (2.9), this can be expressed as [4]:

$$F(t) = 1 - e^{-\mu t} \tag{2.10}$$

It is a measure of unreliability. Mathematical differentiation of this entity yields the corresponding probability density function (pdf) $f(t)$. This is the probability of failure between time t and $t + \Delta t$ [4].

$$f(t) = \frac{dF(t)}{d(t)} = \mu e^{-\mu t} \tag{2.11}$$

The expression for reliability $R(t)$, cumulative distribution $F(t)$, and pdf $f(t)$ are widely used in system analysis and reliability [4, 6]. These functions are closely interrelated. The reliability function is an exponential function which is a simple, easy-to-use distribution. Only one parameter—the failure rate $\mu\left(\frac{\alpha}{\theta}\right)$ specifies the distribution. Θ denotes the mean time to failure in this function. It is extremely important to note the assumptions, under which such a function was derived, the assumption of mutually independent trials and Poisson approximation to the binomial.

The failure rate function, also called hazard function, is a conditional probability distribution $\lambda(t)$ which provides information how a system is aging [4]. It indicates the changing failure rate with aging, for example, a new light bulb may have a 2 % chance of failing in the first 100 h. After this time, the failure rate may increase to 5 % between 100 and 200 h and to 10 % between 300 and 400 h. For a general distribution, the failure rate function is defined as:

$$\lambda(t) = \frac{f(t)}{R(t)} \tag{2.12}$$

For the special case of the exponential distribution, substituting $f(t) = \lambda e^{-\lambda t}$ and $R(t) = e^{-\lambda t}$ in Eq. (2.12), we get

$$\lambda(t) = \frac{\lambda e^{-\lambda t}}{e^{-\lambda t}} = \lambda$$

In other words, for the exponential, the failure rate function does not change with time. The components have a constant failure rate or in other words the probability of future failure is independent of the past operating time [4].

Boolean Algebra

Since fault trees are composed of events which either occur or do not occur (a component either fails or is functioning) connected by logical operators (especially OR and AND) they lend themselves to analysis using Boolean algebra. A fault tree can be viewed as a pictorial representation of the Boolean relationship between different variables. We review some of the basic relationships in Boolean algebra which are essential in the simplification of fault trees. More comprehensive rules of Boolean algebra are available in [4] or any of the many textbooks on the subject. Let us consider a pair of variables X and Y and explore the rules of Boolean algebra and their equivalent engineering symbolism. Let X be the set {2, 4, 6, 8} and Y be the set {1, 3, 6, 8, 9, 10}

1. $X \cap Y$: The set of elements which belong to X AND Y. This is also expressed as $X.Y$ (multiplication). For the example above $X \cap Y$ is the set {6, 8} which belongs to both X and Y. It follows that $X \cap X$ and $X \cup X = X$.
2. $X \cup Y$: The set of elements which belong either to the set X or to Y. For the example above, $X \cup Y$ is the set {1, 2, 3, 4, 6, 8, 9, and 10}. In engineering symbolism, this is represented at $X + Y$.

3a. $X \cap (X \cup Y) = X.\ (X + Y) = X$.

3b. $X \cup (X \cap Y) = X + X.Y = X$. Rules 3a and 3b are called the Law of Absorption.

4. It also follows that $X \cdot X$ and $X + X = X$.

5. $X \cap (Y \cap Z) = (X \cap Y) \cap Z$; in engineering symbolism $X.Y.Z.$ or $(X.Y).Z$ or $(X.Y).Z.$ This is called Associative law where the order of operations for the AND operator does not matter.

6a. $X \cup (Y \cap Z) = (X \cup Y) \cap (X \cup Z)$; in engineering symbolism $X + Y.Z = (X + Y).(X + Z)$.

6b. $X \cap (Y \cup Z) = (X \cdot Y) + (X \cdot Z)$; 6a and 6b are called Distributive law.

7a. $(X \cap Y)' = X' \cup Y'$; in engineering parlance $X' + Y'$.

7b. $(X \cup Y)' = X' \cap Y'$; in engineering parlance $X'.Y'$ (7a and 7b are called De Morgan's laws.)

The symbol X' represents the elements not in X. For conditions such as X represents the event of a component failure, X' represents the logical opposite that it is functional. $X \cap X' =$ the null set since a set cannot have any elements which are in it and not in it at the same time. In safety parlance, a component cannot be failed and functioning at the same time. $X \cup X'$ is the universal set since it represents all possible outcomes. If X and Y represent individual component failures, $(X \cap Y)$ represents the situation when both X and Y have failed, then $(X \cap Y)'$ represents the situation where a combined failure has not occurred. De Morgan's laws state that the event $(X \cap Y)' = X' \cup Y'$ can occur if X does not occur (X') or Y does not occur (Y') i.e., one or the other of X and Y are still functioning [4].

Now that we have reviewed the important Boolean algebra and probability theory basics applicable to fault trees, we proceed towards the development and analysis of fault trees.

FTA Development, Simplification, Minimal Cut Set *Determination*

Once a fault tree is created, it is simplified using Boolean algebra to determine the fault tree's "minimal cut sets." A "minimal cut set is the smallest combination of component failures which if they occur will cause the top event to happen." Simplification of fault trees using Boolean algebra helps avoid redundancies in their estimation. The combination of failures is the smallest necessary set of events needed for the top event to occur. All the failures in the minimal cut set are needed for the top event to occur. Consider the following fault tree example from Fig. 2.9 [4].

The tree can be described as a Top event called T. T happens if events E1 AND E2 happen. The tree is extended to the next level. E1 happens if event A OR event E3 happen. E2 happens if C OR E4 happen. The tree is then extended further to the next level. E3 happens if events B OR C happen. E4 happens if events A AND B happen. At this point, the limit of resolution of the tree is reached and it is not developed further. However, this tree can be simplified using the rules of Boolean algebra developed in the earlier section. Expressing events using the equivalent

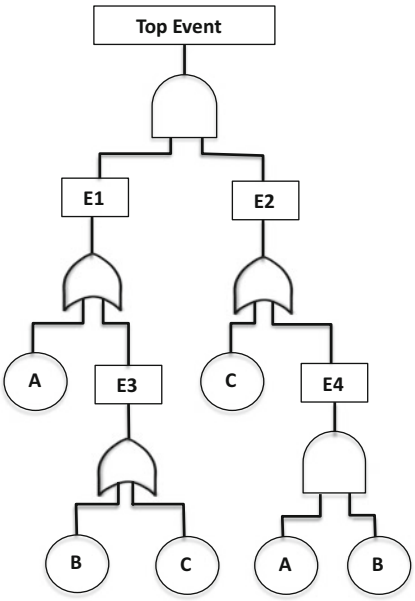

Fig. 2.9 Fault tree example from [4]. See description of events and logical operators above

logical AND (·), OR (+) operators, we can express the tree in the following Boolean algebra form:

$$T = E1 \,.\, E2 \tag{2.13a}$$
$$E1 = A + E3 \tag{2.13b}$$
$$E3 = B + C \tag{2.13c}$$
$$E2 = C + E4 \tag{2.13d}$$
$$E4 = A \,.\, B \tag{2.13e}$$

Substituting for E1 and E2 in the expression for T, we get

$T = (A + E3) \,.\, (C + E4)$ Multiplying and expanding the terms we get :
$T = A \,.\, C + C \,.\, E3 + A \,.\, E4 + E3 \,.\, E4$ Substituting for E3 (Eq. (2.13c)) we get :
$T = A \,.\, C + C \,.\, (B + C) + A \,.\, E4 + (B + C) \,.\, E4$ which simplifies to :
$T = A \,.\, C + B \,.\, C + C \,.\, C + A \,.\, E4 + E4 \,.\, B + E4 \,.\, C$

Now $C \cdot C = C$ and by the law of absorption (all the elements in a set are in common with itself), $A \,.\, C + B \,.\, C + C + E4 \,.\, C = C$. This can be understood somewhat intuitively. A . C, B . C, E4 . C are the elements which are common to A and C, B and C, and E4 and C respectively. These are therefore different subsets of C and when these are combined with the original set, we get the full set of elements in C.

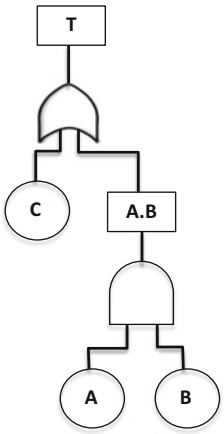

Fig. 2.10 Boolean algebra simplification of the fault tree in Fig. 2.9. T represents the top event

Using this simplification, we get:

$$T = C + A \,.\, E4 + B \,.\, E4 \quad \text{Now substituting for event E4 (Eq. (2.13e)), we get :}$$
$$T = C + A \,.\, (A \,.\, B) + B \,.\, (A \,.\, B) \quad \text{Again, applying the law of absorption we get}$$
$$A \,.\, A \,.\, B + B \,.\, A \,.\, B = A \,.\, B$$
$$T = C + A \,.\, B$$

This expression is considerably simpler than the original expression. This states that the top event T occurs if C happens alone OR A AND B happen together. Therefore the minimal cut sets of the top event are C and $A \cdot B$. The equivalent fault tree is shown in Fig. 2.10. The logical opposite or complement of the fault tree is the success tree. The minimal path set is the smallest combination of primary events whose nonoccurrence prevents the top event from happening. For the example above, the minimal path set can be derived by evaluating the logical opposite or complement of T. Let us denote this using the symbol T′.

$$T' = (C + A \,.\, B)' \quad \text{Using De-Morgan's theorem } (A \cup B)' = A' \cap B'$$
$$T' = C' \cap (A \,.\, B)'$$

Expanding the second term using De Morgan's laws $(A \cap B)' = A' \cup B'$ we get.

$$T' = C' \cap \left(A' \cup B'\right) \quad \text{Using } + \text{ for } \cup \text{ and } (\cdot) \text{ for } \cap, \text{ we get :}$$
$$T' = C'A' + C'B'$$

In other words, the top event T will not happen if C does not happen AND A does not happen or C does not happen AND B does not happen.

A simple illustrative example which has the characteristics of the fault tree in Fig. 2.10 is the electrical circuit in Fig. 2.11.

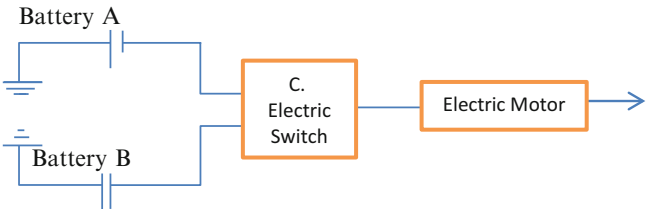

Fig. 2.11 Physical example of fault tree in Fig. 2.10. Battery A or B provides energy to run an electric motor. An electrical switching mechanism selects one of the energy sources to run the motor at any given time. Let T denote top event "No electricity to electric motor." The event A: Battery A fails, B: Battery B fails, C: Electric switch fails. The minimal cut set T happens if either the switching mechanism fails or both batteries fail $(A \cdot B)$ as shown in Fig. 2.10. The corresponding success tree, or "there is electricity to the motor" happens if the switch is functional C' AND Battery A is working $(A' \cdot C')$ OR Electric switch is working C' AND Battery B is working $(B'C')$. Adapted from [4]

Qualitative and Quantitative Evaluation of Fault Trees

Two broad types of results are obtained from fault tree evaluation: qualitative results and quantitative results [1, 4].

Qualitative Results

1. Minimal cut sets: Determine the smallest combination of component failures which can cause system failure. This forms the starting point for quantitative evaluations as well.
2. Qualitative importance: Qualitative ranking of contributions to system failure.
3. Common cause failure: Determine minimal cut sets which are susceptible to a single-component failure.

Quantitative Results

1. Numerical probabilities: Determine the failure probabilities of individual cut sets and calculate probability of system failure.
2. Quantitative importance: Quantitative ranking of contributions to system failure.
3. Sensitivity evaluations: Effects of changes in models and data, error determinations.

Qualitative Results

Minimal Cut Sets

As discussed earlier, in minimal cut set determination, the top event T is represented by an equation of the form:

$$T = F1 + F2 + F3 + F4 + \cdots$$

Assume F1 represents primary event A, F2 event B, F3 event C, F4 event (D·E), F5 event (F·G), F6 (H·I·J), F7 event (I·J·K·L), etc. Therefore:

$$T = A + B + C + (D \cdot E) + (F \,.\, G) + (H \,.\, I \,.\, J) + (K \,.\, L \,.\, M \,.\, N)$$

The top event T thus contains three single component system failures, F1(A), F2 (B) and F3(C); F4(D·E), and F5(F·G) constitute double event failures; F6 triple event and F7 quadruple event failures. The top event therefore has [4]:

three single component minimum cut sets
two double component minimum cut sets
one triple component minimum cut set and one quadruple component minimum cut set

Qualitative Importance

Ranking the minimal cut sets in order of their component size helps with understanding the importance of failures. Single cut sets are listed first, followed by double, then triple, etc. Most computer analysis of fault trees list failures in this order. Since computer complexity increases with size of the cut set, most failures list one, two, and three component minimal cut sets. Higher-order cut sets become important if they show susceptibility to common cause failures (this will be explored further).

Ranking cut sets by size is useful since failure probabilities associated with them decrease by several orders of magnitude as the size of the cut set increases. Let us assume any single component has a 1 in 1,000 chance of failing. Or in other words P (failure of a single component) $= 10^{-3}$. Therefore, a double cut set, which is the probability of two components failing is $10^{-3} \times 10^{-3}$ or 1 in one million. Extending this calculation to three element failures, we get $10^{-3} \times 10^{-3} \times 10^{-3}$ or 1 in one billion for three element minimal cut sets. Therefore, ranking minimal cut sets in terms of size provides a general idea of importance [1, 4].

In the design of fault tolerant systems, in many instances a required criterion for acceptable design or certification is *no single component failure can cause system failure*. The equivalent statement in fault tree terminology is that there are no single component minimal cut sets. The minimal cut sets can be checked to see if this is satisfied [1, 4].

Common Cause Susceptibilities

Common cause susceptibility looks at single failures which cause more than one primary event in the minimal cut sets to occur which can fail the system. A single basic cause may cause multiple failures which can fail the system. In evaluating common cause susceptibility, we are interested in common causes which can trigger all the primary failures in a minimal cut set. This can be performed by identifying common cause categories which can cause component dependence [4]. Common categories of common cause susceptibilities include environment (temperature, humidity, dust, contamination, etc.), manufacturer and operator among others. For example, water main burst causing flooding can cause failure of multiple electrical systems causing all the primary events in a minimal cut set to occur. Another example involves multiple similar components manufactured by the same manufacturer which may fail due to similar manufacturing defects. Software is another potential vulnerability. Once such common cause susceptibilities within categories are identified, the next step is to identify the minimal cut sets whose primary failures are all vulnerable to common cause failure. The minimal cut sets determined to be susceptible to common cause vulnerability are then screened for further action [1, 4].

Quantitative Evaluation of Fault Trees

Following the identification of minimal cut sets, probability evaluations can be performed to provide numerical estimates of probability of system failure. This is performed in a hierarchical fashion, component failure probabilities are first calculated, followed by minimal cut set probabilities followed by the top event or system failure probability [4]. Probabilities are calculated across logical OR and AND gates using rules discussed earlier. This is of course a simplistic description; in actual practice this is substantially more complicated. Common probability models are constant failure rate/h (λ) models—region II of the reliability curve in Chap. 1. The higher failure rates seen during "burn in" and "wearing out" are ignored in this analysis. When time varying models to account for these or a greater precision is required, more sophisticated models such as Weibull and Gamma probability distribution are preferred [4]. The relevant concepts of reliability $R(t)$, cumulative failure probability $F(t)$, and probability density function $f(t)$ were discussed in earlier sections. For small values of λt, $F(t)$ can be approximated by expanding $e^{-\lambda t}$ by its Taylor's series expansion:

$$e^{-\lambda t} = 1 + \frac{-\lambda t}{1!} + \frac{(-\lambda t)^2}{2!} + \frac{(-\lambda t)^3}{3!} + \cdots, \quad -\infty < -\lambda t < \infty$$

Since $F(t) = 1 - e^{-\lambda t}$. For small $-\lambda t$, the higher-order terms can be ignored (since $(-\lambda t)^2$ is much smaller than $-\lambda t$ Therefore we get $F(t) = 1 - (1 - \lambda t)$. Or in other words, for small $-\lambda t$:

$$F(t) \cong \lambda t \quad \text{for small } \lambda \text{ (low failure rates) and } \lambda t \leq 0.1$$

The probability of a minimal cut set is the product of the individual basic event probabilities [1, 4, 5]. The probability of the top event is the sum of the products of the individual probabilities [5]. This is called the sum of products approximation [5]. This is expressed as follows [5]:

$$P(\text{top event}) = \sum P(\text{Minimal cut sets})$$
$$P(\text{Minimal cut set}) = \prod (\text{Basic events in that particular minimal cut set})$$

where $\prod$ denotes multiplication A toy example for an AND gate is given in Fig. 2.12.

For systems whose operating life involves stand-by and active modes, the failure rate is defined as [5]:

$$\lambda = \lambda_0 d + \lambda_N (1 - d)$$

where d is the fractional duty cycle or (total operating time/total mission time), λ_0 is the component failure rate in the operating state, λ_N is the contribution to component failure rate from nonoperating state [5]. Stand-by modes are important in the analysis of latent failures. Conceptually, if a service requires two systems A and B where A is in use most of the time and B is used only if A fails (therefore is a stand-by), a failure involving B would not be detected during the normal operation of A. Since this failure is hidden, it is termed latent failure. Although it does not reduce service delivery, it degrades the safety margin of the system. In general, latent failures can affect systems whose functions are not required during normal operation but provide fail-safe coverage or protection against abnormal operating conditions [1]. The interval between when such a backup system was last known to be operating normally and when it will operate normally again is called exposure time. Such systems require maintenance checks, self-check tests for early detection, and repair to reduce exposure times [1] (Fig. 2.12).

Sensitivity Evaluation

Fault trees can help an analyst estimate how sensitive a system is to particular primary events. Numerical estimation of fault trees using different component failure rates or different exposure times can help with determining if more expensive components can significantly reduce probability of system failure or determine the appropriate maintenance intervals. Quantitative importance for determining the

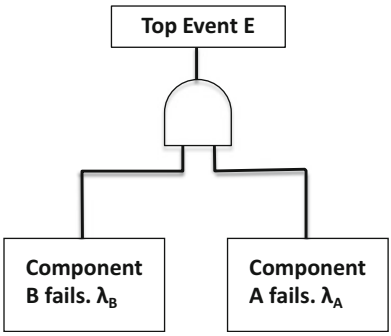

Fig. 2.12 Toy example of quantitative analysis of fault trees. The top event E happens if components A and B fail together. Assume exponential distribution with constant failure rate. For small λ_A and λ_B, $F(t)$ can be approximated by λt. Therefore $P(\text{Top Event E}) = P(\text{Failure of A and B})$ in a given time t is given by $P(\text{A})\,P(\text{B|A})$. If A and B are assumed to be independent, this becomes $\lambda_A \lambda_B t^2$

relative importance of a minimal cut set to top event probability can be performed to rank events in order of their importance. Some methods of doing this are:

(a) Ranking cut sets in descending order of probability.
(b) Calculating cut set importance: for a particular minimal cut set, this is calculated using the formula $= \frac{P(\text{minimal cut set})}{P(\text{top event})}$. This calculates what percentage of the total failure probability is contributed to by the cut set under evaluation.

Other methods include Fussell–Vesley (FV) importance and Birnbaum importance. The interested reader is referred to [1] for further information.

Finally the results of the FTA are presented as a summary. There are numerous methods of doing this [1]. This can take the form of a table where different top events, their respective probabilities, whether safety criteria specified in the PSSA are met, etc. are addressed. The process is iterative, deficiencies identified are addressed and FTA performed again to see if all safety objectives are achieved.

Appendix 2: Dependence Diagrams

DD are similar to fault trees; they represent an alternate method of representing data in a graphical analysis method similar to fault trees. The basic logic operations as in fault trees are OR and AND. However, instead of using logical operator symbols, an alternate method of using serial or parallel linkages between primary events is used. DD are analyzed in a manner qualitatively and quantitatively very similar to FTA [4]. DD are also called reliability block diagrams. The blocks themselves represent system components, the lines represent connections between them. Consider the following toy example in Fig. 2.13 (adapted from [1]).

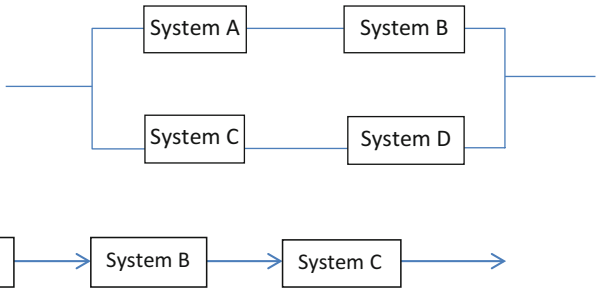

Fig. 2.13 Reliability block diagram

Fig. 2.14 Evaluating system reliability of a series connection of systems A, B, and C with individual reliabilities R_A, R_B, R_C. System reliability $= R_A R_B R_C$

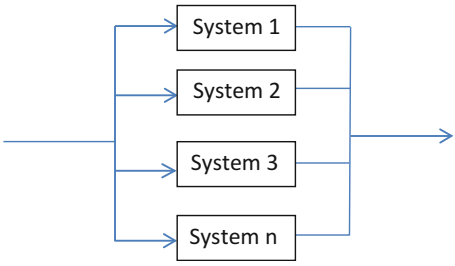

Fig. 2.15 Reliability of a parallel connection of component systems. If any of the systems is functioning, the output is delivered

Let $P(\text{A})$, $P(\text{B})$, $P(\text{C})$, and $P(\text{D})$ represent the respective failure probabilities of systems A, B, C, and D respectively. A series combination represents an OR gate and a parallel combination an AND gate. The top half of the figure shows a series combination of systems A and B. Therefore, a failure of either system A OR system B can cause failure of the top branch. Similarly, a failure of either system C OR D will cause failure of the bottom half. Both top AND bottom branches have to fail for overall system failure to happen. Represented mathematically:

$$\text{P(Failure)} = P(\text{A OR B failing}) \text{ AND } \text{P(C OR D failing)}$$

Applying the + operator for OR and $(\cdot)$ operator for AND we get:

$$P(\text{Failure}) = (P(\text{A}) + P(\text{B})) \cdot (P(\text{C}) + P(\text{D}))$$

The reliability of connected systems is assessed in a similar manner. For series connections (OR), the reliability of a combination is the product of individual reliabilities as shown in Fig. 2.14.

For parallel connections as shown in Fig. 2.15, the system reliability is evaluated differently. From the definition of reliability: Reliability $= 1 -$ System Failure [10].

For the entire system to fail, each of the individual systems has to fail. Let Ri) denote reliability of system i. For a particular system i, the failure probability is given by $1 -$ Reliability of System i $(R(i))$. Therefore, the probability of failure

of system 1 AND system 2 AND system 3. . .AND system N is given by the product of the individual failure probabilities [10].

$$\text{Probability of System Failure} = \prod_{i=1}^{n}(1 - R(i)) \text{ where}$$

$$\text{Reliability of the System, } R(i) = 1 - \text{Probability of System Failure}$$

$$= 1 - \prod_{i=1}^{n}(1 - R(i))$$

Since the basic events are combined using logical OR and AND operators, DD lend themselves well to simplification using Boolean algebra [1] using the same rules as FTA. The analysis of DD involves Boolean algebra simplification to generate minimal cut sets and to perform qualitative and quantitative calculations on them.

Markov Analysis

MA is a method for analysis similar to FTA and DD. It is a powerful tool which can cover a wide range of system behaviors. A Markov chain represents various system states and transitions between them. The states themselves can be operational or nonoperational and the transition from one to the other is determined by the failure and repair rates. At any time, t the probability of being in a particular state can be calculated by solving a set of differential equations. The interested reader is referred to [1, 5] for further introduction to the topic.

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Chapter 3
Fault Tree Analysis for Medical Applications

Abstract This chapter expands fault tree analysis (FTA) introduced in Chap. 2 to medical applications. The history of FTA is discussed to introduce the reader to the diversity of fields in which it finds applications for safety and discovering the root causes of mishaps. FTA is a form of backwards thinking where the investigator starts from an event and searches for the sequence of failures which led to that event. FTA is both qualitative and quantitative, therefore it lends itself well to analysis. In this chapter, a brief review of the material introduced in Chap. 2 is presented followed by case examples where the method helped arrive at the final diagnosis.

Introduction

Fault tree analysis, introduced in Chap. 2 is a tool for "analyzing, visually displaying, and evaluating failure paths in a system, thereby providing a mechanism for effective system risk evaluations [1]." The history of this technique is presented here to introduce the reader to its multi-domain ubiquitous application [1]. The method was first developed by H. A. Watson of Bell Laboratories in connection with the US Air Force contract to study the Minuteman missile launch control system. Dave Haasl, then with the Boeing Company applied FTA to the entire Minuteman missile system. Subsequently, other groups within Boeing began using FTA during the design of commercial aircraft. In 1965 Boeing and University of Washington, Seattle sponsored the first system safety conference. This marked the beginning of a worldwide interest in FTA [1]. Following the lead of the aircraft industry, the nuclear power industry discovered the benefits of this technique and developed it widely. Subsequently the method was adopted by the auto industry, chemical industry, industrial automation, rail transportation, and robotics industries. The technique was used to investigate major accidents in the respective industries. The Apollo 1 launch pad fire on January 27, 1967; Three Mile Island nuclear plant accident on March 28, 1979 were investigated using FTA methods [1]. FTA tends to be used in high-risk applications as part of system safety assessment [1]. Major applications of the technique include: verifying numerical requirements, identification of safety critical components, product certification, product risk assessment, accident/incident analysis and design change evaluation,

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visualizing causes and their consequences, and common cause analysis [1]. The interested reader will find a wealth of information in references [2, 3] and in Chap. 2.

This chapter explores FTA for medical diagnosis which is a form of accident investigation. Starting from symptoms, physical examination, and laboratory evaluation data, we would like to work backwards to the root cause(s) of what we observe. Once we identify the cause(s), we would like to be able to reconstruct all the events which led to the incident under investigation. For the purposes of making this section self-contained, important principles of constructing a fault tree are reviewed here followed by diverse case examples.

Constructing a Fault Tree

The following events and logic gates will be used in the medical case examples discussed in this chapter [2, 3]:

A. Primary events: of a fault tree are those which are not developed further. The most important primary events for the purposes of this chapter are:

A.1: **Basic event**: This is a basic initiating fault which does not require further development.

Medical example: (a) Herpes Simplex is the cause of encephalitis in this patient, (b) myasthenia gravis is the cause of weakness. The investigator therefore needs to define the limits of resolution of his analysis to define the basic event. For the myasthenia gravis example above, we do not extend the analysis further to the next level to define what is the cellular mechanism of weakness from myasthenia gravis.

A.2: **Undeveloped events**: An event which is not developed further, either because developing it further is not relevant for the problem being analyzed or because more information is not available. This usually helps direct investigations and prevents distractions from abnormal lab data which may not be relevant for the investigation on hand. It is represented by a diamond.

Medical example: (a) Thyroid cyst identified on MRI Cervical Spine in a patient with paralysis of the lower extremities. (b) Benign renal cyst on MRI Lumbar Spine performed for foot drop. (c) A Vitamin B12 level of 400 in a patient with paraplegia.

B. Intermediate event: a fault event that happens because of one or more primary events acting through logic gates. It is represented by the rectangle symbol and represents an intermediate step in the analysis.

Medical example: (a). Amyotrophic lateral sclerosis (basic event) led to diaphragm weakness (intermediate event) which led to ventilatory failure.

(b) Myasthenia Gravis (basic event) led to pharyngeal weakness (intermediate event) which led to aspiration (intermediate event) which led to pneumonia.

C. Logic Gates: are the logical combinations of primary and intermediate events (building blocks of the tree) which lead to the undesired top event. The following gates are described here since they find application in the medical case examples discussed in this chapter:

1. **Boolean "OR" gate**: The output occurs if at least one of the input events occurs.

   Medical examples: (a) Hypothyroidism OR Myasthenia led to Weakness. (b) Cardiac failure or COPD caused shortness of breath.

2. **Boolean "AND" gate**: The output event occurs if and only if all the input events occur. Either one or the other input events cannot cause the output to happen.

   Medical example: (a) Diastolic dysfunction AND fluid overload led to pulmonary edema.

3. **The Inhibit gate**: represented by a hexagon is a special case of the AND gate. The output can be caused by a single input, but a qualifying condition must be present for the output to happen. The qualifying condition is represented by a type of primary event called the conditioning oval drawn to the side of the inhibit gate. This can be used to visualize the effect of drug interactions.

   Medical example of Inhibit Gate: (a) Patient on stable dose of carbamazepine became toxic when fluconazole was added for fungal infection [4]. This happened because fluconazole (conditioning event) inhibits hepatic enzymes which are concerned with carbamazepine metabolism leading to toxicity.

The corresponding symbols for the events and logic gates are discussed in detail in Chap. 2. In this chapter, we will use English letters to denote logic gates for ease of discussion. The following rules will be followed for constructing a tree:

1. *State the undesired top level event in a clear, concise statement*. Examples include "Patient is weak and numb below the waist."
2. *Develop the upper and intermediate tiers of the fault tree*: Determine the *immediate*, *necessary, and sufficient* causes to explain the top event and interconnect them by the appropriate logic symbols [2, 3]. For the top event example of "Patient is weak and numb," the immediate, necessary, and sufficient causes are it could happen because of diseases of spinal cord OR diseases of nerves. This is called the "*Think Small*" rule. The investigator identifies only the immediate causes of the top event, not the root causes. Failure modes are identified followed by failure mechanisms as demonstrated in Chap. 2. To the extent possible, at each step failure modes (the manner in which the system has failed) are identified first, followed at the next level of the tree by failure mechanisms (the causes which can lead to the corresponding failure mode.)

3. *Extend each fault event to the next lower level*. The immediate causes of the top event are the subtop events linked together by logic gates. Each subtop event becomes the top event for the next level of the tree. *For each subtop event, identify the immediate, necessary, and sufficient causes for the subtop event to happen*. For the example above, diseases of the spinal cord can happen due to inflammatory conditions, infectious conditions, vascular diseases of the cord, etc. At each level of tree construction, particular attention is paid to the following:

   - Can any single failures cause the event to happen?
   - Are multiple failure combinations necessary for the event to happen?

   In medical fault trees, we can incorporate results of available investigations and develop certain branches of the tree and stop others (undeveloped event). For example, let us assume an EMG study of the above patient shows a severe neuropathy. In that case, disease of spinal cord becomes an undeveloped event.
4. *Develop each event through its immediate, sufficient, and necessary causes till the limit of resolution is reached and root cause(s) are established*. Root cause analysis is explored further as a management method in Chap. 8 of this book. For the example above, we stop developing the spinal cord branch of the tree and explore the immediate, necessary, and sufficient causes of the severe neuropathy. This may be due to immunologic causes like Guillain-Barré Syndrome or toxic causes such as heavy metal poisoning and we design appropriate tests for the same (lumbar puncture for GBS and 24 h urine heavy metal screen for toxic neuropathy). At this stage we have identified the root cause of the top event.
5. *Evaluate the fault tree in qualitative and/or quantitative terms*. Fault trees are qualitative by nature of their construction. At this stage, we can rank root cause(s) in order of probabilities. For the example above, except under unusual circumstances, the probability of Guillain-Barré Syndrome exceeds that of heavy metal poisoning. Therefore, the investigator can direct his attention and further tests to this hypothesis and consider a spinal tap looking for albuminocytologic dissociation.
6. *Once the root cause(s) are identified, the investigator must be able to reconstruct the top event by traversing up the tree*. The idea behind the analysis is to identify the "minimal cut set." A "minimal cut set is the smallest combination of component failures which if they occur will cause the top event to happen" [2]. Therefore, starting from the root cause and walking forwards, the investigator must be able to reconstruct the intermediate events and finally the top event.

Medical Case Examples of Applications of FTA

The first step to performing fault tree analysis is to express the clinical problem in a simple form which forms the starting point of this method.

Case Example 1

P.D. is a 35 y/o male who started exhibiting behavioral changes approximately 2 years ago. Adopted as a child, he was employed as an engineer till matters became increasingly difficult for him because of behavioral abnormalities. This resulted in divorce, a house fire, fights with neighbors, and subsequently loss of employment. He was treated for bipolar disorder with later development of dizziness, poor balance and falls, and oral dyskinesias, possibly a side effect of antipsychotics. Progressive behavioral changes led to nursing home confinement and increasing use of restraints.

Physical examination revealed a severely confused state. Patient had severe impairments in speech, memory, attention, and was unable to follow simple commands. Cranial Nerve examination was normal. Motor strength and gross sensation were normal. Physical examination was consistent with a severe dementia involving multiple domains of memory, executive function.

An MRI Brain done at this stage showed severe abnormalities shown in Fig. 3.1. The key features of this MRI Brain study are the severe global atrophy, a pattern of white-matter signal changes involving the bilateral anterior temporal poles, external capsule and subinsular regions. This constellation of findings raises concerns for

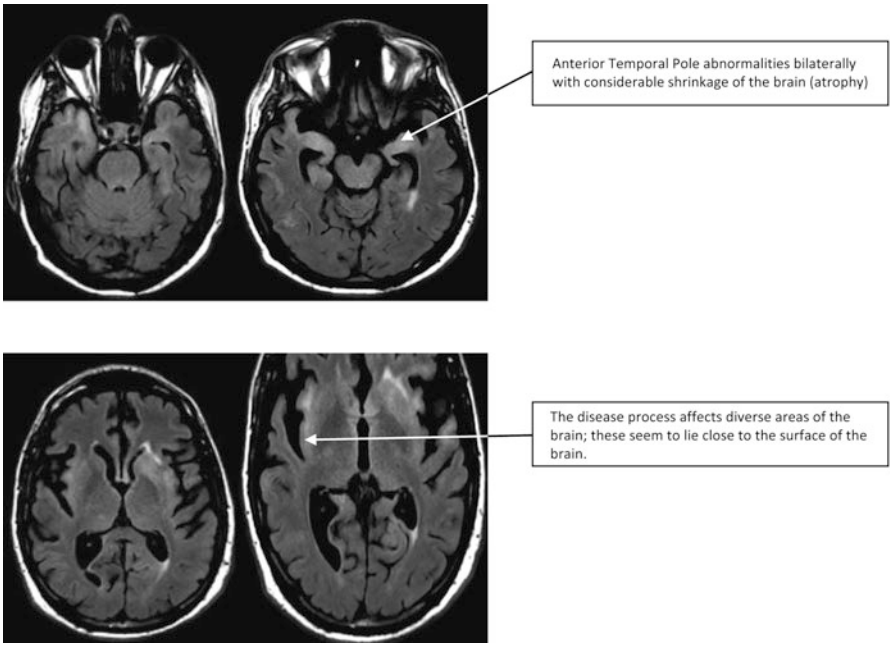

Fig. 3.1 MRI images of a 35-year-old male with rapidly progressive dementia. The pattern of signal changes involves certain key areas of the brain including anterior temporal poles, external capsule, and subinsular regions which can be seen with CADASIL [5]

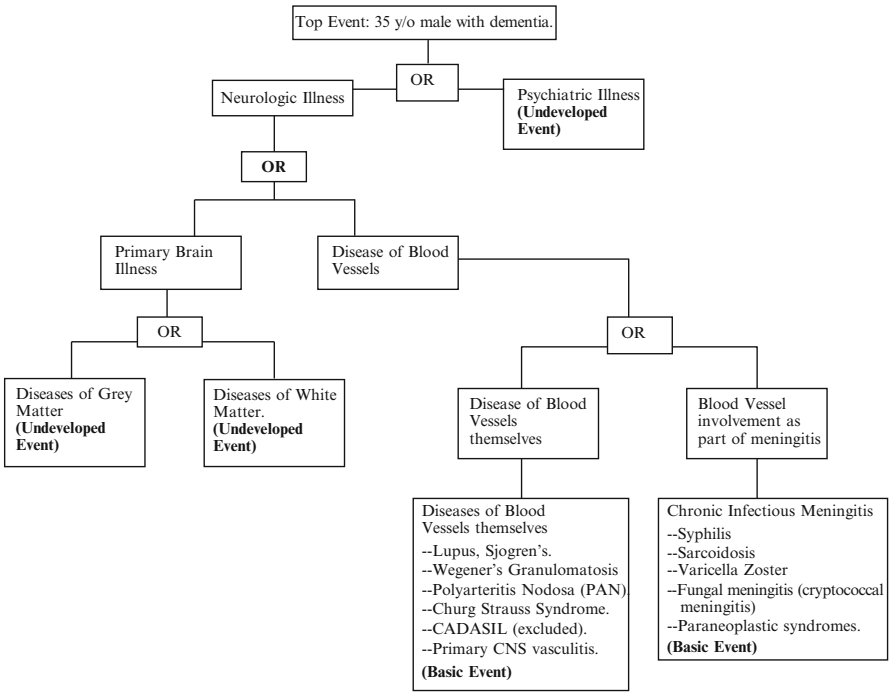

Fig. 3.2 FTA for Case Example 1. The top event is "35-year-old male with rapidly progressive dementia." Using the "think small rule," the investigator works his way down to the root cause (s) of this event and directs confirmatory investigations accordingly

CADASIL—cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy [5]. No contrast enhancement was seen in this study. The referring physician had ordered the corresponding gene test involving the *Notch3* gene on chromosome 19. The gene test has >95 % sensitivity and 100 % specificity [5]. Despite such a suggestive MRI Brain the gene test was negative. Therefore, one of the concerns for the referring physician was whether this patient would benefit from a skin biopsy to diagnose the condition since CADASIL causes deposition of granular osmiophilic deposits around smooth muscles of arterioles in many tissues. These deposits can be seen on electron microscopy and can be used to make the diagnosis of CADASIL when the genetic test is negative [5].

CADASIL is unfortunately not treatable. Limited laboratory data available for review showed a normal result for HIV and Hepatitis B and C viruses. Since this patient's care was fragmented across many institutions, no further data was available. A solution to this case was attempted using FTA shown in Fig. 3.2.

1. **Top Event**: *Formulate the problem in simple terms*: 35 y/o male with rapidly progressive dementia.
2. **Sub-events immediately leading to Top Event**: The *immediate*, *necessary*, *and sufficient* conditions leading to the top event are neurological illness OR

psychiatric illness. The abnormal MRI excludes a primary psychiatric illness; therefore this is an "*Undeveloped event*" and will not be developed further.

3. **Sub-event**: Neurological Illness will be developed to the next level. The abnormalities seen on MRI Brain can be due to a (a) disease of the Brain itself OR (b) due to a disease of blood vessels. CADASIL was explored as a cause of disease of blood vessels.
4. **Sub-event**: (a) Disease of the brain itself can be due to a disease of white matter OR disease of gray matter. MRI shows predominantly white-matter involvement, therefore this is developed further and diseases of grey matter (termed poliodystrophy) will be considered an "Undeveloped Event" and not developed further.
5. **Sub-event**: Diseases of blood vessels can be diseases of blood vessels themselves OR involvement of the blood vessels from chronic inflammation around the surface of the brain—chronic meningitis. Available clinical information did not suggest an ongoing multisystem disease with involvement of lung, liver, or kidneys. Therefore the blood vessels covering and penetrating into the brain could be affected due to inflammation or infection around the brain from chronic meningitis.
6. **Sub-event**: Primary diseases of blood vessels termed "vasculitis," can be isolated to the brain ("primary CNS vasculitis) or be part of a multisystem autoimmune disease like SLE, Wegener's granulomatosis, or polyarteritis nodosa [6]. Given the long duration of illness in this patient, chronic meningitis with this duration of survival without treatment can happen from diseases such as sarcoidosis, syphilis, herpes zoster, fungal (cryptococcal), and tuberculosis infections, the latter two being extremely unlikely [7].

FTA led to the bottom right of the tree since most other conditions along the way were analyzed and felt to be not relevant for the clinical presentation on hand and left as undeveloped events. The formulation has the advantage of permitting the investigator to return to any of these trains of thought and expand them should initial inquiries prove unrewarding.

Following identification of candidate root cause(s), confirmatory tests can be planned for making the final diagnosis. The candidate diagnoses are analyzed further based on available clinical information. For case example 1, this can be performed rigorously using the Bayesian approach (please see Chap. 2 for more details.)

1. Chronic Meningitis Syndromes: We can now determine the probability of the individual diagnosis identified under chronic meningitis syndromes and rank them in descending order of probability to direct investigative resources. Starting with syphilis, we are interested in calculating the joint probability of syphilis and rapidly progressive dementia in this patient, expressed as P(Syphilis AND Rapidly Progressive Dementia). This is expressed as:

$$P(\text{Syphilis, Rapidly Progressive Dementia}) = P(\text{Syphilis}) \times P(\text{Rapidly Progressive Dementia} \mid \text{Syphilis}).$$

P(Syphilis) is a measure of the probability of syphilis. P(Rapidly Progressive Dementia | Syphilis) is a measure of how likely it is to get rapidly progressive dementia from untreated syphilis.

Similarly, we can calculate the remaining probabilities:

P(Fungal Meningitis, Rapidly progressive dementia) = P(Fungal meningitis) × P(Rapidly progressive dementia | Fungal Meningitis).

P(Sarcoidosis, Rapidly progressive dementia) = P(Sarcoidosis) × P(Rapidly progressive dementia | Sarcoidosis).

P(Paraneoplastic Syndrome, Rapidly progressive dementia) = P(Paraneoplastic Syndrome) × P(Rapidly progressive dementia | Paraneoplastic Syndrome).

2. Diseases of Blood Vessels: In a similar manner, we can calculate the respective diagnostic probabilities of this branch of the tree.

   P(SLE vasculitis, Rapidly Progressive Dementia), P(Wegener's, Rapidly Progressive Dementia), P(Primary CNS vasculitis, Rapidly Progressive Dementia) can all be respectively analyzed in this manner. The numbers themselves can be obtained from review papers on these topics, however we are looking for a qualitative feel for the concerned probabilities.

Ranking all the probabilities, we find that P(Syphilis) × P(Rapidly Progressive Dementia | Syphilis) is likely higher than the rest since syphilis is a common infection and untreated syphilis caused neurosyphilis which is a cause of severe dementia. In descending order, we get systemic vasculitis like SLE, Wegener's and Sjogren's syndrome. Primary CNS angiitis is much rarer; therefore it can be investigated if the above approach fails. Based on the results of the FTA, resources can be directed for the next round on testing:

The following tests were requested: **Step 1**: In Blood: Rapid Plasmin Reagin (RPR), Antinuclear Antibodies (ANA), Antineutrophil Cytoplasmic Antibodies (ANCA). **Step 2**: The next step would be testing of the CSF for infections and inflammation. Finally if these do not yield any results, a brain biopsy looking for primary CNS vasculitis can be performed. Each of these hypotheses is a valid minimal cut set. Starting from any of these basic events, we can walk back up the tree and reconstruct the intermediate events leading to the top event.

Serum RPR was positive in very high titer (>1:128). Confirmatory testing for syphilis with FTA-ABS was also positive. A directed examination of spinal fluid showed a positive CSF VDRL confirming neurosyphilis as the root cause of the patient's rapidly progressive dementia. He was treated with high-dose IV penicillin with considerable improvement by the end of the treatment period. He no longer required antipsychotic medications or restraints. At the end of one month he was discharged home to his family with remarkable improvement. The diagnosis in this patient immediately resulted in testing of all contacts by public health authorities.

This case highlights the importance of the methodical, "one small step" at a time approach which is extremely important in constructing fault trees.

Case Example 2

J.W. is a 40 y/o male referred for myasthenia gravis. Patient reports that about 3–4 years ago he developed vertical/diagonal diplopia. This is basically constant all day long and will occasionally get somewhat better after some rest. This is worsened by horizontal gaze, primarily with right gaze. This has remained relatively stable since it began about 4 years ago, however he does state that the images have become further apart over the years. The diplopia completely resolves with the closing of either eye. He denies ptosis or extremity weakness. He does state that he feels his right eyeball is weak and he has grittiness/dryness primarily in the right eye. The patient did have a blow to the head around the time his symptoms began.

Patient first sought care from an eye doctor who felt he had extraocular muscle weakness. He then saw a neurologist in April 2013. He had a CT Chest which did not show evidence of Thymoma or other malignancy. MRI Brain without contrast was obtained and was normal. Blood tests showed: AchR Binding Antibodies: 0.26 (normal <0.25), AchR blocking antibodies negative, AchR modulating AB negative; B12, Folate, TSH, Free T4 normal; ESR 2, CRP 0.6. Patient was initially treated with Pyridostigmine but this did not provide benefit. He was then given IVIG 2 g/kg over 5 days in the last week of April. He saw no improvement with the IVIG. He was placed on prednisone which again showed no benefit. He developed significant side effects from prednisone including rash and weight gain. Since he was a professional truck driver with an international logistics company, he had been unable to work and was on disability.

On focused neurological examination, cranial nerve examination did not show ptosis. The patient had diplopia on right gaze which worsened with left head tilt with weakness referred to the left superior oblique muscle. All other extraocular muscles appeared normal at bedside clinical examination. The remainder of the neurological examination was normal. The reason for referral was for initiating plasmapheresis since IVIG, high-dose prednisone and Pyridostigmine were ineffective. A prior treatment trial with prism glasses had not been successful.

The problem was formulated using FTA methodology with the following results shown in Fig. 3.3:

Step 1: *Top Event*: JW has double vision.

Step 2: *The immediate, sufficient, and necessary causes on the top event are*: Diseases of the central nervous system OR diseases of extraocular muscles OR cranial nerves 3, 4, and 6 (especially 4 based on examination) OR neuromuscular junction disorders.

Step 3: *Sub-event*: Diseases of the central nervous system have been excluded by normal MRI Brain scans. Therefore this is an "undeveloped event." Disease of extraocular muscles are genetic (example mitochondrial disorders), highly unlikely to present this way since they involve multiple muscles and also are associated with ptosis. Therefore this too is an undeveloped event. The following sub-events are chosen for expansion.

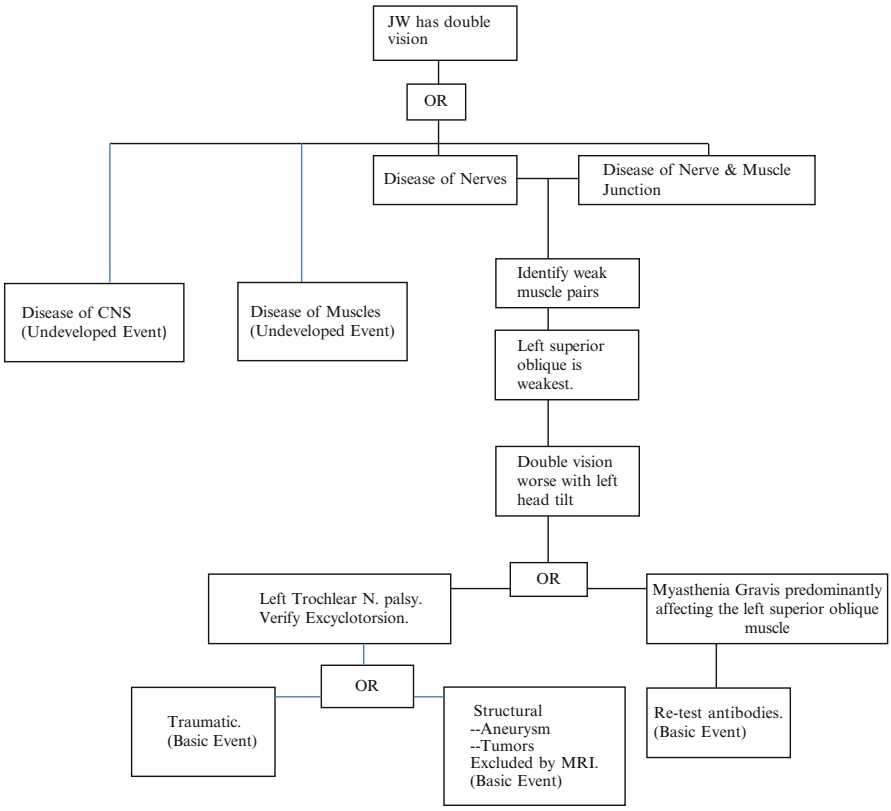

Fig. 3.3 FTA for Case Example 2. By successive application of the "Think Small" rule, the two candidate root cause(s) are left trochlear nerve palsy vs. myasthenia gravis involving the left superior oblique muscle. Confirmatory testing can then be designed to discriminate between the two

Diseases of Nerves: Involving right eye, left eye, or both.
Diseases of neuromuscular junction: myasthenia gravis, Lambert Eaton myasthenic syndrome.

Step 4: *Sub-events: Disease of Nerves*: Identify all weak muscles based on where images are maximally separated. This showed weakness mostly involving the left superior oblique.

Sub-events: **Disease of neuromuscular junction**: identify all weak muscles.

Step 5: *Sub-events*: Examine the back of the eye (Fundus Examination). Is there an outwards rotation of the fundus (termed *excyclotorsion*)?

Sub-event: Look for head tilt—which was right sided in this case. Further, left head tilt made it worse.

Step 6: *Sub-events*: Based on all these, identify the problem either as a left trochlear nerve palsy from head trauma or myasthenia gravis. Design tests to distinguish between two.

Therefore,
Hypothesis 1 (H1): Left Trochlear N Palsy
Hypothesis 2 (H2): Myasthenia Gravis

We need to evaluate which of the two is more probable and define that as the working diagnosis. The alternative becomes the differential diagnosis. The following additional features help with decision making.

(a) The presence of left Excyclotorsion on examination of the left fundus.
(b) The presence of weakly positive AchR antibodies on prior blood work.

Excyclotorsion would explain the difficulty in treating the diplopia with prism glasses in the past. It also favors a left trochlear N palsy over myasthenic weakness of the muscle since it is not a commonly observed phenomenon in the latter. Calculating the joint probability of superior oblique weakness under the two hypotheses, *P*(H1, Left Superior Oblique Weakness, Excyclotorsion, Weakly positive Myasthenia antibodies) vs. *P*(H2, Left superior oblique weakness, Excyclotorsion, weakly positive antibodies), Excyclotorsion favors the former. The physical examination favors H1 over H2; the positive antibodies in low titer may be a false positive. The next step becomes:

(a) Ophthalmology evaluation to confirm fundus findings and verify L trochlear palsy.
(b) Retest antibodies and single-fiber EMG of the left frontalis muscle to exclude myasthenia.

Therefore, the working diagnosis is traumatic left trochlear nerve palsy. A repeat blood test from a reputable lab failed to confirm the initial diagnosis of myasthenia gravis. A single-fiber EMG of the left frontalis muscle was normal, essentially excluding myasthenia gravis. The new diagnosis of left trochlear nerve palsy—likely traumatic was confirmed by a neuroophthalmologist who recommended prism glasses and perhaps corrective surgery if symptoms did not improve. The patient was taken off prednisone 60 mg/day and cleared to return to work much to the delight of the patient and his family.

The exact costs are not available, however the patient reports the costs of IVIG, CT Chest directed towards myasthenia gravis largely from a positive blood test was approximately $45,000. Lost income and disability payments account for a similar figure by the patient's calculations. J.W. example illustrates the enormous savings this approach yields. It helps direct the search for causes from each observation and prevents distractions from misleading or false data which lies at the heart of dependability.

Case Example 3

Mr. A.B. is a 65 y/o male with a progressive, disabling, undiagnosed neurological condition which presented over 8 months. Symptoms initially started with dizziness, associated with nausea and vomiting. Dizziness was initially provoked by head movement and lying down relieved symptoms to some extent. He denied tinnitus, hearing loss at initial presentation. Over the last 8 months, he had developed progressive, bilateral, generalized weakness, confusion, lethargy despite being on anticoagulants and statins for stroke prevention. He had occasional headaches at onset. The identified risk factors were diabetes mellitus and hypertension. He had undergone an extensive stroke workup including a transesophageal echocardiogram, thrombophilia panel looking for common genetic mutations, RPR, Lupus anticoagulant, ANCA, SSA, SSB, complement C3 and C4 levels. CBC, CMP, and urinalysis were also reportedly unremarkable. No associated disease referable to other organ systems was found. There were no skin lesions; oral or genital ulcers were absent. The only significant abnormalities were an abnormal ANA screen positive in 1:1,280 titer. CSF Studies: Normal cell count: 4/hpf, increased protein 126.9 mg/dL; Cytology, RPR: normal. Since undergoing hospitalization recently, he had experienced a progressive decline in consciousness.

Figure 3.4 shows key images from MRI Brain studies obtained during the recent hospitalization. Since recurrent strokes had occurred on MRI Brain in a pattern very unusual for diabetes and hypertension despite anticoagulation and statin therapy, a cerebral angiogram was performed looking for CNS vasculitis shown in Fig. 3.5.

A review of records showed the following formal radiologic interpretations: MRI Brain: "FINDINGS: When compared to prior studies, there has been interval increase in the number of bilateral hemispheric white-matter lesions, some of which show reduced diffusion. One of these lesions is in the right callosal splenium. The findings could still relate to water-shed ischemia. *Is the patient experiencing episodes of hypotension? Vasculitis is in the differential diagnosis*. The remainder of the study is unchanged, including the hyperintense signal in the pons which is nonspecific but can be seen with osmotic demyelination. No reduced diffusion to suggest that this is acute. *IMPRESSION*: Interval development of additional areas of reduced diffusion and T2 hyperintensity within the bilateral hemispheres, for which water-shed ischemia is still a main consideration. *Vasculitis* is in the differential diagnosis."

Cerebral Angiogram: "FINDINGS: On careful inspection, *there is vascular irregularity consistent with the clinical diagnosis of vasculitis, particularly involving the pericallosal branches of the right anterior cerebral artery, some of the posterior middle meningeal branches of the right external carotid, and the superior cerebellar artery on the left side*. The examination is otherwise grossly normal. There is no evidence of AV malformation, dural AV fistula, or aneurysm within the limits of the examination. The dural venous sinuses are patent. **SUMMARY**: *Extremely challenging, less than optimal exam, demonstrating features consistent with vasculitis*.

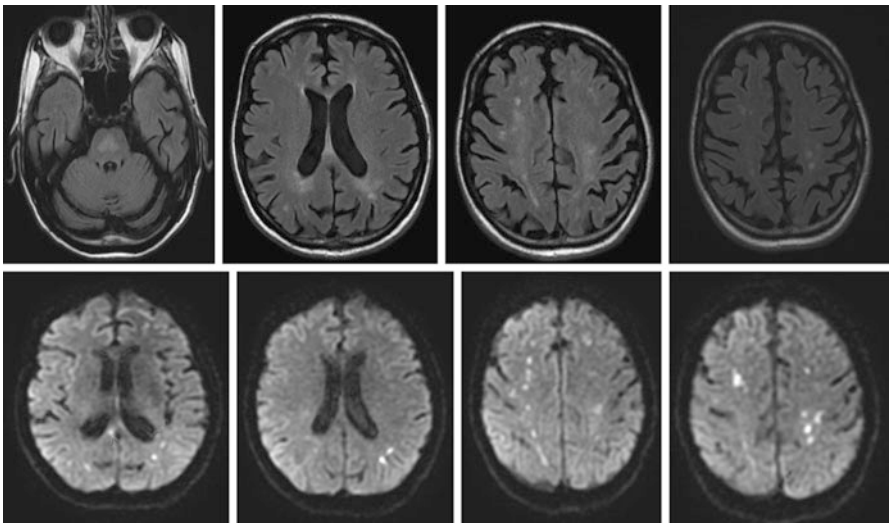

Fig. 3.4 MRI Brain images for Case Example 3. The *top row* shows axial T2 FLAIR images. *Bottom row*: Diffusion weighted imaging (DWI) images which show several areas of diffusion restriction consistent with new strokes appearing as bright spots on imaging

Based on MRI Brain and cerebral angiogram findings, a presumptive diagnosis of CNS vasculitis (perhaps part of a systemic disorder due to positive ANA screen) was made and patient started on pulse IV Methylprednisolone 1,000 mg QDaily for 5 days. His clinical condition worsened with progressive decline in consciousness to coma which required intubation and mechanical ventilation for airway protection. In the few days prior to intubation, the patient had reported not being able to hear too well but had not experienced any visual changes. The main concern for the treating neurologist at this point was whether more aggressive therapy with cyclophosphamide or measures like IVIG, plasmapheresis would help.

An FTA was constructed with one assumption—the imaging findings were real and not artifactual, especially the cerebral angiogram observation of vascular irregularities in multiple circulations. The "*think small*" rule was rigorously applied, shown in Fig. 3.6.

1. **Top Event**: *Stating the top event in simplest form*: Patient has severely decreased mental status.
2. **Sub-events**: *Applying the "think small" rule, the "immediate, necessary, and sufficient" causes of the top event are*: Primary Diseases of Brain (Neurological Disorders) or Systemic Disease.
3. **Sub-events**:

   (a) **Systemic diseases** such as SLE (a major consideration owing to elevated ANA titer) can cause multiple organ system involvement including CNS vasculitis. However, despite a positive ANA screen, evidence of active systemic disease in the form of low complement levels, high ESR/CRP

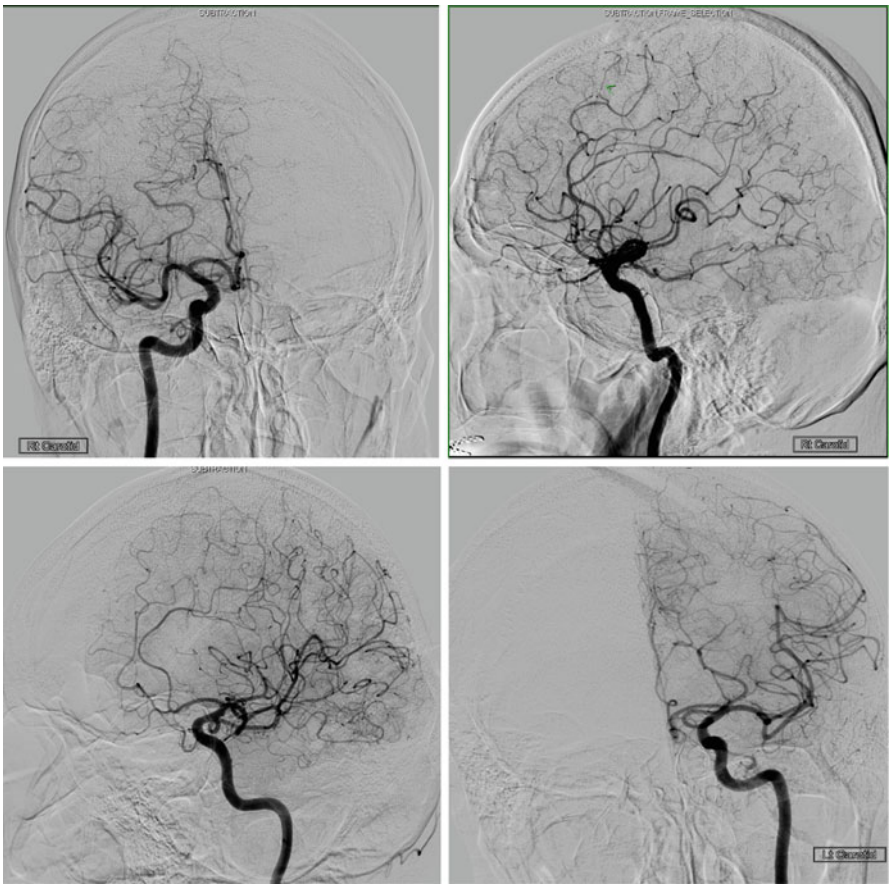

Fig. 3.5 Case Example 3: Cerebral angiogram. Top row shows right carotid injection. Bottom row shows left carotid injection with corresponding AP and lateral views

were lacking. Therefore, while still a valid avenue worth pursing, this is considered an "undeveloped event" for the time being.

(b) **Primary diseases of brain**: We apply available clinical and radiological information from the MRI Brain and cerebral angiogram with the assumption that the angiogram findings are real. Therefore the disease of the brain in this case involves strokes, angiographic evidence of vascular irregularities AND deafness. Progressing one small step backwards, this combination of events can occur due to mitochondrial disorders OR diseases of blood vessels since blood vessels are common to the brain substance, nerves, and inner ear.

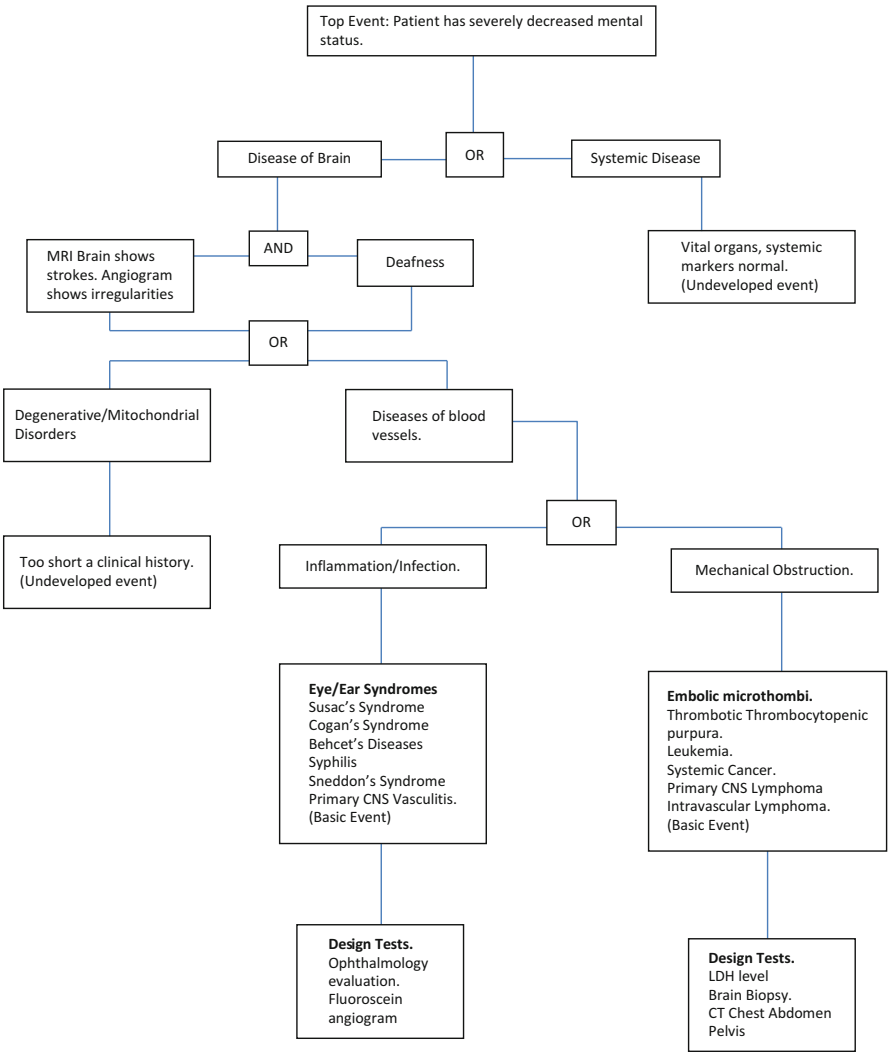

Fig. 3.6 FTA for Case Example 3. Having identified probable root cause(s), we can proceed with diagnostic evaluation to confirm the diagnosis

4. **Sub-events**:

(a) **Mitochondrial disorders** can cause deafness, diabetes mellitus, strokes, and white-matter changes. However, they are unlikely to present with such a short clinical course. Therefore, while a valid clinical concern, they are considered less likely and not developed further ("undeveloped event").

(b) **Disease of blood vessels**: MRI Brain features of strokes, cerebral angiogram features of vessel irregularities all point in this direction. The last clinical observation of deafness progressing to coma also points in this

direction since the disease seems to affect the VIII cranial nerve and the substance of the brain since it causes coma. These may occur due to inflammation/infection OR due to mechanical obstruction.

5. **Sub-events**:

   (a) *Inflammatory/infectious diseases of blood vessels ("vasculitis")* as suggested by the angiogram can be explored further using deafness as an investigative clue. Primary CNS angiitis is therefore a prime consideration for which the patient received empirical treatment with no benefit [6]. Vasculitis like Susac's Syndrome [8], Cogan's syndrome can involve the retina, vestibulocochlear nerve with CNS involvement [9]. Additional considerations include infections like syphilis which can cause stroke and deafness [7]. The broader differential includes rare inflammatory vasculitis of the CNS like Sneddon's syndrome [10] and Behcet's disease [11].

   (b) *Mechanical obstruction of blood vessels*: would also present with vessel irregularities on angiography which mimics vasculitis. The obstruction is mechanical from blood clots or from cells. The patient had been extensively evaluated for blood clots with TEE in the past. Additionally, he had been on therapeutic anticoagulation. The vessels maybe occluded from clumps of debris or cells—the most important diseases which are known to do that are systemic cancers, hematologic malignancies such as leukemia, primary CNS lymphoma or a rare special form of lymphoma called "angiotrophic CNS lymphoma" [12]. These constitute the "basic events" of our analysis from which further diagnostic testing can be planned.

FTA yields two classes of disease which are worth pursuing for narrowing the diagnosis further. Diagnostic tests can now be chosen to further distinguish between these possibilities since they are treated differently. The major hypotheses as a result of our analysis are:

(a) Hypothesis 1: Vasculitis syndromes. This can be evaluated further by requesting an ophthalmology evaluation and a fluorescein angiogram to look for any vasculitis of the retinal vessels.

(b) Hypothesis 2: Mechanical obstruction. Many diagnostic considerations are essentially excluded (by normal TEE, normal platelet counts, absence of systemic cancer and evidence of other organ involvement) to just 2: Intravascular lymphoma (also called angiotrophic large cell lymphoma) and primary CNS lymphoma. Given the current mode of presentation with vascular involvement, intravascular lymphoma is the preferred hypothesis. Eighty-five percent of patients with intravascular lymphoma are reported to have an elevated lactate dehydrogenase (LDH) level [12].

Hypothesis 1 was immediately evaluated and no signs of ocular involvement were found. LDH levels were mildly elevated. A brain biopsy was requested specifically for evaluating intravascular lymphoma. A right frontal lobe biopsy reported "numerous vessels filled with markedly atypical large lymphocytes

consistent with intravascular lymphoma. The malignant lymphocytes stain strongly for B cell markers (CD 20). There is no staining for T cell markers or for AE 1/3." This is an extremely rare but aggressive lymphoma where early diagnosis followed by aggressive chemotherapy can prolong survival [12].

Unfortunately, given the delays in recognition and diagnosis, the patient died without a chance for aggressive chemotherapy to be instituted.

This example shows how FTA facilitates the same objective finding to be explored from different perspectives. In this case, the report of "irregularities" in the angiogram led to the assumption the process is inflammatory with CNS vasculitis being the only possibility. However, identifying the failure mode (see Chap. 2) as blockage of blood vessels prior to exploring failure mechanism led to consideration of "mechanical factors" which led to the diagnosis.

Case Example 4

K.L.H. is a 75 y/o male with hypertension, hyperlipidemia, transient ischemic attack, rheumatoid arthritis, and coronary artery bypass grafting who presented with progressive cognitive decline for close to 8 months. An MRI Brain done at an outside institution was concerning for meningitis or meningoencephalitis. He had been having severe, intractable headaches for this time. He had several other health problems around this time including unintentional weight loss, syncope, new diagnosis of diabetes mellitus, and granulomas (possibly caseating) found on lung needle biopsy. The patient's granulomas were felt to be due to a rheumatological cause and he was placed on prednisone 60 mg daily. Subsequently he was started on sulfasalazine. His headaches worsened while on the sulfasalazine which necessitated discontinuation of the drug. Later the rheumatoid arthritis diagnosis was questioned and the steroids were tapered to a low dose (5 mg) and he was started on methotrexate. The patient was examined by neuroopthalmology and treated with high-dose steroids for possible temporal arteritis. However, he continued to experience headaches. Given that he did not have visual impairment or jaw claudication, the medication was discontinued. He was noted to have a high ESR ~ 100 mm during the course of the illness.

The patient was readmitted after a recent MRI Brain at an outside hospital demonstrated several areas of increased signal on DWI of the cerebral convexities as well as increased signal intensity of the cerebral gyri. Additionally, post-contrast imaging demonstrated moderate enhancement of the leptomeninges concerning for meningitis or meningoencephalitis. The radiologist's concerns were for inflammatory processes such as sarcoidosis or intracranial hypotension. The patient was admitted for further evaluation and treatment. He continued to have daily headaches which were bifrontal and his cognition continued to worsen.

On focused neurological examination: mental status examination showed the patient to be awake, oriented to person but not to place or time. He was cooperative and followed simple one step commands consistently. However, attention span and

concentration were impaired. Speech and language were normal. Cranial nerve examination revealed: grossly normal visual fields to confrontation; normal symmetric, reactive pupils; normal extraocular movements without nystagmus; normal jaw closure strength and normal facial sensation. He was felt to have a mild degree of right lower face weakness. Auditory acuity was grossly normal. He had normal palatal elevation and shoulder shrug with right tongue deviation without atrophy or fasciculations. Motor examination revealed normal strength in the left upper extremity, a pronator drift in the right arm. In the lower extremities he had 4−/5 strength in the right iliopsoas, 4/5 on the left; 4/5 in the right hamstring, 4+/5 in the left hamstring; 5/5 in the quadriceps bilaterally. Foot dorsiflexors were 5/5 on the left and 4/5 on the right. Deep tendon reflexes were trace in the upper extremities, 2+ in the lower extremities. Plantars were equivocal bilaterally. There was mild finger-to-nose dysmetria and sensation was grossly intact to light touch.

Summary of investigations to date: An MRI/MRA done during a prior admission 2 months ago demonstrated dural thickening. An LP done at the same time demonstrated WBC 151 (tube 1), 187 (tube 4), RBC 0; with 42 % mononuclear cells and 58 % polysegmented leukocytes; glucose 41 and protein 220. Cytology, fungal culture, CSF tests for CMV, VDRL, VZV, HSV, AFB, Lyme, and bacterial cultures were normal. An EEG demonstrated continuous generalized slowing with superimposed intermittent left frontal slowing in the delta range. A CUS/TCD demonstrated no stenotic flow. An SPEP demonstrated 2 M spikes in the Gamma region estimated at 0.14 and 0.12 g/dL. A hematology/oncology consult revealed that the paraproteinemia could possibly be secondary to monoclonal gammopathy of unclear significance (MGUS) or smoldering myeloma. Multiple myeloma was felt to be less likely. A bone marrow biopsy and osseous survey were obtained during his previous admission and both were unremarkable. Figure 3.7 shows MRI images for Case Example 4.

The problem can be formulated in FTA terms as follows, shown in Fig. 3.8.

1. **Top event**: *Stating the top event in simplest form*: 74 y/o male with headaches and cognitive decline.
2. **Sub-event**: *Applying the "think small" rule, the "immediate, necessary, and sufficient" causes of the top event are*: Paraneoplastic Syndrome OR Diseases of CNS blood vessels (vasculitis) OR Meningitis/Encephalitis.
3. **Sub-event**:

   (a) Paraneoplastic syndrome: The MRI Brain features show prominent meningitis which is unusual for Paraneoplastic syndromes. While possible, these are therefore considered less likely and not developed further at this point. Therefore this is an undeveloped event.

   (b) Diseases of Blood Vessels "vasculitis": are most certainly plausible and would likely need exploration. However since meningitis is a prominent feature of this patient's illness and vasculitis may occur as a consequence of meningitis, this will be explored if investigations along the lines of meningitis are not successful.

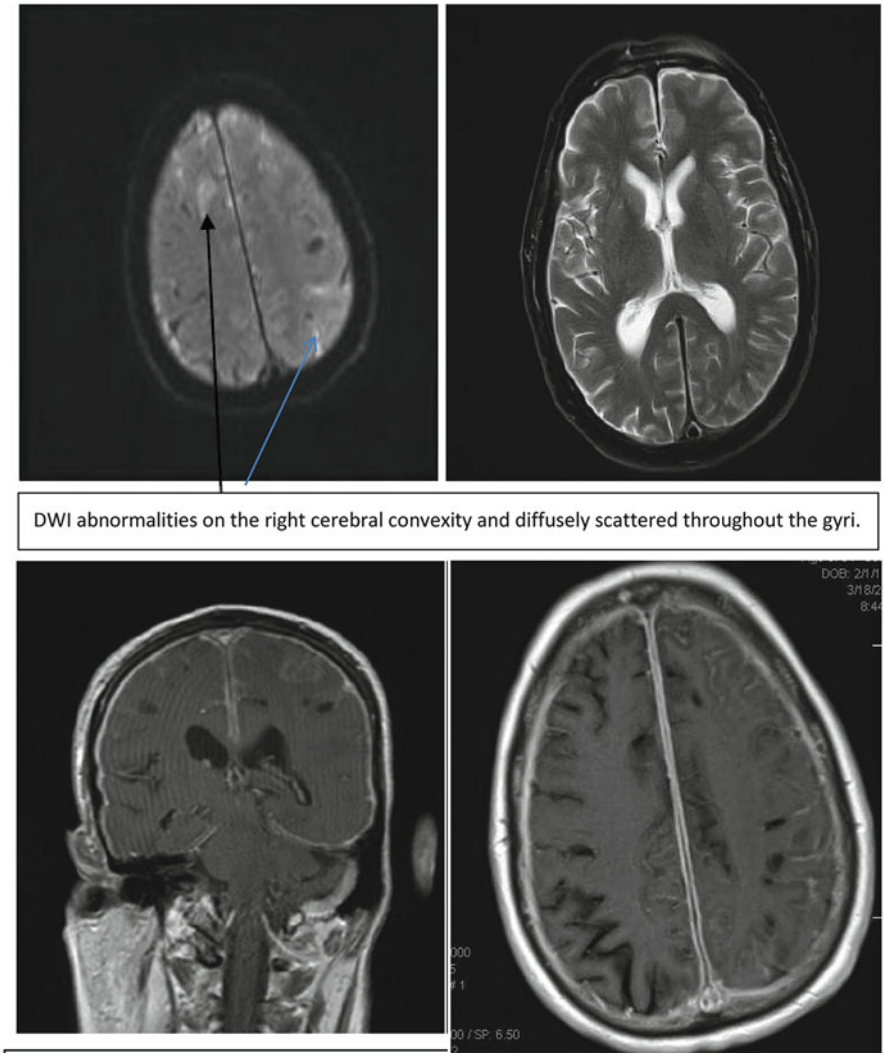

Fig. 3.7 MRI Brain images from Case Example 4. Top row (*left*): DWI images showing diffusion restriction scattered diffusely throughout the cerebral convexities. Top row (*right*): a surprisingly unremarkable axial T2 weighted image. Bottom row shows diffuse dural and leptomeningeal enhancement in a pattern consistent with pachy and leptomeningitis

(c) Meningitis/Encephalitis: This would be developed further given MRI Brain evidence of meningoencephalitis and LP findings of pleocytosis and high protein consistent with the same. Additionally, MRI Brain shows features of leptomeningitis and pachymeningitis with a limited differential [13].

4. **Sub-event**: Exploring leptomeningitis and pachymeningitis further, the radiological differential diagnosis can be classified further into chronic infections OR

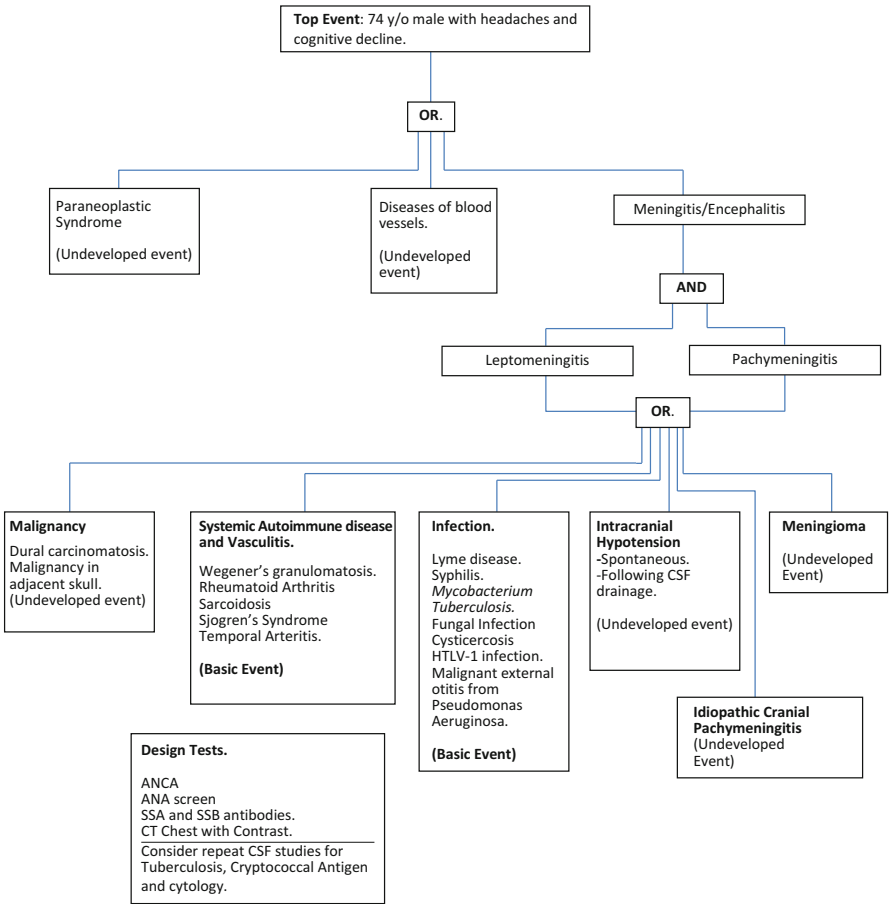

Fig. 3.8 FTA for Case Example 4. The candidate basic events can now be selected based on probabilitistic analysis for further investigation [13]

autoimmune OR systemic malignancy OR benign intracranial neoplasms like meningioma OR idiopathic cranial or spinal pachymeningitis OR intracranial hypotension. These constitute candidate basic events. We have reached the limit of resolution of the tree and can select our candidate hypotheses and rank them in order of probabilities.

Candidate basic events have been grouped into five major categories. We can now look at each major category and identify conditions within each category which are probable. From left to right:

Category 1: **Malignancy**: *P*(Dural Carcinomatosis with 8 month untreated survival) = extremely low. Similarly *P*(Malignancy in adjacent skull) is also extremely low since imaging of the skull has been normal.

Category 2: **Systemic Autoimmune Diseases and Vasculitis**: Exploring individual conditions in this category

(a) Wegener's granulomatosis (Granulomatosis with Polyangiitis—GPA): *P* (Wegener's Granulomatosis, KLH clinical, radiological, LP profile) = Reasonably high. Additional features supporting this diagnosis include the high ESR. It is possible patient would still be alive after 8 months untreated, although obvious clinical features of this disease elsewhere in the body are lacking. Since we are giving this serious consideration, this can be explored with checking Serum Antineutrophil cytoplasmic antibodies (c-ANCA). Additionally, a CT Chest with contrast can look for evidence of Wegener's granulomatosis in the lungs.

(b) Rheumatoid Arthritis: *P*(Rheumatoid Arthritis, KLH clinical, radiological, LP profile) = Reasonably High. The absence of joint involvement is unusual. The high ESR and long duration of illness make this plausible. This can be screened using rheumatoid factor initially and if suspicion persists checking anticyclic citrullinated peptide (Anti-CCP) antibodies.

(c) Sarcoidosis: *P*(Sarcoidosis, KLH clinical, radiological, LP profile) = Reasonably High. Isolated neurosarcoidosis is possible and presents as a chronic meningitis [13]. Silent pulmonary involvement can be screened using a CT Chest with Contrast.

(d) Sjogren's Syndrome: *P*(Sjogren's Syndrome, KLH clinical, radiological, LP profile) is reasonably high. This can be tested using anti-SSA and -SSB antibodies for initial screening [13].

(e) Temporal Arteritis: *P*(Temporal Arteritis, KLH clinical, radiological, LP profile) is lower than the rest given poor response to steroids in the past, continued preservation of vision untreated. A temporal artery biopsy can be considered if the rest of the workup is unrevealing.

Therefore, we have identified Wegener's Granulomatosis, Sarcoidosis, Sjogren's Syndrome as high probability events, Rheumatoid Arthritis as being intermediate in probability due to absence of obvious arthritis elsewhere and Temporal Arteritis as lower in probability. A CT Chest with Contrast, ANCA, Anti-SSA and -SSB antibodies and Rheumatoid Factor are reasonable immediate tests to screen for these conditions. Based on the results of these a brain biopsy can be considered.

Category 3: **Infections**. It would be very unusual for an untreated CNS infection to last 8 months with continued survival in the absence of antibiotics/antivirals/antifungals and in the presence of immunosuppression the patient was exposed to. Therefore *P*(Infection, KLH clinical, radiological, LP profile) is very low with the following exceptions.

(a) Fungal Meningitis: *P*(Fungal Meningitis, KLH clinical, radiological, LP profile) = Intermediate and cannot be excluded. Fungal meningitis can be longstanding [13]. This was initially screened for in the LP and fungal

cultures were negative based on records. However, a repeat tap maybe considered and CSF Cryptococcal antigen checked.

(b) CNS Tuberculosis: *P*(CNS Tuberculosis, KLH clinical, radiological, LP profile) = Low to intermediate but cannot be excluded. CNS Tuberculosis too can be longstanding . This too can be checked in CSF by PCR and Culture.

(c) Lyme Disease: *P*(Lyme Disease, KLH clinical, radiological, LP profile) = Reasonable probability. However initial tests for the condition have been negative. A repeat serology can be checked which if negative essentially excludes the disease given the duration of illness.

(d) Syphilis: *P*(Syphilis, KLH clinical, radiological, LP profile) = Reasonably High as Case Example 1 shows. This has been evaluated with prior CSF studies and found to be negative based on records. However, to verify a repeat RPR can be checked in blood.

Therefore, we have identified Syphilis, Lyme as being reasonably high in probability; fungal and tuberculous meningitis as being low to intermediate and other infections being unlikely and not explored further ("undeveloped event"). Based on this probabilistic analysis: RPR, Lyme serology can be done on blood and CSF studies for fungal meningitis (Cryptococcal antigen, cultures) can be done if initial tests are unrevealing and clinical suspicion remains high.

Category 4: **Intracranial Hypotension**: *P*(Intracranial Hypotension, KLH clinical, radiological and LP profile) is an event of low probability given the persistent cognitive decline, inflammatory CSF. Therefore tests for the same such as a CT Myelogram can be deferred ("undeveloped event").

Category 4: **Meningioma**: *P*(Meningioma, KLH clinical, radiological, and LP profile) too is an event of low probability given the persistent leptomeningitis and imaging findings which are unusual for a meningioma ("undeveloped event").

Category 4: **Idiopathic Cranial Pachymeningitis**: *P*(idiopathic cranial pachymeningitis, KLH clinical, radiological, and LP profile) is an event of intermediate to high probability given the persistent leptomeningitis and imaging findings. This is a diagnosis of exclusion.

Based on this probabilistic analysis, further investigations can be planned. The following results were obtained in short order:

(a) **CT Chest with contrast**: "The previously demonstrated *right upper lobe nodule has increased in size from 7 to 13 mm and is now cavitary*. Additionally, there are nodular opacities in the medial right base. These parenchymal findings may relate to recurrence of an inflammatory/infectious process similar to the findings demonstrated on the outside CT from July 2011. Given the cavitary appearance, differential considerations would include Wegener's granulomatosis, rheumatoid nodules, squamous cell carcinoma, tuberculosis and septic emboli."

(b) **c-ANCA**: *Positive. Antiproteinase 3 (PR3): Positive 1:86 (normal < 6). Rheumatoid Factor: 1:320 (positive, normal < 20).* Anti Myeloperoxidase antibody (MPO): Negative. *Serum IgG4 level 154 mg/dL (normal 4–86 mg/dL).*

A Brain dural biopsy was requested but declined. A pulmonary biopsy performed of the right upper lobe nodule identified on the CT Chest showed granulomatous inflammation without malignancy. Cultures were negative for tuberculosis.

Based on the positive c-ANCA, anti-PR3 antibodies and lung biopsy findings of granulomatous inflammation, KLH was diagnosed with Wegener's granulomatosis of the central nervous system. The new name for this disorder is Granulomatosis with Polyangiitis (GPA). It is considered a type of IgG4 disorder [14, 15]. He had a paucity of systemic involvement which is what made his presentation so unusual and difficult to diagnose. However, FTA followed by probabilistic analysis directed investigations which helped make the diagnosis in 3 days after 8 months of undiagnosed illness [14, 15]. This case example will be studied further as an example of Plan-Do-Study-Act (PDSA) cycle in Chap. 8.

Case Example 5

D.J. is a 47 y/o female with progressive leg symptoms for the past 3 months. Symptoms include pain in both thighs extending below the knees with transient accompanying pins and needles sensation. She also experienced a sensation of heaviness in both legs making it difficult to walk. The onset was relatively sudden over days with weakness progressing over weeks. Initially it was difficult to walk, progressively she has to use her arms to rise from a sitting position. She denied any symptoms in the hands. She was empirically placed on Prednisone 60 mg for 5 days which helped symptoms for a few days prior to regressing. She has experienced 30 lbs.-weight loss in the last 3 months associated with fatigue, dry mouth, and difficulty with sleep. She denied associated alopecia, bleeding/clotting problems, fevers, new headache, oral ulcers, pleurisy, rashes/photosensitivity, Raynaud's, seizures, bloody loose stool or eye inflammation. Patient also denied history of asthma, sudden loss of vision, wrist/foot drop, or recurrent genital ulcerations. Past medical history was significant for hypertension, hypokalemia for which she was on treatment. She was never placed on statins.

On focused examination, she weighed 276 lbs, blood pressure 148/88, and pulse 80/min. Neurological examination revealed normal mental status, cranial nerves, upper extremity strength, sensation, and reflexes. Lower extremity strength was 4−/5 in the right hip flexors, 3/5 in the left hip flexors; 4/5 in the bilateral leg flexors and extensors; 4+/5 in the bilateral tibialis anterior, and 5/5 in bilateral medial gastrocnemius. She had trace reflexes at the knee and absent ankle jerks. Despite reported numbness and pain, sensation was intact to pinprick at the bedside.

Table 3.1 Needle EMG findings for case example 5

Muscle name and side	EMG findings
Right Vastus Lateralis	Increased insertional activity, 1+ fibrillations, and positive sharp waves. Normal motor units with normal recruitment and activation
Right Tibialis Anterior	Increased insertional activity, 2+ fibrillations, and positive sharp waves. Normal motor units with slightly reduced recruitment, normal activation
Right Medial Gastrocnemius	Increased insertional activity, 1+ fibrillations, and positive sharp waves. Normal and slightly large motor units with normal recruitment and activation
Right iliopsoas	Increased insertional activity, rare fibrillations, and positive sharp waves. Normal and small motor units with mildly increased polyphasia with normal recruitment and activation
Right Gluteus Medius	Normal save mildly increased polyphasia
Right L5 paraspinal	Normal

Examination revealed diffusely increased spontaneous activity without motor unit changes

TEST RESULTS: to date showed normal CBC, CMP showed normal liver and kidney function save persistent hypokalemia. ESR 70 (0–30), CRP 23.8 (0–10), HBA1c: 5.7, TSH 1.380 (0.40–5.50); ANA SSA, SSB antibodies were normal. CK 30 (normal). Serum and Urine immunofixation normal. LDH 166 (90–271). Rheumatoid Factor 10.

She underwent a nerve conduction/EMG study as part of initial evaluation. Nerve conductions showed normal sural sensory responses, diffusely low-amplitude peroneal motor responses; normal distal tibial amplitudes and latencies, a 70 % fall with behind knee stimulation which was felt to be due to technical difficulty with maximal stimulation from obese body habitus. She had a normal repetitive nerve stimulation study of the right ulnar nerve. Needle EMG was diffusely abnormal with findings outlined in Table 3.1.

The formal EMG conclusion was: "This is an abnormal study. There is electrophysiologic evidence of diffuse spontaneous activity in multiple muscles without accompanying motor unit changes. These findings are consistent with inflammatory myopathies (polymyositis, dermatomyositis, overlap myositis, inclusion body myositis) or neurogenic etiologies. Based on the normal nerve conduction studies, we favor evaluation for the former. If a biopsy is considered in the future, the best muscle for biopsy would be the left medial gastrocnemius.

A firm diagnosis was far from evident. A few days later, patient came to the ER with worsening weakness and numbness. She felt numb to the umbilicus, weakness had worsened to the point she was unable to rise from a toilet seat. She denied any urinary or bowel incontinence. Based on these findings and worsening numbness, she underwent an MRI Cervical, Thoracic, and Lumbar Spine with and without Gad. Images are shown in Fig. 3.9.

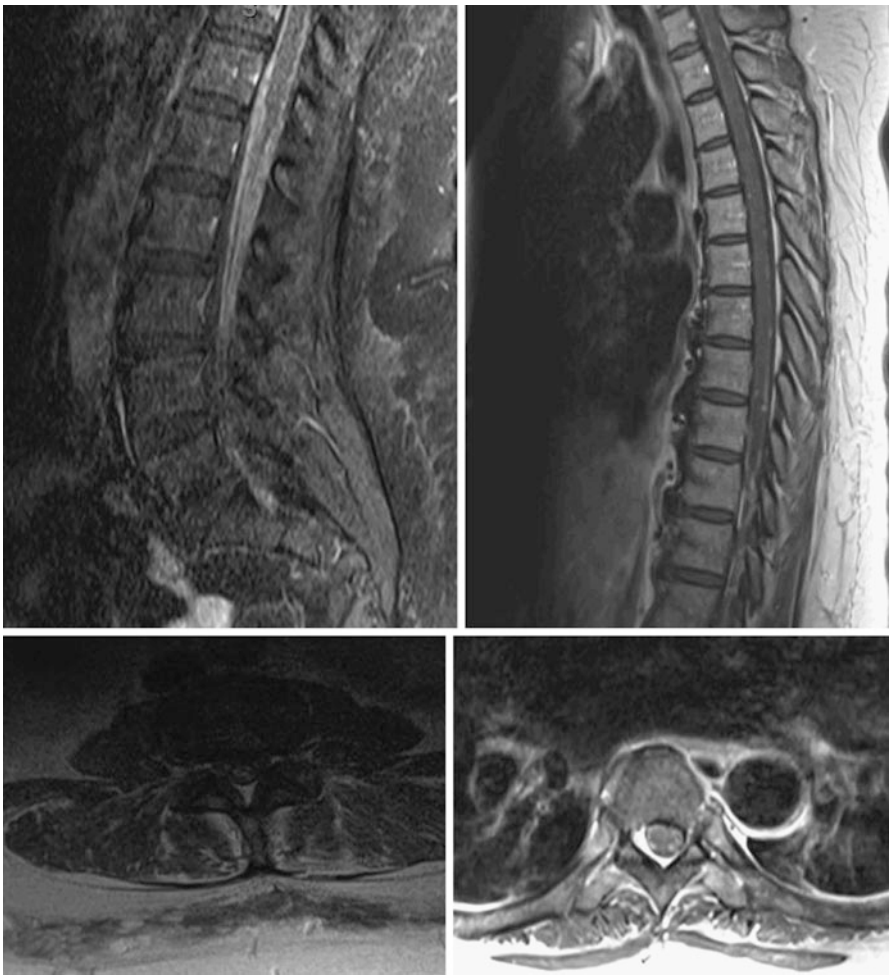

Fig. 3.9 MRI Lumbar and Thoracic Spine for Case Example 5. There is diffuse nodular enhancement of the spinal cord concerning for inflammatory polyradiculoneuropathy (CIDP), systemic malignancy, granulomatous disease, lymphoma, CNS neoplasms with drop metastasis

An FTA can guide further evaluation and narrow between these possibilities. Following the steps used in the prior cases:

1. **Top event** can be stated in simple terms as "Rapid weakness and numbness below the waist."
2. **Sub-events**: *The immediate, necessary, and sufficient* causes of the top event are Diseases of Brain OR Diseases of Spinal Cord AND Nerve root (myeloradiculopathy) AND Diseases of Muscle. Concurrent diseases of neuromuscular junction are also a possibility.

3. **Sub-events**:

   (a) Diseases of brain are considered less likely, but patient reported sudden onset diplopia during hospitalization for which reason this was pursued. The study was essentially normal, therefore diseases of the brain were not pursued further ("undeveloped event").
   (b) Diseases of the spinal cord AND nerve root are demonstrated on MRI therefore will be developed further. MRI imaging shows the disease process involves the surface of the spine in a nodular manner without causing signal changes or enhancement within the cord. Therefore, the disease process involves the leptomeninges diffusely which narrows the differential diagnosis considerably.
   (c) Diseases of neuromuscular junction are essentially excluded given the imaging findings ("undeveloped event").
   (d) Diseases of muscle remain a consideration in the differential diagnosis given the diffuse irritability of the muscles. As noted in the EMG conclusion, it is possible the diffuse irritability of the muscles maybe due to involvement of motor nerves as they traverse the subarachnoid space. It is interesting to speculate whether such pathologies would be expected to involve the dorsal root ganglion cells (thereby causing abnormal sensory responses) since the cause of such a polyradiculoneuropathy is inflammation and infiltration and not compression (which spares sensory responses).

4. **Sub-events**:

   (a) Diseases of spinal cord which predominantly involve the surface and not the intrinsic cord itself are inflammatory conditions such as sarcoidosis; neoplastic conditions such as lymphomas, carcinomatous meningitis, hematologic malignancies, and CNS gliomas with drop metastasis; infections such as Lyme disease, HIV, HTLV 1, syphilis, and Hepatitis. We can also consider metabolic conditions like Vitamin B12, Vitamin E, and copper deficiencies though the imaging findings are less likely. We have now reached the limit of resolution and these possibilities will be considered the basic event.
   (b) Diseases of Nerve roots include inflammatory conditions such as Guillain Barre Syndrome and CIDP. Given the long duration of the illness, GBS is excluded. CIDP is unlikely because it is not expected to produce nodular enhancement on the surface of the cord. A myeloradiculopathy pattern can be seen with inflammatory conditions like sarcoidosis, infectious, and neoplastic conditions listed above. We have now reached the limit of our resolution and these possibilities will be considered "basic events."
   (c) Diseases of muscle with concurrent disease involving spinal cord AND nerve root include sarcoidosis (causing sarcoid myopathy AND myeloradiculopathy); collagen vascular diseases such as SLE, Rheumatoid Arthritis, Sjogren's syndrome; systemic vasculitides such as Wegener's granulomatosis, polyarteritis nodosa (PAN), and Churg Strauss Syndrome.

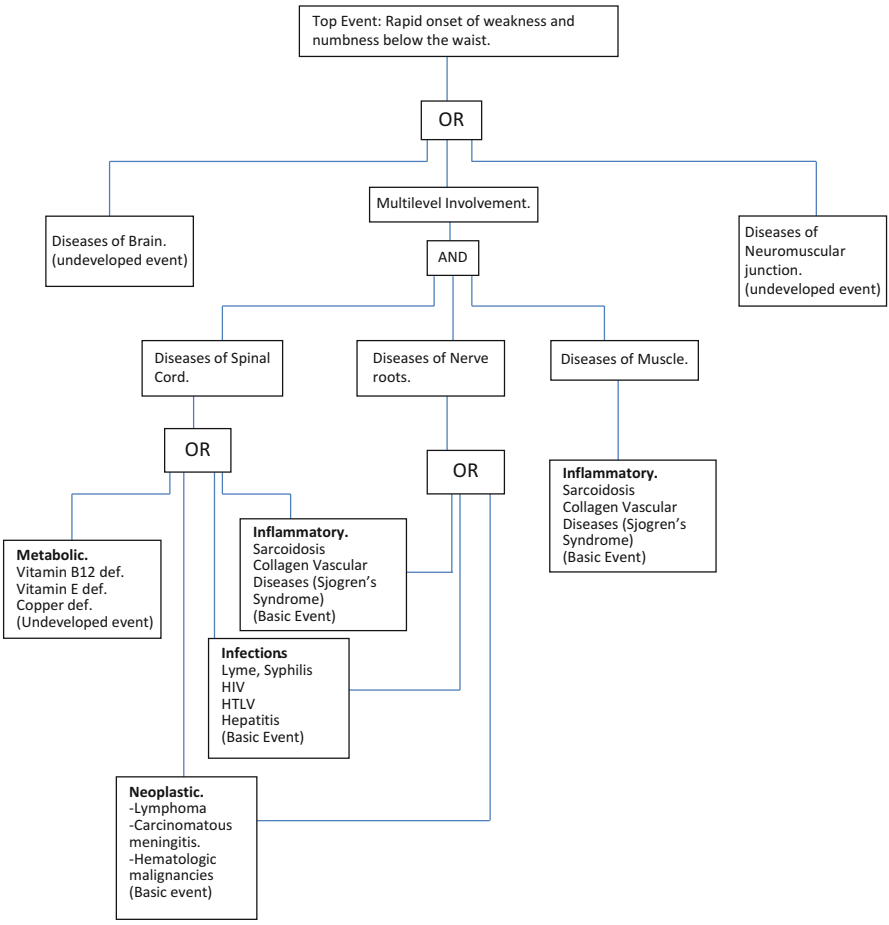

Fig. 3.10 FTA for Case Example 5. Basic events common to spinal cord AND nerve root AND muscle disease can be pursued to arrive at the final diagnosis

We speculate there is direct muscle involvement in this instance without adequate proof. These possibilities will constitute the basic event.

The corresponding FTA for Case Example 5 is shown in Fig. 3.10. Further tests can be designed based on probabilistic analysis of the conditions identified by FTA. Ranking the possibilities in the descending order of probability [16]:

1. **Sarcoidosis**: Probability (Sarcoidosis, DJ clinical, radiological, and lab profile) ranks among the very top given all the features of this case. Sarcoidosis is an etiology common to spinal cord AND nerve root AND muscle disease which are features of this case. This can be investigated by a CT Chest looking for pulmonary involvement. An LP looking at the composition of the spinal fluid will also be invaluable.

2. **Neoplastic etiologies**
   (a) Lymphoma ranks extremely high on the neoplastic differential. *P*(Lymphoma, D.J.'s clinical, radiological, and lab presentation) is high. This would rank amongst the very top with sarcoidosis. A few features make this less likely—muscle involvement is not commonly seen in lymphoma. Further, spinal cord involvement is usually seen after there is diffuse involvement of paravertebral lymph nodes with metastatic spread. This was not observed on the MRI LS Spine. A CT Chest Abdomen and Pelvis can evaluate this possibility without the need for PET scanning. CSF cytology and flow cytometry looking for clonal expansion of mononuclear cells if found will be helpful.
   (b) Hematologic abnormalities, multiple myeloma would also involve the spinal cord AND nerve root only with extensive spread. Therefore normal CBC excludes leukemias and makes multiple myeloma less likely. A normal Serum and Urine immunofixation excludes myeloma.
   (c) Carcinomatous meningitis is in the differential. Occult primaries originating in the gastrointestinal tract can cause such a pattern of involvement without causing other abnormalities. Therefore, if initial evaluation for sarcoidosis and lymphoma is unrewarding, a follow-up colonoscopy, endoscopy can be considered.
3. **Infectious etiologies**
   (a) Lyme disease: *P*(Lyme disease, D.J.'s clinical, radiological, and lab presentation) is high among the infectious etiologies. This can be tested using Lyme serology and CSF Lyme studies.
   (b) HIV, HTLV-1, Hepatitis, and Syphilis are common infections with some features of such a presentation. For example HIV can cause myelopathy, polyradiculoneuropathy, and myopathy. Though unlikely, given the high incidence of these conditions these can be tested in blood. Therefore HIV, HTLV-1, and RPR can be tested in blood.
4. **Metabolic etiologies**
   (a) Vitamin B12, E, and copper deficiency are extremely unlikely but can be easily tested in blood.

Therefore, at the end of FTA, the top two hypotheses are Sarcoidosis closely followed by Lymphoma. A spinal tap and CT Chest Abdomen and Pelvis were done to evaluate between these possibilities. The following results were obtained:

1. Spinal Fluid: CSF WBC: 696, RBC 313; Protein 628 mg/dL, Glucose 24 mg/dL. Angiotensin converting enzyme (ACE) level: 7. Fungal, Tuberculosis, Viral tests normal. 5 CSF Oligoclonal Bands were seen. CSF Cytology and Flow cytometry took several days to complete but showed a polyclonal population of cells.
2. CT Chest Abdomen and Pelvis: CONCLUSION

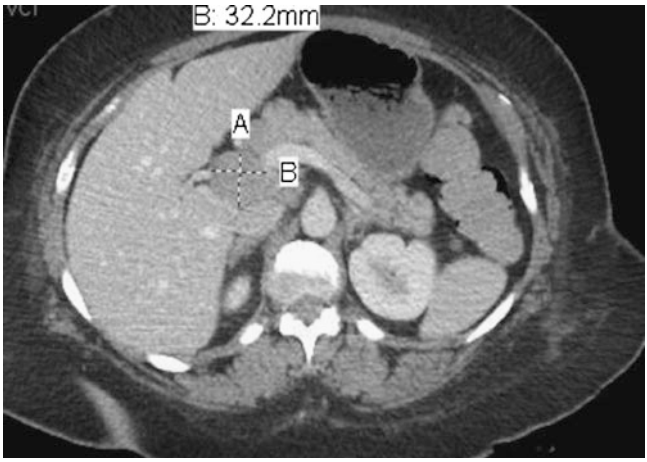

Fig. 3.11 CT Abdomen showing enlarged portal lymph node which was selected for endoscopic ultrasound guided fine needle biopsy

2.1. Several enlarged portocaval lymph nodes are suspicious for primary lymphoma. Metastasis from an unknown primary is also possible but less likely. Biopsy via endoscopic ultrasound (EUS) may be helpful (see Fig. 3.11).
2.2. Indeterminate 2.5 × 1.3 cm left adrenal nodule can be observed on follow up
2.3. No acute cardiopulmonary abnormality. No pulmonary findings to suggest sarcoidosis
2.4. Hepatomegaly

Despite this report where no pulmonary involvement was seen and large portocaval lymph nodes were seen which the radiologist reported as concerning for primary lymphoma, the polyclonal cell population in the CSF made $P(\text{Sarcoidosis}) > P(\text{Lymphoma})$. An endoscopic ultrasound-guided fine-needle biopsy was performed of the largest involved lymph node. The results showed "scattered non-necrotic granulomas and a limited number of lymphoid cells. Benign columnar epithelium and mucus. No malignancy identified."

A systematic FTA and probabilistic analysis helped arrive at the diagnosis of sarcoidosis. The patient was treated with IV Methylprednisolone 1,000 mg/day for 5 days followed by oral prednisone 60 mg for 3 weeks and subsequent gradual taper. By the end of 1 week, she regained her ability to walk unassisted and returned to work. Her numbness also improved considerably. She continues to make excellent progress with low-dose prednisone and azathioprine started as adjunct steroid sparing therapy.

Conclusions

This chapter shows the clinical utility of FTA in solving complicated neurological problems where the diagnosis had been difficult to establish. FTA helped narrow the field of possibilities, incorporate available knowledge to date, rank diagnostic possibilities in order of probabilities to guide further testing. The investigator is able to rank his suspicions in a Bayesian framework and establish lines of investigation that are worth pursuing. The method also facilitates communication and hand offs, for example as the care is being transferred from one clinician to the other it helps understand the assumptions that were made, lines of inquiry which were not pursued. This method will be discussed further in future chapters and incorporated into other forms of decision making, especially in cases where tests yield uncertain and unreliable results.

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Chapter 4
Failure Modes and Effects Analysis

Abstract This chapter extends the principles of failure modes and effects analysis (FMEA) introduced in Chap. 2 with medical case examples. This chapter explores inductive reasoning or "forwards thinking" in the context of neurological diagnosis and treatment. FMEA facilitates understanding of symptoms from disease along physiological lines and helps predict effects on diverse organ systems. This facilitates treatment planning and implementing mitigation strategies in cases where the underlying disease itself is not directly treatable. It provides a framework to understand symptoms from a systems failure perspective, thereby optimizing the treatment response and preventing over- and undertreatment. FMEA also helps understand and implement strategies to anticipate, monitor, and mitigate side effects of many treatment regimens.

Introduction

Chapter 2 introduced failure modes and effects analysis (FMEA) from a systems safety assessment (SSA) perspective. It presented an application of FMEA in performing SSA for treatment of chronic inflammatory demyelinating polyneuropathy (CIDP) with pulse steroids. FMEA helped identify diverse failure modes, failure severity, high-risk patient populations, and mitigation strategies in planning this intervention. This chapter extends the discussion on FMEA with more case examples spanning a more diverse spectrum of diseases. FMEA helps guide choice of therapy when there is a broad armamentarium of therapeutic strategies with a wide range of costs and side effects to choose from. In conditions where there is no direct treatment for the underlying disease, FMEA helps direct palliative and mitigation strategies which help quality of life and care. References [1–3] present the theoretical principles behind the method. As discussed in Chap. 2, failure classification to determine the consequences of failure is an integral part of FMEA. Chapter 1 presented safety assessment and failure classification for a range of critical industries ranging from aerospace, railways, nuclear, automobile, and industrial automation [4–7]. For the purposes of this chapter, we adopt a similar failure classification methodology with minor changes to adapt them to clinical medicine and neurology [1–7]. The following framework shown in Table 4.1 is used in this chapter, adapted from Chaps. 1 and 2.

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Table 4.1 Failure classification adapted for medical applications from US FAA's AC 25.1309

Failure classification	Effect on patient	Comments
Catastrophic	High probability of loss of life despite all corrective medical interventions	1. Faults, errors triggering catastrophic consequences must be extremely rare 2. Extremely rare is defined to be probability of occurrence in the 10^{-4} to 10^{-6} (probability of occurrence in the thousands or millions) 3. From Chaps. 1 and 2, catastrophic events must not happen from single point failure or simple combination of failures in dependable systems 4. Systems resulting in catastrophic consequences (humans, procedures, medications) must confirm to the highest skill, operational guidelines, and quality levels, equivalent to DAL A in the computer and engineering literature
Hazardous	Moderate risk for loss of life; permanent damage to vital organ systems like liver, kidney, heart especially if not urgently corrected and mitigation strategies effectively deployed	1. Faults and errors triggering hazardous consequences must be extremely rare, similar to catastrophic category 2. Rest as above
Major	Low potential for loss of life; reversible but moderate to severe damage to vital organ systems like heart, liver, kidney. This also includes conditions with lasting impact such as development of hypertension, diabetes mellitus, coronary artery disease, etc.	1. Faults and errors triggering major consequences must be rare 10^{-2} to 10^{-3} (probabilities in the 100s to 1,000s) 2. Rest as above
Minor	No potential for loss of life; reversible, mild, abnormalities in vital organ systems like heart, liver, kidney. This also includes conditions with lasting impact such as development of mild edema, impaired glucose tolerance, osteopenia, and mild osteoporosis	1. Faults and errors triggering minor consequences can be more frequent than major category: 10^{-1} to 10^{-2} (probability of occurrence in the 10s to 100s) 2. Corresponding DAL can be lower 3. Single point failure is permissible
No safety effect	No potential for loss of life, no effect on major organ systems. Effects limited to pain, discomfort lasting a few days to week. Symptoms easily mitigated with rest, fluids, analgesics, and antidotes	1. Faults and errors triggering such events may be frequent 2. Single point failure is permissible 3. Lowest possible DAL

Failure classification intimately links to allowable probabilities of occurrence in terms of triggering faults and errors and corresponding development assurance levels (DAL—see Chap. 1)

FMEA in Therapy Planning

This section explores using FMEA for treatment planning in situations with a wide range of side effects ranging from no safety effect to catastrophic. This is especially advantageous for the treatment of chronic conditions with medicines having side effects which are dependent on dosing and duration. Casting the treatment in an FMEA framework has the advantage of classifying them by significance and directing mitigation strategies accordingly. Consider the example of two commonly used therapies in neuromuscular medicine—prednisone and intravenous immunoglobulin (IVIG).

FMEA for Prednisone Therapy

Prednisone is one of the most frequently used medicines in immunosuppression for the treatment of a wide range of inflammatory and autoimmune conditions across a variety of specialties. Prednisone is cheap, available in oral formulation, with well-recognized and predictable side effects. These include effects on numerous organ systems: cardiovascular, endocrine/metabolic, musculoskeletal, ocular, gastrointestinal systems among others. Additionally, immune suppression from prednisone increases the susceptibility to many infections. Generally, operating practice has been to use prednisone for cases where the benefit exceeds the risk, the side effects themselves being considered to some extent inevitable. Adopting the FMEA methodology, it is possible to mitigate side effects of prednisone to a great extent and deploy it effectively against a barrage of diseases, even in diabetic patients. FMEA report on prednisone can be created from a review of the literature [8] and is shown in Table 4.2. While the following is adapted from the myasthenia gravis literature, the methodology has potentially widespread application [8].

The FMEA analysis demonstrated in Table 4.2 shows that prednisone therapy is best implemented in partnership between the patient and the physician. Failure modes can be viewed from patient and physician perspectives and responsibility devolved for mitigation strategies and timely intervention. It helps identify populations at higher risks and vulnerabilities such as patients with frequent shingles outbreaks, diabetes mellitus, hypertension, osteopenia, and helps institute specific preventive strategies. The prednisone information sheet has been successfully used in many of the case examples presented here.

FMEA for Intravenous Immunoglobulin Therapy

IVIG is used for a variety of autoimmune conditions in neurology, common examples being myasthenia gravis, Guillain-Barré Syndrome, CIDP among many others.

Table 4.2 FMEA approach to prednisone therapy

Failure mode	Failure classification/failure frequency	Patient responsibility	Physician responsibility	Comments
Abnormal blood glucose	Major (wide fluctuations possible, ranging from mild elevation to life threatening coma ~1,000 mg/dL) Frequency: extremely common	1. Maintain blood glucose log 2. Reduce calorie intake. Follow suggested nutrition recommendations	1. Check basic metabolic profile, HBA1c, random glucose 2. Encourage purchase of glucometer 3. If patient does not have glucometer, provide prescriptions for checking blood glucose once a week to every 2 weeks	1. If already diabetic, closely monitor sugar profile 2. May require additional insulin in the form of sliding scale, long-acting insulin. Work closely with endocrinologist
High blood pressures	Minor (higher average pressures, rarely in hypertensive urgency range) Frequency: extremely common	1. Monitor blood pressures once a day if hypertensive, once a week if normotensive 2. Reduce salt intake	1. Adjust antihypertensive dosing if patient is already hypertensive	1. Consider adding a diuretic for improving blood pressure control 2. Apply defense in depth (see Chap. 9)
Bone loss	Minor to major Frequency: extremely common	1. Calcium and vitamin D intake 2. Bisphosphonates as indicated by age and sex, baseline bone health	1. Consider baseline DEXA scan in high-risk populations 2. Annual DEXA scan 3. Check vitamin D level	Educate patients about bone health, benefits of exercise
Weight gain	Major Frequency: extremely common	1. Monitor calories. Low calorie, low fat, high-protein diet 2. Follow nutrition recommendations (see Appendix of Chap. 9) 3. Maintain weight chart	1. Closely monitor weight during each visit 2. Monitor and encourage compliance with nutrition	Request formal nutrition consult if there is excessive weight gain between visits

Cataracts/glaucoma	Minor to major Frequency: common	1. Regular eye exams, especially if diabetic	1. Monitor closely	
Aseptic necrosis of hip	Major Frequency: rare	Inform physician of any new hip pain	Obtain X ray hip if there is new development of hip pain	May require hip replacement
Vertebral compression fractures	Minor to major depending on severity Frequency: generally uncommon except in prior osteoporosis	Inform physician of any new persistent back pain	Obtain X-ray Thoracic and Lumbar spine for any new back pain, observed loss of height	High-risk populations include women with prior osteopenia/osteoporosis
Fluid retention/leg swelling	Minor Frequency: common	Monitor weight Reduce salt intake	Consider low-dose diuretic	
Abdominal pain/heartburn, nausea	Minor to major Frequency: very common	1. Over the counter omeprazole for steroid ulcer prophylaxis 2. Inform physician if there is new or severe heartburn	Reduce dose Monitor and treat for gastritis, steroid ulcer	Watch for bleeding in stools and vomitus
Easy bruising, thin skin	Minor Frequency: very common	None	None	
Insomnia, mild anxiety, feeling wired	Minor Frequency: common	1. Reduce caffeine intake 2. Maintain sleep hygiene	Low-dose clonazepam, lorazepam while on high-dose steroid therapy	Reassurance, provide adequate counseling
Psychosis, steroid mania	Major Frequency: uncommon to rare	1. Stop prednisone 2. Inform physician 3. Seek assistance in ER immediately	1. Screen risk factors: prior bipolar disorder	Seek immediate psychiatry consult to prevent harm
Infection	Major Frequency: common	1. Watch for shingles, genital herpes and oral thrush break out. Inform physician immediately	1. Monitor closely 2. Evaluate skin rashes immediately 3. Institute acyclovir or Valacyclovir prophylaxis	Consider Trimethoprim/Sulfamethoxazole (Bactrim) prophylaxis for pneumocystis pneumonia

(continued)

Table 4.2 (continued)

Failure mode	Failure classification/failure frequency	Patient responsibility	Physician responsibility	Comments
		2. Get killed flu vaccine 3. Avoid live vaccines	in patients with frequent shingles or genital herpes outbreaks 4. Nystatin swish and swallow as first line for oral fungal infections. Consider adding oral fluconazole early if needed	
Addison's crisis	Major Frequency: uncommon to rare	Inform physician of tiredness, weakness, or recent steroid therapy even if prednisone has been discontinued	Monitor closely. Blood cortisol levels. Monitor hypothalamic pituitary adrenal axis. Consider stress dose steroids, fluids for persistent hypotension	Consider Addisonian crisis in all patients with steroid therapy and hypotension
Miscellaneous Rare CNS infections like fungal meningitis, progressive multifocal leukoencephalopathy (PML), pseudotumor cerebri	Major Frequency: uncommon to rare	Inform physician about headache, somnolence, and change in mental status	MRI Brain Low threshold for spinal tap after MRI Brain for CNS infection	Educate patient and family about mental status changes

Failure modes, potential preventative and mitigating strategies are identified and instituted to prevent cascading failure. The prednisone FMEA should be used in conjunction with immunosuppression checklist discussed in Chap. 7. Prepared with assistance from David Mayans, MD. Adapted from [8]

Similar to steroid therapy, IVIG has a plethora of side effects ranging from minor to potentially life threatening. During the course of treating CIDP with IVIG and steroids, one fatality was seen. Based on the available EMS reports, it is possible that patient developed a deep venous thrombosis (DVT) and pulmonary embolism given reported symptoms of shortness of breath and cardiac arrest with pulseless electrical activity. An FMEA approach helps classify failure modes associated with IVIG and direct prevention and mitigation strategies accordingly [9]. This is shown in Table 4.3.

Table 4.3 FMEA for IVIG therapy, adapted from [9]

Failure mode	Failure classification/ frequency	Risk factors	Mitigation strategy
Infusion-related symptoms (chills, nausea, myalgia, headache)	Minor Frequency: frequent	None	1. Plenty of fluids 2. Premedicate with IV Benadryl, oral acetaminophen 3. IV Methylprednisolone 50 mg if severe or IV Hydrocortisone 50–100 mg 4. Subcutaneous epinephrine if shock
Anaphylaxis	Major Frequency: infrequent	1. Common variable immunodeficiency 2. IgA deficiency	1. Although not mandated, consider checking IgA levels 2. IgA poor formulations
Thromboembolism (myocardial infarction, stroke, central retinal vein occlusion, deep venous thrombosis, pulmonary embolism)	Hazardous/ catastrophic Frequency: 3 %	1. Elderly 2. Preexisting vascular disease 3. Immobility	1. Identify high-risk patients following IVIG checklist (see Chap. 7) 2. Monitor closely including EKG monitoring. Follow IVIG checklist for possible thrombotic complication
Reversible vasospasm	Minor to major Frequency: infrequent	None	MRI/MRA/MRV Brain Hydration
Headache, aseptic meningitis	Minor Frequency: frequent, up to nearly 60 %	None	NSAIDs IV Fluids

(continued)

Table 4.3 (continued)

Failure mode	Failure classification/ frequency	Risk factors	Mitigation strategy
Abnormal renal function	Major Frequency: infrequent	1. Preexisting renal disease 2. Diabetes mellitus 3. Sepsis 4. Concomitant nephrotoxic drugs 5. Age > 65 years 6. Hypovolemia	1. Fractionate doses. Slow infusion rates 2. Maintain hydration 3. Sucrose-free formulations
Decompensated congestive heart failure	Hazardous/ catastrophic Frequency: infrequent	1. Preexisting CHF 2. Unstable angina	1. Identify high-risk patients 2. Monitor closely in high-risk patients
Rash (urticarial, eczema, erythema multiforme, purpura, maculopapular rash)	Minor to major Frequency: ~6 %	None	1. IV Benadryl 2. Steroids
Hematologic	Major Frequency: rare	None	1. Monitor for hemolysis 2. Monitor for transfusion reactions 3. Monitor blood counts

The FMEA summary should be used in conjunction with IVIG checklist discussed in Chap. 7

Case Example 1: Treatment of Inflammatory Neuropathy Using FMEA Principles

PM is a 61 y/o diabetic female seen one and a half years after developing sudden onset of severe bilateral upper extremity weakness, numbness, and pain. Onset was abrupt, noticed on waking in the morning with a popping sensation in the neck followed by severe neck pain. She went to local urgent care and underwent X-rays of the neck. While waiting in urgent care, she experienced severe weakness, electric shock-like paresthesias initially in the right arm followed a few hours later by the left. During the course of hours, she developed severe bilateral upper extremity weakness. She denied any lower extremity symptoms. Prior to this illness, despite being diabetic she denied any numbness or tingling in her feet or hands. She reports ongoing electric shock-like painful paresthesias in her thumb and index fingers bilaterally with severe bilateral wrist drop and right greater than left shoulder weakness. MRI Cervical spine showed moderate degenerative changes in the neck without significant stenosis to explain the hand weakness and numbness.

Past medical history includes diabetes mellitus, stable coronary artery disease, s/p coronary artery bypass grafting (CABG) a few years ago, hypertension and hypothyroidism. She had undergone bariatric surgery also several years ago with weight loss. Medications included famotidine, insulin, hydrochlorothiazide, levothyroxine, a multivitamin, and potassium chloride. At the time, she was a current every day smoker.

Focused neurological examination revealed normal neck flexion and extension strength, deltoid strength. The right triceps had less than antigravity strength being 2/5, the left triceps showed mild weakness with MRC 4+/5 strength. Further distally she had absent movement with MRC 0/5 in the wrist extensors bilaterally. The wrists and fingers were maintained in flexion with little functional usage possible for the hands. Additionally, there was ulnar deviation of the wrist. The flexor pollicis longus showed 3/5 strength on the right, left was 4+/5; the Abductor Pollicis Brevis (APB) had only trace strength bilaterally with First Dorsal Interosseous showing 2/5 strength. These were tested with the hand passively placed in neutral position by extension of the wrist and fingers. The lower extremities showed normal symmetric strength in both legs. Deep tendon reflexes were normal in the biceps, absent elsewhere. The sensory examination was normal in the lower extremities and patchily decreased diffusely in the bilateral upper extremities.

Nerve Conduction/EMG study data is shown in Table 4.4.

Laboratory findings: Cerebrospinal fluid studies (CSF): 1 WBC/hpf, 4 RBC/hpf. CSF Glucose 140 mg/dL. CSF protein 71 (normal < 45 mg/dL). CSF Lyme, VDRL, ACE negative. Complete Blood Count (CBC): WBC 11.8 μL^{-1}, Hb: 11.6 g/dL, Platelets: 274. TSH: 0.143 (normal 0.40–5.50). HBA1c: 8.8 %. Anti SSA, SSB antibodies, ANA screen, ANCA negative. ESR: 46 mm. Serum and Urine Immunofixation: Normal without M spike. Blood copper: 106.

The constellation of findings was considered most consistent with an inflammatory neuropathy, likely autoimmune given the fulminant onset. The three inflammatory neuropathies in the differential diagnosis included forms of CIDP such as multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), idiopathic brachial plexitis (Parsonage Turner Syndrome), and diabetic cervical radiculoplexus neuropathy. Given the one and half years since onset, continued presence of pain and weakness without any improvement, the concern is for ongoing nerve damage preventing reinnervation and repair. The functional impairment on the patient was severe; she was unable to care for herself with the severe bilateral hand weakness, unable to even brush her hair due to shoulder weakness. The constant pain and numbness added to the debility from this disease. The anatomical involvement is patchy and diffuse with severe involvement of radial nerves bilaterally with right greater than left involvement.

The following systematic solution approach using system safety assessment and FMEA was attempted.

Functional Hazard Assessment

1.1. Loss of bilateral proximal motor function—muscles about shoulder joint.
1.2. Loss of distal motor function involving hands—fingers and wrist.
1.3. Loss of normal sensation leading to numbness.
1.4. Loss of normal pain perception with constant pain.

Table 4.4 NCS/EMG report for Case Example 1

Nerve, stimulation site and side	Latency (normal limit)	Distance	Amplitude (normal)	Velocity (normal)	F waves
Median motor (right)					
Wrist	5.1 (<4.4 ms)	70 mm	2.2 (>4.0 mV)		36.2 ms (<31 ms)
Elbow	10.4		1.3	41 m/s (>49 m/s)	
Ulnar motor (right)					
Wrist	4.2 (<3.5)	70 mm	4.4 (>6 mV)		33.0 ms (<32 ms)
Below elbow	8.6		3.8	44 (>49 m/s)	
Above elbow	11.0		3.1	44 m/s	
Ulnar motor (left)					
Wrist	3.6 (<3.5)	70 mm	3.1 (>6 mV)		35.2 ms (<32 ms)
Below elbow	7.8		2.9	44 (>49 m/s): forearm segment	
Above elbow	10.3		2.7	42 m/s	
Tibial motor (left)					
Ankle	6.6 (<6.0 ms)	80 mm	1.5 (>3.0 mV)	32 m/s	70.3 ms (<58 ms)
Pop fossa	18.6		1.2		
Median sensory (right)	4.2 (<3.5 ms)	150 mm	3 (>22 μV)		
Ulnar sensory (right)	Absent	140 mm			
Radial sensory (right)	Absent	100 mm			
Sural sensory (left)	4.5 (<4.2 ms)	140 mm	5 μV (>6 μV)		
EMG findings					
Muscle (side)	*Description of findings*				
Deltoid, C6, C7 paraspinals (right)	Normal				
Triceps (right)	1+ fibrillations, positive sharp waves; few normal motor units interspersed with enlarged polyphasic motor units with reduced recruitment				
Biceps (right)	Absent spontaneous activity. Mildly enlarged but otherwise normal motor units with reduced recruitment				
Extensor digitorum communis (right)	Profuse, 3 to 4+ spontaneous activity. Absent motor units				
First dorsal interosseous	Absent spontaneous activity. Mildly enlarged motor units, essentially normal recruitment				
Tibialis anterior, medial gastrocnemius, vastus lateralis (right)	Normal				

Standard distances and normative data are within brackets for each nerve. The upper extremity nerves show mild demyelinating features with the lower extremities being more normal than the upper. This study was interpreted as a severe sensorimotor polyneuropathy with demyelinating features. Conditions in the differential include forms of chronic inflammatory demyelinating polyneuropathy (CIDP), idiopathic brachial plexitis (Parsonage Turner Syndrome) and diabetic cervical radiculoplexus neuropathy

The following assumptions are being made to guide treatment.

(a) The nerves are involved at multiple different sites along their course in a patchy distributed manner. The most proximal site of involvement is almost at the brachial plexus itself since the right triceps shows severe involvement. This cannot be confirmed since the nerves cannot be biopsied.
(b) Recovery is likely to be slow and prolonged. It is assumed we can arrest ongoing nerve inflammation. With inflammation and ongoing damage arrested with treatment, the nerves will get a chance to grow back in a length-dependent manner. The nerve regrowth process itself cannot be accelerated.

The following FMEA report can be constructed as shown in Table 4.5.

Based on the above Functional Hazard Assessment (FHA), SSA, the patient was treated as an inpatient with IVIG 2 g/kg in five divided doses. IV Methylprednisolone was added as adjunct therapy and initially administered as 1,000 mg every day for 5 days. Patient did not report any chest pain, EKG, or shortness of breath. Renal function was stable. Blood glucose levels rose markedly for between 48 and 72 h (between 400 and 500 mg/dL) after each methylprednisolone infusion which was treated with sliding scale insulin and maintaining hydration. No clinical complications of hyperglycemia were experienced.

The patient was provided with the prednisone, IV Methylprednisolone FMEA sheets and counseled on nutrition. Since she lived over 4 h away with regular disruptions from weather during the winter, she maintained close followup via telephone. Sample blood sugar logs showed the blood sugar profile shown in Table 4.6 on the day of (Day 0) and up to 2 days after the infusion.

Blood pressure logs were stable with values ranging from 113/75 to 132/86. Baseline weight prior to treatment was 120 lb which increased to 127 lb with observed fluid retention in the legs during the first 6 weeks of treatment. Ten months into treatment, it decreased to 121 lb and has remained stable since.

Following initial therapy, she received weekly pulses of 1,000 mg IV Q weekly for six doses. Given observed fluid retention, the dose was reduced to 500 mg IV every 10 days for another six doses. Patient reported the same therapeutic benefit at the lower dose but observed less hyperglycemia and fluid retention. By 4 months, she was completely pain free and had regained antigravity strength in her right triceps and normal strength in her left triceps. She regained MRC 2/5 left wrist extension and a flicker on the right. Finger extension remained 0/5. She was evaluated by a physical and occupational therapist who made her a wrist and finger extension brace which passively extended the fingers into a more functional position. There were initial troubles with the brace from abrasive edges and skin excoriations, these were improved with smoothening sharp edges and using effective padding.

After 6 months, she received one more round of treatment with IVIG at 1 g/kg in two divided doses followed by IV Methylprednisolone at 500 mg Q weekly for another five doses. By this time, she had regained considerable functional use of both hands enabling her to perform self-care and perform household tasks such as cooking and cleaning. Triceps strength was normal bilaterally. Wrist extensors

Table 4.5 PSSA for Case Example 1

Failure mode	Failure classification	Treatment strategy	Risk factors/precautions	Risk and morbidity mitigation strategy
Loss of proximal motor function around elbow and shoulder	Major (unable to perform to most basic tasks)	1. Treat nerve inflammation with IVIG and IV Methylprednisolone 2. Likely multiple rounds of treatment will be needed 3. Repeat treatment favors IVIG, steroids over plasmapheresis since they can be given IV	1. The following risk factors were identified in this patient's case—refer Table 4.3 for FMEA for IVIG and Chap. 2 for FMEA for IV Methylprednisolone 1. CABG 2. Cardiac stents 3. Renal failure 4. Hypertension	1. CABG: determined stable based on good functional capacity, absence of angina in the last 6 months 2. Cardiac stents: as above. Thrombotic risk–low given absence of symptoms for 6 months 3. Given identified cardiac risks, the first round of IVIG should be given as an inpatient with cardiac monitoring 4. Diabetes mellitus: monitor when inpatient. Use data to guide outpatient therapy. Follow steroid/IV Methylprednisolone FMEA 5. Renal insufficiency: monitor renal function with daily Basic Metabolic Profile measurement. Maintain hydration 6. Hypertension: stable on current therapy. Risks of hypertensive urgency/emergency deemed low 7. Shoulder strengthening exercises

Loss of distal motor function in wrist and fingers	Major (unable to perform basic tasks such as cooking, eating, writing)	1. Treat nerve inflammation with IVIG and IV Methylprednisolone 2. Reinnervation assumed to be in a length-dependent manner. Therefore this function if it improves is expected to take nearly 1 year	1. As above	1. As above 2. Passive range of motion exercises to prevent contractures 3. Bilateral radial braces to passively extend fingers and improve functional usage of the hands
Loss of normal sensory function with numbness	Minor	None	1. As above	None
Loss of normal pain perception with continuous pain	Minor	1. Treat nerve inflammation to treat underlying cause 2. Analgesics	1. As above	None

CHF, cardiac stents, renal insufficiency, and diabetes mellitus were identified as the major risks to treatment during the PSSA process. Mitigating strategies for initial round of therapy and long-term treatment based on risk factors identified in column 3 till improved functional recovery are discussed in column 5

Table 4.6 Sample blood sugar profiles on the day of and up to 2 days following IV Methylprednisolone 500 mg infusion

Fasting	Afternoon	Evening
Day 0: 126 mg/dL (prior to IV Methylprednisolone infusion)	519 mg/dL	412 mg/dL
Day 1: 228 mg/dL	124 mg/dL	Not available
Day 2: 124 mg/dL	Not available	74 mg/dL

This pattern of a transient hyperglycemia without clinical decompensation for less than 48–72 h was seen frequently during the infusion cycle

attained MRC 2/5 strength bilaterally with the left being stronger than the right which enabled better functional performance with the assistance of bracing. Finger extensors continue to show 0/5 strength. At this time, all further treatment was stopped since patient had experienced a durable remission with a slow length-dependent reinnervation anticipated in due course of time. Retreatment would be initiated if recurrences occur. If there is arrest of progress over time, a referral to orthopedics would be considered for tendon transfer surgery for improving functional positioning of the fingers.

Case Example 2: Treatment of Diabetic Lumbosacral Radiculoplexus Neuropathy

LM is a 64 y/o female with longstanding diabetes mellitus, high HBA1c's (>12) presenting with pain, frequent falls and weakness of the right lower extremity for the last 5 months. Symptoms started subacutely 6 months ago with pain about the knee. Subsequently, the pain became diffuse spreading to the corresponding hip and groin with weakness which developed between 2 and 3 months later. She describes progressive weakness with buckling of the right leg and falls. She does not think matters are at nadir yet, she continues to experience severe pain and weakness to the point of requiring a wheelchair. She has some numbness and tingling in her feet from diabetes for many years. Her hands also are numb with some tingling. There was an initial concern for multiple sclerosis which has been excluded based on unremarkable MRI films and an EMG (see report) consistent with a severe radiculoplexus neuropathy. She denies bowel or bladder symptoms. She affirms ongoing asymmetry of her symptoms; the left leg is much stronger and less painful than the right. She has been taking one tablet of acetaminophen–hydrocodone for pain relief every 4–6 h for the last 6 months for reasonable relief of pain.

Past Medical History: Diabetes mellitus, Diabetic macular edema. Diabetic proliferative retinopathy with neovascularization of the iris, vitreous hemorrhage, cataracts, and hypertension. Edema of the lower extremities, Depression and Right leg weakness.

Medications List: Atenolol, Sliding scale insulin, oral cyanocobalamin, celebrex, enalapril, vitamin D, escitalopram, gabapentin, glyburide, hydrochlorothiazide, acetaminophen–hydrocodone (Norco), metformin, and regular insulin.

Review of Systems: Sugars have been in the 140s fasting. BP fluctuates, highest 180/90s. Overall she feels blood pressure control is reasonable with numbers mostly in the 150–170 range. She has diabetic proliferative retinopathy and macular edema for which she is being treated by ophthalmology.

Initial vitals showed: BP 140/70|Pulse 76/min|Wt. 86.592 kg (190 lb 14.4 oz)|BMI 29.44 kg/m^2.

Physical Examination showed normal cranial nerves with the exception of the fundus examination which showed diabetic retinopathy. Neck flexion/extension strength was normal. Upper extremity strength was normal. In the lower extremity, the left side showed normal strength save mild foot dorsiflexion weakness. In the right lower extremity, she had barely antigravity strength in the iliopsoas and quadriceps muscles. More distally, strength was symmetric with the same degree of observed dorsiflexion weakness as the other side. Deep tendon reflexes were 1+ in the upper extremities, trace at the knees, and absent at the right ankle. It was 1+ on left. Plantars were downgoing bilaterally. Sensory examination revealed loss of sensation below the knees bilaterally with severely reduced pinprick and joint position sense at the toes and asymmetry in pinprick sensation involving the right thigh when compared to the left.

Review of imaging showed normal MRI Brain. MRI Lumbar Spine and Pelvis showed degenerative changes in the lumbar spine without adequate compression of nerve roots to explain her symptoms and findings. Nerve Conduction and EMG study data are in Table 4.7.

Table 4.7 NCS/EMG report for case example 2

Nerve, stimulation site and side	Latency (normal limit) ms	Distance	Amplitude (normal)	Velocity (normal)	F waves
Peroneal nerve to extensor digitorum brevis muscle (right), tibial motor (right and left)	Absent		Absent		
Peroneal nerve to tibialis anterior (right)					
Fib. head	6.2	100 mm	2.8		
Pop fossa	8.9		3.0	50 m/s	
Median motor (right)					
Wrist	8.5 (<4.4 ms)	70 mm	4.0 (>4.0 mV)	35 m/s (>49 m/s)	41.0 ms (<31)
Elbow	14.5		3.7		
Ulnar motor (right)					
Wrist	3.9 (<3.5)	70 mm	9.3 (>6 mV)		34.3 ms (<32)

(continued)

Table 4.7 (continued)

Nerve, stimulation site and side	Latency (normal limit) ms	Distance	Amplitude (normal)	Velocity (normal)	F waves
Below elbow	8.5		9.2	43 (>49 m/s)	
Above elbow	10.6		8.3	59 m/s	
Median motor (left)					
Wrist	6.1 (<3.5)		7.0 (>6 mV)	43 (>49 m/s)	37.2 ms (<31)
Below elbow	11.5		6.9		
Median sensory (right)	Absent	150 mm	Absent		
Ulnar sensory (right)	3.0 (<3.2)	140 mm	6 μV (>10 μV)		
Radial sensory (right)	2.0 (<2.2)	100 mm	7 μV (>22 μV)		
Sural sensory (right)	Absent	140 mm			
EMG findings					
Muscle (side)	*Description of findings*				
Tibialis anterior (right)	2+ fibrillations (fibs) and positive sharp waves (psw). Mix of normal and mildly enlarged polyphasic units with slightly reduced recruitment				
Medial gastrocnemius (right)	1 to 2+ fibs, psw; mix of normal motor units interspersed with enlarged polyphasic motor units showing normal recruitment				
Vastus lateralis (right)	2+ fibrillations (fibs) and positive sharp waves (psw). Mix of normal and mildly enlarged polyphasic units with reduced recruitment				
Iliopsoas (right)	Same as corresponding vastus lateralis				
Adductor longus (right)	2+ fibrillations (fibs) and positive sharp waves (psw). Mix of normal and mildly enlarged polyphasic units with slightly reduced recruitment				
Vastus lateralis (left), tibialis anterior (left); L4/5 and S1 paraspinal (right)	Normal				

Standard distances and normative data are within brackets for each nerve

Conclusion: This is an abnormal study. There is electrophysiologic evidence most consistent with a severe, length-dependent sensorimotor polyneuropathy with prominent demyelinating features. These findings are most consistent with a severe background diabetic neuropathy. Additionally demonstrated is a severe, subacute, right-sided lumbar radiculopathy/plexopathy (or combined femoral and obturator neuropathies) most consistent with diabetic lumbosacral radiculoplexus neuropathy (DLRPN) or diabetic amyotrophy. The main differential diagnosis for these findings is a form of inflammatory demyelinating neuropathy—CIDP, especially asymmetric forms such as the Lewis Sumner variant (MADSAM). Clinical correlation is requested.

Laboratory findings: CRP: 4.4 (normal), ANCA: negative, ANA 1:80 (nonspecific), CK 46, Anti SSA, SSB: Normal. TSH: 1.117 (Normal). Lyme Serology: negative. Serum and urine immunofixation: Normal without M Spike. HBA1c ranged between 10.5 and 10.9.

Therefore, the combination of clinical features, physical examination findings, electrophysiology is most consistent with DLRPN, also called diabetic amyotrophy. The traditional approach has been to exclude other causes, analgesia for the pain and physical therapy. Case reports in the literature have reported benefit from steroid therapy early in the condition within the first 2 months of onset [10]. The disease has been understood in recent years to be a microvasculitis causing inflammation and ischemia to the nerve [10, 11]. A few limited series of immunotherapy early in the disease report good improvement in symptoms although clear guidelines are lacking. In this case the presence of ongoing, severe, unremitting pain and weakness 6 months into the illness without any improvement in strength since onset led to consideration of immunotherapy. Further, the patient had been unable to work or live in her own home due to the severe weakness and was wheelchair dependent. SSA for planning therapy led to the following plan:

Functional Hazard Assessment

2.1. Loss of proximal motor function in right leg.
2.2. Partial loss of bilateral motor functions distally in both legs.
2.3. Loss of sensory function in both legs.
2.4. Loss of normal pain sensation with continuous pain in right leg.

The working diagnosis which can be rigorously verified using a fault tree analysis (FTA) favors an inflammatory process (DLRPN, Asymmetric CIDP variants, Vasculitis). A biopsy or spinal fluid studies may not yield discriminating information between the three since similar findings of elevated CSF protein without cells would be seen in all three. PSSA then proceeds with FMEA.

FMEA for Case Example 2

The following assumptions were made for performance of FMEA:

1. A biopsy is difficult to perform in this instance due to involvement of deep motor nerves which cannot be biopsied.
2. The working diagnosis is a form of inflammatory neuropathy: more specifically DLRPN which has been shown to be a microvasculitis [10, 11]. Conditions in the differential include inflammatory conditions such as asymmetric forms of CIDP, vasculitic neuropathy. Therefore immunotherapy with steroids may potentially benefit all these conditions owing to similar pathogenesis.

3. Firm guidelines in the literature are lacking. Given severe pain and weakness without any improvement over 6 months, it is assumed that ongoing pain indicates active nerve inflammation and microvasculitis, therefore immunotherapy to reduce inflammation is worth considering despite the patient being more than 2 months into the disease.
4. Reduction in pain following initiation of steroid therapy suggests a response to treatment. Motor function would take longer to recover. Since proximal leg muscles are involved it is assumed clinical improvement may start to occur in 2–3 months and be complete by 6 months.

The patient was treated according to the FMEA plan in Table 4.8. Prior to initiating therapy, she contacted her primary care physician and obtained diabetic supplies in the form of test strips, sliding scale insulin, and agreed to monitor glucose closely. The author discussed these above assumptions and recommended therapeutic plan with the primary care physician who knew the patient well. Responsibilities were clearly identified and demarcated and treatment started. The patient received her first two doses of IV Methylprednisolone 500 mg on consecutive days. She reported an immediate 50 % relief in pain a few days after the second dose. In the week following initiation of therapy she could skip at least one or two doses of acetaminophen hydrocodone for pain relief but could not go a full 24 h without it. She maintained regular contact with her PCP and reported peak glucose values between 400 and 500 mg/dL for 36–48 h after therapy followed by decline to her baseline levels. She reported experiencing a mild form of the acute infusion syndrome with palpitations, mild insomnia, and anxiety; however none of these required specific treatment.

She went on to receive seven doses total of IV Methylprednisolone 500 mg, the first two given on consecutive days and subsequent doses once a week for 5 weeks. She was seen back in clinic soon afterwards, approximately 3 months into treatment. She reported being pain-free approximately 4 weeks into treatment without the need for any tablets of acetaminophen–hydrocodone. Soon after pain subsided, she was able to stand and started hip strengthening exercises. She could walk with the assistance of a walker. She denied any falls since starting therapy. She was also able to move back into her own home and take care of herself. At her return visit, the following motor examination findings were observed in the clinically affected muscles: Right hip flexors: 4+/5, Right knee extensors (quadriceps): 5−/5. She continued to have mild weakness in the tibialis anterior muscles bilaterally which remained MRC 4+/5 in strength. She was able to walk without any difficulty with a walker. A renewed prescription for physical therapy was provided to improve right hip strength and for gait and balance training to mitigate the established damage from diabetic neuropathy. At her return visit, her blood pressure measured 136/63, weight 196 lb (gain of 6 lb since beginning therapy). Blood pressure over the past 3 months ranged between 150 and 170 mm systolic, the highest being 180/90. Blood sugars were in the range of 140 mg/dL fasting after completion of therapy. The only reported persistent side effect noticeable to the patient was the development of persistent right lower extremity edema which was not present prior to treatment.

Table 4.8 FMEA for case example 2, treatment of severe, right sided diabetic lumbosacral radiculoplexus neuropathy (DLRPN) with IV Methylprednisolone

Failure mode	Failure classification	Treatment strategy	Risk factors/precautions	Risk and morbidity mitigation strategy
Loss of proximal motor function in the right leg	Major (unable to stand with frequent falls from weakness. Consequently unable to live independently)	1. Treat nerve inflammation with IV Methylprednisolone 500 mg weekly for 4–5 doses 2. An initial dose of 1,000 mg IV will be given over 2 days 3. Reinnervation assumed to be in a length-dependent manner. Since proximal nerves and muscles are involved, improvement in function expected to take 3–6 months	1. The following risk factors were identified in this patient's case.—Refer Chap. 2: FMEA for IV Methylprednisolone 1. Severe diabetes mellitus 2. Hypertension 3. Edema	1. Diabetes mellitus: follow steroid/IV Methylprednisolone FMEA. Patient will contact primary care physician, procure insulin supplies, establish close followup with PCP for receiving guidance on glycemic control 2. Hypertension: stable on current therapy. Risks of hypertensive urgency/emergency deemed low. Based on prior experience with similar patients (see Case Example 1), a rise of 20–30 mm in systolic and 10–20 mm in diastolic is anticipated 3. Physical therapy: initially range of motion exercises till pain improves (first 2 months) 4. As pain control improves, right hip strengthening exercises (2–3 months to 6 months) 5. When standing improves, patient will benefit from gait and balance training for underlying diabetic neuropathy (3–6 months)

(continued)

Table 4.8 (continued)

Failure mode	Failure classification	Treatment strategy	Risk factors/precautions	Risk and morbidity mitigation strategy
Loss of distal motor function in both legs	Minor (mild distal foot weakness without foot drop)	1. Improve glycemic control to prevent progression	1. As above	1. As above 2. Distal exercises to strengthen leg muscles, especially Tibialis anterior. This can start immediately given lack of pain distal to the knees 3. Gait and balance training starting 2–3 months into treatment
Loss of normal sensory function with numbness	Minor	1. Diabetic foot care	1. As above	None
Loss of normal pain perception with continuous pain	Minor	1. Treat nerve inflammation to treat underlying cause 2. Analgesics	1. As above	Continue acetaminophen hydrocodone for the time being till there is a durable response

Treatment of Ocular Myasthenia Gravis Using FMEA Principles

Case Example 3

Ms. KJ is an 88 y/o female presenting with ocular myasthenia gravis. She has severe bilateral ptosis which prevents her from seeing. During the few times in the day her eyelids are open, she has severe double vision. She props an eyelid open using one hand to view through one eye at a time. She was diagnosed with myasthenia gravis based on positive AchR antibodies (acetylcholine receptor antibodies). Treatment was tried initially with Pyridostigmine which was not helpful. Subsequently she was placed on oral steroids at an unknown dose which too was not well tolerated and therapy abandoned. She was referred to ophthalmology for eyelid surgery but was referred for one last trial of medical therapy before permanent surgical procedures could be attempted. Symptoms started approximately 2 years ago, since then she denies any dysarthria, dysphagia, dyspnea, and extremity weakness.

Past Medical History includes severe asthma, hypertension, and hypothyroidism.

Medications list: L-Thyroxine, nasal steroids, cetirizine, hydrochlorothiazide, singulair, omeprazole, and simvastatin.

On initial evaluation, vitals were BP 144/100, pulse 100. Weight 167 lb. Focused neurological evaluation revealed severe bilateral ptosis with diplopia in all directions of gaze referable to weakness of multiple extra-ocular muscles. The rest of her cranial nerves, extremity muscles were normal.

The clinical history and physical examination in conjunction with the serology was most consistent with ocular myasthenia gravis. The patient and daughter were keen to try treatment but were highly skeptical regarding medical management given their prior experience. Although a single debilitating side effect was not identified with prednisone therapy, the patient and her daughter felt she was extremely anxious, jittery and not her normal self when it was tried in the past. The following treatment shown in Table 4.9 was started based on the SSA process.

Functional Hazard Assessment of Case Example 3

3.1. Loss of eyelid control leading to inability to open eyes.
3.2. Loss of extra-ocular muscle strength leading to double vision.

The patient was started on prednisone 20 mg in 5 mg increments over the course of a week. She discontinued treatment 2 weeks later since she did not like the side effects of jitteriness and did not want to try adjunct lorazepam to reduce anxiety. On review in clinic 2 months later, she admitted that her eyes had shown consistent improvement with the ability to stay open for many hours a day. With further education and encouragement she was willing to try once again provided anxiety and insomnia could be controlled. She was restarted on gradually increasing doses of prednisone to a goal dose of 20 mg/day with adjunct Alprazolam 0.25 mg, half to

Table 4.9 FMEA for case example 3

Failure mode	Failure classification	Treatment strategy/ risk factors	Comments
Loss of eyelid control	Minor (since myasthenia has been ocular for 2 years, it is unlikely it will generalize)	1. Initiate low-dose prednisone. Follow oral steroid FMEA 2. Risk factors: (2a) Hypertension (2b) Osteoporosis given patient being elderly female (2c) Anxiety/ jitteriness	1. Oral prednisone gradually titrated to 20 mg/ day in 5 mg increments over the course of 1 week 2. Hypertension: well controlled. No worsening anticipated 3. Osteoporosis: start calcium and vitamin D3 1,000 i.u. day. Risk assumed low since dose of prednisone is low. Annual DEXA scans 4. Anxiety and jitteriness: provide prescription for Lorazepam or Alprazolam 0.25 mg PO QHS PRN 5. If medical therapy unsuccessful after 3–4 months, refer back to ophthalmology for eyelid surgery
Loss of extra-ocular muscle strength leading to double vision	Minor	1. As above	1. As above except for #5 2. If eyelid surgery is required for refractory ptosis, then patch one eye to suppress diplopia

The failure modes are minor without safety consequences except if patient sustains a fall from poor vision

1 tablet at bedtime as needed for anxiety and insomnia. On review 2 months later, she was doing very well with no periods of complete ptosis, many hours of normal conjugate vision, and the ability to resume activities of interest like playing the piano. Physical examination at the time continued to show mild ptosis and mildly disconjugate eye movements. Since patient was tolerating the therapy well, the dose was increased further to prednisone 25 mg/day. She was maintained on that dose for another 2–3 weeks with sustained improvement except for minimal double vision on left gaze. Since that point, a gradual taper was initiated over 3 months with durable improvement with eyelids open throughout the day, mild intermittent nondisabling diplopia and minimal side effects. She is currently maintained on prednisone 5 mg/day with blood pressure of 141/67, weight of 173 lb (gain of 6 lb), calcium and vitamin D supplements with a full return to her normal life.

Case Example 4: Improved Myasthenia Gravis Treatment Using FMEA Principles

WA is a 69 y/o male with a right sided corneal ulcer from past herpes zoster infection. He always considered it his weak eye. Symptoms started as sudden onset of right eye ptosis in Mar 2011. Intracranial causes such as aneurysm were excluded with normal MRI Brain scans. Subsequent antibody testing for myasthenia gravis was positive with high titers of acetylcholine receptor binding antibodies. CT Chest was negative for thymoma. On initial examination in May 2011, he had mild right ptosis. There was prominent bilateral exotropia. There was severe left medial rectus weakness which resembled a left internuclear ophthalmoplegia (INO). Weakness was more prominent in right extra-ocular muscles with severe inferior oblique, medial rectus weakness. He had mild eye closure weakness, but strength was otherwise normal in all muscle groups. The following approach was taken to treatment (shown in Table 4.10):

Table 4.10 FMEA for case example 4

Failure mode	Failure classification	Treatment strategy/risk factors	Comments
Loss of eyelid control	Minor	1. Initiate low-dose prednisone. Follow oral steroid FMEA 2. Risk factors: (2a) Hypertension (2b) Osteoporosis given patient being elderly male (2c) Ocular Herpes Zoster infection: with high risk of recurrence with prednisone therapy (major/hazardous)	1. Oral prednisone 20 mg/day with gradual taper based on response 2. Adjunct pyridostigmine 60 mg up to four times daily as needed 3. Hypertension: well controlled. No worsening anticipated given low doses of prednisone 4. Osteoporosis: start calcium and vitamin D3 1,000 i.u. day. Risk assumed low since dose of prednisone is low. Annual DEXA scans 5. Herpes Zoster: start valcyclovir prophylaxis while on higher dose prednisone. If there is any risk of break out, he will see his ophthalmologist immediately
Partial loss of extra-ocular muscle strength leading to double vision	Minor	1. As above	1. If prednisone therapy is unsuccessful, then patch one eye for suppression of diplopia

The failure modes are minor without safety consequences except if patient develops recurrence of ocular herpes zoster infection which is major/ hazardous

Functional Hazard Assessment of Case Example 4

Functional Hazard Assessment of Case Example 4: is very similar to case example 3.

4.1. Loss of eyelid control leading to inability to open eyes.
4.2. Partial loss of extra-ocular muscle strength leading to double vision.

Over the next 3 months, patient attained satisfactory control of symptoms with gradually tapering doses of prednisone. No zoster break outs were seen and he was taken off Valcyclovir as therapy progressed and prednisone doses were decreased. He continued to experience mild diplopia with very fine tasks which were not limiting. He maintained poor compliance with recommendations and self-discontinued therapy when he became symptom-free. A year later he developed sudden numbness of his left thumb and digits I–III which was initially felt to be carpal tunnel syndrome. However given acute onset of symptoms, an MRI Brain was performed which showed a subacute right lacunar infarct which had not been present in his initial scan done for development of ptosis and diplopia. A stroke work up was performed, including EKG, 2D Echocardiogram with saline bubble contrast, carotid dopplers which were all negative. He was started on atorvastatin which was subsequently changed to pravastatin 40 mg/day, aspirin 81 mg/day, and advised to maintain strict control of blood pressure and do regular aerobic exercise. Blood sugars were rigorously monitored and were normal.

Over the next 2 years, there were repeated cycles of therapy for intercurrent eye weakness. Each was treated with prednisone 20 mg/day which was then gradually tapered to a maintenance dose of 5 mg/day. However, patient would discontinue therapy with symptom-free intervals of several months prior to coming back to clinic with recurrent eye weakness. In Oct 2013, he had a persistent spell of weakness which responded poorly to prednisone 20 mg/day. The dose was increased to 30 mg/day for another 2 weeks but patient was subsequently lost to followup. He established care with neighboring providers but requested a return appointment 3 months later for worsening generalized myasthenia gravis perhaps needing rescue therapy with IVIG or Plasmapheresis. He had severe generalized weakness and required a walker to stand and walk. He had sustained falls due to severe hip weakness. On review in end Jan 2014, physical examination showed a weight of 165 lb, BP 151/65. He had moderate right eye ptosis, sluggish right eye movements referable to multiple muscles. Neck flexors, extensors, and deltoids showed 5−/5 strength; biceps, triceps 4+/5 on the right, and 5−/5 on the left. The remaining upper extremity muscles were normal. In the lower extremities he had severe hip flexor weakness which were MRC 4/5, quadriceps showed 5−/5 strength bilaterally, and the tibialis anterior muscles were 4+/5 bilaterally.

The major concern was for steroid myopathy over decompensated myasthenia gravis. He had been on a high dose of prednisone without close monitoring for over 2 months. The following approach was adopted based on the SSA principles (shown in Table 4.11).

Table 4.11 FMEA for case example 4

Failure mode	Failure classification	Treatment strategy/risk factors	Comments
Loss of eyelid control	Minor	1. Continue myasthenia gravis therapy but use low doses of prednisone 2. Risk factors: (2a) Hypertension (2b) Osteoporosis given patient being elderly male (2c) Ocular Herpes Zoster infection: with high risk of recurrence with prednisone therapy (major/hazardous)	1. Reduce prednisone to 20 mg/day immediately 2. Start adjunct Mycophenolate Mofetil 1,000 mg twice daily given persistent eye weakness which seems poorly responsive to prednisone. Start regular blood count monitoring for side effects 3. Hypertension: well controlled. No worsening anticipated given low doses of prednisone 4. Osteoporosis: start calcium and vitamin D3 1,000 i.u. day. Risk assumed low since dose of prednisone is low. Annual DEXA scans 5. Herpes Zoster: Consider Valcyclovir prophylaxis if needed. Since he did not have a breakout with prednisone 60 mg/day, it is unlikely this may happen. If there is any risk of break out, he will see his ophthalmologist immediately
Partial loss of extra-ocular muscle strength leading to double vision	Minor	1. As above	1. If prednisone therapy is unsuccessful, then patch one eye for suppression of diplopia
Partial loss of strength in bilateral proximal upper extremities	Minor	1. Reduce and maintain prednisone below 20 mg/day	1. Start physical therapy to strengthen the upper extremities
Severe loss of proximal muscle strength in lower extremities	Major	1. As above	1. Start physical therapy for lower extremity strengthening 2. Reduce and maintain prednisone below 20 mg/day 3. Continue using a walker to ambulate for the time being

(continued)

Table 4.11 (continued)

Failure mode	Failure classification	Treatment strategy/risk factors	Comments
			4. If there is continued worsening with reducing the dose of prednisone, call immediately since that is suggestive of worsening myasthenia gravis as a cause of symptoms 5. Increase protein in the diet
Partial loss of sensory function in left hand from stroke	Minor	1. Aspirin 81 mg/day 2. Pravastatin 40 mg/day 3. Continue blood pressure control with Lisinopril	1. Resume aerobic exercise as lower extremities strengthen 2. Continue monitoring sugars and general health maintenance with primary care physician

The patient now has one major failure mode from proximal muscle weakness in the lower extremities and one major/hazardous mode should herpes zoster break out in the eye

FHA for Case Example 4

4.1. Loss of eyelid function.
4.2. Partial loss of eye movement function.
4.3. Partial loss of strength in bilateral proximal upper extremities.
4.4. Severe loss of proximal muscle strength in lower extremities.
4.5. Partial loss of sensory function in left thumb, fingers from stroke.

FMEA Assumption: FHA conditions 4.3 and 4.4 are assumed to occur due to steroid myopathy and less likely due to worsening myasthenia gravis.

Adopting the above FMEA principles, patient was reduced down to prednisone 20 mg/day for possible steroid myopathy as a cause of his weakness and falls. While worsening myasthenia gravis is in the differential, it would be unusual for it to present over 2 months into high-dose prednisone therapy. Tests such as repetitive nerve stimulation could help but lack sensitivity and specificity [8]. He was started on adjunct Mycophenolate Mofetil given continued extra-ocular muscle weakness despite prolonged high-dose prednisone therapy. Emphasis was placed on physical therapy, muscle strengthening exercises to reduce the severity of steroid myopathy. He was expected to need a walker for ambulation for the next 8 weeks due to the severity of the hip weakness but expected to make a faster recovery in the proximal upper extremity muscles due to the relatively mild involvement.

Over the next 2–3 months, he continued to show steady improvement without the need for a walker. He did not sustain any further falls. Strength in the proximal upper extremity muscles also improved. On examination in Jun 2014 he had normal

neck flexion/extension strength; biceps, triceps showed 5−/5 strength, hip flexors were 4+/5 with normal quadriceps strength. Strength was normal in the remaining upper and lower extremity muscles. Cranial nerve examination showed mild right ptosis, mild weakness of the right superior rectus and persistent diplopia which was less than prior examinations. Blood pressure remained 132/65 and weight remained stable at 156 lb. Over time, the dose of prednisone was tapered to 5 mg/day and he has maintained compliance with his regimen. This example illustrates how a disciplined approach using SSA principles can considerably assist long-term therapy.

Treatment of Parkinson's Disease Using FMEA Principles

Case Example 5

RB is a 85 y/o male presenting with progressive difficulty walking, balance, falls, softening speech for the last 6 months to 1 year. He has a history of back pain with radiation to the right lower extremity and weakness for the last 3 years. He has received steroid shots to the spine with modest improvement. There is significant urinary incontinence for the last several months. Wife denies any prominent visual hallucinations or REM sleep disorder. Falls occur due to give way of the right lower extremity. Some falls have been backwards, including some with loss of consciousness. Speech has become progressively soft but is unchanged for a few months. There is some drooling and jaw tremor. Patient and wife deny dysphagia but admit swallowing has been difficult over the last 1 year. Past medical history from a review of the medical record includes hypertension, diabetes mellitus, lumbar spinal stenosis, back pain, and mild dementia.

Medications list includes losartan, metformin, glipizide, and aspirin.

Physical examination revealed blood pressure of 155/75, pulse 65/min; soft, hypo nasal speech; decreased facial expression; normal motor strength and coordination, normal reflexes in the upper extremities with absent reflexes in the lower extremities, upgoing toes bilaterally. The jaw jerk was mildly brisk with right greater than left cogwheel rigidity, mild axial rigidity, and prominent bradykinesia. MRI Brain showed moderate atrophy with mild secondary ventriculomegaly and periventricular white matter disease. MRI Lumbar spine showed multilevel central stenosis and multilevel right greater than left foraminal stenosis.

Based on the clinical history, physical examination findings, and radiological features, a diagnosis of Parkinson's disease was made and treatment recommended [12]. Over the next few months, lightheadedness, dizziness, and falls with loss of consciousness became more prominent. A tilt table test for the same showed blood pressure decreasing from 181/54, pulse rate 69/min to 91/40 with pulse rate of 67/min confirming orthostatic hypotension. During the course of treatment, a formal SSA approach was adopted towards treatment (shown in Table 4.12).

Table 4.12 FMEA for loss of motor function for patient RB in case example 5 above

Failure mode	Failure classification	Mitigation strategies	Comments
Slowness of movement of the extremities (bradykinesia)	Minor (significant morbidity but without affecting lifespan or causing life-threatening complications)	Levodopa/carbidopa as initial therapy Add Dopa agonists, MAOB inhibitors as needed	None
Difficulty swallowing	Major (potential for aspiration pneumonia, debility and weight loss all of which are potentially life-threatening)	1. As above 2. Formal swallowing evaluation if not better with levodopa/carbidopa therapy	1. Consider speech and swallowing evaluation for exercises, aspiration precautions 2. Dietary changes 3. Nutrition consult if there is progressive weight loss
Mechanical falls without loss of consciousness	Hazardous (potential for fall with hip/vertebral fracture, subdural hematoma all of which with potential for loss of life)	Levodopa/carbidopa as initial therapy followed by Dopa agonists, MAOB inhibitors as needed	1. Walker/Cane/avoid uneven surfaces 2. Physical therapy for gait and balance training concomitant with dopamine replacement therapy

5.1. *FHA*: Top Level FHA for the patient includes the following problems:

(a) Loss of Motor Function from Parkinson's disease.
(b) Loss of cognitive function.
(c) Loss of Autonomic function from Parkinson's disease. In a top-down manner this can be subdivided into:

(i) Loss of Blood Pressure control.

- Loss of blood pressure control when standing (orthostatic hypotension).
- Loss of blood pressure control when lying leading to overshoot (supine hypertension).

(ii) Loss of urinary bladder control.
(iii) Loss of swallowing function.

5.2. *FMEA* for failure conditions identified in FHA above:

5.2.1. *Loss of motor function from Parkinson's disease*: This is manifest in the form of poor mobility, mechanical falls from poor balance, drooling, and overall slowness of movement. The mechanical falls from postural

imbalance need to be separated from falls from orthostatic hypotension. The latter are associated with dizziness and lightheadedness, the former are not.

Applying the methodology described in Table 4.12, swallowing function was completely restored, slowness of movement improved considerably, and mechanical falls were almost completely eliminated with gradually increasing doses of levodopa-carbidopa 25/100 mg tabs, two tabs three times daily with an additional tablet as needed during the day. Patient was able to regain considerable functional independence performing tasks like mowing the lawn and walking through a grocery store which he had been unable to perform earlier. Over the subsequent several months, autonomic features became more prominent for which the following FMEA was adopted in close collaboration with his cardiologist.

5.2.2. *Loss of autonomic function from Parkinson's disease*: This is a prominent feature of Parkinson's disease in the late stages. The following strategy was adopted in RB's case:

Assumptions: 1. Autonomic Failure is largely a consequence of Parkinson's disease and less likely due to diabetic neuropathy.

Adopting the above methods [12, 13], orthostatic hypotension did well on Pyridostigmine, reducing and discontinuing current antihypertensive regimen and substituting to a low dose of metoprolol 25 mg at night time in close conjunction with his cardiologist. A blood pressure chart maintained by the patient and his wife showed acceptable control with the highest blood pressures and resting heart rates at night times within the limits defined in row 2, Table 4.13 without further precipitous drops and loss of consciousness. The dose of metoprolol was subsequently increased to 25 mg in the morning and 50 mg at night. The patient denies syncopal spells since the changes were made. Cognitive decline was mild; therefore an FMEA analysis was not performed. As an initial step, antidepressants were maximized to treat the cognitive component resulting from depression.

Table 4.13 FMEA for treating autonomic failure in case example 5

Failure mode	Failure classification	Mitigation strategies	Comments
Loss of blood pressure when standing (orthostatic hypotension)	Major (potential for falls causing injuries such as subdural hematoma, fractures with threatening complications)	1. Tight stockings 2. Pyridostigmine therapy for symptomatic relief 3. Midodrine if 1 and 2 are not successful 4. Monitor blood pressure and pulse rates at home, especially when dizzy	1. Provide pictures showing methods to tighten calf muscles when standing 2. Avoid excessive dopamine

(continued)

Table 4.13 (continued)

Failure mode	Failure classification	Mitigation strategies	Comments
Loss of supine blood pressure control (supine hypertension)	Minor to major (potential for stroke, heart attack, hypertensive urgency)	1. Titrate night time antihypertensive dosing for maximal efficacy 2. Maintain blood pressure chart 3. Reduce dose of antihypertensives permitting a higher band of resting blood pressures between 160–180 systolic and 90–100 diastolic	Institute changes in blood pressure regimen. Antihypertensive therapy changed to metoprolol 25 mg at night time. Adopt the following ranges as acceptable if orthostatic hypotension is controlled and no cardiac side effects develop (a) Less than 160/90: acceptable control (b) 160–180/100: monitor, acceptable if only few times/week (c) >180/100: attempt additional control
Loss of urinary bladder control	Minor	Monitor for retention, urinary tract infection	Urology referral and evaluation as needed

Please note that blood pressure parameters used in this case are derived from monitoring patient logs, symptoms to optimize therapy with the conflicting goals of minimizing supine hypertension (with blood pressure goals closer to 150/90 goal in elderly aged > 80 years [13]) and preventing orthostatic hypotension and syncope

Conclusions

This chapter presents several examples of patients with multiple medical comorbidities successfully treated using SSA principles. Treatment approach starts in a top-down manner with a FHA followed by a PSSA which identifies failure modes and their effects in the FMEA, links therapeutic strategies to specific risks, and allows planning of mitigation strategies. Further examples will be presented in future chapters integrated with other treatment tools to extend the concept.

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Chapter 5
Machine Learning Methods with Applications to Diagnosis

Abstract This chapter extends probabilistic analytical methods introduced in Chap. 2. The principle of transformation of medical information into data visualization is introduced in this chapter. This enables transforming a diverse array of clinical problems into simple, standard forms which lend themselves more easily to diagnostic solutions. Data distillation followed by data visualization allows clinical problems to be formulated into decision making "nodes" which lend themselves to graphical methods of problem solving. This method is exploited widely in computer science and forms the basis for many optimization algorithms used ubiquitously. Candidate diagnosis, differential diagnosis can be selected and evaluated probabilistically. Like Fault Tree Analysis, these methods can be qualitative and quantitative. Illustrative case examples are provided following introduction of the theoretical fundamentals.

Medical Problem Solving: The Computer Science Perspective

In this chapter we explore principles from computer science that can help with medical problem solving. Machine learning refers to a branch of computer science which involves learning from data and making decisions [1]. At their heart, many algorithms in machine learning can be understood to be forms of mathematical optimization. Frequently, this involves defining and solving a "cost function" such that the best solution to the problem minimizes the error between the predicted solution and the real solution [1].

Certain cost functions lend themselves well to standard solutions. Therefore, a lot of machine learning involves transforming diverse problems into a few standard forms and then obtaining solutions to the transformed problem. Basic probability principles developed in Chap. 2 are used in this chapter.

One of the most famous optimization algorithms in computer science is the traveling salesman problem (TSP). Given a list of cities and distances between pairs of cities, what is the shortest route that visits each city only once and returns to the original city [2]? Many different problems in the real world can be transformed into the TSP and the same solution method applied. Examples include vehicle routing for logistics companies, designing electronic circuit boards where the cities

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represent locations of different electronic components which need to be placed and linked together. Once the problem is converted into standard form (such as the TSP), the solution approach remains the same, despite a vastly different application.

While machine learning attempts to create intelligence in computers modeled along human lines, this chapter travels in the reverse direction. Can applying machine learning methods help with diagnosis? Can physicians think like computers or formulate problems like computers and work it out on pen and paper? I will present some case examples of successful results from formulating challenging diagnostic problems along computer science lines. Such research is already underway at many research centers, the interested reader is encouraged to study IBM "Watson" [3] for more information [4].

The main idea with medical diagnosis is to go from manifestations of disease-termed symptoms to the underlying condition that produced them. The challenge lies in the fact that the mapping between disease and symptoms is *many to one*, i.e., many diseases look alike in terms of symptoms. For example tumors, strokes, dementias, nerve disease, and muscle disease can all produce the symptom of swallowing difficulty or slurring of speech. The diagnostic tests depend on the physician's a-priori thought and judgment—tumors and strokes are best diagnosed with an MRI Brain with contrast while nerve and muscle diseases are best diagnosed with blood tests for diseases such as myasthenia gravis and nerve conduction/EMG tests. Since these tests are very expensive (several thousand dollars and restricted in resource availability), initial problem formulation is exceedingly important for avoiding wasteful testing and making timely diagnosis.

Discovering the relationship between manifest data and underlying processes (which are hidden) that generate them forms the basis of statistical inference. Such methods are in use every day for numerous real-world applications. For example, based on observed temperature, wind, cloud data, a prediction can be made about whether the weather will be stormy, clear, etc. Speech recognition is another example. In this instance, statistical inference maps the observed pattern of sound changes to the underlying word that was spoken. Hidden Markov Models (HMM), form the basis of many speech recognition algorithms [1]. Neural networks, support vector machines are other powerful algorithms which are commonly used. A detailed discussion of all such techniques is beyond the scope of this chapter. The interested reader is directed to an excellent textbook by Trevor Hastie et al. for further information [1].

These techniques are highly data and computation intense. However, the abstract algorithmic principles behind them can be applied to individual problem solving and often can help the investigator form a solution. This section will demonstrate case examples of applications of graph theoretical methods which facilitate problem solving once a problem has been expressed graphically. The main advantage with this method is that it helps with *data visualization* and representation. Data visualization is a very powerful tool for conceptual understanding of a problem and helps with solutions planning. The clinician can build various hypotheses connecting different symptoms (observed random variables in statistical parlance) in parallel, assigning different degrees of belief to each hypothesis (possible

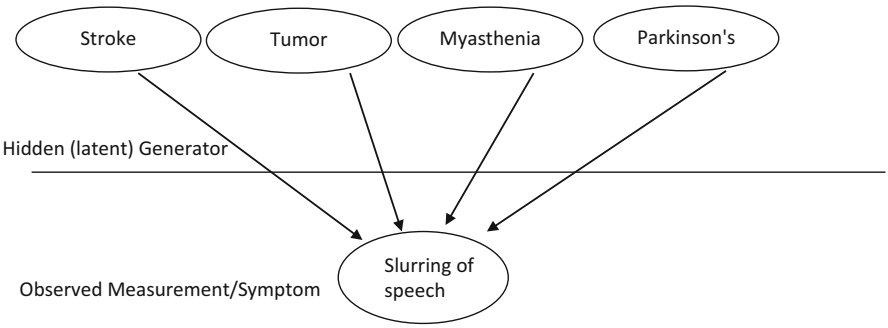

Fig. 5.1 The many to one mapping from underlying diseases to manifestations of disease (symptoms)

diagnosis) for investigation in parallel. A special type of graph theoretical model called Bayesian network is a powerful tool for analyzing such problems where probabilities can be assigned between symptoms and a disease hypothesis where a relationship between the two can be postulated to exist. For the example in Fig. 5.1, the symptom is slurring of speech and one of the possible diagnostic hypotheses is "myasthenia gravis".

First, a quick introduction to *graph theory* and Bayesian networks. Graph theory is the study of graphs. A graph is a collection of *vertices* or *nodes* and connections between them when a relation exists between any pair of vertices called *edges* [1, 4]. An example of this in day-to-day life would be a road map with nodes being cities and edges being the highways connecting a pair of cities. Directed graphs have edges where direction is important, such as a one-way street that connects two cities where cars can go only in one direction and not the other. Quantification in this simple model can be attained by assigning distance or travel times between cities to give an idea about the strength of a connection between any city pair.

Combining graph theory with probability theory leads to a structure called Bayesian Network (BN). Bayesian networks are also called belief networks. They belong to the family of probabilistic graphical models where observed random variables (example: symptoms such as fever, headache, etc. for applications in medicine) are represented as nodes of a graph and the probability of co-occurrence of a pair of random variables can be encoded by an edge. It is a powerful tool for visualizing and understanding data and has broad applications. For example, a connection or an edge can exist between nodes such as "fever" and "vomiting" since the two symptoms happen together in the common flu, meningitis, gastroenteritis, and other underlying infectious diseases while "hair loss" and a "fracture" probably are unrelated and cannot be connected by an edge. Bayesian networks are examples of directed graphical models where the edges have direction and (directed) connections between nodes have cause-and-effect implications. For day-to-day applications, we will drop the requirement that edges be directed and will depart from classical BN theory and work with undirected graphs. Undirected graphs are also called Markov random fields or Markov networks. We will use this

structure to enhance data visualization and formulate problems in graphical form to search for solutions [1]. (*For the mathematically pure*, *inference need not be Bayesian in Bayesian networks; frequently these are maximum likelihood-based inferences*.) The advantages with this architecture are:

1. It provides a simple, intuitive, visual understanding of key aspects of a problem.
2. Helps direct searching large databases like Pubmed for co-occurrences and generating candidates for underlying hypotheses.
3. Helps evaluate multiple diagnoses in parallel with different likelihoods assigned to different hypothesis.
4. Can be scaled easily when new observations or symptoms appear.
5. Can help direct search for new nodes to generate disease patterns.

Once a problem is expressed in the form of nodes, the idea is to construct edges which reflect a relationship between them under a specific hypothesis. In a sense, we are trying to construct a disease "trail" and see how far we can go and connect the nodes with a particular hypothesis or diagnosis in mind. In graph theory a "Trail" is a sequence of edges between vertices which are distinct. We use the term more loosely to mean the sequence of nodes which can be connected together by edges under a particular hypothesis. Based on the principle of Occam's razor, the better hypothesis is one which can construct a better joint conditional probabilistic relationship between nodes and incorporate more of them under a single diagnosis [1]. As a toy example, a patient comes in with fever, headache. He also reports feeling confused, not remembering where he was when he woke and experiencing neck pain which is worse when looking down. Based on this description, the nodes are the constellation of "fever", "headache", "neck stiffness", "confusion" and the investigator is evaluating whether the underlying condition is Flu or meningitis (Fig. 5.2).

Step 1: Problem formulation in graphical form.
Step 2:

(a) *Evaluate the hypothesis of meningitis*: Starting with chief symptoms fever, see if meningitis can cause fever and confusion and connect the two nodes. More rigorously, for the mathematically inclined what is the joint conditional probability of fever and confusion occurring if the underlying condition is meningitis? This is expressed as P (Fever, Confusion | Meningitis)? Fairly

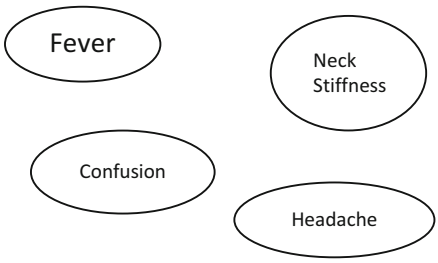

Fig. 5.2 Data visualization. Creating important decision making nodes

high, therefore a strong edge can be connected between the two which incorporates our strong belief that the two can happen together if the underlying disease is meningitis. Consider the next node "Headache"; can meningitis connect the pair {fever, confusion} with "headache"? Definitely it can connect the two. Finally can meningitis connect {Fever, confusion, headache} with "neck stiffness"? Definitely. Meningitis can connect all the nodes quite well under our beliefs and we represent this using thicker arrows.

(b) *Evaluate hypothesis of Flu*: Going through the above reasoning, Flu can connect Fever, Headache quite well as everyone who has suffered it knows. However connecting the pair of {fever, headache} with confusion? May be. We are not dismissing it so we will connect them with a thinner edge. Can flu connect {Fever, confusion, headache} with "neck stiffness"? Neck soreness as part of body ache can happen, but neck stiffness is unlikely, unless the flu causes viral meningitis/encephalitis in rare instances. Therefore a thinner arrow is used to link such a weak joint probability between them (Fig. 5.3).

Now the graphical model becomes for meningitis:

Applications of this technique for a few real case examples will be presented. Examples selected are ones where formal application of this structure helped make rare and obscure diagnosis which were elusive for many years and saved costs and

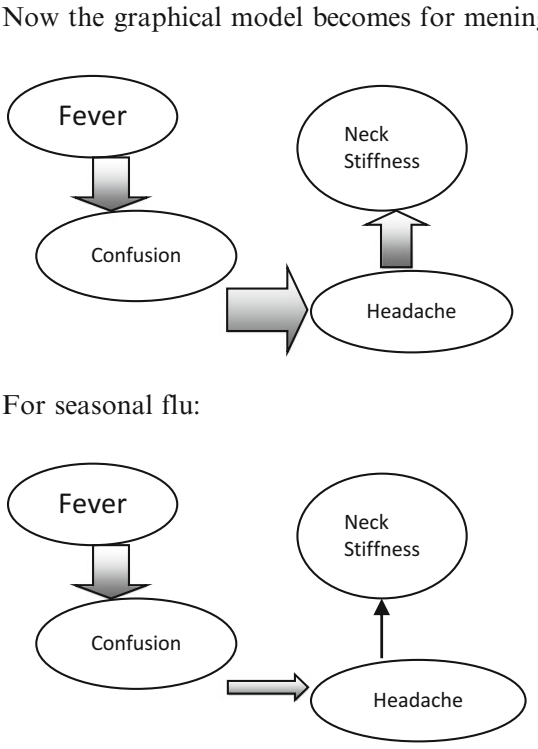

Fig. 5.3 Using graphical methods to construct competing hypothesis for the toy example of a patient presenting with fever, headache, confusion, and neck stiffness

directed appropriate treatment. The historical narrative from patient records is presented to demonstrate the great degree of initial filtering required for representing the problem in canonical form for application of these techniques. *Case Example 1 is presented with almost all details included from patient records to show the degree of data distillation that is required to perform decision making with medical data. The remaining case examples are edited considerably.*

Case Example 1

"BH is a pleasant 65-year-old diabetic female who presents to clinic with her husband for further workup of her sensory ataxia. She has 3 years of progressive sensory ataxia and 6 years of peripheral neuropathy.

She has been having 1–2 falls each week. Her husband states that there is significant staggering when she walks. She relies on a cane and her husband's help to walk now. The most recent episode was a fall a few days ago. She fell backwards and hit her head without dizziness or loss of consciousness. Balance is worse after sitting for a long time. Patient also complains of fatigue that has been worsening over the past year. She has not broken any bones. She endorses difficulty with memory, remembering names of people and following instructions. She did not notice any changes in her speech or swallowing difficulties. She spends most of the day lying in bed and has experienced some shoulder/neck pain on the left side that is being treated by her primary care doctor. The following tests have been done:"

EMG/NCV: (uncertain date, 2010 or prior) legs showed severe sensory/motor polyneuropathy (diffuse nerve damage). Arms showed bilateral carpal tunnel, left worse than right.

Imaging: 4/27/10 noncontrast MRI brain (per report): no cerebellar/pontine atrophy, no mass/structural lesion, scattered periventricular white matter disease.

7/7/10 carotid duplex: 60–80 % stenosis (narrowing) of proximal left internal carotid artery, 40 % stenosis of proximal right internal carotid artery.

8/4/10 carotid/VA duplex: vertebral artery patent with anterograde flow, left carotid artery shows "a small fibrocalcific plaque at the bifurcation which extends into the origin of the internal carotid artery producing a stenosis (narrowing) in the upper category of 40–59 %."

Serum: Borderline abnormal TSH (thyroid tests); Normal B12/folate, B1, Vitamin E, Normal electrolytes, liver function, blood counts. Anti Nuclear Antibody normal. Normal serum protein electrophoresis and negative cryoglobulins. Negative anti-Hu, anti-Yo antibodies. Tests for diabetes show well-controlled sugars.

8/17/11 Lumbar puncture—Cerebrospinal Fluid is within normal limits. No abnormalities found.

Medications

1. SYNTHROID 112 MCG TABS (LEVOTHYROXINE SODIUM)—daily
2. FUROSEMIDE 40 MG TABS (FUROSEMIDE)—twice daily
3. TRAZODONE HCL 100 MG TABS (TRAZODONE HCL)—at bedtime
4. LANTUS INSULIN 18 UNITS AT BEDTIME ()
5. PROTONIX 40 MG TBEC (PANTOPRAZOLE SODIUM)—daily
6. DEPAKOTE 250 MG TBEC (DIVALPROEX SODIUM)—one pill three times a day
7. PROZAC 20 MG CAPS (FLUOXETINE HCL)—three pills daily
8. LORTAB 5 5–500 MG TABS (HYDROCODONE-ACETAMINOPHEN)—one pill every 6 h as needed
9. LISINOPRIL TABS (LISINOPRIL TABS)
10. NORTRIPYTLINE HCL CAPS (NORTRIPTYLINE HCL CAPS)
11. SIMVASTATIN TABS (SIMVASTATIN TABS)—one tab qD
12. NORFLEX SOLN (ORPHENADRINE CITRATE SOLN)—100 mg one tablet two times a day
13. VOLTAREN 1 % GEL (DICLOFENAC SODIUM)

Allergies

1. NSAIDS—hives, itch

Past Medical History: Appendectomy, Blepharoplasty, L carotid stenosis, cholecystectomy, depression with psychotic features, gastric bypass, reflux disease, hypothyroidism, hysterectomy.

Heart failure, fibromyalgia, depression, type II diabetes, hypertension.

Family History
Negative for: psychiatric, neurologic disease.

Social History
Marital status: married; Lives: at home; Number in household: 2; Lives with: spouse; Number of children: 0, Occupation: on disability, Tobacco Use: past, quit in 1981, Alcohol use: never, Drug use: never

Physical Exam

VITALS: Weight: 177.9 lbs., BP: 134/67, Pulse: 83, Resp. Rate: 14.
GENERAL: Bilateral ptosis, temporal wasting, persistent mouth pursing.
CRANIAL NERVES: CN 3, 4, 6: *unable to move eyes horizontally more than a few degrees*. Vertical gaze impaired, but less so. Up gaze worse than down gaze. CN 5 (Trigeminal): weak bite, mildly weak jaw opening. CN 7 (Facial): weakness of eye closure, able to maintain lip closure. CN 8 (Auditory): decreased hearing on right. CN 9, 10 (Glossopharyngeal): The uvula is midline, the palate elevates

symmetrically. CN 11 (spinal accessory): Bilateral sternocleidomastoid weakness. CN 12 (Hypoglossal): tremulous, no fasciculation.
COORDINATION: Limited exam, no obvious difficulties.
SENSATION: decreased proprioception at fingers. Touched eye when trying to touch nose. She has decreased vibration and pinprick sensation to the knees in the lower extremities and to the wrists in the upper extremities.
GAIT: *Wide based, very off-balance. Tends to fall either back or to the left if not supported*. Able to walk with hands held. Comments: significant ideomotor apraxia.

Neuromuscular Exam

Muscle Strength:

- Deltoids: (R): 5− (L) 5−
- Biceps: (R): 5− (L): 5−
- Triceps: (R): 5− (L): 5−
- Pronators: (R): 4+ (L): 4+
- Wrist Extensors: (R): 5− (L): 4
- Wrist Flexors: (R): 5− (L): 4
- Flexor Pollicis Longus: (R): 4+ (L): 4
- Finger Flexors: (R): 4+ (L): 4
- Hip Flexors: (R): 4+ (L): 4+
- Quadriceps: (R): 5− (L): 4+
- Hamstrings: (R): 5− (L): 4+
- Adductors: (R): 5 (L): 5

Deep Tendon Reflexes: 1+ at the biceps bilaterally, absent elsewhere.

A repeat EMG study was requested to evaluate for neuropathy. At this time she was noticed to have dysarthria as well. The EMG showed a severe sensorimotor axonal polyneuropathy without evidence of a coexistent myopathy.

Solving a problem involving ataxia, especially an inherited genetic one is extremely challenging. The genetic tests are ordered as a battery, are time consuming and expensive. However, after picking out the most important aspects of this presentation from the medical data and reformulating the problem in the form of a graphical model, solutions can be attempted as discussed above. From a review of all the clinical information and clinical data, the decision making nodes are ataxia, severe neuropathy, dysarthria, and ophthalmoplegia. The equivalent graphical model which enables data visualization is shown in Fig. 5.4. This enables a directed search of medical databases searching for diseases which can manifest with this combination of symptoms and signs.

Candidates include forms of Spinocerebellar ataxia (SCA) inherited in an autosomal dominant or recessive manner, multiple systems atrophy, and a peculiar disease entity called sensory ataxic neuropathy with dysarthria and ophthalmoparesis

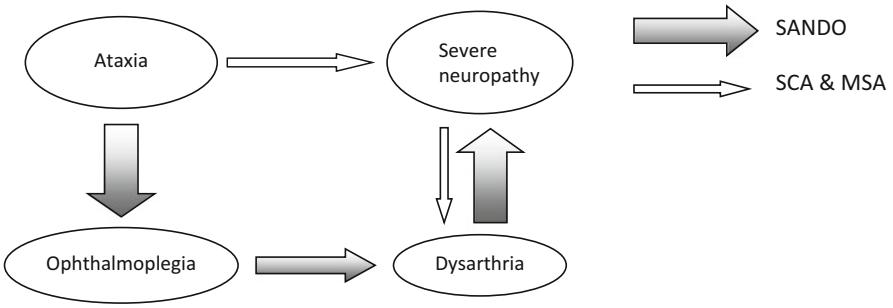

Fig. 5.4 Graphical model formulation of case 3. SANDO (*shaded arrow*) can link more nodes than alternate hypothesis; therefore it remains the preferred hypothesis. (SANDO: sensory ataxic neuropathy dysarthria and ophthalmoparesis, SCA: spinocerebellar ataxia, MSA: multiple systems atrophy.)

(SANDO) [5]. Each of these hypotheses can be evaluated in the manner described above in the graphical model that has been constructed.

Consider ataxia as the first node.

(a) Hypothesis 1 (SANDO): The probability of ataxia given underlying SANDO, given by P (Ataxia | SANDO) is high. Starting from this node, let us see if SANDO can cause ophthalmoplegia. The joint probability is given by P (Ataxia, Ophthalmoplegia | SANDO). SANDO can cause this as well; therefore, the two can be linked by a strong edge. Similarly SANDO can cause dysarthria and severe neuropathy enabling a strong edge to be drawn connecting each of the nodes. Building the set we get: {Ataxia, Ophthalmoplegia, Severe Neuropathy, and Dysarthria | SANDO}. Applying Bayes rule (from Chap. 2), the posterior probability of SANDO given BH's clinical presentation is given by:

P (SANDO | Ataxia, Ophthalmoplegia, Severe Neuropathy and Dysarthria) = by P (SANDO) × P (Ataxia, Ophthalmoplegia, Severe Neuropathy, and Dysarthria | SANDO)/P (Ataxia, Ophthalmoplegia, Severe Neuropathy and Dysarthria).

The first term represents the a-priori probability of SANDO; the second term is the *likelihood* that SANDO can produce the constellation of ataxia, neuropathy, dysarthria, and ophthalmoplegia [5]. (The denominator P (Ataxia, Ophthalmoplegia, Severe Neuropathy and Dysarthria) is common to all the hypotheses, therefore can be ignored while evaluating probabilities. We will follow this convention in all future examples.)

(b) Hypothesis 2 (SCA): The probability of ataxia given SCA given by P (Ataxia | SCA) is high. Moving to the next node, forms of SCA can cause severe neuropathy as well. The corresponding probability is given by P (Ataxia, neuropathy | SCA). A strong edge can connect ataxia, severe neuropathy under the hypothesis of SCA. Moving on SCA can cause dysarthria as well.

Therefore P (Ataxia, Neuropathy, Dysarthria | SCA) is high and corresponding edges can be drawn as shown in Fig. 5.4. SCA can cause mild eye movement abnormalities, but does not cause ptosis and ophthalmoplegia. Therefore an edge cannot be drawn between these nodes. Building the set of nodes connected by edges under the hypothesis of SCA we get {Ataxia, Severe Neuropathy, Dysarthria | SCA} with ophthalmoplegia outside the set. The corresponding Bayesian probability is given by:

P (SCA | Ataxia, Ophthalmoplegia, Severe Neuropathy, and Dysarthria) can be approximated by P (SCA) × P (Ataxia, Ophthalmoplegia, Severe Neuropathy, and Dysarthria | SCA).

(c) Hypothesis 3 (MSA): In a manner similar to Hypothesis 2, we get the set {Ataxia, Neuropathy, Dysarthria | MSA} under the hypothesis of MSA with the unconnected node ophthalmoplegia lying outside. The corresponding probability becomes:

P (MSA | Ataxia, Ophthalmoplegia, Severe Neuropathy, and Dysarthria) can be approximated by P (MSA) × P (Ataxia, Ophthalmoplegia, Severe Neuropathy, and Dysarthria | MSA).

Since all these disorders are relatively rare, we can assume prior probabilities are similar and equal. Therefore, the first terms become equal and the corresponding likelihoods determine which hypothesis is the preferred one. Since a thick edge can connect all the nodes under the hypothesis of SANDO while it cannot under SCA and MSA, it becomes the working diagnosis. The other conditions SCA and MSA become the differential diagnosis.

Based on this analysis, genetic testing of the DNA Polymerase Gamma gene was requested. Genetic testing revealed three pathogenic mutations in the POLG1 gene. One allele was found to have two sequence variants: c. [752C > T; 760C > T] which led to amino acid substitutions [THR > ILE; PRO > LEU]. The other allele had a compound heterozygous mutation of c.1399G > A which resulted in substitution of Threonine for Alanine. These mutations have been reported in other case reports of mitochondrial disorders [6]. Therefore, a review of the clinical data followed by data distillation, graphical representation helped establish a difficult diagnosis.

Case Example 2

Mr. KL is a 48-year-old male referred for numbness, weakness, and progressive gait difficulties. The main reason for referral is concern for SCA. He was well until about 6 months ago. At that time, he developed numbness and tingling in the middle finger of his right hand. Over the next 2–3 months, this progressed to right hand and arm numbness and tingling and right foot numbness. He was seen by his primary care physician who was concerned for stroke. Over the next month, he began losing strength in his right hand and right leg. He has since noticed that his left leg is also

tingling. He believes the involved limbs are also getting progressively weaker. A CT head was reportedly normal. During this time, he has had multiple other symptoms including recurrent respiratory problems requiring inhalers and a 50–60 lbs. weight loss over the last 9 months. He believes he is losing weight because his appetite is poor and experiences early satiety. Over the past month, he has also been vomiting after meals. He is certain that no one in his family has a history of balance disorders, weakness, or sensory changes. He reports that he began drinking heavily since last fall and is now drinking 1–2 pints of liquor per day. He has a one pack per day smoking history for over 20 years.

On focused neurological examination, mental status and speech are normal. Eye movements showed slow saccades without nystagmus. Motor examination shows normal neck flexion/extension strength, normal symmetric deltoid strength. He had a mild, right-sided hemiparesis with 4+/5 to 5−/5 strength in the muscles of the right upper and lower extremity. The left upper and lower extremities were normal.

Deep tendon reflexes were diffusely absent. He had an upgoing left plantar response. Tests of coordination revealed an action tremor in both hands and dysmetria on heel to shin testing, worse on the right. Sensory examination revealed severely decreased vibration, decreased pinprick in the right hand and leg. Gait was wide-based, very unsteady with mild toe walking. He was unable to tandem. The gait abnormality was far more pronounced than finger to nose and heel to shin tests of cerebellar function. No labs were available to review.

Based on a review of the symptoms and physical examination findings, the following decision making nodes can be identified:

(a) Cerebellar ataxia: based on presenting symptom of balance problems, difficulty with gait and abnormalities on heel to shin and finger to nose.
(b) Neuropathy: based on areflexia, sensory loss.
(c) Weight loss of 60 lbs.
(d) Weakness: as manifest by right hemiparesis.

The nodes are as shown in Fig. 5.5.

A focused search of the literature raises the following candidate hypothesis: Paraneoplastic Syndrome, Alcohol-related disorders (Wernicke's encephalopathy and alcohol-related cerebellar degeneration) and SCAs [5]. As in Example 1, starting with cerebellar ataxia, these can be evaluated as follows:

(a) *Hypothesis 1*: Paraneoplastic Syndrome: P (Cerebellar Ataxia | Paraneoplastic Syndrome) is very high [7]. Examining the next node, Paraneoplastic syndrome can cause neuropathy. The joint probability can be expressed as P (Cerebellar Ataxia, Neuropathy | Paraneoplastic Syndrome) under the hypothesis of paraneoplastic syndrome. Therefore a strong edge can connect the two. Similarly, Paraneoplastic syndrome can cause weight loss and weakness which enables a strong edge to connect all the nodes. The set {cerebellar ataxia, neuropathy, weakness, weight loss | Paraneoplastic syndrome} contains all the nodes. Applying Bayes' rule the posterior probability, given by P (Paraneoplastic Syndrome | Cerebellar ataxia, neuropathy, weight loss,

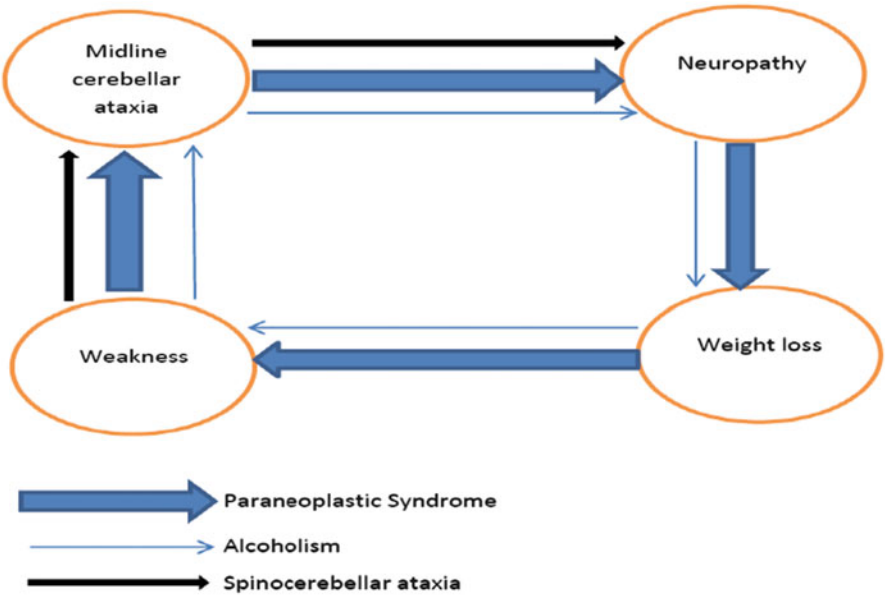

Fig. 5.5 Cerebellar ataxia, neuropathy, weakness, and weight loss form the nodes for case Example 2. The main candidate hypotheses are Paraneoplastic syndrome, alcoholism (including Wernicke's encephalopathy and alcoholic cerebellar degeneration) and spinocerebellar ataxia

weakness) is approximated as P (Paraneoplastic Syndrome) × P (Cerebellar ataxia, neuropathy, weight loss, weakness | Paraneoplastic Syndrome).

(b) *Hypothesis 2*: Alcoholism: The high daily alcohol consumption is most certainly the most common cause of these symptoms since alcohol is toxic to the cerebellum. Additionally, given weight loss, poor nutritional intake, and vomiting, Wernicke's encephalopathy is also a major consideration [8]. Therefore all the nodes can be connected under the hypothesis of alcoholism by strong edges. The corresponding posterior probability applying Bayes' rule becomes:

P (Alcoholism | Cerebellar ataxia, neuropathy, weight loss, weakness) is approximated by P (Alcoholism) × P (Cerebellar ataxia, neuropathy, weight loss, weakness | Alcoholism).

(c) *Hypothesis 3*: SCA: This hypothesis can cause ataxia, therefore P (Ataxia | SCA) is very high. It can also cause neuropathy, therefore the two nodes can be connected by a strong edge. Weakness may also be seen in many types, therefore this node can be connected as well. However it should not cause weight loss. Therefore, the corresponding set contains the nodes {cerebellar ataxia, neuropathy, weakness} but does not include weight loss. In addition the time course is too short. Therefore the corresponding posterior probability is given by:

P (SCA | Cerebellar ataxia, neuropathy, weight loss, weakness) is approximated by P (SCA) × P (Cerebellar ataxia, neuropathy, weight loss, weakness | SCA).

In evaluating these probabilities, P (Alcoholism) is greater than P (Paraneoplastic Syndrome) and P (SCA). Therefore, alcohol becomes the primary diagnosis. However, given the rapid progression and clinical features in this instance, a paraneoplastic syndrome must be evaluated. Although this is an event of low probability, estimated at 1 in 10,000 patients with cancer [7], the expected loss (P (Paraneoplastic Syndrome) × Total Loss if this is not detected) is extremely high in terms of financial risk and potential irreversibility of something that may have been treatable. Therefore, our two top hypotheses must be evaluated in parallel. This can be evaluated by checking paraneoplastic antibodies in blood and by imaging. Given the patient's smoking history lung cancer becomes the top cancer that must be considered. Therefore, the most immediate test becomes a Chest X-ray, and a paraneoplastic panel in blood. If the antibody panel is positive and Chest X-ray is negative, a CT Chest Abdomen and Pelvis can be performed to investigate this hypothesis further.

A Chest X-ray done the same afternoon showed an "irregular nodular opacity in the left lung apex, with adjacent pleural-parenchyma scarring concerning for primary neoplasm vs. infection, including tuberculosis." A follow up CT Chest performed 4 days later showed a primary pulmonary neoplastic disease in the left upper lobe with intrapulmonary, hilar, and mediastinal nodal spread of disease. Images are shown in Fig. 5.6. Weeks later, the serum paraneoplastic profile showed positive Antineuronal Nuclear Antibody (ANNA)—1 (Anti Hu) which has been associated with such a presentation [7]. A graph theoretical method followed by probabilistic analysis of potential diagnoses, expected loss helped guide testing which established the diagnosis in a few hours. Following the diagnosis, the patient established care with another facility, follow-up information is therefore not available.

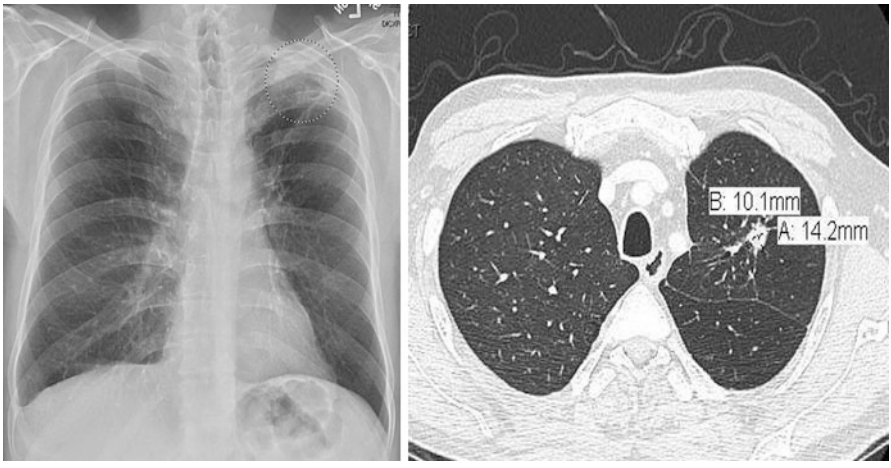

Fig. 5.6 Chest X-ray (*left*) and CT Chest images for case Example 2. There is a lesion involving the upper lobe of the left lung highly suspicious for malignancy. 3 weeks later, Anti Hu antibodies were found to be positive in very high titer

Case Example 3

RJ is a 33-year-old male with left ICA dissection, right hemiparetic, aphasic stroke since June 2011. He has had multiple strokes due to cervical dissections. No obvious etiology for the dissection such as fibromuscular dysplasia was found. It was felt these dissections were spontaneous and he was treated with anticoagulation. Following hospitalization, admission, clinical stabilization and completion of stroke work up, he was transferred to inpatient rehabilitation where there was continued progression of weakness. On review in neurorehab clinic, patient had worsening diffuse weakness; especially paraparesis which the patient and his family felt was relentlessly progressive since the stroke. Patient's mother mentioned there is a cousin who is reported to have a neuropathy.

Focused neurological examination revealed aphasia and dysarthria from his prior stroke(s). He had a mild right facial droop consistent with prior stroke. Motor examination revealed 3 to 4−/5 strength in bilateral upper extremities with marked atrophy in multiple muscle groups. Hand grips were 2−3/5 bilaterally. Hip flexors showed 2/5 strength in bilateral hip flexors and hamstrings. Ankle dorsiflexors were 0/5. Muscle tone showed expected spasticity in the upper extremities but deep tendon reflexes were absent throughout. A reliable sensory exam could not be performed but showed distal sensory loss.

Such a progressive pattern was quite unexpected for cervical dissection and stroke. Since there was considerable atrophy, a nerve conduction/EMG study was requested. The first EMG study done in September 2011 showed:

Nerve and side	Latency in msec (Normal)	Amplitude (Normal)	Velocity (Normal)	F waves
Median (Right) Wrist	5.3 (<4.4)	4.2 mV (>4.0)		42.6 ms (<32 ms)
Elbow	11.6	3.2 mV	35 m/s (>49 m/s)	
Ulnar (Right) Wrist	3.8	9.2 mV (>6)		44.2 ms (<32 ms)
Below elbow	9.5	8.2 mV	40 (>49 m/s)	
Above elbow	12.5	7.4 mV	40	
Median sensory (Right)	3.4 (<3.5)	17 μV (>20)		
Ulnar sensory (Right)	2.9 (<3.2)	18 μV (>10)		
Muscle and side	*EMG findings*			
R. Tibialis Anterior	Profuse spontaneous activity. Moderately enlarged motor units with reduced recruitment			
R. First Dorsal Interosseous	Absent spontaneous activity. Moderately enlarged motor units with reduced recruitment			

The study was interpreted as consistent with a moderate, sensorimotor polyneuropathy. Given the intermediate velocity slowing in the forearm, absence of conduction block, the neuropathy was likely to be an inherited neuropathy rather than an acquired one. Further, in the context of an affected relative, there was increasing concern the neuropathy is inherited. The patient continued to deteriorate

and was readmitted to the hospital with worsening weakness in spring of 2012. He underwent a repeat nerve conduction study which showed a complete absence of responses in the right median and ulnar nerves. Needle EMG performed of limited muscles of the right upper extremity showed profuse spontaneous activity in the right FDI with the patient being unable to activate any motor units. The right deltoid and biceps showed chronic neurogenic changes without spontaneous activity. Given the rapid progression in neuropathy over 6 months, this was interpreted as consistent with a severe sensorimotor acquired polyradiculoneuropathy which can be seen with chronic inflammatory demyelinating polyneuropathy (CIDP), vasculitic neuropathy, and forms of mononeuritis multiplex. Figure 5.7 shows MRI Brain and Spine images:

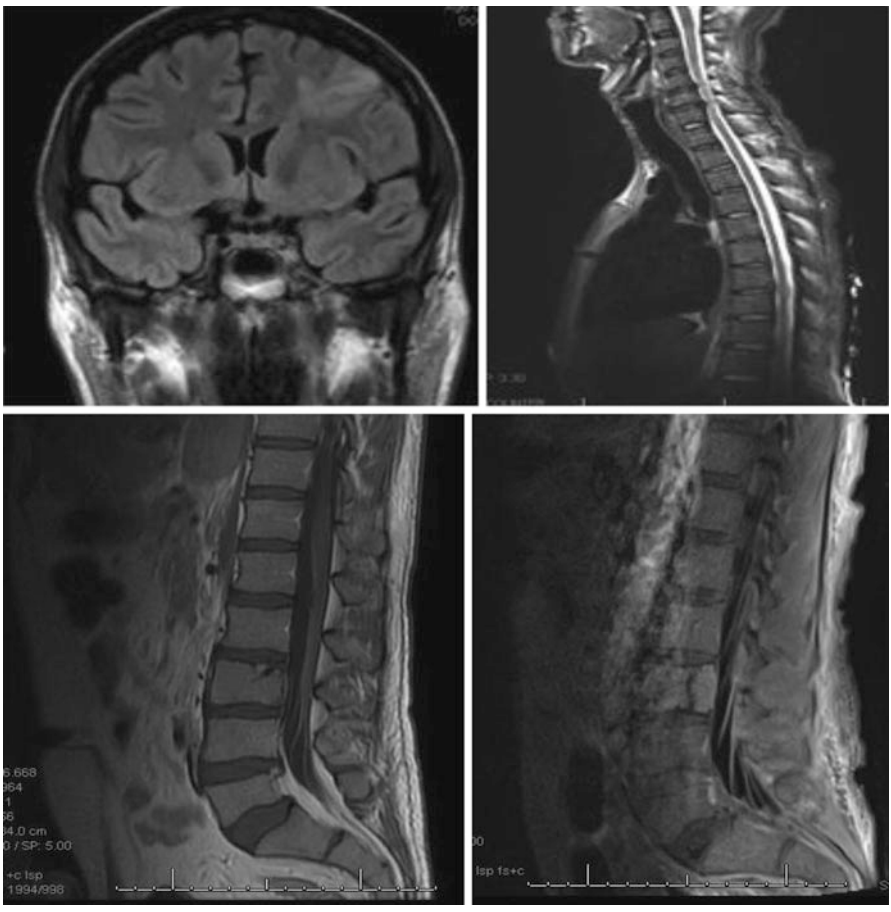

Fig. 5.7 MRI Brain images for case Example 3. *Top Left*: MRI Brain showing left frontal stroke. MRI C Spine showing moderate stenosis without cord compression. MRI Lumbar Spine showing diffuse enhancement of nerve roots. The radiologist also reported an aggressive appearing lesion involving the L3 vertebral body concerning for tumor. The radiological differential diagnosis for this lesion includes primary lymphoma, inflammatory neuropathy, melanoma, primary bone tumor, and metastatic disease

Lab Studies to date: showed CSF protein 256 mg/dL, 0 WBC, 166 RBC, CSF Glucose 65 mg/dL, CSF Flow Cytometry was normal. A blood thrombophilia panel showed a low-protein S level. An interventional radiology-guided biopsy of the L3 spine lesion showed hemangioma. SPEP and UPEP did not show any M Spikes. Plasmapheresis and steroids undertaken for presumed inflammatory neuropathy such as CIDP did not show any benefit.

Following the second EMG study, this relentlessly progressive problem was cast into a graphical framework. The following nodes were identified: Recurrent Strokes, Recurrent Dissections, Severe Neuropathy and Spine Tumor and a search done of medical databases. Based on the results of this search, the following candidate hypotheses were identified as shown in Fig. 5.8.

Hypothesis 1: POEMS Syndrome, also called Crow Fukase's disease stands for polyneuropathy, organomegaly, endocrinopathy, M spike, and skin changes. Not all patients show the classic syndrome, revised diagnostic criteria are discussed in [9]. Serum vascular endothelial growth factor (VEGF) is elevated in 68 % of patients with POEMS [9]. VEGF is believed to play a role in the pathogenesis of this syndrome. Starting with the first node stroke, there is a higher risk of stroke in patients with POEMS syndrome [10]. Therefore P (Stroke | POEMS) is moderately high. POEMS is characterized by a severe neuropathy which is frequently

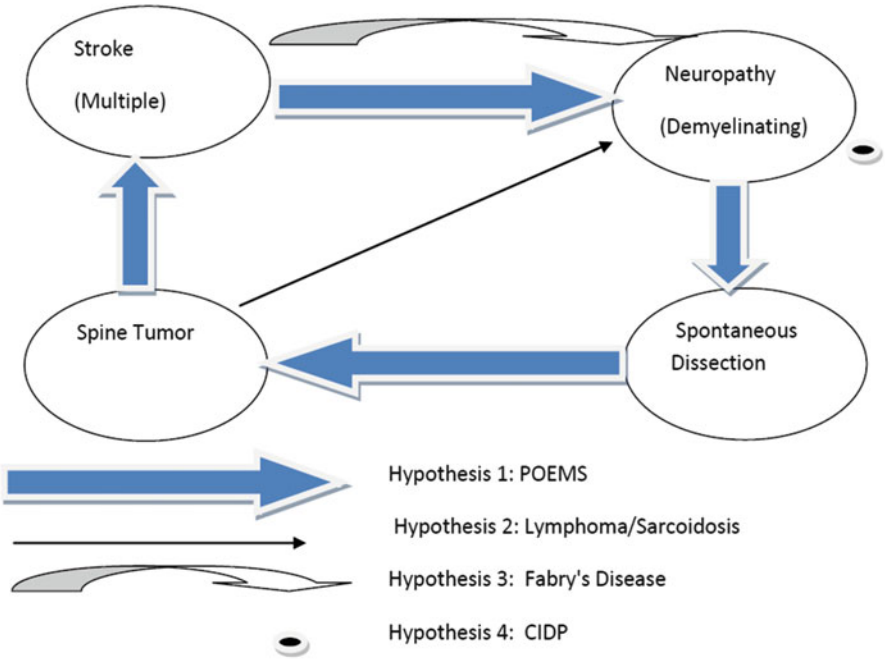

Fig. 5.8 Case Example 3 expressed in a graphical framework. The nodes are multiple strokes, demyelinating neuropathy, spine tumor, and spontaneous dissections. Candidate hypothesis that can connect these nodes are POEMS, Fabry's disease, CIDP, lymphoma and sarcoidosis

demyelinating. Therefore, POEMS can connect a strong edge between stroke and neuropathy. The mechanism of stroke is variable, but it is reported that one mechanism is to cause vascular dissection from endothelial dysfunction [10].

There is an increased risk of dissections in patients with POEMS [10]. Therefore an edge can be connected between neuropathy and dissection. Finally, POEMS is usually due to a plasma cell tumor, therefore it can connect the last node too of spinal tumor. Therefore the set {stroke, demyelinating neuropathy, dissection, and spine tumor | POEMS} can connect all the nodes.

Hypothesis 2: Lymphoma/Sarcoidosis: Lymphoma can cause spine tumor. Therefore it can account for one node. By infiltrating into the spinal canal, it can cause a progressive severe radiculoneuropathy. It may also cause a neuropathy by paraneoplastic means [7]. Therefore it can connect a strong edge between the two. However, it would be very difficult for it to connect stroke and dissections. Therefore the set contains the nodes {spine tumor, neuropathy | lymphoma}. Sarcoidosis can be evaluated in a similar manner.

Hypothesis 3: Fabry's Disease: Fabry's disease can cause stroke, therefore P (Stroke | Fabry's) is high. It can also cause neuropathy, therefore the two can be connected by a strong edge. However, it would not connect the nodes spinal tumor or dissection. Therefore the set contains the nodes {Stroke, Neuropathy | Fabry's Disease} under the hypothesis of Fabry's disease [11].

Hypothesis 4: CIDP: CIDP can cause a severe demyelinating neuropathy. Therefore P (Neuropathy | CIDP) is high but it cannot connect anything else. Therefore the set contains only one node under this hypothesis.

Ranking the hypotheses in order as discussed above, further investigation for POEMS was pursued. A serum immunofixation performed after the second EMG showed an IgA Lambda M Spike. A biopsy was performed of the spine lesion which showed a plasmacytoma. Subsequently, patient was treated with chemotherapy and radiation following current protocols with clinical stabilization and a slow recovery [9]. On review of records, VEGF level was 157 (normal < 86). CT Chest Abdomen and Pelvis showed anasarca which completed all criteria for POEMS syndrome.

Case Example 4

AF is a 67-year-old female with bilateral lower extremity weakness and numbness since August 2011. She was referred for treatment of CIDP. She noticed she was walking slower for about a month before she noticed numbness in her toes which moved up to her knees in 2 months. In the mean time she started getting weaker and had trouble walking due to her toes catching. The symptoms were symmetrical in both legs to start with, over time her left leg became weaker than the right. She also had some numbness in her hands and some pain in her lateral foot. She started to develop dark hair over her face which she attributed to being a side effect of

treatment with prednisone. She denied skin rashes, palpitations, sweating issues, dry mouth, bone pain, swallowing, or breathing difficulties. EMG testing was consistent with a severe demyelinating neuropathy leading to a diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP).

As part of work up, an IgA Lambda spike was discovered for which she underwent bone marrow biopsy and a skeletal survey. The patient had also noticed worsening swelling of the legs for the last several months since starting prednisone. After extensive work up by her hematologist, it was felt she had IgA Lambda MGUS which did not need treatment but annual surveillance for conversion to malignancy. According to standard treatment guidelines, the low levels of paraprotein did not necessitate treatment with chemotherapy or radiation at this time.

For treatment she had three IVIG (intravenous immune globulin) infusions and prednisone but felt no durable improvement. She perceived a benefit for about 10 days with the first dose of IVIG which was given over 4 days. Her subsequent IVIG infusions were given over 2 days, totaling 70 g on a monthly basis. She was also started on prednisone in December with an initial dose of 80 mg by mouth every day. She did not feel any benefit and the dose was reduced gradually to 40 mg every day without noticeable deterioration. Physical examination showed severe weakness and sensory loss in the legs, especially below the knees. Cranial nerves and upper extremity strength and sensation were normal. Motor exam showed 5−/5 strength in the right quadriceps, 4+ on the left. The right tibialis anterior was 4+, left 4. Eversion was 4− on the right and 3 on the left. EHLs showed 2/5 strength bilaterally. The medial gastrocnemius was 4 bilaterally. Muscle tone was decreased in the distal leg muscles. Sensation was decreased to pinprick to the mid shin level. She had a steppage gait. All reflexes were absent which is frequently seen in CIDP. NCS/EMG studies are shown in Fig. 5.9.

EMG was consistent with a severe sensorimotor demyelinating polyneuropathy. Given the prolonged F waves, the main condition to consider is CIDP with an IgA

Nerve and Side	Latency	Amplitude	Velocity	F waves (ms)
Peroneal (right and left), tibial (right).	**Absent**			
Ulnar Left				
Wrist	3.1 (<3.5 ms)	11.9 (> 6 mV)		40.6
Below Elbow	5.9	11.0	57 m/s	
Above Elbow	8.5	10.8	38 m/s	
Median Left				
Wrist	4.5 (<4.4 ms)	6.6 (> 4 mV)		40.6
Elbow	9.5	5.7	37 m/s	
Sural Left	Absent			
Ulnar Sensory Left	3.1	21 μV		

Muscle and Side	Findings
Tibialis Anterior Left	Moderate spontaneous activity. Moderately enlarged motor units with reduced recruitment.
Medial Gastrocnemius Left	Moderate spontaneous activity. Moderately enlarged motor units with reduced recruitment.
Vastus Lateralis Left	Mildly enlarged and mildly polyphasic motor units.
FDI, TFL, L5 and S1 paraspinals	Normal.

Fig. 5.9 NCS/EMG for case Example 4. The F waves are prolonged with prominent denervation changes in multiple muscles

lambda monoclonal gammopathy which had been diagnosed before. The poor response to IVIG was intriguing. As part of routine evaluation, a complete blood count was ordered which showed WBC 15 K and Platelet count of 879,000. A review of records showed a gradually increasing platelet count for several months for which no cause had been uncovered. Patient was being evaluated for essential thrombocytosis by her hematologist.

Visualizing data, the key decision making nodes are demyelinating neuropathy, IgA Lambda spike, edema, poor response to treatment and thrombocytosis. A focused search of the literature revealed the following candidate solutions.

Hypothesis 1: The initial formulation shows that she has CIDP with an IgA Lambda spike. The platelet count and edema are immaterial. This hypothesis cannot form any relation between the nodes save a link between CIDP and IgA Lambda M spike which are connected by an edge.

Hypothesis 2: CIDP, IgA Lambda Spike as related events with edema as a consequence of prednisone, physical inactivity (which are commonly seen) and Essential Thrombocytosis to account for the platelet count. (Essential Thrombocytosis is a condition where the platelet count rises because of a mutation in JAK2 gene.)

Hypothesis 3: POEMS syndrome [9]. While this is a completely different presentation from case example 3, the underlying disease remains the same. Applying the analysis developed before, POEMS can connect the nodes of demyelinating neuropathy, IgA Lambda spike, thrombocytosis, edema, and poor treatment response to IVIG by strong edges [9]. Therefore the set {Demyelinating neuropathy, IgA Lambda Spike, Thrombocytosis, Edema and Poor response to IVIG | POEMS} under the hypothesis of POEMS includes all the cardinal manifestations in this case.

The graphical model can be formulated as shown in Fig. 5.10.

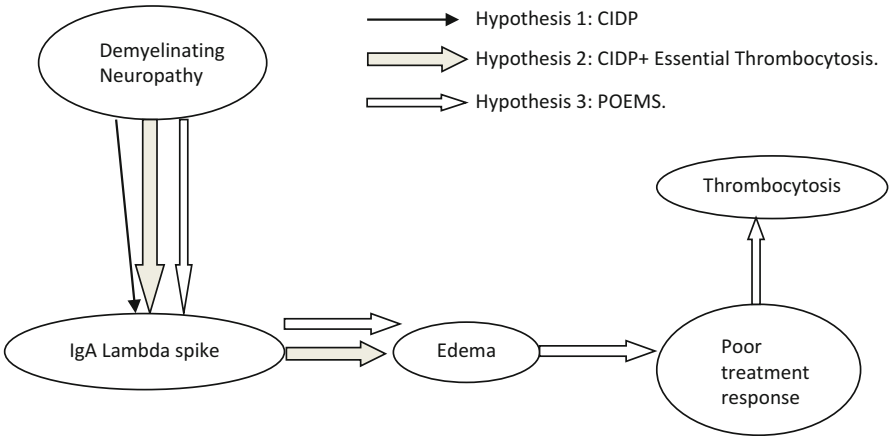

Fig. 5.10 Case 4: Hypothesis 3 forms the longest trail connecting all the nodes of this patient's presentation. Hypothesis 1 and 2 form shorter trails and although they are more intuitive, they are considered much less likely

However, once POEMS was considered the likely hypothesis, a blood test for VEGF was performed. Serum VEGF level was 987 which was elevated to five times the normal value. Unlike example 3, no source was found despite extensive skeletal surveys, CT Chest Abdomen Pelvis, and PET scans. Patient was treated with lenalidomide and dexamethasone by her hematologist with stabilization and mild improvement.

Conclusion

Distilling data, followed by data visualization to help identify key decision making nodes can be a valuable tool in diagnosis and guiding testing. These methods are borrowed from machine learning algorithms and simplify understanding of a problem and guide a focused search for a solution. The methods discussed in this chapter are similar to fault tree analysis (trees are a type of graph) discussed in Chap. 3. This method lends itself well to qualitative and quantitative analysis and is helpful in diagnosing syndromes where connections between nodes from multiple organ systems need to be made to yield the underlying diagnosis.

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Chapter 6
Byzantine Medical Problems: Decision Making with Misleading, Imperfect Information

Abstract Medical diagnosis and treatment decision making traditionally hinges on clinical judgment, available evidence from the literature and "test results". This information is highly imperfect and can be erroneous or frankly misleading. This chapter borrows from digital fly-by wire paradigms for processing information from unreliable sources for guiding diagnosis and treatment. A brief overview of the principles and architectures used in Airbus and Boeing Fly-By Wire systems is presented. The relevant architectures are used to inspire similar methods of thinking for medical diagnosis and treatment. This chapter extends the theory of fault tree analysis and probabilistic methods developed in prior chapters for guiding decision making in the face of uncertainty and misleading clinical information. Costs and treatment risks are incorporated into uncertainty associated with poor quality information. Medical examples are presented.

Byzantine Faults

A famous problem in computer science is the Byzantine Generals problem [1]. In this hypothetical situation, two or more byzantine generals need to attack an enemy fort. Each does not have the strength to attack alone and only a coordinated attack will succeed. They must coordinate and communicate their attack plans through unreliable, potentially treacherous messengers who can fail to deliver the message, can distort the message to mislead the other army or be intercepted by the enemy. Similarly in the dependability literature, byzantine faults refers to unpredictable system failures where failures manifest not merely as lack of output but as unpredictable and misleading system output. As shown in Fig. 1.6 of Chap. 1, such faults can cascade across systems with potentially catastrophic consequences.

Fault tolerant systems must deal with Byzantine faults [1]. To a great extent, medical decision making and treatment must deal with byzantine faults. Patient-reported symptoms, physical examination findings, laboratory findings, radiological findings, and neurophysiology (EEG, EMG) findings are prone to errors in understanding and interpretation which can mislead decision making with deleterious consequences. *While there is no solution to the Byzantine generals problem, approximate solutions are used in day-to-day applications to deliver dependable service* [1].

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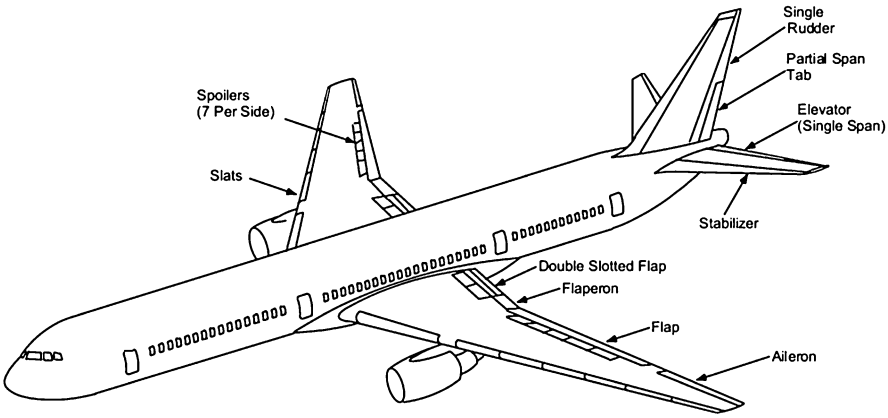

Fig. 6.1 The Boeing 777 control surfaces. Slats and Flaps increase the curvature of the wing to increase lift during take-off and landing. The rudder moves the plane in the "yaw" axis (moves the nose of the plane right or left). The ailerons are used to move the airplane in the "roll axis", where it rotates along its length to raise one wing and dip the other. The elevators and horizontal stabilizers move the plane in "pitch" axis where the nose goes up or down. © [1998] IEEE. Reprinted, with permission, from [4]

In traditional passenger airplanes, mechanical linkages in the form of hydraulics are used to transmit inputs from the pilot to movable sections of wings, horizontal stabilizers (elevators), rudder, called control surfaces to fly the airplane. This is shown in Fig. 6.1. The first analogue electrical flight control system, Fly-By-Wire (FBW), for a civil aircraft was designed by Aerospatiale for the Concorde [2]. In fly-by-wire systems, mechanical linkages are replaced by electrical wires which move the control surfaces using actuators (an actuator is a mechanism, usually electrohydraulic that physically moves the control surface) to control the airplane. The most exacting fault tolerant architectures which deal with byzantine faults are used in digital fly-by wire (DFBW) systems. This chapter briefly presents the chief features of DFBW used in Boeing and Airbus airplanes to describe two major architectures which are fault tolerant and capable of making safe decisions in the face of Byzantine faults [2–5].

In DFBW airplanes, pilot inputs are interpreted by flight control computers to make the necessary movement of control surfaces to make desired flight path modifications [2]. In autopilot mode, the flight control computers take their orders from the autopilot flight director computers (AFDC). The heart of the fly-by wire system is the primary flight computers (PFCs). They receive inputs from the pilot flying the aircraft, information from sensors (such as ADIRU, accelerometers, and rate-gyro) and perform complex signal processing on these data [2–5]. The Air Data and Inertial Reference Unit (ADIRU) perform two critical functions: providing air data (airspeed, attitude, altitude) and inertial navigation information to the PFCs and pilots on the electronic flight display. The PFCs use these inputs to calculate control laws to compute the control surface position commands. These commands are then transmitted to the control surfaces using an electrical data bus. To meet extremely

high functional integrity and functional availability requirements, multiple redundant hardware resources are required. *FAR/CS 25. 1309 standards specify that any combination of failures of this system which can cause catastrophic consequences be "extremely improbable" with probability of occurrence less than 1 in 10 billion per flight hour of operation* (*see Chap. 1*). *The fault tolerance for trustworthy FBW system design should consider all known and unknown causes of problems, failures, and errors known as common mode failure and single point failure* [4]. Based on these principles, the following sections look at the architectures used in Boeing and Airbus airplanes. Less technically inclined readers can skip sections "The Boeing 777/787 FBW Computers" and "Airbus Fly-By-Wire" and resume at section "Lessons from Digital Fly-By Wire".

The Boeing 777/787 FBW Computers

The Boeing 777, which debuted in 1995 is the first commercial DFBW airplane manufactured by Boeing. This was followed by the 787 in 2011 with common principles governing the design of the flight control system. The key principles of the Boeing 777/787 flight control design philosophy are [5]:

(a) The automation is an aid but does not replace the pilot.
(b) The pilot has the highest authority.
(c) The pilot and copilot must be aware of each other's input.
(d) Control functions will assist the pilot in avoiding or recovering from exceeding operational boundaries.
(e) Control laws reduce pilot workload and improve ride quality.
(f) Reliable alternate control mechanisms will be available to deal with failures.

The 777 uses a triple–triple modular redundancy design (TMR) for achieving fault tolerance [4]. TMR was introduced in Chap. 1 as a means of achieving fault tolerance.

The triple–triple modular system uses three identical channels termed left, center, and right PFC for redundancy. The outputs are transmitted to the control surfaces using three redundant ARINC (Aeronautical Radio, Inc.) 629 buses. There are three dissimilar computing lanes within each channel as shown in Fig. 6.2.

The PFCs are designed to comply with the following safety requirements:

(a) No single fault, including a common mode hardware fault, regardless of probability shall result in erroneous transmission of output signals without indicating failure [4, 5].
(b) No single fault, including a common mode hardware fault regardless of probability of occurrence shall result in loss of function in more than one PFC [4, 5].

Each PFC has three dissimilar computing lanes with three different processors using the ADA programming language. This is shown in Fig. 6.2. The three processors are the AMD 29050, Motorola 68040, and Intel 486 DX4 [4, 5].

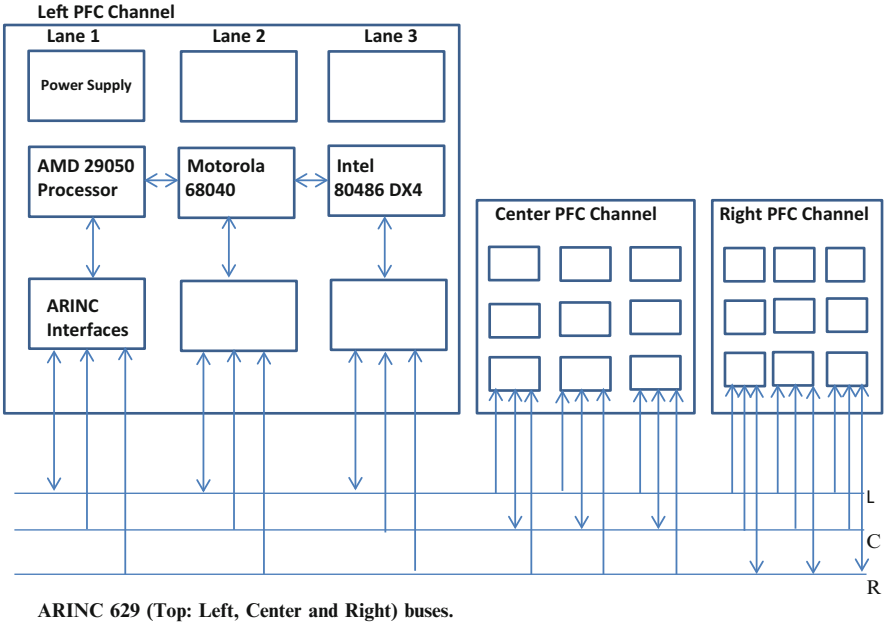

Fig. 6.2 The Boeing 777 Primary Flight Computers (PFC's). The DFBW system consists of three identical channels (*left*, *center,* and *right*), each of which is composed of three dissimilar computing lanes powered by different microprocessors. Each PFC receives and transmits on one ARINC 629 bus but receives all three bus lanes. Adapted from [4, 5]

As discussed in Chap. 1, failures can occur when certain input patterns combine with latent system faults and states to produce erroneous, unstable outputs. Using dissimilar processors manufactured by different companies in parallel mitigates this to a great extent since they are unlikely to fail together when presented with the same challenge, thereby mitigating against byzantine faults in the most complex component (microprocessor) of the system [4, 5].

Each PFC channel transmits on a preassigned data bus and receives on all the buses. This prevents one bad channel from disrupting all the communications. The three PFC channels are placed in different locations of the aircraft to prevent damage from structural causes from causing service failure of all systems.

In normal operation, the PFCs exchange information with each other for critical variable equalization to maintain convergence between PFC channel outputs. Each PFC lane operates in two modes—command role or monitor role. Only one lane in each channel is allowed to be in command mode [4, 5]. The PFC lanes in monitor role will perform a "selected output" monitoring of their command lane. If an error is detected in the command lane by the monitor lanes of a particular channel, it is declared bad and taken offline [4–6]. One of the spare lanes is upgraded to command assignment. The PFCs perform their calculations and exchange their proposed surface command outputs with each other. The proposed output from each channel is voted by a median value select algorithm in PFC hardware to produce the

selected PFC command output. They declare the selected median value as the actual computed control value. The command lane will send the selected actual surface command to its ARINC 629 bus [4–6]. This prevents structural fatigue from force fights induced by asynchronous PFC channel operation [4, 5].

The median value select method provides fault blocking against PFC faults until completion of fault detection, identification, and reconfiguration via PFC cross lane monitoring [4, 5].

Therefore, nine distinct computing lanes organized in three PFC channels, using three different sets of microprocessors communicating via three different ARINC 629 data buses provide redundancy in calculating DFBW output. This prevents a byzantine fault in any one lane from producing erroneous output compromising stable flight [4, 5]. Since their debut in 1995, excellent in-service reliability, six times better than predicted has been achieved. No unsafe events have occurred in over 20 million flight hours with more than 1,000 airplanes in service [5].

Airbus Fly-By-Wire

The Airbus A320/A330/A340/A380 and soon to debut A350 XWB family of aircraft are all DFBW. The Airbus A320 which entered service in 1988 is the first of the current generation of DFBW airplanes [2]. The striking feature of the entire Airbus family of airplanes is that control laws electrically drive all the control surfaces; the pilot sets objectives and not directly a control surface position [2, 3]. In all Airbus planes, conventional control columns are replaced by sidesticks. Therefore control surface positions are the sum of pilot inputs and stabilization orders [3]. As stated previously, the flight control computers take their orders from the pilot or from the AFDC. The flight control computers consist of five to seven computers and the autopilot system of two. The Airbus flight control system supports four main functions [2, 3]:

(a) Acquisition and monitoring of crew requests through sidesticks and associated sensors.
(b) Acquisition and monitoring of aircraft response.
(c) Piloting the aircraft via control laws so that the aircraft achieves the objectives set by the crew.
(d) Control of actuators so that control surface position appropriately changes the aircraft position.

To meet extreme dependability and safety requirements, the flight control computers should not produce an erroneous signal. The basic element of the Airbus architecture is the command (COM) and monitoring (MON) failsafe computer [2, 3]. This is shown in Fig. 6.3. These computers are subject to draconian safety requirements and are functionally composed of a command channel and a monitoring channel. The system incorporates a high degree of redundancy to deliver fault tolerance.

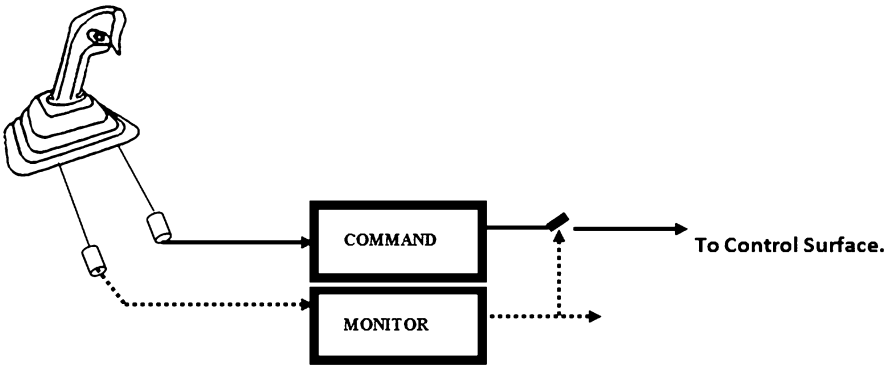

Fig. 6.3 Airbus FBW control-monitor architecture. One of the PFCs is in command role and the other in monitor role. When an error is detected, the command computer is disengaged by the monitor which is shown by the open switch in the above figure. Adapted from [2, 3]

The command channel ensures the function allocated to the computer (control of a mobile surface). The monitoring channel ensures the proper functioning of the command channel. These two computers have different functions and software. Both computers are simultaneously active [2, 3]. If the monitor computer senses an error and deselects the command order, it disables a solenoid valve on the corresponding actuator and it goes into stand-by mode. Two types of computers are used in the A320 FBW system: the ELAC (elevator and aileron computers) and the SEC (spoiler and elevator computers). Each computer includes a command channel and a monitoring channel. Therefore four different systems are used: the ELAC command channel, ELAC monitoring channel, SEC command, and SEC monitoring channel. This leads to four different types of software for redundancy [2, 3]. On the A320, two other computers are used for rudder control, the flight augmentation computers (FAC). The A320 has two ELAC computers, three SEC computers, and two FAC computers for redundancy.

On other DFBW Airbus planes (A330/A340 and A380), two different computers are used called PRIM (primary computers) and SEC (secondary computers). On these planes, rudder control is integrated into the PRIMs and SECs [2, 3].

Each channel (whether command or monitoring) includes one or more processors, associated memories, input and output circuitry, power supply and specific software [2, 3]. Each computer processes its inputs using different processors and software to avoid common mode faults. When the results of one of these two channels diverge sufficiently, the channel that detected the failure cuts the connection between the computer and the outside. The failure detection is achieved by comparing the difference between the command and monitoring orders with respect to a given threshold [2, 3]. This scheme allows the detection of consequences of a computer component failure and prevents the spread of the resultant error outside of the computer. Error detection is supplemented by monitoring the correct execution of the program and encoding of memories [2, 3].

Redundancy is managed at the system level. System functions are divided among all the computers so that each is constantly active on at least a subset of its functions [3]. For a given function, a computer is active, others are on stand-by (hot spares). As soon as the active computer interrupts its functioning, one of the computers in stand-by mode passes almost instantly into active mode with only a minimum perturbation of the control surfaces. These computers constantly transmit a signal of good health, when a failure is detected the signal is discontinued at the same time as the functional outputs to the actuator [3].

In the A340-600, four command and monitoring computers are used, with one being sufficient to power the aircraft [3]. In normal operation, one of the computers (PRIM1) provides control of the surface. The other computers control the other control surfaces. If PRIM1 or one of the actuators it controls fails, PRIM2 picks up the relay. Following the same type of failure, PRIM2 can pass on the task to SEC1 and then eventually to SEC2. In addition to redundancy, the system is capable of self-diagnosis. The DFBW system uses sensors distributed throughout the aircraft to sense failure and perform diagnosis.

Control laws need to be reconfigured in case of loss of some of the sensors, especially the ADIRU. For redundancy, each airplane has three ADIRUs. If all three ADIRUs are available as in the normal case, the pilot has full authority within a safe flight envelope since PFCs are able to make decisions with a high degree of accuracy and corroboration. If there are system failures and only 1 ADIRU is available, it is partly monitored by comparison to other independent sources of information. If all ADIRUs are lost, the protections provided by the PFCs are lost and control law finds itself in a limited degraded mode called direct mode which allows control similar to a conventional aircraft [2, 3]. The Airbus family of aircraft has accumulated a rich, extremely dependable experience in service [2, 3] with over 4,000 airplanes in service and over 80 million hours flown.

Lessons from Digital Fly-By Wire

Both Boeing and Airbus DFBW systems are extremely dependable and safe and have become the standard in civil aviation. The previous sections showed the greatly different systems used to achieve dependability. There are invaluable lessons for decision making to be learnt from the design principles of these systems which we will later extend to medical decision making.

1. Information processing by the PFCs assumes Byzantine faults at all levels. The PFCs attempt to verify and corroborate information from multiple different sources (ADIRU's, accelerometers etc.), so that no single or combination of byzantine faults can mislead the PFCs into making unsafe outputs. Therefore, under most circumstances, a faulty speed reading from a sensor cannot fool the PFC since it will be verified with data from a second and a third ADIRU prior to decisions being made.

2. The Airbus and Boeing systems use enormous diverse redundancy using different computers driven by different microprocessors and software to make decisions. This mitigates against byzantine faults in hardware and software which prevents a single hidden flaw in the system from making unsafe outputs.

Therefore as hypothesized by Dr. Dionysius Lardner in 1834, reproduced in Chap. 1, Airbus and Boeing FBW systems embody the principle that *the most certain and effectual check upon errors which arise in the process of computation, is to cause the same computations to be made by separate and independent computers; and this check is rendered still more decisive if they make their computations by different methods.*

In medicine, frequently such an approach is not made. A single error in one medical test or a single misdiagnosis will act as the basis for decision making downstream causing error propagation and system failure as shown in Chap. 1. Applying DFBW principles learnt above can prevent or mitigate against such byzantine medical errors. Borrowing from DFBW, assume the following decision making principles:

(a) All medical information whether they are patient-reported symptoms, physical examination findings, diverse test results, and radiology images should be considered unreliable and potentially misleading to varying degrees. The degree of unreliability varies from test to test: for example needle biopsies are highly fraught with sampling error, whereas large masses after they are resected are much less vulnerable to this susceptibility but still liable to errors in interpretation. This must be factored into medical decision making.
(b) In complex medical cases, an important diagnosis should not be susceptible to single point failure—in other words, the assumptions and test results for a diagnosis should be clearly analyzed and not be vulnerable to a single point of failure. As seen in case Example 2, Chap. 3, a weakly positive AchR-binding antibody titer should not form the absolute basis for a diagnosis of myasthenia gravis and be used to direct $50,000 worth of unnecessary treatment.
(c) Competing hypotheses must be entertained throughout the lifecycle of complex cases where a firm diagnosis is difficult to establish. In such cases, there should be constant striving to differentiate between the current working diagnosis and competing hypothesis. Fault Tree Analysis, Bayesian methods described in Chaps. 3 and 5 are some tools which can generate competing hypotheses and enable their continuous refinement and discrimination.
(d) Borrowing from these DFBW systems, each healthcare professional has latent (hidden) vulnerabilities in knowledge and judgment just as each microprocessor and its related software does (byzantine faults). These faults become activated when faced with specific unforeseen clinical challenges (just as a microprocessor and its software produce errors when faced with specific input patterns which expose vulnerabilities). In a manner similar to these systems, this can be overcome only by using knowledge redundancy—seeking the independent, unbiased opinion of colleagues and professionals (with different vulnerabilities) in a concurrent manner facilitating knowledge and

professional teamwork. It is assumed these concurrent opinions (analogous to the control-monitor role in Airbus planes or nine independent computation lanes in Boeing FBW) will reach conclusions using "different, independent" methods. A decision where there is reasonable consensus between two experts inspires greater confidence than a divergent one. If there is disagreement, the degree of disagreement and the degree to which it alters treatment decision making must be factored. For example, if expert 1 feels a patient has CIDP, expert 2 feels patient has vasculitic neuropathy (control-monitor role), while there is disagreement, there is commonality in both experts agreeing this is an inflammatory neuropathic condition and is likely to respond to anti-inflammatory measures like steroids and IVIG. Therefore, to a great degree there is concurrence and treatment maybe initiated. In a hypothetical case where expert 1 feels a patient has CIDP and expert 2 feels it is a variant of diabetic neuropathy, there is considerable divergence between their opinions and the matter maybe put to vote with a third concurrent opinion (similar to Boeing FBW) and the median value or majority vote selected prior to initiating treatment with expensive options like IVIG. The emphasis is on concurrent opinion where a matter is discussed and understood concurrently rather than delays waiting for second and third opinions. If a concurrent opinion is not possible, then the same professional must evaluate a different diagnosis as a virtual second opinion and discriminate between the two.

(e) Similar to flight control systems, medical diagnosis and treatment could be managed based on the degree of uncertainty in their foundations. The draconian standards applicable to the PFCs are not applicable to the in-flight entertainment system and food warming system. The in-flight entertainment system can produce output to the relevant screen even if there is some degree of uncertainty in the choice of movie selection. A similar paradigm can be applied to guide treatment in such circumstances as shown in Fig. 6.4.

Diagnostic Accuracy can be divided into three groups:

1. Low: These include diagnosis made on:
   (a) Weak test results, such as antibodies positive in low titer, mild elevation of muscle enzymes where unequivocal proof has not been well established.
   (b) Symptoms, especially self-reported experience of pain, numbness which is difficult to measure using objective means. Examples include fibromyalgia, forms of complex regional pain syndrome.

   In such cases, it is reasonable to embark on low cost and risk to intermediate cost and risk treatments as shown in Fig. 6.4. High treatment risk or cost is very likely not justified.

2. Intermediate: These include diagnosis made based on more objective physical examination findings (such as muscle strength, deep tendon reflexes) and test data. In such cases, there is some reproducible mild to moderate abnormality on physical examination findings or radiological data, however there is still room for uncertainty. Examples include abnormalities on MRI Brain raising concerns

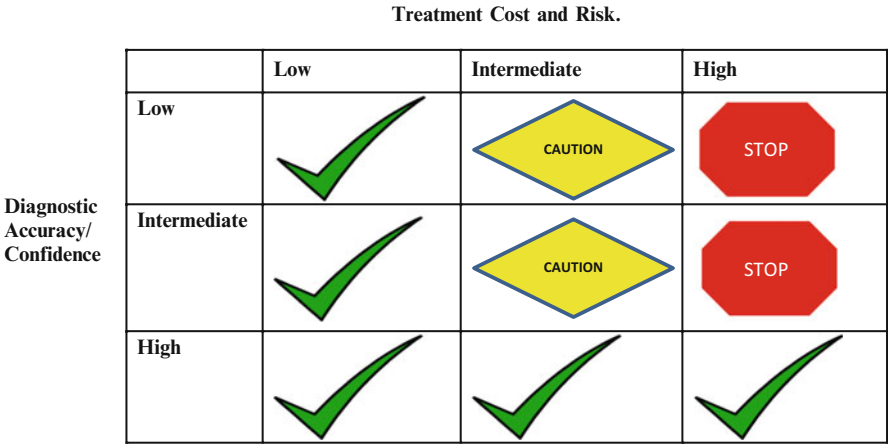

Fig. 6.4 A paradigm for treatment decision making in the face of uncertainty in diagnostic accuracy. The risks and costs associated with different treatments can be weighed in terms of confidence that is placed on the accuracy of the diagnosis

for multiple sclerosis. This situation is frequently encountered with neurophysiological measurements such as EEG, EMG, and visual evoked potentials. These information sources are fraught with poor diagnostic criteria, subjective errors in interpretation, and mild abnormalities form the basis of diagnosis leading to a nonnegligible probability of misclassification with huge ramifications for treatment costs and risks. This situation is also frequently encountered with biopsies due to sampling errors. Two real examples:

(a) GE is a 75-year-old female who suffered a right frontal hemorrhage several years ago requiring evacuation. She was subsequently admitted for waxing and waning mental status. Routine video EEG recording showed frequent abnormalities with possible seizures originating from her right cerebral hemisphere. She was started on phenytoin (later switched to carbamazepine) and levetiracetam (Keppra). Subsequent prolonged video EEG recordings were read as concerning for partial status epilepticus and the dose and treatment changed to carbamazepine since phenytoin and Keppra were not helping. Despite this, there was no improvement in her mental status. Based on frequent seizures on EEG, a recommendation was made to initiate propofol or midazolam as part of general anesthesia. Fortunately, prior to initiating general anesthesia, applying the Byzantine generals model, a concurrent review of her EEG was requested. Review of her EEG by an experienced epileptologist reported none of the prior EEG recordings were seizures. Therefore, there was substantial disagreement between two experts which exceeded the threshold for unequivocal diagnosis of seizures. Based on lack of corroboration of seizures, propofol or midazolam were not initiated and their costs and risks (general anesthesia

and intubation) avoided. The patient did develop severe transaminitis from carbamazepine which was managed conservatively.

(b) ND was a 54-year-old female who noticed a lump on the side of her tongue. The lump was not painful and showed a mild increase in size over 6 months. She was evaluated by an oral surgeon who did a biopsy from the edge of the lesion. This was reported as a benign lesion. No further workup was done over the next 6 months. Approximately 1 year later, it had started showing ulcerative features concerning for malignancy. Surgical excision proved it was carcinoma of the tongue, by when it had metastasized to the neck lymph nodes. Despite wide excision and radiation, the disease proved fatal within 2 years.

When a diagnosis is made with intermediate confidence in its veracity, it is reasonable to embark on low and intermediate cost and risk treatment as shown in Fig. 6.4.

3. High accuracy: This includes those rare happy situations where multiple sources corroborate a diagnosis and consequent treatment. Examples include conclusive biopsies, pathognomonic CT/MRI scans where the imaging features are unambiguous. Neurological examples include biopsy proven nerve vasculitis. In some conditions like CIDP which are difficult to diagnose, diagnostic accuracy is increased by multiple features which are corroborative. For example, mild-to-moderate nerve abnormalities alone may have only intermediate diagnostic accuracy. However, when combined with the typical clinical picture of areflexia, symmetric proximal and distal weakness, high spinal fluid protein, the combination increases the diagnostic accuracy even though no one feature is conclusive in itself. This is analogous to the condition described in Chap. 1 where multiple lower development assurance level (DALs) can be used in lieu of a single higher DAL.

In such circumstances, it is reasonable to embark on treatments involving high costs and risks if needed since the treatment is based on high confidence in the diagnosis. The high confidence stems from the diagnosis being supported by more than one feature, thus making it resistant to single point failure or a simple combination of failures. This principle is illustrated in Fig. 6.4. Case examples of medical decision making in the face of byzantine faults is presented below.

Case Example 1

KK is a 39-year-old female referred for weakness in both hands. This has been present for at least 4–5 years but may have been present for longer. 4–5 years ago the patient had surgery on a ganglion cyst on her right wrist. After the surgery when her cast was removed the physician noticed weakness and wasting in both

Abductor Pollicis Brevis muscles. Because of this she was referred to a neurologist who thought she may have a neuropathy as the cause. Eventually it was felt that she had a myopathy and needed evaluation at a university medical center. She feels the weakness is in her hands and distally in her legs. She has mild foot drop but this hasn't caused any falls and she tries to remain active and athletic. The weakness is painless but now it is starting to cause some functional problems with opening jars. She feels that her right side is slightly worse than her left. She had a CK checked and it was in the 2000s. She has never had any change in her urine color. The weakness doesn't fluctuate. She has not had any rashes or skin changes with this. She has no difficulties with raising her arms above her head, fixing her hair, walking up stairs, or rising from a chair. The patient is of English heritage, has a normal 16-year-old daughter and denies any similar illness or known neurological condition in her parents or siblings.

On examination no skin/nail changes characteristic of Dermatomyositis was seen. She had normal strength in her neck flexors and extensors, deltoids, biceps, and triceps. The right wrist extensors were 4+/5 and the left were similar. Wrist flexors were 5/5 bilaterally. Finger extensors were 4−/5 bilaterally. The flexor pollicis longus was 5−/5 bilaterally. The hand intrinsics showed severe weakness and wasting involving thenar eminences, hypothenar eminences, and FDI. Hip flexors showed only mild weakness being 5−/5. The quadriceps and hamstrings were normal. Bilateral tibialis anterior showed 4/4 strength with a mildly steppage gait. The medial gastrocnemius was normal showing 5/5 strength bilaterally. Deep tendon reflexes showed normal 2+ reflexes in the biceps, triceps, brachioradialis, knee, and ankle jerks. The sensory examination was normal. She was able to toe walk but unable to stand on her heels. The remainder of the clinical examination was normal. A review of records from outside showed high CK levels, ranging between 1,000 and 2,000 for a female weighing 55.8 kg or 123 lbs. The most recent CK measurement was 1962 performed in September 2012. Laboratory investigations for ANA, ANCA, SSA, SSB, HIV, and Syphilis were negative. Other data included HBA1c: 5.0, TSH 1.135 and CRP: 2.7. A NCS/EMG (shown in Table 6.1) was reported to be "consistent with a moderately severe distal myopathy with denervation potentials noted on EMG." Based on the EMG findings, the right tibialis anterior was considered the best muscle to biopsy. The patient was steroid naïve at this point. An FTA was performed as shown in Fig. 6.5. The main conclusions of the FTA can be divided into two groups—Inflammatory Myopathies and Distal Myopathies [7, 8].

A right tibialis anterior muscle biopsy was performed to evaluate for the two major classes of muscle disease: inflammatory myopathy vs. inherited distal myopathies. The muscle biopsy was reported to show an "inflammatory myopathy". The Gomori trichrome stain showed no evidence of rods, ragged red fibers, rimmed vacuoles, or increased connective tissue. Overall the pathologist favored polymyositis which merited consideration of immunosuppression.

The problem was formulated in a Byzantine generals framework. Since the condition requires long-term treatment with immunosuppression with potentially severe side effects there needs to be extremely high corroboration about the

Table 6.1 NCS/EMG for case Example 1

Nerve and side	Latency	Distance (mm)	Amplitude	Velocity	F waves
Median motor (Left)					
Wrist	4.3 (<4.4 ms)	70	1.0 (>4 mV)	52 m/s (>49 m/s)	30.3 ms (<31)
Elbow	8.2		0.2		
Ulnar motor (Left)					
Wrist	4.1 (<3.5 ms)	70	3.8 (>6 mV)		
Below elbow	7.1		3.6	58 m/s (>49 m/s)	31.9 ms (<32 ms)
Above elbow	8.9		3.6	61 m/s	
Peroneal motor (Left)					
Ankle	6.0 (<6.1 ms)	90	3.1 (>2 mV)		50 ms (<56 ms)
Fibula	12.8		3.0	42 m/s (41 m/s)	
Pop Fossa	15.7		2.8	38 m/s	
Tibial motor (Left)					
Ankle	6.0 (<6.1 ms)	80	3.4 (>3 mV)		45.6 ms (<58 ms)
Pop Fossa	15.5		1.7	38 m/s (>41 m/s)	
Ulnar left sensory	2.9 (<3.2 ms)	140	44 (>10 μV)		
Median left sensory	2.7 (<3.5 ms)	150	67 (>22 μV)		
Sural left	3.8 (<4.2 ms)	140	9 (>6 μV)		
Muscle and side	*Findings*				
Tibialis anterior (Left)	2+ Fibrillations and positive sharp waves. Small amplitude, small duration, polyphasic motor units with normal recruitment				
Vastus lateralis (Left)	No spontaneous activity. Mix of normal and small motor unit potentials showing mild polyphasia, normal recruitment, and activation				
Ext. Dig. Communis (Left)	2+ fibrillation and positive sharp waves. Small amplitude and duration motor units with polyphasia and early recruitment				
First dorsal interosseous (Left)	2+ fibrillations and positive sharp waves with small amplitude and duration motor units with polyphasia, normal recruitment				

Standard normative data are in brackets. The motor nerve conduction studies are abnormal demonstrating low amplitudes. The corresponding sensory potentials are normal which argues against a neuropathy. EMG findings showed small amplitude, duration motor unit potentials with considerable polyphasia consistent with a myopathic process

diagnosis for initiation of high-risk treatments. The following features need to be reconciled for adequate diagnostic accuracy:

(a) The EMG data is internally consistent, consistent myopathic features were seen in multiple muscles.
(b) The pathology sample is also highly definitive. Inflammatory features were observed on the biopsy with a definite conclusion by the pathologist.
(c) The clinical picture is not completely consistent—the pattern of involvement is remarkably distal, involving extensors of the wrist and fingers more than

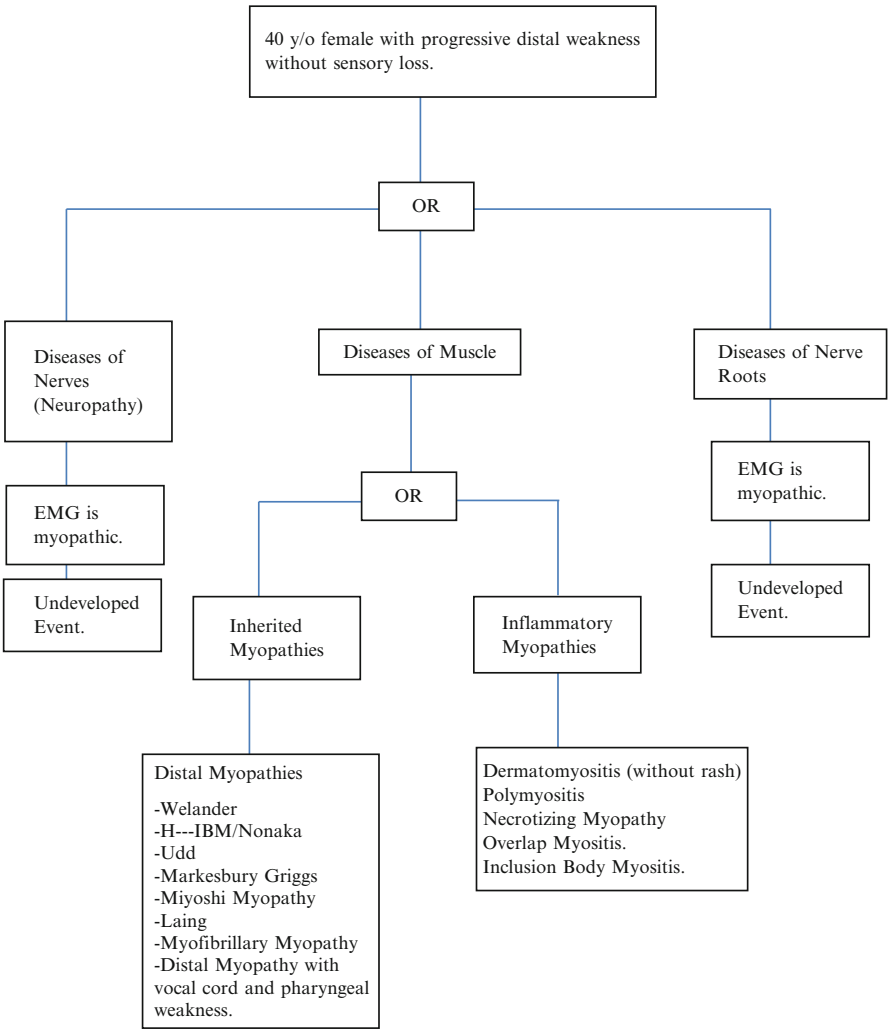

Fig. 6.5 FTA for case Example 1. The two major hypotheses are a form of distal myopathy vs. an acquired inflammatory myopathy

flexors and ankle dorsiflexors more than plantarflexors. This would be unusual for the inflammatory myopathies since they are usually proximal > distal. Distal inflammatory myositis with unusual features resembling polymyositis and focal myositis has been described in the literature, but these would be the exception than the rule [9].

The pathology sample is prone to Byzantine faults from sampling error. To mitigate against byzantine faults in pathology, the sample was sent to a nationally reputable institution, in a manner analogous to the control—monitor architecture.

Table 6.2 The clinical differential diagnosis of rimmed vacuoles on muscle biopsy

Differential diagnosis of rimmed vacuoles
Inclusion body myositis
Hereditary inclusion body myopathy
– h-IBM2 or Nonaka type distal myopathy
– hIBM with Paget disease and frontotemporal dementia
– h-IBM3 (myosin heavy chain IIa)
Distal muscular dystrophies
– Welander type
– Markesbery-Griggs type
– Udd type
Myofibrillary myopathy
Other muscular dystrophies/myopathies
– Reducing body myopathy
– Emery-Dreifuss
– LGMD2G
– Oculopharyngeal muscular dystrophy (PABP2-GCG triplet)
– Acid maltase deficiency
– Danon disease (LAMP-2)
– X-linked myopathy with excessive autophagy (VMA21)

Adapted from [10]

The pathologist concluded "necrotizing myopathy with lymphocytic inflammation, expression of MHC-Class 1 and deposition of complement C5b—9". In the body of the report, the pathologist was unable to confirm or refute the presence of "rimmed vacuoles" since the sample showed freezing artifacts. Specialized staining showed "caveolin +, dysferlin +, MHC-1 +ve, Embryonic Myosin Heavy Chain +ve, C5b—9 +ve". The two pathologic conclusions do not differ substantially; therefore they are within the convergence thresholds of inflammatory neuropathy.

Therefore two independent pathology experts were in concurrence about an inflammatory process (Table 6.2).

A decision making structure using three lanes was used in a manner similar to Boeing FBW. The first lane is clinical presentation. The second lane is Laboratory Information. The third lane is biopsy information.

Based on the above analysis, the tentative diagnosis was an inflammatory myositis with intermediate accuracy. The differential diagnosis is a form of distal myopathy (Welander, h-IBM2/Nonaka) being the leading considerations. Since diagnostic confidence was intermediate, from Figs. 6.6 and 6.7, low and intermediate cost and risk treatments were considered appropriate. The following were considered permissible in this instance from the treatment options for inflammatory myositis [7].

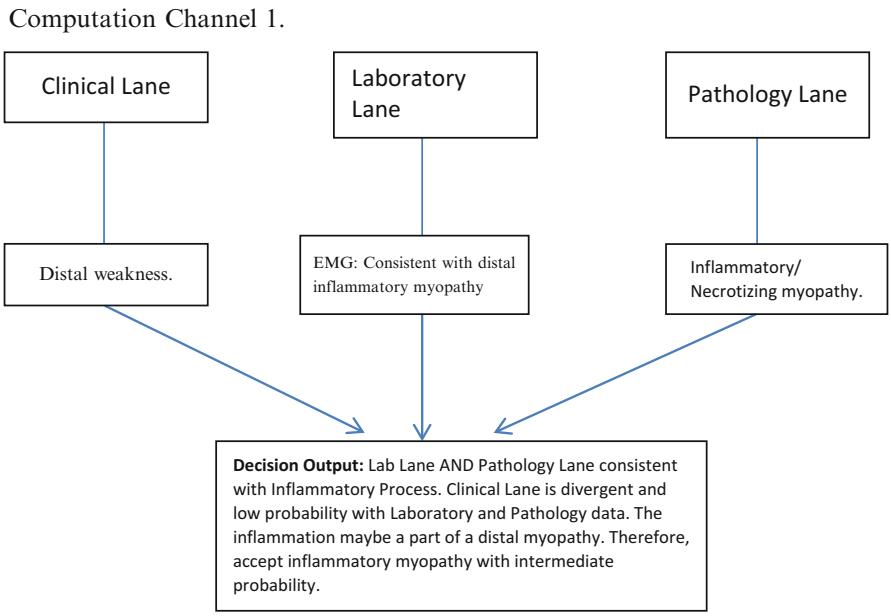

Fig. 6.6 Byzantine formulation of case Example 1. Each computation channel (physician in this instance) would integrate three different lanes of information and try to corroborate all features under one diagnosis with low, intermediate, or high probability to guide treatment

Fig. 6.7 Cost vs. Risk treatment matrix for options in inflammatory myositis [7]

Low Risk/Low Cost Prednisone Methylprednisolone	**Low Risk/High Cost** IVIG Rituximab
High Risk/Low Cost Azathioprine (Acceptable With reservations) Methotrexate	**High Risk/High Cost** None.

The matter was discussed in detail with the patient and her family. Since an inflammatory disorder is treatable, it was decided to try low and intermediate risk and cost treatments to see if there is improvement. The following assumptions were made in choosing treatment.

(a) The choice of therapy should be such that its worst failure mode would be minor side effects which are reversible and/or treatment failure.
(b) No treatment choice with major or lasting side effects in addition to treatment failure would be instituted. This excluded options like Methotrexate which can cause pulmonary fibrosis [7] and diagnostic accuracy is not high enough to warrant their usage. Azathioprine could be considered.

She was started on oral Prednisone and monitored closely in terms of subjective (self-experienced improvement in strength, dexterity in hands) and objective features (CK level, Strength on MRC scale). The oral prednisone FMEA was closely followed. After 2 months of treatment, her CK dropped to 202 but patient herself did not perceive significant benefit. No change was experienced in the hands. The dose was reduced to 40 mg/day and over 4 months to 20 mg/day. At some times she felt her right leg was stronger. Therefore, improvement was modest and close adherence to FMEA prevented significant adverse side effects. At her return visit 6 months later, she had modestly better strength in her right dorsiflexors which were 4+ to 5−/5 on the right and 4+/5 on the left. The remainder of the examination was unchanged. The patient felt more optimistic at this time and was interested in considering prolonged immunosuppression therapy with methotrexate, azathioprine, or IVIG.

Since patient had stopped experiencing benefit and physical examination did not show continued improvement, a second biopsy was planned. Three objectives were set for this biopsy:

(a) Primary Objective: A repeat search for rimmed vacuoles.
(b) Secondary Objective: If rimmed vacuoles are not found, look for evidence of decreased inflammation and regeneration of muscles. This would indicate treatment success and make a case for options such as IVIG, Azathioprine, and Methotrexate.

The patient was also referred to a top national university center for a second opinion. While there was no conclusive opinion, there was concern for a distal myopathy. A second biopsy done approximately 9 months into treatment showed "chronic myopathy with mild lymphocytic inflammation and rimmed vacuoles." Electron microscopy performed on the sample showed vacuoles containing membranous whorls (called myeloid bodies) which are the ultrastructural correlate of rimmed vacuoles. These are shown in Fig. 6.8. This suggests that the underlying process is a distal myopathy and not an acquired inflammatory myositis, therefore very likely untreatable. She was weaned off steroids but reported subjective and objective evidence of worsening leg weakness after the taper. The patient had not developed any adverse events at the end of therapy with stable weight, glycemic control, and blood pressure at the end of a trial of FMEA-guided steroid therapy.

Casting the problem in a Byzantine generals framework avoided use of IVIG, methotrexate, and azathioprine which have high costs or risks based on the misleading initial biopsy findings. The approximate cost of Prednisone and ancillary supplies for 1 year of therapy is estimated at less than $200. Evaluation for genetic etiologies is underway. *GNE* (UDP-N-Acetylglucosamine 2 epimerase/N Acetylmannosamine kinase) and *TIA1* gene tests for h-IBM and Welander's myopathy were negative. Further genetic testing will be pursued as costs fall.

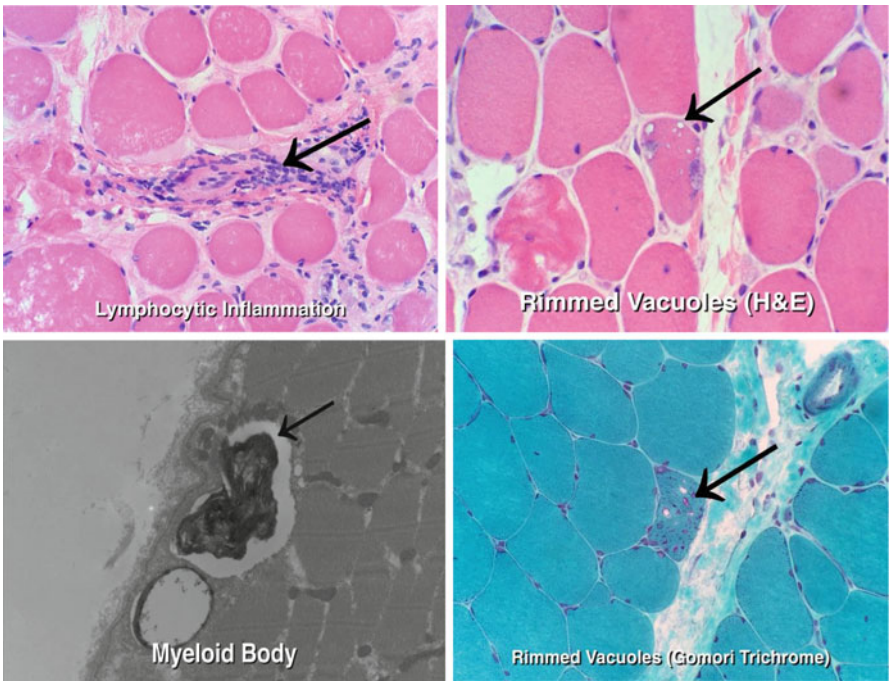

Fig. 6.8 Second biopsy slides for case Example 1. The *top* row shows lymphocytic inflammation and muscle fibers showing rimmed vacuoles. *Bottom* row *left* shows electron microscopy correlate of the rimmed vacuoles called myeloid bodies. Picture courtesy: Ryan T Mott, MD

Case Example 2

RM is a 58-year-old man with severe sensorimotor neuropathy due to monoclonal gammopathy of unknown significance presenting for further evaluation. His symptoms started almost 7–10 years ago with numbness and tingling in his fingers associated with some degree of pain. It progressed to involve his feet and he had significant balance problems. Currently he experiences numbness in his arms. He had many falls in the past and he went to a neurologist and had EMG/NCS that showed a predominantly axonal sensory neuropathy. Workup revealed MGUS due to an IgM monoclonal spike. This was diagnosed in 2005 after bone marrow biopsy and since that time he has been having skeletal surveys, CT scans, and blood work that has never shown a focus of myeloma, amyloidosis, or lymphoplasmacytic lymphoma. He feels he may have started experiencing weakness over the last few months. He has never been treated with IVIG or plasmapheresis. He has had repeated ENT and chest infections since childhood and used to get injections of IVIG as treatment. He was never diagnosed with a specific immune deficiency syndrome. Infections were due to pseudomonas, streptococcus, and pneumococcus. Repeated NCS/EMG studies showed steady progression of his neuropathy. His last

EMG/NCS in June 2010 (approximately 1 year prior to this evaluation) showed "large fiber sensorimotor neuropathy, primarily sensory and axonal". He denied any bowel or bladder symptoms or other symptoms of autonomic dysfunction such as orthostatic hypotension.

Past Medical History: Axonal neuropathy associated with IgM MGUS, Barrett's esophagus, hypertension, hyperlipidemia, unknown immune deficiency syndrome with frequent respiratory infections, gout, obstructive sleep apnea, and nasal polypectomies. Family History is concerning for father having a neuropathy.

Focused neurologic examination revealed normal mental status and cranial nerves. Motor examination was normal. Sensory examination revealed severe loss of joint position sense at the toes with severe sensory ataxia. Pinprick was decreased in a glove and stocking distribution. He was diffusely areflexic with a cautious gait. Review of medical records confirmed an IgM spike on multiple occasions. EMG conclusions were recorded as consistent with axonal polyneuropathy. The patient had an upcoming appointment in 4 weeks with a nationally renowned specialist at a top university.

The clinical picture was cast in a Byzantine framework as shown in Fig. 6.9. The clinical lane showed severe sensory loss, areflexia which is consistent with a demyelinating neuropathy. However, repeated EMG data is reported as axonal. IgM spikes with reactivity to anti-myelin-associated glycoprotein (anti-MAG) antibodies are frequently demyelinating [11]. The distinction is important since demyelinating neuropathies are treatable and inherited neuropathies are not.

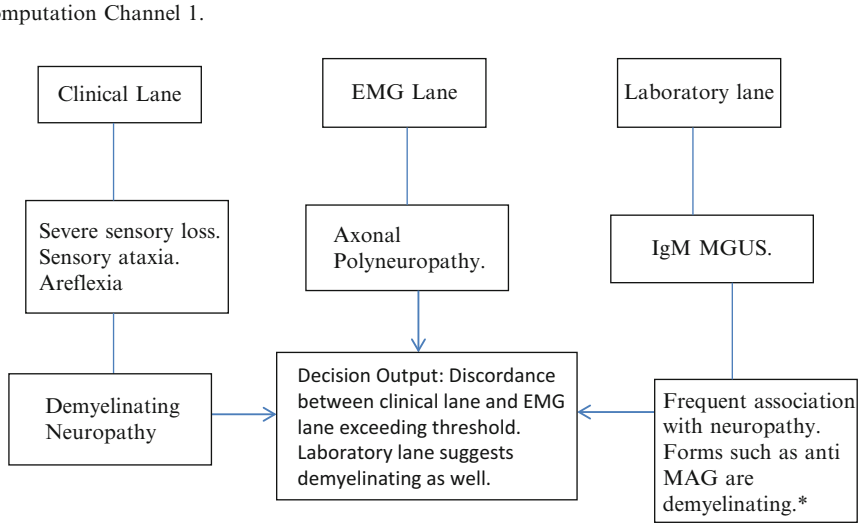

Fig. 6.9 Formulating Case Example 2. There is discordance in the outputs of the three lanes. The clinical lane suggests a demyelinating process while EMG data is reportedly axonal. (*Anti MAG antibody: anti-myelin-associated glycoprotein.)

Table 6.3 Nerve conduction data for case Example 2

	Left				Right			
Nerve	Latency (ms)	Amplitude (mV)	Velocity (m/s)	F waves (m/s)	Latency (m/s)	Amplitude (mV)	Velocity (m/s)	F waves (ms)
Median motor	6.3	6.1			6.4	5.8		
		5.7	41	40.7		5.0	45	26.4
Peroneal motor	6.5	6.0						
		5.9	33	60.8				
		5.4	34					
Ulnar motor	4.2	10.6			4.2	8.8		
		9.9	47	44		7.6	60	
		8.7	52			7.1	51	
Median, ulnar, sural sensory	Absent				Absent			

Their normative data is not available, but it can be assumed to be similar
EMG data is not available since only limited information is available from the other institution

A repeat EMG study was performed by the top medical center. A copy of the report is presented in Table 6.3.

The study was reported to show: "This is an abnormal study. There is electrophysiologic evidence for a motor and sensory polyneuropathy with features of mild uniform demyelination. The differential diagnosis includes intermediate forms of Charcot Marie Tooth (CMT) disease. There was no evidence for segmental demyelination (no conduction blocks or temporal dispersion) to support paraproteinemic or inflammatory neuropathy. There was relative prolongation of median vs. ulnar distal latencies which may suggest superimposed bilateral carpal tunnel syndromes".

While this study classifies the disease as a demyelinating neuropathy, it still differs considerably from the output of the clinical lane. The CMT disorders are not treatable, whereas acquired demyelinating neuropathies are treatable. The criteria such as conduction block and temporal dispersion can often be lacking, therefore this test is prone to Byzantine faults where an acquired treatable condition can be misclassified as an untreatable one [12]. Given the late onset, rapidly progressive debilitating course, the main concern was for an IgM-associated demyelinating neuropathy. A spinal tap showed CSF Protein 100 mg/dl, normal glucose, and 0 WBC.

The patient established care at the other institution. Following this study at the other institution, the patient underwent genetic testing for the CMT (axonal and demyelinating) disorders. This was negative. After a review of these results, a long discussion followed with the other institution where the EMG data was analyzed in light of the clinical picture. It is possible that nerve demyelination is confined to the nerve roots which causes only mild slowing along the course of the nerve without conduction blocks but nevertheless results in prolonged F waves in nerve studies. Therefore, nerve conduction tests are fraught with byzantine faults in this scenario.

An alternate interpretation of this data as an acquired demyelinating disorder associated with IgM spike was suggested. With this hypothesis, the outputs of the three channels will be concordant and reach a mutually supported conclusion. A third computation channel was created with another expert who expressed agreement with an acquired demyelinating neuropathy hypothesis. The outputs of the channels are shown in Fig. 6.10.

A tentative hypothesis for IgM spike-associated acquired demyelinating neuropathy was made and patient followed treatment at the other institution. After the initial genetic testing panel was normal, he underwent testing for subtypes of IgM antibodies associated with neuropathy. The anti-MAG antibody was normal. He was found to have high titers of Anti GD1a IgM antibodies. He was admitted for plasmapheresis at the other institution and experienced considerable improvement after the first five sessions. He continues to be treated with IVIG at this time with sustained, modest benefit.

This is an example where strict application of rules for interpreting EMG data leads to misleading information, potentially setting the clinician for misclassifying a treatable disorder as an untreatable one. Casting the problem in the Byzantine generals framework seeking corroboration from multiple parallel lanes of data (clinical lane, EMG lane, and laboratory lane) led to the correct conclusion in the face of Byzantine faults.

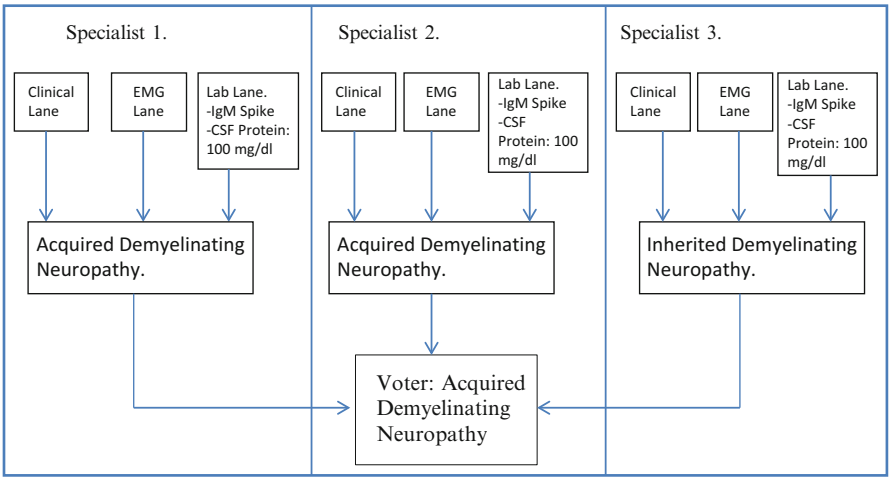

Fig. 6.10 Majority voting using three independent channels (three different specialists) led to a majority vote in favor of an acquired demyelinating process using triple modular redundancy (TMR) architecture

Case Example 3

BL is a 19-year-old female with a 2-week history of progressive diffuse weakness. Symptoms started approximately 2 weeks prior when she began to experience difficulty with grip strength and paresthesias in both hands. This progressed symmetrically and proximally over the next few days to include the entirety of both arms up to the shoulders. She then experienced paresthesias in her central chest. After about 1 week the weakness and paresthesias spread to her proximal legs and progressed further distally over the course of about 2–3 days. Over the next several days she developed progressive difficulties with gait. She denied any bowel or bladder incontinence.

MOTOR: Muscle Strength: Strength—4/5 in bilateral grip strength, wrist extensors and flexors; 4+/5 in bilateral biceps/triceps/and deltoid. Lower extremities show 4/5 strength throughout except for bilateral plantar flexors which appears 5/5.

Muscle Tone: Tone and muscle bulk were normal in the upper and lower extremities. Deep tendon reflexes were 3+ at both patellar tendons, otherwise 2+ and symmetrical in all four extremities; plantar responses were flexor bilaterally. Coordination showed intact finger-to-nose, heel-to-shin, and rapid alternating movements without tremor. Sensory examination showed decreased sensation to light touch, vibration, pinprick which was maximal in the proximal lower extremities and reduced diffusely throughout the upper extremities. Gait: Patient was unable to ambulate due to weakness and poor balance. She was able to stand with assistance.

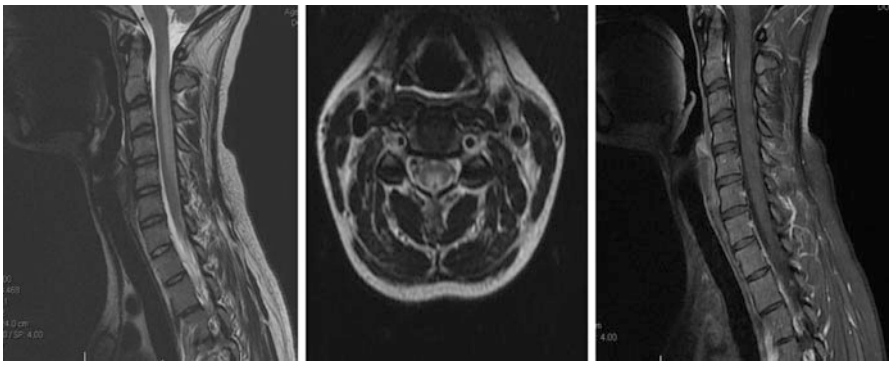

Fig. 6.11 MRI imaging for case Example 3. *Left* T2-weighted sagittal images, *middle* axial T2 images, and *right* sagittal T1-weighted postcontrast images. The images show abnormal signal predominantly in the dorsal columns and the lesions are not contrast enhancing. Courtesy: Pearse Morris, MD

Patient had MRI Brain, Cervical, Thoracic, and Lumbar Spine scans performed outside which were reported to show longitudinally extensive transverse myelitis (LETM). An extensive workup was initiated looking for common etiologies of the same. Outside records indicated that vitamin B12 level was 300 (nominally >200), ANA screen, SSA, and SSB antibodies were negative. HTLV, Lyme antibodies were pending. CSF studies showed 0 WBC, Protein 32 mg/dL; HSV, VZV, CMV, and EBV PCR were normal.

She was treated with IV Methylprednisolone 1,000 mg QDaily for transverse myelitis. Supportive care included physical therapy with mild improvement at the end of a 5-day course of methylprednisolone. The main question and reason for transfer was whether to initiate plasmapheresis for presumed neuromyelitis optica (NMO) since she had such limited improvement with methylprednisolone. A repeat MRI C Spine w/wo Gad was obtained shown in Fig. 6.11. (Prior images performed at the outside institution are not available for comparison.)

Casting the problem in a Byzantine generals framework helps guide further decision making [13, 14]. This is shown in Fig. 6.12.

The pattern of spinal cord involvement with preponderance of dorsal column involvement, lack of enhancement is consistent with subacute combined degeneration (SCD) of the spinal cord [14]. Vitamin B12 deficiency is one of the commonest causes of SCD. Even though the B12 level was 300 which is considered normal, this is misleading information. A serum methylmalonic acid level (MMA) level which is a better indication of vitamin B12 deficiency was checked which was 10,800 (normal <300) [14]. This helps establish the diagnosis as SCD of the cord from B12 deficiency. The patient was treated with IM cyanocobalamin 1,000 μg Qdaily for 5 days followed by monthly supplementation. Three weeks later, the results of CSF Oligoclonal bands were obtained and were negative [14]. Subsequently, the results of NMO antibody testing returned (approximately 70 % sensitive) negative [13].

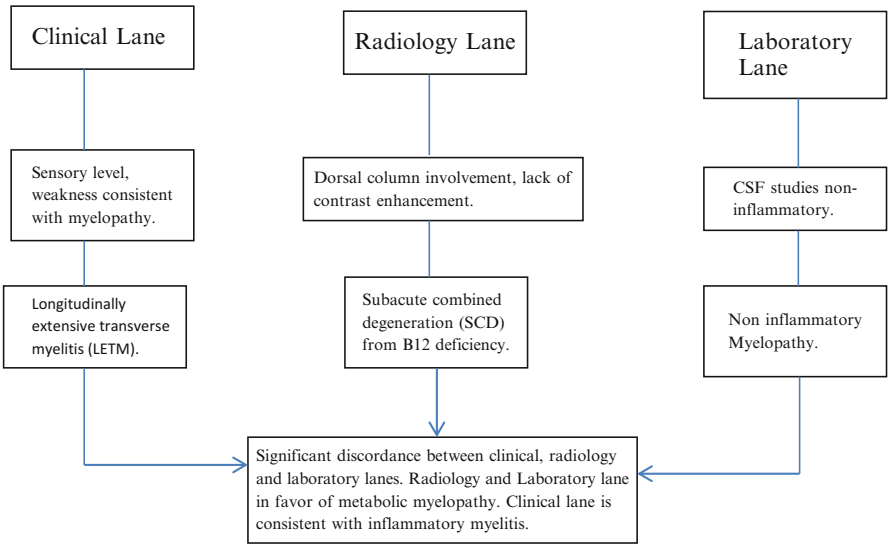

Fig. 6.12 Formulating Case Example 3. There is discordance in the outputs of the three lanes with the radiology and laboratory lanes favoring a noninflammatory cause. The clinical lane favors an inflammatory etiology

Casting the problem in FBW framework where there was a lack of information corroboration between the clinical, radiological, and laboratory lanes helped establish the diagnosis. This led to the following changes in the patient's treatment:

(a) Plasmapheresis did not need to be performed.
(b) Long-term immune suppression with medications like Rituximab, mycophenolate mofetil (MMF), azathioprine, and/or oral prednisone which are instituted in patients with LETM for preventing future episodes were avoided. With the exception of prednisone, these are expensive and have serious side effects [13].
(c) Correct treatment with high-dose parenteral cyanocobalamin could be instituted.

The cause of the severe B12 deficiency (infections, pernicious anemia, nitrous oxide abuse, nutritional) was not established since patient and family transferred her care out of state and were lost to follow up.

Case Example 4

EWS is a 49-year-old male presenting with symptoms of progressive weakness over the last 8 weeks. These symptoms were initially noticed after he was started on atorvastatin 40 mg QHS for hyperlipidemia. Subsequently the dose was increased

to 80 mg. He started noticing weakness in his hips bilaterally. He denies any cramps, myalgias or muscle aches, and pains. A CK level checked at the time was around 500 according to the patient. These symptoms gradually progressed and he started noticing weakness in his shoulder muscles. He also reports sometimes having noticed difficulty keeping his eyes open. He states that at times in the day, the eyes shut off on him. There is some day-to-day variation, but he denies having noticed that symptoms are worse at night. He has noticed it is a little difficult for him to breathe lying flat during this period. Even though statins were stopped, he feels that the symptoms are progressively worsening. He is unable to work at this time. He denies any diplopia. He does report that at times his vision feels different and he feels dizzy, but he denies any true vertigo or nausea associated with it. He denies any dysarthria or dysphagia. He denies any numbness or tingling in his upper or lower extremities. The referring physician's major concern was for statin-induced myopathy.

MEDICATIONS LIST: Fish oil, Aspirin, Metoprolol, Lisinopril. Recently stopped medications include varenicline, atorvastatin, and fenofibrate which were stopped for the last 4 weeks.

Past Medical History includes coronary artery disease, s/p stenting, hypertension, and hyperlipidemia.

SOCIAL HISTORY: He quit smoking 9 weeks ago. He reported social use of alcohol and denied any drug use.

On focused neurological examination, mental status was normal. Cranial nerve examination showed mild-to-moderate fatigable bilateral ptosis. Extraocular movements were conjugate, symmetric without evidence of diplopia. There was mild diplopia and bilateral exotropia elicited with 1 min of sustained upgaze. Curtain sign was positive bilaterally. He had minimal eye closure weakness. Cheek puff, jaw closure, jaw opening, facial sensation, and hearing were normal bilaterally. The uvula was midline with normal elevation of the soft palate. The tongue protruded in the midline with normal side-to-side movements.

Examination of the motor system revealed he had mild neck flexion weakness, which was 5−/5. Neck extensors were 5/5. The deltoids showed 4/5 strength bilaterally and were fatigable. The biceps, triceps, wrist flexors, extensors, and intrinsic hand muscles showed normal strength. In the lower extremities, the hip flexors were 4/5 in strength. He had normal strength in his hip adductors, abductors, knee extensors, knee flexors, plantar and dorsiflexors. Deep Tendon Reflexes were 1+ in the upper extremity, 2+ at the knees and 1+ at the ankles. Sensory examination and cerebellar examination were both normal. He had a waddling gait. Additionally he was unable to stand up from the floor without using his arms (positive Gower maneuver when arising from the floor).

A NCS/EMG was performed for further evaluation. The data is shown in Table 6.4. The nerve conduction studies were normal without evidence of neuropathy (based on normal sensory, motor responses, F waves). Repetitive nerve stimulation (RNS) studies of the right spinal accessory nerve recording the corresponding trapezius muscle were normal. RNS of the right facial nerve

Table 6.4 NCS/EMG findings for case Example 4 performed for progressive weakness noticed after high-dose statin therapy

Nerve and side	Latency	Distance	Amplitude	Velocity	F wave
Peroneal right					
Ankle	4.9 ms (<6.1 ms)	90 mm	4.0 mV (>2 mV)	45 m/s (>41 m/s)	51.8 ms (<56 ms)
Fibular head	11.6 ms		3.9 mV	42 m/s	
Popliteal Fossa	14.0 ms		3.9 mV		
Tibial right					
Ankle	4.8 ms (<6.1 ms)	80 mm	4.5 mV (>3 mV)	41 m/s (>41 m/s)	
Popliteal Fossa	14.1 ms		4.3 mV		55.4 ms (<58 ms)
Sural right	3.4 ms (<4.2 ms)	140 mm	9 μV (>6 μV)		
Muscle and side	*EMG findings*				
Right Deltoid, Biceps, Triceps, Vastus Lateralis, Tibialis Anterior, Medial Gastrocnemius, T8 paraspinals	Normal				
Repetitive nerve stimulation (RNS):	1. Stimulating right spinal accessory recording trapezius: Normal				
	2. Stimulating right facial nerve recording the nasalis: >10 % decrement				

Standard normative data are in brackets. The abnormal decrement in the repetitive nerve stimulation (RNS) study recording the nasalis muscle confirms a neuromuscular junctional disorder which in the presence of normal motor amplitudes is consistent with myasthenia gravis

recording the nasalis muscle showed a greater than 10 % decrement. Verification of the waveforms showed adequate quality for clinical decision making since the nasalis is a difficult muscle to record due to low amplitudes and motion artifact. Needle EMG of the right deltoid, triceps, biceps, vastus lateralis, tibialis anterior, medial gastrocnemius, and T8 paraspinals were normal. There was repair of the decrement after 10 s of exercise. Based on these findings, the NCS/EMG was reported as "this is an abnormal study consistent with a defect of neuromuscular junction transmission such as myasthenia gravis."

A Mayo Clinic Myasthenia Gravis panel checking antiacetylcholine receptor antibodies (blocking, binding, and modulating) was normal. A CT Chest for excluding Thymoma was requested but there was delay in obtaining the results. The patient was started on treatment with Prednisone 60 mg/day and Pyridostigmine 60 mg QID with modest benefit. At his return visit in 6 weeks, he reported experiencing improvement in ptosis but continued to experience difficulty standing from a seated position and walking. Given this unexpected clinical course, the problem was cast in the FBW framework as shown in Fig. 6.13.

The less than anticipated improvement at the follow-up visit led to the following FTA in Fig. 6.14.

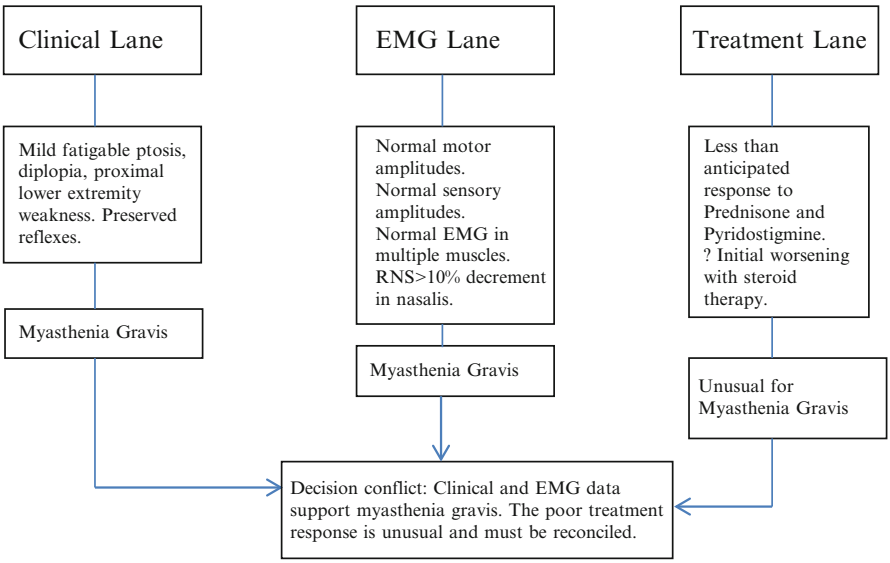

Fig. 6.13 FBW framework for case example 4. The clinical and EMG lanes based on published data are consistent with myasthenia gravis. However the lack of response to prednisone and pyridostigmine is somewhat unusual

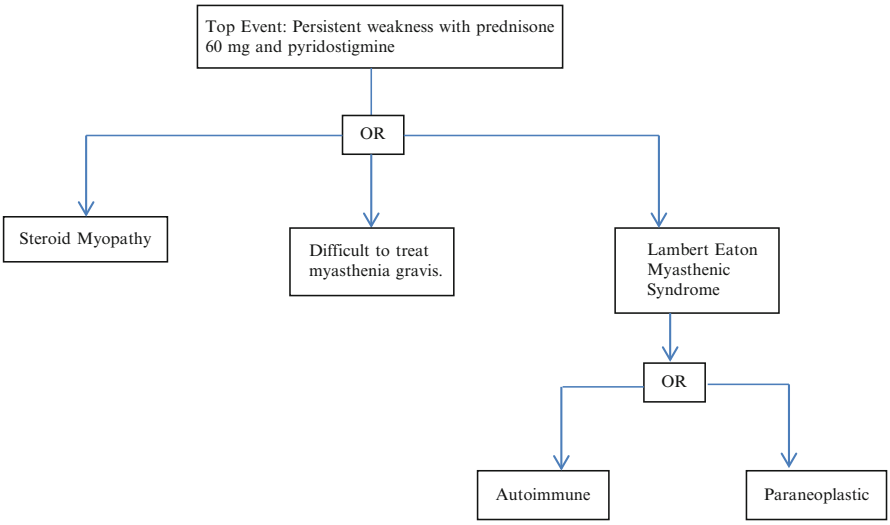

Fig. 6.14 FTA for case Example 4 for top event of poor response to Prednisone 60 mg daily

Difficult-to-treat myasthenia gravis is the natural conclusion. Blood anti-MUSK (muscle-specific tyrosine kinase) antibodies were ordered. This is usually treated with plasmapheresis or IVIG and is a fairly frequent occurrence in the treatment of

myasthenic patients. Lambert Eaton Myasthenia Syndrome (LEMS) is a consideration in the right branch of the tree [15]. While LEMS has features which are very similar with myasthenia gravis, the prominent limb girdle weakness argues in favor of LEMS. However two characteristic diagnostic features of the disease are missing: areflexia on clinical examination and low-motor amplitudes on nerve conduction studies [15]. A decrement on repetitive nerve stimulation is common to both myasthenia gravis and LEMS, however low-motor amplitudes are seen in LEMS and not myasthenia gravis. (The low motor amplitudes improve with 10 s of maximal isometric exercise in a phenomenon called facilitation.) Since motor amplitudes were normal, facilitation was not performed. Considering these to be byzantine faults from EMG, the possibility of LEMS was investigated by the following:

(a) Single-fiber EMG to confirm a junctional disorder.
(b) Check Voltage-Gated Calcium Channel Antibodies (VGCC): this was done as part of a Mayo Clinic Paraneoplastic Panel. (Approximate turnaround time 3–4 weeks)
(c) Encourage the patient for expediting scheduling and completion of his CT Chest given the suspicion for a paraneoplastic disorder (LEMS).

CT Chest was reported to show "Large middle mediastinal masses with extensive mediastinal lymphadenopathy, concerning for lymphoma. Other differential considerations include primary bronchogenic carcinoma and sarcoid, both felt less likely. Several of the mediastinal lymph nodes and the subcarinal mass would be amenable to transbronchial biopsy. 13 mm left upper lobe pulmonary nodule."

A single-fiber EMG of the frontalis muscle showed increased jitter and blocking consistent with a junctional disorder. Based on the CT Chest results, patient underwent mediastinoscopy followed by biopsy of the lymph nodes. These were reported to be "consistent with small cell lung cancer." Three weeks later, the results of his paraneoplastic panel showed positive VGCC P/Q (0.82, normal <0.02) and *N* type (0.19, normal <0.02) antibodies.

The management of this patient will be discussed again in Chap. 10 since it represents a success of collaboration and teamwork. Casting the problem in a byzantine framework, seeking information corroboration and performing an FTA led to the pursuit of LEMS instead of pursuing IVIG and plasmapheresis for presumed poorly controlled myasthenia gravis. This proved to be lifesaving since it allowed institution of aggressive chemotherapy and radiation for treatment of small cell lung cancer. The patient is alive and well 3 years after the diagnosis, while the usual survival for untreated small cell cancer is less than 1 year [16].

Case Example 5

This patient was seen for NCS/EMG, therefore only a brief history was taken as narrated by the patient and his parents to perform the test. TS is a 16-year-old male who developed symptoms of numbness, tingling, and weakness a few days after

Table 6.5 NCS/EMG data for case Example 5

Nerve and side	Latency (ms)	Distance	Amplitude (mV)	Velocity (m/s)	F waves (ms)
Sural, ulnar, and median sensory (right)	Absent				
Tibial motor (Right)	Absent				
Peroneal motor (Right)					
Ankle	9.9 (<6.1 ms)	90	2.5 (>2 mV)		
Fibular head	18.6		2.2	37 (>41 m/s)	50.4 (<56 ms)
Popliteal Fossa	22.6		1.8	25	
Ulnar motor (Right)					
Wrist	7.6 (<3.5 ms)	70	6.4 (>6 mV)		
Below elbow	12.2		5.7	46 (>41 m/s)	47.8 (<32 ms)
Above elbow	16.0		3.3	29	
Median motor (Right)					
Wrist	8.7 (<4.4 ms)	70	4.7 (>4 mV)		48.2 (<31 ms)
	15.2		4.4	37 (>49 m/s)	
Muscle and side	Findings				
Tibialis anterior (Right)	No spontaneous activity, mildly enlarged stable motor units. Mildly reduced recruitment				
Vastus lateralis (Right)	Normal				

Standard normative data are presented in brackets

sustaining a concussion 5 months prior. He was playing football and he was tackled several times. He denied any loss of consciousness. Symptoms improved to some extent spontaneously, however they continued to cause poor balance, numbness, and tingling in the feet. He denied any family history of neuropathy. Physical examination revealed mild weakness of dorsiflexion bilaterally, mild sensory loss distally, and diffuse areflexia. Patient had normal arches, so did accompanying family members.

NCS/EMG showed the following pattern, shown in Table 6.5.

The key features are prolonged distal latencies, uniform slowing, absence of conduction blocks with the only amplitude drop being in the right ulnar motor response with slowing across a compression site (elbow). Needle EMG did not show any evidence of denervation. Based on these features, the EMG was reported to show "This is an abnormal study. There is electrophysiologic evidence most consistent with a length-dependent, uniform, sensorimotor demyelinating polyneuropathy. The uniform slowing, absence of temporal dispersion or conduction block favors an inherited etiology over an acquired one like CIDP. Given this pattern, major etiological considerations would be CMT1, CMT X, and especially given the additional slowing across compression sites hereditary neuropathy with liability to pressure palsies (HNPP) [17]".

This conclusion was arrived at based on the description of trauma prior to the perceived symptoms and by the unique features observed in this study. This report was sent to the ordering neurologist who based on this report proceeded with genetic testing for the CMT (especially PMPP22 duplication/deletion) disorders. Testing was negative, but that is possible in a small percentage of cases (~10–15 %). The patient and his family were counseled on the CMT disorders which led to rethinking the patient's participation in contact sports.

Over the next several months, patient showed substantial improvement. A repeat study was ordered by the same neurologist for comparison 9 months later which showed the data in Table 6.6.

A comparison of the two studies in Tables 6.5 and 6.6 shows substantial improvement in nerve conduction data that correlates well with the reported clinical improvement. Based on this evolution the following conclusion was reported

Table 6.6 NCS/EMG for case Example 5 performed 9 months later

Nerve and side	Latency (ms)	Distance	Amplitude	Velocity (m/s)	F waves (ms)
Sural (Right)	3.9 (<4.2 ms)	140 mm	4 μV		
Ulnar (Right)	3.3 (<3.2 ms)	140 mm	13 μV		
Median (Right)	3.3 (<3.5 ms)	150 mm	12 μV		
Peroneal motor (Right)					
Ankle	6.6 (<6.1 mV)	90 mm	6.4 (>2 mV)		
Fibular Head	14.1		5.2	41 (>41 m/s)	62 ms (<56 ms)
Popliteal Fossa	16.8		4.6	38	
Tibial right					
Ankle	7.4 (<6.1 ms)	80 mm	1.9 (>3 mV)		54 ms (<58 ms)
Popliteal Fossa	18.5		1.5	36.0 (>41 m/s)	
Median right					
Wrist	5.9 (<4.4 ms)	70 mm	8.5 (>4 mV)		35.3 ms (<32 ms)
Elbow	11.6		8.0	47 (>49 m/s)	
Ulnar right					
Wrist	4.7 (<3.5 ms)	70 mm	11.1 (>6 mV)		
Below elbow	8.7		9.9	54 (>49 m/s)	40.8 ms (<32 ms)
Above elbow	12.5		9.4	32	
Muscle and side	EMG findings				
Tibialis anterior (Right)	Normal				

Normative data are presented in brackets. There is considerable improvement with all motor and sensory nerves showing better velocities, amplitudes, and latencies compared to the initial study

"This is an abnormal study. There continues to be electrophysiologic evidence of a moderate sensorimotor demyelinating neuropathy. The overall pattern of prolonged latencies, slowing across compression sites, absence of conduction block favors, an inherited processes such as HNPP with CIDP being less likely. When compared to his prior study dated February 2012 there is considerable interval improvement in all nerve studies, especially the sensory responses which were absent earlier are now present and there is improvement in motor responses. Clinical Note: Please consider evaluating the patient for acquired neuropathies such as CIDP (spinal tap) given the marked changes in nerve conduction studies."

The above sequence of events had led to considerable difficulties for the family and the ordering physician. There was considerable unpleasantness caused to the ordering neurologist. These conclusions were reviewed by independent experts who agreed with the interpretation of data since it met accepted rules for diagnosing and classifying demyelinating disorders, nevertheless, this case was a major failure.

This could have been avoided if the byzantine fault method had been consistently applied. Unlike other cases where a heavy burden was placed on information corroboration between multiple lanes, in this case conclusions were made solely based on one channel of information (EMG) and the rules regarding its interpretation. Section "Byzantine Faults" showed that FBW systems never make decisions from a single source of information or rely on a single channel. The history of trauma immediately preceding the development of symptoms was also misleading. A more important factor that was not mentioned in the history at the time of initial NCS/EMG was that the patient had a sore throat and mild febrile illness 4 weeks prior to onset of symptoms. Therefore if the matter had been analyzed in the byzantine generals framework as performed in the other cases, it would have led to a significant disagreement in the information in the EMG and clinical lanes thereby preventing the misdiagnosis. Casting the problem in the byzantine generals framework would have suggested investigating this case as an acquired form of inflammatory demyelinating neuropathy such as Guillain-Barré Syndrome. It would have merited consideration of a spinal tap which may have further strengthened the case for a trial of treatment with plasmapheresis or IVIG. It is only a matter of pure chance that no serious harm came to the patient from untreated Guillain-Barré Syndrome [17, 18].

This example shows the pitfalls of making major diagnosis based on one channel of information. The other case examples are ones where such fallacies were avoided solely because of the need for information corroboration.

Conclusions

There are valuable lessons for medical decision making from FBW. This chapter describes different paradigms for medical decision making borrowed from Boeing and Airbus FBW which follow different architectures but attain similar extreme dependability standards. At the heart of this extreme dependability lies the principle

of considering all information as potentially erroneous, misleading, and relying on design diversity for fail safe decision making. A greater degree of confidence can be placed on decisions made from misleading data if different information sources and decisions corroborate and different systems (or experts) arrive at the same conclusion using different computation methods.

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Chapter 7
Process Driven Methods in Diagnosis and Treatment

Abstract This chapter explores processes for establishing diagnosis and guiding treatment in a dependable manner. It introduces the idea of creating a workflow to visualize, monitor, measure, and improve the steps involved in diagnosis and treatment. It presents variance reduction methods like six sigma, checklists, and describes potential applications to medicine and neurology. A process driven method can make matters more efficient by providing opportunities for integrating operations and running many processes in parallel. The benefits of integrated, multidisciplinary clinics like the Amyotrophic Lateral Sclerosis (ALS) clinic are presented. This chapter also borrows ideas from the field of product lifecycle management (PLM) to develop similar principles for managing diseases across their lifecycle called disease lifecycle management (DLM). In a manner similar to prior chapters, the principle is presented first followed by medical case examples drawn from daily practice. This chapter forms a bridge that extends the journey from the first part of the book that emphasizes decision making and diagnostics into the second half that explores improving treatment.

Introduction

This chapter looks at the application of manufacturing principles to healthcare. Manufacturing enables consistent duplication and delivery of the same product to different customers without variation. A sequence of predefined steps is necessary in creating the final product which constitutes the assembly line. The ideas and science behind it form the basis of management and engineering—how do we organize production efficiently to guarantee the highest quality, least defects and variations and minimum cost? The Oxford dictionary defines a process as "a series of actions or steps taken in order to achieve a particular end" [1]. This chapter will borrow established ideas from management and engineering and apply it to healthcare delivery by creating a process. For the most part, these initiatives are zero cost and serve to adapt successful manufacturing industry principles for healthcare processes; therefore no investments in equipment or drugs are necessary.

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The Benefits of Defining a Process

The world of manufacturing is driven by tangible inputs and outputs—such as a company manufactures a certain number of cars of a certain quality or produces a certain number of metric tons of steel. The input is tangible and well defined. For the example of a car plant it is steel, rubber, plastic, paint, modular components (such as engine assemblies, gearboxes, etc.) and the output is finished cars. Once the process is defined, metrics can be applied for input and output. For a particular model, annual production takes x millions tons of steel, y gallons of paint, etc. for manufacturing z number of cars. For each input and output, a sequence of steps or a "manufacturing process" is defined to convert raw materials into finished cars. A process itself leads to subprocesses such as manufacturing a gearbox which feeds into the larger automobile manufacturing process of including the gearbox as a component of the finished automobile. Between the raw input and final finished output, there are a number of intermediate stages where products pass from one step of the manufacturing process to the next, often in an assembly line to yield the final product. The following are several advantages to formulating a *process* for a product:

1. The input is well defined.
2. The output is well defined.
3. Intermediate stages are well defined.
4. Metrics for the process can be defined.
   (a) Processing times for each step of the process.
   (b) Labor and technology requirements.
   (c) Quality can be defined.
   (d) Costs can be defined.

Once process metrics are defined, improvements can be planned. Such improvements can be radical, including rethinking the product or process itself or incremental. At some level, striving for improvement constitutes innovation. An example of radical rethinking for the above toy example would be to do away with the current machining process for manufacturing gears and use 3-D printing instead for manufacturing gearboxes. Incremental innovation usually involves refining the process or making minor modifications to finished products for lowering costs or improving quality. For example, given the same levels of manpower and shop floor equipment can we reorganize how we do things to increase output of gearboxes by 15 %? This innovation will be discussed further in Chaps. 8 and 9.

A process therefore is like an algorithm in computer science. It is a sequence of steps that must be followed from beginning to end for each iteration. Every car, every ounce of steel has been through the same steps in manufacturing. While it is difficult to say there is only one way to do things, once a process is defined and becomes measurable, it can lead to continuous experimentation for better ways to do things in terms of the defined metrics. As Lord Kelvin, the famous nineteenth

century physicist once said "if you cannot measure it, you cannot improve it." Therefore, innovation applied to processes leads to gradual maturation and a path towards the best way to do things.

Systems Engineering and the Traditional V Model

Systems engineering is described as "a methodical, disciplined approach for the design, realization, technical management, operations, and retirement of a system. A system is a construct or collection of different elements that together produce results not obtainable by the elements alone. The elements or parts can include people, hardware, software, facilities, policies, and documents [2]." Systems engineering is interdisciplinary by its nature [2]. It is concerned with a system's performance, interactions of its subsystems with each other, interactions with the user, and other interacting systems [3].

The classic systems engineering model is called the V model as shown in Fig. 7.1.

The traditional model assumes a *sequential* development process and starts at the top of the left arm of the V. It proceeds stepwise from left to right along the arms of the V. The first step is defining and understanding customer requirements. Based on customer demands and understanding of needs, a system specification is arrived at—termed validation. Validation refers to confirming that the system being

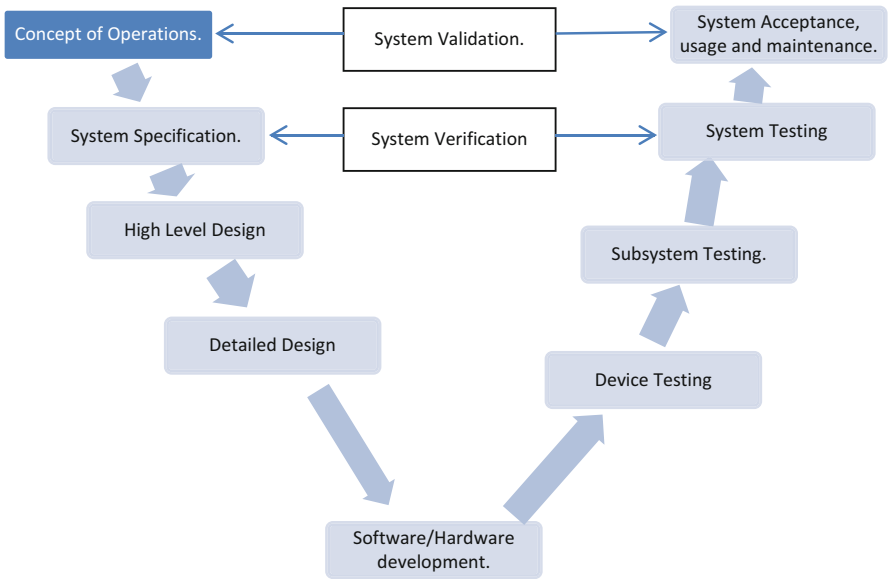

Fig. 7.1 The traditional V model for systems development. Adapted from [2, 3]

developed conforms to the user's needs and expectations [3]. The system specification is implemented in a top-down manner by first specifying the high level design of the system. For the example of an automobile, high level design would include decomposing system development into platform, engine, transmission, braking, and electronic control systems. Subsequent development proceeds by systematically decomposing each high level system into component subsystems (detailed design) and ultimately to component level detail [2, 3]. The idea is to attain system decomposition into component subsystems which can be implemented in parallel to speed product development [3]. Each step of the process requires detailed documentation since it is expected that the personnel may leave the project along the development lifecycle.

The right branch of the V is where components and devices are initially verified before being integrated into subsystems. Verification refers to determining that the system being designed meets all the predefined specifications. This step confirms the design is robust, maintainable, and each component behaves as expected [3]. Individual components/devices are then integrated into subsystems. Each subsystem subsequently undergoes rigorous verification before integration into the final system. Verification is then performed on the completed system to ensure that the entire product conforms to requirements specified in detailed design stage of development [3]. This is followed by validation to ensure it meets the customer's requirements.

Understanding customer needs and getting the right system specification is extremely important prior to proceeding with system development. This is because making changes after detailed design is complete is extremely difficult since it involves redoing a lot of the development work to meet the new requirements. Therefore, the traditional model lays great emphasis on the first step of understanding customer needs and specifications prior to system design with a sequential implementation as a consequence.

The Lack of Processes in Healthcare

A common theme in many healthcare problems is the wide variability in patient experiences. The elapsed time between onset of symptoms and final diagnosis and instituting treatment varies from days to weeks to several years. Events such as a clinic visit or a laboratory test happen haphazardly, there is a period of some activity followed by quiescence. Similarly, costs are also extremely variable for the same diagnosis and comparable outcomes. This chapter will explore methods for creating processes which will have the advantages listed in Section "The Benefits of Defining a Process".

Defining Patient Processes and Creating a Virtual Assembly Line

A similar V-shaped model can be created for healthcare delivery. To a great extent, matters happen in isolation in healthcare with all too great an emphasis on the physician. The first step is to define a healthcare process and create a virtual assembly line or a V model for each patient. No two people have the same disease or require the same treatment making it difficult to create standardized flowcharts in healthcare. However, a process can be created for each patient to improve healthcare delivery. The following steps can be identified:

Step 1: Define patient symptoms and needs: This step is analogous to "concept of operations" in systems engineering. This step involves two major objectives:

(a) Understanding patient symptoms to direct diagnosis.
(b) Preliminary understanding of patient requirements and needs to define initial objectives of care.

Step 2: The next step involves subsequent information gathering performed during the clinic visit—clinical examination, review of medical records as the necessary background for clinical decision making.

Step 3: Clinical Diagnosis step: This step involves formulating a working diagnosis. This step can take any of the forms discussed in prior chapters such as Fault Tree Analysis (FTA), Graphical Methods, and Probabilistic methods. Additionally, the problem maybe cast in a Byzantine framework for decision making in the face of byzantine faults as discussed in Chap. 6.

Step 4: Direct appropriate diagnostic testing: In this step, the clinician directs diagnostic testing based on possibilities identified in step 3. If the diagnosis is validated he proceeds to the next step, if rejected he proceeds with alternate hypothesis (such as other hypothesis identified in the FTA or graphical method).

As shown in Fig. 7.2, this step is iterative and must be traversed repeatedly until the correct diagnosis is established. The speed with which this loop is iterated and diagnostic possibilities examined varies depending on the severity of the problem, as will be discussed later.

Step 5: Diagnosis confirmed: In this step, the clinician establishes both the diagnosis and the degree of confidence in the conclusion. This helps direct the choice of treatment. As described in Chap. 6, it is useful to define the working diagnosis in the byzantine framework. Treatment can be selected based on the confidence-cost/risk matrix in Fig. 6.4 of Chap. 6.

Step 6: High-Level Treatment planning: In this step, the clinician and patient can discuss an appropriate treatment plan that conforms to the extent possible with patient expectations identified in step 1. Patient goals, intermediate milestones are identified and established in this step. Examples include "be able to walk

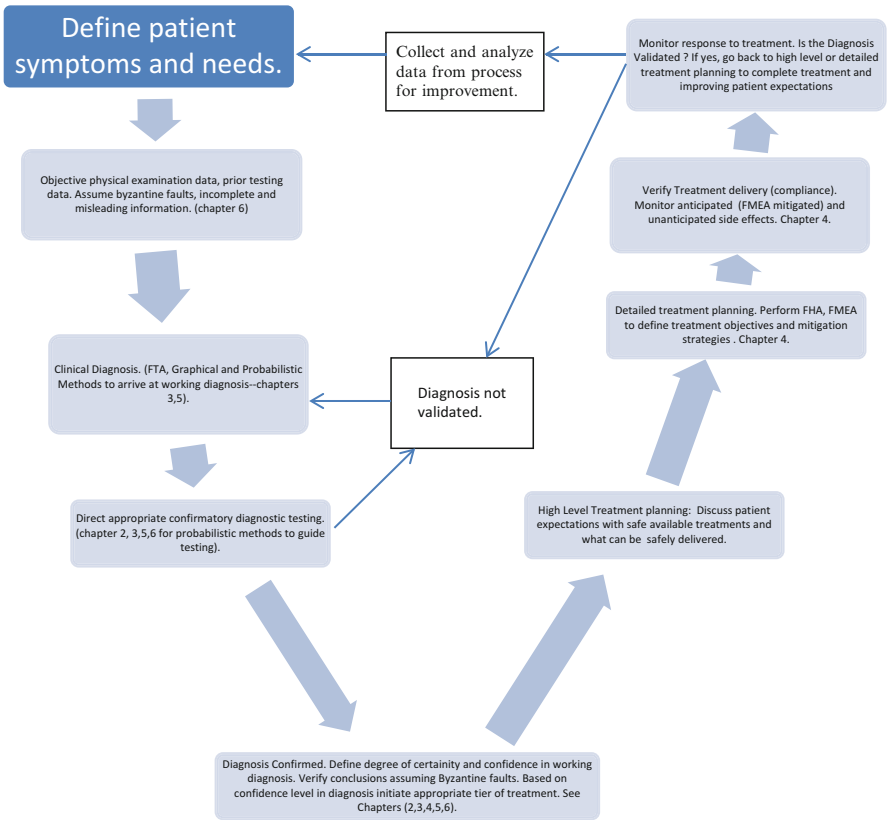

Fig. 7.2 Creating a patient process analogous to the systems engineering V model

with a walker in 2 months and with a cane in 4 months." In this step, the decision making is along the lines of broad generalities such as "Immunosuppression" and "Physical Therapy" or "Symptomatic Treatment" instead of immunosuppression for "myasthenia gravis".

Step 7: Detailed treatment planning: This step involves defining the low level fine details involved in formulating treatment. It involves performing a preliminary system safety assessment (PSSA), followed by system safety assessment (SSA). Functional hazard assessment (FHA), failure modes and effects analysis (FMEA), and particular risks analysis (PRA) are performed to guide therapy. Methods to perform these are described in detail in Chaps. 1, 2 and 4.

Step 8: Verification: In this step, treatment delivery is verified, are medications being taken as directed? Is therapy focusing on the right goals and objectives? At this stage side effects, anticipated and unanticipated are reviewed and mitigated. This step also includes appropriate therapeutic monitoring for dose corrections such as INR monitoring for warfarin.

Step 9: Monitor response to treatment: This is a strong validation step which affirms the veracity of the first 8 steps and enables corrective action if anticipated goals are not met. If there are shortfalls these imply:

(a) Imperfections in diagnosis: this is addressed by going back to step 4 and performing FTA, graphical methods or byzantine generals framework analysis to improve the diagnosis.
(b) Imperfections in treatment: Treatment can be refined by using the Plan-Do-Check-Act (PDCA) cycle which will be discussed in Chap. 8.

Step 10: Collect and analyze data for Quality Assurance and Knowledge building: This step connects back to step 1 where the process can be iterated again for a similar clinical condition with the benefit of lessons learnt from prior experience.

The systems engineering approach yields a few important lessons:

(a) Successful care delivery is a multistep process which must work harmoniously. It is greater than the sum of its parts.
(b) The process is dependent on different skills and expertise at different steps of the journey. Therefore, it must necessarily be more than one person, the physician and must involve teamwork.
(c) While the steps involved are very similar between different clinical problems, the speed with which the cycle must be traversed differs greatly depending on the acuity of the problem. Severe, life-threatening problems would require rapid process times (in minutes to hours) while for chronic outpatient problems, the process can be traversed over days.
(d) The model allows for factoring time, cost, and expertise at each stage of the process. During early stages, the emphasis is on the left arm of the V since most of the effort needs to be expended in determining the diagnosis. In later stages, the emphasis shifts to the right arm of the V since the diagnosis is firmly established and it is refining treatment that is typically important. This model provides a foundation for transitioning to the Disease Lifecycle Management (DLM) model which borrows ideas from Product Lifecycle Management (PLM).

The traditional V model finds great applications in single provider settings, where diagnosis and treatment is essentially dependent on one physician or a group of physicians. In the case of clinical problems involving more than one type of physician (such as a multisystem disease with cardiac, renal, hematological involvement) or where expectations are dynamic and goals need continuous refinement, newer systems engineering models are advantageous and they will be described later with case examples. Detailed implementation of steps in the V will be studied further in the Reliance Microplanning method in Chap. 9.

Defining Processes Based on Time

Based on time, complexity, and number of systems involved, problems can be labeled as follows:

Open problems: These are problems where a diagnosis has not been established. Based on acuity, severity, and duration these are classified as "Open-Chronic" and "Open-Urgent/Acute". Most of the cases discussed in prior chapters are examples of "Open-Chronic" where the physician has time (measured in days to weeks) to guide thoughtful analysis and testing. In these cases, the V can be traversed in weeks or months. "Open-Acute/Urgent" problems are the most dangerous, since the patient's condition is rapidly changing and unless appropriate action is instituted in a timely manner, there is potential for irreversible injury and loss of life. Such problems may need correction of life-threatening anomalies to be instituted before a root cause can be established and treated. Examples include rapidly declining ventilatory function which requires immediate intubation prior to determining if this is from myasthenia gravis or Guillain-Barré Syndrome (GBS).

Open–multidisciplinary: These cases involve more than one specialty, therefore a multidisciplinary approach is necessary. In other cases, the diagnostic workup threw open a Pandora's Box of frequently overlooked information which requires partnership and assignment of responsibility for appropriate treatment. This classification is important for improving dependability in healthcare. "Open–Multidisciplinary" are cases where the devil is in the details and a small little thing buried in a test report which means very little to the physician who ordered it, probably will snowball into the most important thing in the years to come.

Closed: All aspects of the presenting symptom(s) have been addressed and no further diagnostic workup or treatment is necessary. The aim of traversing the V is to go from open to closed status.

Case Example 1: Open-Acute—Urgent Problem

JH is a 35-year-old male, s/p kidney transplant who presented to the hospital with diarrhea and dehydration. Medical comorbidities include hypertension and diabetes mellitus. During the course of his admission, he was treated with supplementation of IV fluids, electrolytes, and monitored closely for renal function. He awoke one morning with weakness of the left arm. He also had mild left shoulder pain and did not feel there was any difference in sensation. On examination, he had diffuse weakness involving the left arm involving all muscle groups with normal reflexes everywhere. Sensory examination was normal.

The history and physical examination did not yield an immediate solution. The weakness was too diffuse to be attributed to the commonest reason—radial palsy.

Given the sudden onset, diffuse weakness and risk factors of kidney disease, high blood pressure, and diabetes mellitus the most pressing concern was for a stroke. An urgent MRI Brain was requested. The patient was beyond all windows for IV or intra-arterial tissue plasminogen activator (tPA). The patient was initially seen in the afternoon around 3:00 P.M. The MRI Brain was planned within the next 2–3 h as soon as scheduling permitted. If this was negative, the plan was to proceed with an MRI of the Cervical Spine to see if this was due to lesions of the spinal cord like transverse myelitis. If this was negative as well, the plan was to perform an EMG to look for brachial plexus lesions. The problem was classified as Open-Acute/Urgent which necessitated a solution had to be found in hours.

By 7:30 P.M., MRI Brain was performed. The MRI Brain was reviewed later that evening and was found to be normal. No evidence of stroke was found. Proceeding down the algorithm mentioned above, MRI C Spine was ordered urgently. While waiting for this, a thorough review was performed, including consideration of the rare and obscure (West Nile infection, CMV infection etc.) which though possible given the immunosuppression were obviously not the cause here. MRI C Spine was completed around 10:00 P.M. and was normal as well.

Since no solution had been apparent by 10:00 P.M., a second examination was performed of the patient around midnight, approximately 8 h since initial examination. By now, the patient had woken from a nap and was paralyzed below the neck. Breathing, eye movements were normal. Curiously speech and sensation were normal and he had no urinary or fecal incontinence. Since no firm hypothesis was formed, reevaluating the entire data looking for new clues became the priority. An intense review of all data to date performed around 1:00 A.M. showed a fact that had been overlooked in the afternoon, a low potassium level of 2.8 meq/L. An urgent repeat level was ordered which showed it had slid lower to 2.0 meq/L with the potential for life-threatening cardiac arrhythmias. This was not suspected or sought aggressively initially since low potassium is not a common consideration in focal weakness.

The solution had been determined but only just in the nick of time. An urgent EKG showed findings of severe hypokalemia such as U waves and frequent ectopics. The patient was immediately transferred to the ICU. Potassium was urgently replenished with complete recovery. The root cause of the problem was identified as loss of potassium from diarrhea and changing acid base balance.

This case would have been fatal if the hunt for the solution had been delayed until next morning. Therefore, a problem status has to be defined and the V model has to be intensely applied until the problem is solved within the acceptable timeframe. As discussed above, approaching this as a process has the advantage of imposing intermediate processing times for each step of the diagnostic approach with alternate ideas being explored in a time bound way driven by the urgency and importance of solving the problem.

Case Example 2: Open-Chronic

WH is a 60-year-old male with symptoms of bilateral arm weakness. He did not remember when the problems started, it could have been many years ago, but it progressed very slowly. The first symptoms he noticed were difficulty retrieving objects from shelves. He had no difficulty with closing his eyes, speaking, chewing, swallowing, breathing, or walking. He had no problems with sensation. On physical examination, he had severe weakness about the shoulder. The mildest movements would lead to displacement of the shoulder blade so that the deltoid muscle was rendered mechanically ineffective. The deltoid muscles themselves showed only mild weakness. The serratus anterior and rhomboids were severely wasted and weak with prominent scapular winging. The face, forearm, hands, and legs were normal. Sensation was normal. No diagnosis had been arrived at to-date. FTA performed for this case is shown in Fig. 7.3. Based on this analysis, the prominent scapular winging an initial working diagnosis of Facioscapulohumeral dystrophy (FSHD) was considered [4]. Neuropathic etiologies which can cause scapular winging, (usually in a scapuloperoneal pattern) include Davidenkow's syndrome [5]. A gene test for FSHD (D4Z4 repeats on chromosome 4q35) was requested [6], patient was provided a return appointment in the next 4 months as results of diagnostic testing were obtained. The patient was also set up for EMG.

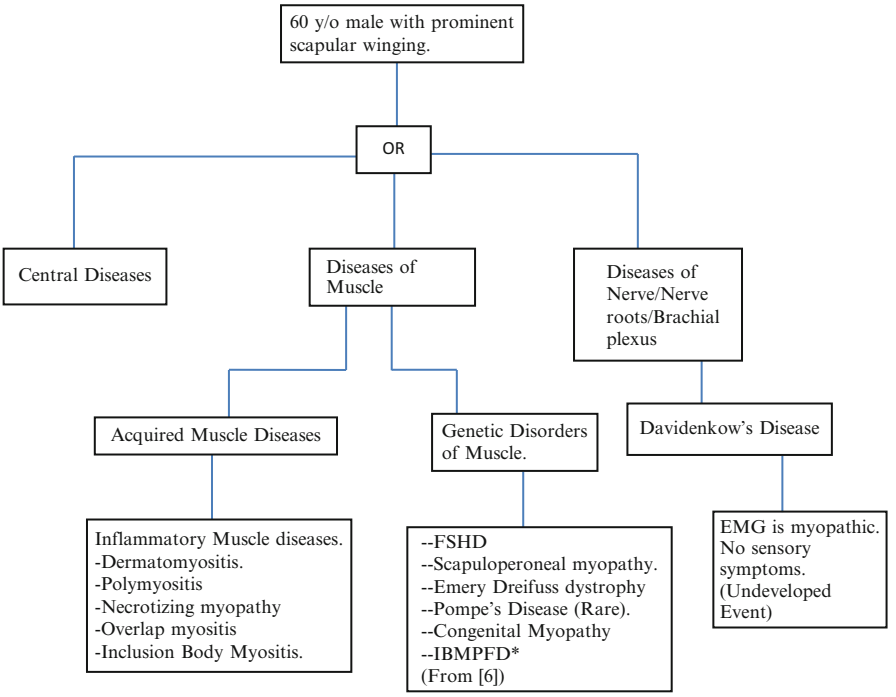

Fig. 7.3 FTA for Case Example 2. *IBMPFD: Inclusion Body Myositis with Paget's disease and frontotemporal dementia

The patient underwent an EMG performed by another physician which confirmed a myopathic process. Genetic test for FSHD was negative which can happen in ~2 % of cases [4]. This necessitated going back to steps 3, 4 to examine alternative hypotheses from the FTA and direct further testing. Since the gene test was negative, a muscle biopsy was requested based on raw EMG data. Though clinically weak, commonly biopsied muscles such as biceps were reported to be normal on EMG. Based on EMG description, the findings in the infraspinatus were interpreted to be reasonable for biopsy. The biopsy was however indeterminate since the sample was essentially end stage muscle. Since the patient lived far away, the muscle biopsy was performed concomitantly with blood testing for Acid Maltase (Pompe's disease) activity level, which is considered a rare cause of scapular winging [6]. Pompe's disease is classically described to produce limb girdle weakness and respiratory weakness which was not the case here [6]. The Acid Maltase activity level was low confirming this to be an unusual presentation of Pompe's disease. Pompe's disease can cause respiratory weakness but is treatable with enzyme replacement therapy, therefore it was a surprising outcome [7]. While Acid Maltase deficiency itself is a very rare disease even for most skilled neuromuscular clinicians, this presentation of it is even rarer. Application of this rigorous process yielded a solution instead of attributing his problem to a variation of FSHD. Pulmonary Function tests showed moderate diaphragmatic weakness.

Solutions Process

The diagnosis was confirmed by genetic testing to be Pompe's disease. At this stage, the transition began to the right arm of the V.

The next steps of High level treatment planning, treatment goals, including supportive care were discussed in detail with the patient. This is vital since Pompe's disease causes severe ventilatory weakness which can shorten life expectancy and is treatable. The patient transferred care to another clinic for the same.

We will jump ahead to the Quality Assurance and building knowledge part. The following errors were observed in this case:

1. Poor choice of muscle biopsy due to poor muscle selection. The test yielded no useful information and left the patient with a bill which he is still struggling to pay off. The root cause of this was poor interpretation of EMG data since this was done by another clinician. This could have been avoided if a discussion and review had been performed with the physician performing the EMG so that he could advice on the best choice for biopsy. Therefore there was failure of communication and teamwork.
2. Incomplete EMG: The thoracic paraspinal muscles were not studied in this EMG. The thoracic paraspinal muscles can show a peculiar pattern of electrical abnormality called electrical myotonia which could have tipped the clinicians in that direction [7].

Lessons from WH, Plans for Solution Improvement

1. The best muscle to biopsy should always be stated explicitly in the report. If this is not the case, always discuss with the physician performing the EMG which is the best muscle to biopsy.
2. In all cases where primary muscle disease is suspected, perform EMG of the thoracic paraspinals. This is to look for electrical myotonia and also to look for very proximal muscle involvement which can be seen in inflammatory myositis like dermatomyositis and polymyositis.

The lessons learnt from WH helped improve the diagnostic process for patients with similar problems because this experience was incorporated into future cases and no future negative biopsies were encountered.

Open-Chronic Ancillary Multi-Specialty Problems and Related Processes

This section discusses creating ancillary processes for unexpected information encountered during the diagnostic process in steps 3 and 4 which are not the core area of the physician who initiated the process. Teamwork in the care of complex multisystem patients is discussed separately in subsequent chapters, this example guides a process driven approach to information unexpectedly encountered while traversing the V.

Advances in imaging technology and laboratory diagnostic medicine have created immense amounts of ancillary information which are discovered serendipitously during the course of searching for something else. A major problem has been the lack of a rigorous disciplined approach to handling such unexpected information when they are not the focus of the ordering clinician. Numerous examples abound in virtually all areas of medicine with radiology being the common denominator in most instances. Successful modern management in industry involves defining problems and subproblems and assigning responsibility appropriately. Such details must not be omitted and must be addressed by applying the correct skills. For each thread of unsolved information, a process must be defined and responsibility fixed so that a problem does not get neglected and become incurable, especially in those happy instances when a long lead time would have benefitted treatment. Assigning responsibility is key. The following example illustrates this principle:

Case Example 3

MA is a 65-year-old male smoker with symptoms of double vision, fatigue, and weakness for several months. Strokes, aneurysms were excluded by normal MRI Brain scans. He was diagnosed with myasthenia gravis. The diagnosis was

fairly straight-forward, blood work was positive for the antiacetylcholine receptor-binding antibodies (AchR-Binding antibody) which established the diagnosis. Since a percentage of cases are related to a tumor of the thymus gland located in the chest, a CT scan of the chest usually follows this diagnosis. In MA's case, it was anticipated that his treatment would involve suppression of the immune system with steroids such as prednisone. For this reason, precautions were taken to check vitamin D levels, thyroid function, establish whether he was diabetic or not and perform a skin test for tuberculosis along the lines of FMEA discussed in Chap. 4.

The CT chest was negative for thymoma, but showed pulmonary nodules which are a frequent finding in CT scans of the chest as scanners became better. Blood testing showed he was already diabetic without knowing it. Thyroid function testing revealed hypothyroidism. Additionally, vitamin D levels were low. Given this constellation of abnormalities, responsibility and follow through were defined for the subproblems:

(a) A copy of the CT chest report was provided to the patient identifying the size and location of the nodules. A repeat scan was recommended by the radiologist in 6 months to see if there was any growth suspicious for lung cancer given his smoking history. This responsibility was transferred to the primary care physician and patient so that it was not overlooked in the course of treatment of his myasthenia gravis.
(b) The constellation of diabetes mellitus and hypothyroidism was treated by referral to an endocrinologist. The anticipation that he will need steroids which will worsen diabetes considerably and that be factored into treatment planning was made and responsibility assigned. By the time of his return visit in 2 months, both these problems had been well treated. This enabled safe use of prednisone for this patient with minimal complications of worsening diabetes since the sugars were well controlled and the treating endocrinologist had formulated contingencies for perturbations in sugar control with the use of Prednisone at a moderate dose for 2 months. Addressing thyroid abnormalities helped with overall metabolism, decrease in fatigue and improved exercise ability which made myasthenia gravis easier to treat.

Therefore, what started out as one symptom had multiplied into four problems—lung nodules, diabetes mellitus, hypothyroidism, and myasthenia gravis. Each required meticulous attention and follow through which was beyond the scope of one person. Defining a *problem list* where each of these entities is enumerated with an appropriate physician taking responsibility for each problem was defined. In a sense, it is similar to the graph theoretic structure described earlier except the idea is not to define an edge between the nodes but to establish a thread of responsibility and follow through. The advantage with defining such problem lists is that every subproblem gets labeled and gets adequate attention, expertise, and follow through. The recent requirement for creating, maintaining, and updating such problem lists is a step in this direction.

Continuous Engineering and the Integrated Workflow Model

The traditional V systems engineering model suffers from one drawback. It is very sequential. It lays extreme emphasis on understanding customer needs and defining requirements prior to initiating detailed design. The model performs poorly when customer needs are evolving—this can happen as a consequence of customers not knowing what they want or being unclear about their exact needs and from changing market conditions. In recent times, the traditional V model has been supplanted by more integrated models which see customer needs as flexible and therefore need refinement throughout the system design process. This model is referred to by many different names in different industries, one term that is applied is *continuous engineering* [3].

Continuous engineering involves "continuous verification and validation throughout the product development process [3]". The basic steps are similar with the left side involving definition and decomposition and the right involving integration and validation. The different steps of the V happen massively in parallel and iteratively as system design is continuously refined and changes implemented [3]. Given constantly evolving needs, system design changes, continuous verification and validation, continuous engineering needs very high transparency, teamwork, knowledge collaboration, and excellent communication [3]. Emphasis is placed on modular designs which are interchangeable across product lines. Reusing components, software, knowledge, and assets during different product development cycles helps manage cost and time [3].

An integrated approach has been well adopted in many industries, especially the auto industry. In earlier times, model changes happened sequentially—first the design, then the engineering, then investments in tooling, production planning and finally sales. This led to an all too common problem—conflicts between stages in development and expensive redesign. A design may not be the optimum one to manufacture for time or skill reasons which would then require redesign and slowing of product development. Automakers have increasingly relied on integrated approaches where downstream processes such as manufacturing, sales are built into the design stage itself and a car is designed to manufacture and sell. This can be carried to a further level where automakers have increasingly adopted component sharing across product lines which has reduced product development costs considerably and led to benefits from economies of scale. Additionally, companies have moved from building a single product with firm specifications to a family of products spanning a spectrum of specifications catering to a diverse need. This has considerably reduced lead times or cycle times in the auto industry where model replacements now happen on average every 4 years from the usual 8–9 years in the sequential approach. This is referred to as platform-based product development. Formally, a platform-based approach is described as "a collection of the common elements, especially the underlying core technology, implemented across a range of products" [8, 9].

The integrated, platform approach allows for ideas from all levels of the process to be applied at the very beginning and may potentially resolve conflicts before they happen. In this chapter, we borrow the term platform approach since it brings together multiple different skills in a platform to deliver the maximum in one clinic visit similar to what happens in industry. The interested reader will find a wealth of information on integrated approaches to healthcare in [10].

Such an integrated approach can be applied to healthcare to potentially speed diagnosis and treatment. An example is the general neurology clinic which is usually run in the sequential workflow model. In the classic healthcare model (especially for large teaching hospitals), a patient sees a consultant who then orders some tests, imaging studies, seeks the assistance of another consultant, and finally based on putting all these together comes up with a treatment. Medical records are sought and reviewed when they are received. The treatment itself may take the form of physical therapy or occupational therapy with further stages in coming to fruition. Adopting the platform approach led to the following solution method in a general purpose clinic.

Step 1: Review the problem—the specific question asked by the referring physician which may take the form of "Evaluate for nerve damage", or "Evaluate for muscle damage," etc. If the question is not well formulated, make an a-priori hypothesis. This is akin to understanding customer needs before even seeing or talking to the customer.

Step 2: Assess acuity and offer an appointment. If EMG testing is necessary, offer an appointment on a day when the two—a clinic visit and an EMG visit can be integrated.

Step 3: Seek pre-certification from insurance companies so that patient is approved for clinic visit and EMG and the two can happen in a smooth sequence.

Step 4: Plan the range of blood tests that maybe necessary—special blood work for immune system disorders or genetic disorders.

Step 5: Plan for additional consultant expertise—does the patient need a biopsy of a muscle or nerve? Select the one which is anticipated and reduce lead times further by requesting the required appointment or procedure well before seeing the patient. This may not be needed after the clinic visit and EMG based on the results obtained, therefore such an appointment can be flexibly overbooked in most instances.

Step 6: Split the visit into two parts, the first half dealing with diagnostic history, physical examination proceeding straight onto the EMG part of the study. Integrating the two in the same room saves a lot of time and helps make the process parallel. Once this is done, the second half can be reserved for discussing potential diagnosis and treatment plans.

Step 7: Perform blood work; patient sees the surgeon for potential biopsy or other consultant whose services are requested.

This method is appreciated by patients who sometimes wait several months for an appointment and drive several hundred miles. The classic method disconnects all these processes, sees each step in isolation and requires many visits to the hospital/clinic separated by weeks and at considerable cost and delay.

The platform approach therefore involves problem anticipation, solution planning in a manner similar to the microplanning method which will be described later.

Integrated Clinic: Amyotrophic Lateral Sclerosis Clinic

One of the best examples of the integrated platform approach is the ALS (Amyotrophic lateral sclerosis) clinic. While there is no specific treatment for this condition, once the diagnosis is confirmed, patients are referred to the ALS clinic which is dedicated to the long-term care of such patients. Riluzole has a modest effect at slowing down the progression of the disease. Since the disease is frequently relentlessly progressive with involvement of breathing and swallowing muscles at different stages of the disease, great teamwork is needed to ameliorate deterioration and maximize quality of life. The classic sequential approach in a debilitated patient is very difficult given the physical and logistical difficulties in going from one appointment to the other, sometimes over great distances. The care of the ALS patient is discussed in [11, 12]. The ALS clinic uses an integrated or platform approach to deliver very high quality, dependable, supportive care [11]. This model can be adopted in other clinics to deliver better care and dependability. The clinic seeks to address the greatest challenges faced by patients during each visit. Figure 7.4 shows the integrated patient care model of the ALS clinic.

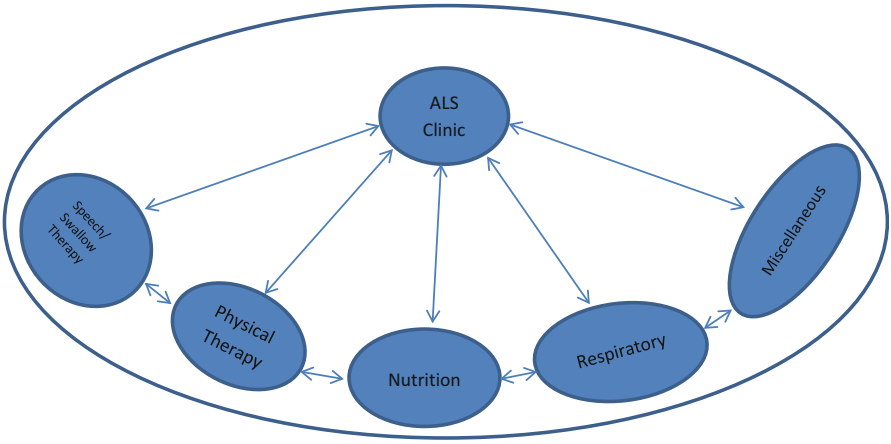

Fig. 7.4 Multidisciplinary ALS clinic, an example of an integrated systems engineering model. The ALS clinic can be seen as an integration of multiple subsystems such as speech therapy, physical therapy, nutrition requirements, respiratory assessment, and miscellaneous (blood work monitoring, eligible clinical trials, social aspects of care). An integrated approach permits these processes in parallel and integrates the effect of these subsystems

1. Progression of the clinical condition is usually evaluated by an MD.
2. Riluzole monitoring requires blood work for monitoring liver function tests. This requires a blood draw performed by the nurse or nursing assistant.
3. Monitoring swallowing function to see if weakness has affected the swallowing muscles. If it has and the patient is at risk for aspiration, appropriate precautions in the form of changing the diet, changing the consistency or in advanced cases a feeding tube called PEG (percutaneous endoscopic gastrostomy) tube needs to be inserted into the stomach to overcome swallowing difficulty. This is performed by a speech and swallow therapist.
4. Monitoring breathing function to see if there is weakness of the breathing muscles. This is performed by a respiratory therapist.
5. Physical therapy for appropriate exercises. This is performed by a physical therapist.
6. Occupational therapy for ameliorating functional limitations from weakness. This is performed by physical and occupational therapists.
7. Speech therapy (performed by speech therapists) to assist with speech and communication. In very advanced disease this may include use of sophisticated computers to assist with speech from movement of vocal cords. Speech therapy works with assistive technologies to facilitate speech.
8. Monitoring weight, especially if there is weight loss and making appropriate nutritional recommendations. This is performed by a dietician.
9. Assistive devices which range from electric wheelchairs to lift assist devices to other mechanical aids for patients.
10. Monitor any clinical trial data if patient is enrolled in a trial.
11. End-of-life planning such as instituting hospice if life expectancy is of the order of 6 months or less.

The ALS clinic also includes contributions from social worker, nutritionist, neuropsychologist, and ALS association chapter representative. Additionally, the ALS clinic partners with the same surgeon and gastroenterologist for PEG placement owing to their experience and familiarity with special needs of ALS patients.

The clinic usually involves vendors performing many of these services such as home health agencies, respiratory care companies. The last step involves integration, something which is most important and only rarely ever done in medicine. At the end of the clinic there is a meeting of all the personnel to compile their different perspectives and make recommendations for their respective areas. A copy of the letter is then sent to the patient after the visit to reinforce the conclusions. For example, the swallow therapist may recommend a plan for a PEG tube in 3–6 months since there is a decline in swallowing function during his/her assessment.

Therefore, at minimum, the ALS clinic integrates services of an MD, RN, nutritionist; physical, occupational, speech and swallow, respiratory therapists; home health agencies and vendors for assistive devices at one visit. Since such expertise usually exists only at a few institutions in a particular state, repeat visits for each of these evaluations would be monumentally difficult for the patient and their families if such integration is not skillfully performed. In some ALS clinics,

the patient is assigned a room and all the providers enter, provide their services, and leave one after the other which saves time in going from one clinic area to the other. Some clinics use the classical model of patient moving from room to room or from area to area to get the appropriate service.

The ALS clinic has a clinic coordinator who is central to the operations of an ALS clinic. The clinic coordinator is perhaps a good example of the industry equivalent of an effective *middle manager*. In general what makes middle managers very effective is their knowledge of the processes with which they are involved with. While there is no shortage of middle managers at all levels of the healthcare bureaucracy, the *middle care manager*, someone who can coordinate care processes effectively for day-to-day patient care is generally lacking.

The ALS coordinator coordinates all aspects of care, from extending an appointment to a patient with suspected ALS, providing disease related information, ensuring and coordinating all diagnostic testing, managing appropriate follow up visits, coordinating care through primary care physicians for patients living far away with a specific need such as care of aspiration pneumonia, working with vendors to name a few. The ALS coordinator plays a major role in integration and validation of care of ALS patients. They play a great role in understanding and facilitating broader living needs like social security disability, provision of appropriate supportive devices like power wheelchairs which require a lot of time and effort to meet regulatory approval. They help understand mental health concerns and coordinate help in that direction through neuropsychologists. The ALS coordinator is able to facilitate interventions like feeding tube placement and more recently diaphragmatic stimulator placement through knowledge of the processes involved in getting these done. The integrated clinic model allows these to be planned well in advance before progressive weakening can make anesthesia more challenging.

Case Example 4

This example briefly illustrates the unique aspects of ALS care delivered through the clinic. The following letter is reproduced from patient records, courtesy of the ALS clinic.

"Dear. . .. . .,

Thank you for attending the ALS clinic. We certainly appreciate all your efforts to come. At each clinic the ALS team holds a post clinic conference. At this conference the team discussed your need for the following:

1. Continue taking Riluzole. Lab work for comprehensive metabolic profile (CMP) today and every 3 months while in clinic.
2. You were screened for the BENEFIT study today. You are still too strong to qualify, but you can be re-evaluated if you remain interested.
3. We discussed the Diaphragmatic Pacing System today and it can be combined with a gastrostomy (feeding) tube.

4. Outpatient and Physical Therapy do not report any new needs.
5. Social Work: Advanced directives are in place.
6. Speech and Swallow Therapy: Your clinical swallow evaluation was very poor. We recommend a swallow test now, please call to schedule. We also recommend a boogie board or an iPad for communication.
7. Respiratory Therapy: Your Forced Vital Capacity (FVC) is stable at 81 %.
8. Cognitive Assessment: Cognition needs assessment at your next clinic visit.

Your next ALS clinic visit will be in October of 2013. Our clinic coordinator will contact you to schedule your next appointment. If you have any questions or concerns about your visit, please do not hesitate to call us as at . . . .

Sincerely,

ALS-Center Medical Director".

A few other clinics have adopted a similar model. In neurology alone these include movement disorders clinic where patients with Parkinson's disease get a similar integrated approach. It is exceedingly difficult to manage patients with diseases with similar morbidity and relentless progression without such clinics. Therefore, an integrated clinic model has great advantages since it is implicitly process driven.

Product Lifecycle Management

Product Lifecycle Management or "PLM is a term used to describe the process of managing the entire life cycle of a product from its conception, through design and manufacturing, to service and disposal" [13]. The term refers to the knowledge, skills, technology, and resources that enable an enterprise to "effectively and efficiently innovate and manage its products and related services throughout the entire business life cycle" [13]. PLM transcends a single organization and refers to the collaborative relationships that exist with suppliers, technology partners, and customers to manage the product lifecycle from conception to obsolescence [13]. PLM facilitates updated information sharing across multiple stakeholders involved with a product or service. PLM refers to the constellation of knowledge, technology, and processes that manage the entire product lifecycle. It is of significant importance in several industries requiring high safety like aerospace and automobiles.

For the example of an automobile, during the conception phase, understanding customer needs and conceiving an initial design is vital in the initial phases. During the detailed development phase, the focus shifts to detailed design of component systems, often in partnership with suppliers. This requires extensive collaboration across organizations to ensure the correct specification is being developed at any given time. The next step involved manufacturing which requires precise collaborations with machine tool suppliers to ensure that designs on paper are precisely translated into metal. Raw material suppliers like steel, aluminum, composites,

plastics, and paint play a great role in this phase of product development. Following launch and product maturity, knowledge related to maintenance, anticipating, and correcting defects plays a major role. Finally, when the model reaches obsolescence, developing efficient recycling methods becomes important. The knowledge gained from the entire lifecycle can then be applied to new model development. In some industries such as aerospace which have extremely long and complicated product lifecycles spanning decades, documentation and validation plays an extremely crucial role to ensure safe and effective product performance.

The automobile example above illustrates the changing needs across the entire lifecycle. The knowledge and processes required are substantially different across different phases of the lifecycle, for example—tooling plays an important role during the mature manufacturing phase but is not the focus of the recycling and obsolescence phase. Borrowing from industry, the idea of *DLM* can be conceptualized and defined for many chronic conditions.

We define DLM as the knowledge, skills, processes, and collaborative relationships between all stakeholders involved in the care of a specific disease in a particular patient across its expected lifecycle. Similar to PLM, DLM involves the following key components:

(a) Understanding customer (patient, families, physicians') needs and requirements.
(b) Developing knowledge, skills, and processes to diagnose and treat the disease across different phases of its lifecycle in an efficient and dependable manner. (The term dependable is used here in the same strict sense as the definition of dependability in Chap. 1—a service which can be justifiably trusted by the user.)
(c) Perform analysis of the DLM experience to innovate across the disease lifecycle.

DLM helps adapt and evolve with different healthcare needs across the disease lifecycle. Knowledge and resources can be directed appropriately instead of being fixated with a single idea or process. During the initial phases DLM emphasizes the diagnostic aspect. During later stages, DLM helps transition to efficient care delivery. In the subsequent sections, two commonly encountered diseases across their disease lifecycle—myasthenia gravis and chronic inflammatory demyelinating polyneuropathy (CIDP) are discussed.

DLM of Myasthenia Gravis

Myasthenia Gravis is an excellent example of a chronic, potentially lifelong disease which would benefit from DLM. The disease lifecycle can be conceptualized as shown in Table 7.1.

Consider the case of severe myasthenia gravis requiring intubation and mechanical ventilation. As shown in Table 7.1, knowledge and skill requirements

Table 7.1 Disease lifecycle management of myasthenia gravis

Interventions	Initial diagnostic phase (days to weeks)	Initial treatment phase (weeks)	Mature treatment phase (weeks to months)	Long-term phase (months to years)
Diagnostic tests	1. Antibody tests (AchR, MUSK)	None	None	None
	2. Repetitive nerve stimulation			
	3. Single-fiber EMG			
	4. Exclude mimics—LEMS, Botulism, ALS, CIDP variants, etc.			
	5. CT chest without contrast for thymoma			
Disease severity	Decrement on repetitive nerve stimulation, jitter, blocking on single-fiber EMG	FHA/FMEA/PSSA to define severity to direct treatment	Usually controlled, moderate disease severity	Low severity
Immunosuppression	None	1. Ocular: Mild to none. Symptoms treatment with Pyridostigmine	Moderate-to-low immunosuppression	Moderate-to-low immunosuppression
		2. All others moderate-to-severe immunosuppression	1. Prednisone: 20–40 mg/day in decreasing doses	1. Prednisone dose 5–7.5 mg/day
		(a) Generalized: Moderate-to-severe immunosuppression	2. Mycophenolate Mofetil (MMF): 1,000–1,500 mg Bid	2. MMF: 1,000–2,000 mg/day
		(b) Pre-crisis/bulbar involvement: Plasmapheresis/IVIG and steroid combination. Follow prednisone FMEA	3. Azathioprine: 150–200 mg/day	3. Azathioprine: 150–200 mg/day
		3. Thymectomy for Thymoma and young persons	4. Occasional rescue treatments with IVIG or plasmapheresis	4. Ca/Vit. D and / Bisphosphonates
				5. Annual killed flu vaccine

(continued)

Table 7.1 (continued)

Interventions	Initial diagnostic phase (days to weeks)	Initial treatment phase (weeks)	Mature treatment phase (weeks to months)	Long-term phase (months to years)
Adverse effects/ Monitoring	None	1. Pyridostigmine: Mild	1. Prednisone: See FMEA: Main complications include diabetes mellitus, hypertension, weight gain, edema, osteopenia, and osteoporosis	1. Prednisone: See FMEA: As in column 4
		2. Prednisone: Follow prednisone FMEA. See col. 3	2. Mycophenolate Mofetil (MMF): Diarrhea, Blood count abnormalities. Frequent CBC	2. Mycophenolate Mofetil: Malignancy risk. Lymphoma, skin
		3. IVIG: follow IVIG FMEA	3. Azathioprine: Flu-like reaction. Blood count abnormalities. Frequent CBC, CMP	3. Azathioprine: Malignancy risk, skin, lymphoma, hematological
		4. Plasmapheresis: Line-related complications, infection		4. Unusual infection risk
		5. Mycophenolate Mofetil, Azathioprine: See col. 4		5. Annual DEXA scan
		6. Thrombotic risk from IVIG and hospitalization		6. Biannual HBA1c
Ancillary therapies/ Physicians	1. Respiratory: Mechanical ventilation/BiPAP	1. Respiratory as in column 2	1. Decreasing respiratory needs	1. Minimal respiratory needs
	2. Swallow therapy in cases of bulbar weakness	2. Swallow as in column 2	2. Swallow needs anticipated to be complete	2. Internal medicine/ Endocrinology/ Hematology–Oncology
		3. Internal medicine/Hospitalist/ Critical care/Cardiothoracic surgery	3. Internal medicine/ Endocrinology	

See Chap. 4 for detailed FMEA information [14]

through the myasthenia disease lifecycle initially involves a neurologist to establish the diagnosis followed by critical care for managing intensive care unit treatment, plasmapheresis nurses, and respiratory technologists. As the patient overcomes the crisis, general neurologists or internal medicine hospitalists become the dominant knowledge and skill required. The knowledge and skill contribution from respiratory technologists, speech and swallow therapists decreases at this point. Subsequently, as the patient is transitioned to the home environment, the contribution from primary care physicians becomes extremely important. At this stage, the primary care physician provides detailed treatment and the neurologist provides high level guidance of treatment. This phase of the disease lifecycle evolves into the long-term phase where the disease is usually well controlled, chronic side effects and safety become the most important and the neurologist provides an advisory role. In this phase, management of weight gain, osteopenia/osteoporosis, monitoring for malignancy, monitoring/treating diabetes mellitus, and hypertension become the overriding concerns.

Myasthenia Gravis is best managed as a disease lifecycle and not in a piecemeal manner as the following examples demonstrate.

Case Example 5: Myasthenia Gravis—Traditional Approach

JC is a 76-year-old male with a history of seropositive myasthenia gravis. The diagnosis was based on positive acetylcholine receptor antibodies done at an outside facility. His original presentation in August 2013 involved generalized weakness and dysphagia for 1 week. He noticed that his symptoms of weakness would be normal in the morning, however it would progress throughout the day. He also began to notice worsening diplopia and dysarthria throughout the day. He began to have difficulty holding his head up. He was treated with prednisone followed by IVIG at an outside facility prior to being transferred for possible plasmapheresis. Since he had only recently received IVIG, plasmapheresis was withheld in the anticipation that IVIG would begin to exert full therapeutic effect in the next several days to a week. This strategy proved successful and the patient was progressively advanced to a mechanically soft diet prior to being discharged on Prednisone 60 mg/day.

The patient chose not to follow up at our facility and instead followed up with his local neurologist. He was referred back to the emergency department by his neurologist 5 months later in January 2014 with worsening weakness and concerns for worsening myasthenia gravis requiring plasmapheresis. On examination in January 2014, he was found to have normal speech, bulbar strength, mild proximal upper extremity weakness, but significant proximal lower extremity weakness which was around 4/5. The tibialis anterior muscles showed 4−4+/5 strength, medial gastrocnemius was normal. Standing and walking was difficult due to proximal weakness.

Since discharge from the hospital, the patient was continued on Prednisone 60 mg/day for the next 5 months. He also had an approximately 14 lbs. weight

gain and notable ankle edema. Based on the pattern of weakness involving solely the proximal lower extremity muscles, this was determined to be steroid myopathy and not worsening of myasthenia gravis by the neurology service. The patient was advised that plasmapheresis would not be helpful and he was discharged home with his prednisone dose reduced to 40 mg/day. He was advised close follow-up despite a longer distance in 1 month. At his subsequent clinic visit, there was clinical stabilization and improvement. An aggressive taper followed with the prednisone dose being reduced to 20 mg/day followed 4–6 weeks later by reduction to 10 mg/day. At this stage, mycophenolate mofetil was started as adjunct therapy with prescriptions provided for blood work monitoring through his primary care physicians.

The above is all too frequent a story. A patient gets treated for myasthenic crisis, gets discharged home on a high dose of prednisone, sporadically establishes care with a local neurologist who views the problem in a piecemeal manner. Subsequently, weakness from steroid myopathy sets in which is usually treated with IVIG or increasing the prednisone dose further. As the condition worsens, the patient is referred back for plasmapheresis for "worsening myasthenia gravis".

Based on the PLM model, myasthenia gravis should be managed along its disease lifecycle. The patient and physician need to adhere to the disease lifecycle which starts in the hospital but extends for many years as an outpatient. Appropriate transitions in therapy with tapering doses of prednisone, appropriately adding adjunct therapies like mycophenolate or azathioprine and their safety monitoring must be performed for dependable outcomes. Piecemeal approaches as in this example are wasteful and harmful.

Case Example 6: Myasthenia Gravis: DLM Approach

LEB is a 70-year-old female with hypertension, myasthenia gravis diagnosed based on positive acetylcholine receptor antibodies, a positive repetitive nerve stimulation study showing significant decrement and clinical symptoms of progressive dysarthria, dysphagia, recent onset of left ptosis, along with generalized weakness and head drop. She required the assistance of a feeding tube during her severe illness. She underwent five sessions of plasmapheresis and was started on prednisone 60 mg and pyridostigmine 60 mg four times daily. She did well since discharge. Her dysarthria and dysphagia, as well as head drop resolved along with ptosis. She develops transient fatigue after a workout session or after cleaning the house which resolves with rest. She feels pyridostigmine helps her swallowing. She has no trouble breathing. She was also discovered to have some thyroid nodules though workup for this had turned out to be benign. CT Chest for Thymoma was negative. The prednisone made her "jittery", and also caused her to eat more. She had an 18 lbs. weight gain and her blood pressures have been in the 170/86 mmHg range. During the course of the next 6 months, her prednisone dose was gradually tapered to 10 mg/day with adjunct pyridostigmine to help with ptosis and improve throat strength prior to eating.

Despite onset with severe disease, she was never again hospitalized for severe disease. She made steady progress and her care was assumed over the entire disease lifecycle. She closely communicated her status by telephone to make appropriate transitions in therapy. She attained good blood pressure control through hydrochlorothiazide and her weight gain stabilized over the next 2 years at 10 lbs. above her baseline. During year 2 and 3 of her disease she was seen biannually by the neurologist, much more frequently by her family physician who provided close treatment of her hypertension. Annual DEXA scans showed osteopenia which is being treated with oral calcium supplements and vitamin D. On review 2 years into her illness, she experienced no symptoms from myasthenia and her dose of prednisone was further dropped to 5 mg/day on Monday–Wednesday and Fridays and 2.5 mg on Tuesday, Thursday, Saturday, and Sunday, a dose at which she has remained for the last 1 year. She continues to take pyridostigmine as needed. She never developed diabetes mellitus. Vitamin D levels were periodically monitored and verified to be in normal range. She now remains in durable remission requiring only annual follow up.

Following initial diagnosis, intense inpatient treatment, the monthly disease treatment cost is less than $10/month since prednisone and calcium/vitamin D are commonly sold in most retail pharmacies for around $4/month. The following factors helped this successful outcome:

(a) Collaboration between all stakeholders: patient, neurologist, neurology clinical nursing assistant (CNA), and primary care physician. The patient understood this is a chronic condition with changing needs over time which requires careful transitions at all stages.
(b) Great collaboration from the primary care physician who provided excellent care of hypertension, osteopenia and provided seasonal killed flu vaccination.
(c) Most importantly, an extremely competent and hardworking CNA who took ownership and responsibility for managing all patient communications and ensuring timely clinic appointments.

DLM of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

CIDP is another disease which lends itself well to DLM principles. It should be noted that the following lifecycle is presented from experience with patients treated with steroids and not chronic IVIG or plasmapheresis therapy.

Table 7.2 shows the different phases of the CIDP lifecycle in patients treated at least partially with steroids. As treatment progresses into the mature and long-term phase, it is postulated that active nerve inflammation is being arrested and a gradual re-innervation process will take place. Therefore the mature phase requires decreasing doses of IVIG, steroids, and increasing emphasis on physical therapy and side-effect monitoring. The proximal muscles of the upper and lower extremities are the

Table 7.2 Disease lifecycle management of CIDP

Interventions	Initial diagnostic phase (Days to weeks)	Initial treatment phase (Weeks)	Mature treatment phase (Weeks to months)	Long-term phase (months to years)
Diagnostic tests	1. NCS/EMG	None	1. Repeat limited select NCS to monitor progression, response to therapy	None
	2. CSF studies			Monitor for recurrence
	3. Serum/Urine immunofixation			
	4. Specialized antibody tests			
	5. MRI Lumbar, cervical spine with and without Gad			
Disease severity	Mild: Sensory symptoms only	FHA/FMEA/PSSA to define severity to direct treatment	As in column 3	As in column 3
	Moderate: Mild distal weakness			
	Severe: Proximal and distal weakness with difficulty ambulating			
Immunotherapy	None	1. Plasmapheresis OR IVIG and steroid combination	1. IVIG or plasmapheresis as needed	1. Moderate-to-low dose prednisone/methylprednisolone
		2. Follow IVIG FMEA	2. Moderate steroid doses based on response	2. Rare IVIG or plasmapheresis
		3. Follow prednisone or pulse methylprednisolone FMEA as appropriate	3. Ca and Vitamin D	3. Ca/Vit. D and/Bisphosphonates

Adverse effects/monitoring	None	1. Prednisone: Follow prednisone FMEA.	1. Prednisone: See FMEA: Main complications include diabetes mellitus, hypertension, weight gain, edema, osteopenia, and osteoporosis	1. Prednisone/methylprednisolone and IVIG: See FMEA: As in column 4
		2. IVIG: follow IVIG FMEA		2. Annual DEXA scan
		3. Plasmapheresis: Line related complications, infection		3. Biannual HBA1c
		4. Thrombotic risk from IVIG and hospitalization—Heparin or Enoxaparin		
Ancillary therapies/physicians	None	1. Physical therapy: range of motion exercises	1. Decreasing pharmacology needs	1. Minimal pharmacology needs
		2. Stand and transfer with walker	2. Increase physical therapy needs: (a) Proximal muscle strengthening (b) Distal muscle range of motion (c) Ankle Foot Orthosis (AFO's) (d) Progress gait from walker to cane	2. Increasing therapy needs focus on distal muscles in lower and upper extremities. Progress gait to independent or with cane
		3. Internal medicine/hospitalist	3. Internal medicine/endocrinology	3. Internal medicine/endocrinology/hematology–oncology

See Chap. 4 for detailed FMEA information [14]

first to regain strength, re-innervation in the distal muscles happens slowly over months to years. Re-innervation is facilitated to a great extent by physical therapy. Therefore, over several months, the disease lifecycle requires decreasing pharmacotherapy and increasing physical therapy. Physical therapy itself evolves initially from range of motion exercises to increasing strength building exercises, first proximally and then distally. Several case examples of managing the CIDP lifecycle will be presented in Chap. 9.

Statistical Control, Monitoring Variations, Six Sigma Principles in Healthcare

Walter Shewhart, one of the titans of statistical quality control, introduced the concept of variation in a process as an important parameter in understanding quality control. Variation in a process is to be avoided and improving quality involves the control of variation [15]. Since most processes are random, a certain degree of variation is to be expected due to noise. Control charts are a simple but powerful data visualization tool that helps understand variation in a process [15, 16]. Figure 7.5 shows an example. A control chart involves plotting the outcome measure on the *y* axis and time or the sequence of samples on the *x* axis. For example, the process may involve manufacture of screws of a certain diameter. To assist data interpretation, on the *y* axis the data is centered about the mean or median of the outcome measure and upper and lower control limits (usual choices include 3 standard errors about the mean or 3 standard deviations) are plotted about the mean. These define the natural limits of the process, or in other words

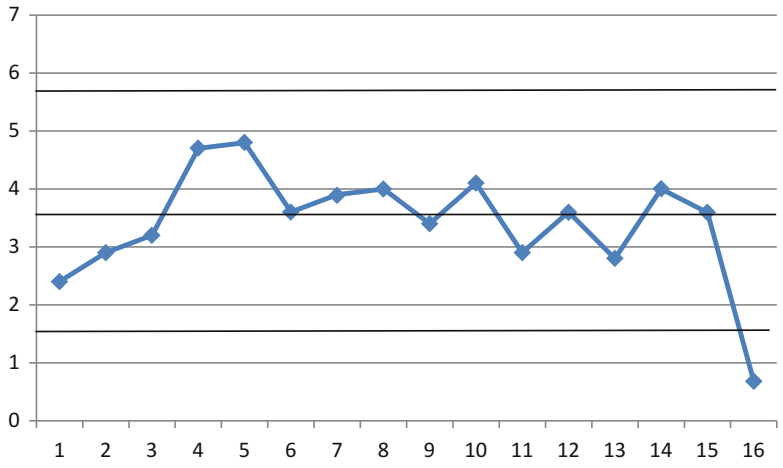

Fig. 7.5 Control chart for screw diameter (*y* axis) example plotted against sample number (*x* axis). The mean and upper and lower control lines for the process are plotted

the variation that can be expected due to the random nature of the process. (Note, this does not mean that all products within these confidence limits are acceptable to the customer, the specifications of the customer may fall within a narrower band.) If the upper and lower control limits are chosen to be 3 standard deviations about the mean, the probability of a sample falling above or below these limits is less than 1 in 1,000.

Control charts provide a simple, powerful, and convenient tool for understanding variation [16]. Based on the graphical representation demonstrated above, Walter Shewhart described two types of variations—common cause variation and special cause variation [16, 17]. Common cause variation is intrinsic to a process and relates to the inherent statistical nature of a process [17]. Samples fall within a predictable distance of the mean (within the upper and lower control lines) and in Fig. 7.5, the first 15 samples fall within a band which is consistent with common cause variation. Special cause variation refers to a new, unpredictable event which causes unforeseen variation in data, when a sample falls outside the upper and lower control limits. In such an instance, the probability is less than 1 in 1,000 that the variation is due to chance. In the example below, the first 15 samples fall within the upper and lower control lines, however the 16th sample is below the lower control line which has a less than 1 in 1,000 probability of occurrence. Therefore, a special cause such as machine malfunction must be sought and corrected. A process where the data fall within the control bounds is said to be "in control" [17].

Control charts present a simple, adaptable, and flexible method for visualizing data and with the advent of smart phones and tablet computers, lend themselves to quick implementation for day-to-day application in medicine. At the current time, these are used mainly by hospital administration for quality control in services such as patient scheduling, wait times for registration, admission, etc. A more powerful application would be when these are used for managing treatment by doctors and nurses.

Variables such as blood pressure, blood counts, respiratory rates, pulse rate, disease rating scales such as manual myasthenia rating scale (which measures individual muscle strengths) lend themselves to such analysis to guide changes in treatment. If these variables are "in control", adjustments to treatment can be avoided. If special cause variation is observed, its causes can be carefully investigated—such as missed doses, drug interactions, treatment failure, etc.

Six-Sigma

Six sigma is based on the concept that variation in manufacturing or services is the cause of all defects. Eliminating variation can eliminate defects. Extending the process of controlling variability, six sigma refers to a process where there are less than 3.4 defects per million [18]. The name is derived from the Greek letter sigma which is used to denote standard deviation in statistics. The roots of the idea themselves lie in the work of Walter Shewhart, Joseph Juran, and W Edwards

Deming. Controlling variability to achieve a defect rate of 3.4 defects per million was adopted by Bill Smith at Motorola in the 1980s [18]. Six Sigma is a registered trade mark of Motorola. One of the most successful implementations of this technique has been by General Electric whose success generated considerable interest in the technique. Six Sigma is being applied widely in healthcare, but its true value maybe underestimated at this time since it is rarely used by practicing doctors and nurses. Many healthcare institutions today lay claim to being six sigma at some level. A review of six sigma in healthcare is beyond the scope of this chapter, this section will focus on six sigma from a doctor's viewpoint as a process to reduce variation in diagnosis and treatment.

A word of caution is necessary here. Patient care does not lend itself easily to the rigid standardization that is sometimes understood to be the goal of six sigma. No two patients have been the *same*, therefore *blind* standardization of processes to reduce variation is difficult to implement and may even be harmful in some instances. Blanket approaches such as if disease *X*, then drug *Y* may even be harmful in some instances which can easily undermine the six sigma standards. The patient maybe on a drug *Z* which can interact dangerously with drug *Y*, therefore a reasonable alternative needs to be chosen. In a narrow sense, this alternate choice of medication does not meet six sigma norms. Numerous processes can however be standardized in healthcare such as ER wait times, infection control rates, antibiotic administration times for sepsis and other dangerous conditions, scanning protocols where patient to patient variation is not expected. The philosophy behind six sigma—that of reducing variation and understanding processes—has important applications in day-to-day medicine from a doctor's perspective. Its application as a slogan or an end in itself has been less successful and perhaps of less consequence. This section will view Six Sigma purely as a variation reducing method and will explore some ideas that serve this goal in diagnosis and treatment.

Order Sets

Order sets provide a set of standard instructions for the care of a patient. These can be general—applicable to any patient admitted to a hospital, or they can be diagnosis specific—such as orders relating to the care of a patient with stroke. More advanced order sets implement established "evidence-based" best practices where the orders are backed by data from clinical trials or other objective assessments. When implemented electronically, a simple mouse click can activate a sequence of orders which are complete without potentially vital information being omitted. Generally, the following parameters are specified at the time of admission: Working diagnosis, type of bed (whether with cardiac monitoring or not), diet, activity level, IV fluid needs, required tests, medications list, allergies, Do Not Resuscitate status, etc. Some general order sets mandatorily implement certain hospital and professional society guidelines such as blood thinners like heparin for preventing blood clots and stomach acid suppressing drugs to prevent ulcers. Early in the author's training, admissions were performed manually.

Invariably, one parameter or the other would be omitted when these were entered manually leading to a frustrated nurse paging the doctor to complete the orders. An electronic order set monitors for all these aspects of care being specified and often does not allow signature till all these criteria are met.

Order sets can be disease specific where a set of orders are linked to further investigate or treat a working diagnosis. Let us consider the example of a stroke order set. In addition to the above, it involves orders for MRI Brain scans (usually with and without Gadolinium dye), vessel imaging in the form of ultrasound or MRA or CT Angiography, cardiac evaluation in the form of 2D echo with saline bubble contrast, EKG, cardiac enzymes, and rhythm monitoring for abnormalities such as atrial fibrillation; swallowing, and speech tests [19]. The therapeutic aspect of a stroke order set would include choice of antiplatelet drugs such as aspirin, clopidogrel or more potent blood thinners like heparin or warfarin for cardiac rhythm abnormalities. These would also involve using statins and at minimum blood tests for diabetes, thyroid disease, lipid panels among others. Blood pressure parameters and treatments when the values fall outside these boundaries can be specified. It would also order appropriate supporting therapies in the form of speech and swallow therapy, physical and occupational therapy to limit morbidity. Order sets prevent omission of a sequence of orders. For example, vessel imaging is exceedingly important in the evaluation and management of stroke. This can be easily performed in one setting during performance of the MRI Brain scan. If vessel imaging is neglected, a potentially treatable cause of recurrent stroke—such as critically narrowed carotid artery will be missed with significant attrition in quality of care and higher error rate. At worst, a patient will need to be rescanned which imposes constraints on patient mobilization and transport. Order sets for particular diagnosis prevent such omissions and specify tests the right way. For example, echocardiography studies for stroke are best performed with agitated saline bubble contrast to look for any patent foramen ovale (PFO) [19]. Echo studies for other applications such as heart infections do not need this specification. Similarly, MRI Brain for a patient with a seizure is performed differently using an epilepsy protocol and vessel imaging is not required. This can be addressed using a similar epilepsy order set. For more resource intensive challenges such as care of ICU patients admitted with treatable but life-threatening conditions, order sets allow numerous variables to be monitored and treated by nurses in an autonomous manner without the need to get individual instructions for abnormalities.

Currently their use is heavily in the in-patient setting for treatment. Order sets can be used successfully in the outpatient setting for diagnostic workup as well. They are especially useful when they are disease specific which help thoroughness in evaluation and treatment. For example, a myasthenia gravis order set could include blood tests for antibody testing, CT scan of the Chest without contrast looking for Thymoma as a cause of the disease, testing for Tuberculosis (either using PPD or blood test called Quantiferon) prior to initiating suppression of the immune system; blood tests for glucose, vitamin D levels, bone scans, medications used for treatment such as prednisone, calcium, vitamin D, bisphosphonates to prevent bone loss when being treated with steroids; omeprazole for suppressing

stomach acid when on steroids; lung function and swallow tests as needed. This ensures that all aspects of diagnosis and treatment are addressed and nothing is omitted [14].

Diagnosis Related Processes

For a few critical conditions, a diagnosis-related process has been instituted. In these conditions, standards have been established nationally and internationally which mandate a certain treatment or intervention within a certain time frame. This prevents deterioration and complications due to delay in instituting proper care. The best examples for these are stroke and myocardial infarction. For myocardial infarction current protocols are very process driven and emphasize an expedited revascularization time. At the current time, the treatment of myocardial infarction requires a "Door to Balloon" time to be as early as possible, based on guidelines from the American Heart Association [20]. Such a process lends itself well to standardization since the treatment approach is the same in all patients as opposed to a condition like office-based migraine treatment where the choice of treatment is heavily influenced by cost, side effect, gender (some medicines like Valproic Acid work well in men but are best avoided in women for pregnancy risk reasons) considerations and such standardization is hard to define and achieve.

Stroke has benefited tremendously from such a process driven approach. Stroke severity is measured on a standard stroke scale which provides a numerical measure of severity and facilitates risk vs. benefit assessment. In the past decade, clot dissolving drugs such as IV tissue plasminogen activator (IV-tPA) have become available which are best used very early to restore circulation and rescue brain function. There are numerous criteria and safeguards for their use. The classical limit on their use IV was 3 h which in most cases can be extended to 4.5 h under certain conditions [21]. It can be extended up to 6–8 h through intra-arterial catheters delivering the drug into the blocked blood vessel in some conditions.

The criteria for whether a patient should receive or not receive IV-tPA has been standardized and implemented in most certified institutions in the form of a *checklist* [21]. This prevents errors when a complicated sequence of critical safety criteria is evaluated. Scanning protocols such as—time to CT Brain scan, scanning protocol itself, time for scan to be read and results communicated by radiologist to neurologist or emergency department physician to institute treatment have been standardized [21]. The most recent guidelines are listed in Table 7.3. Immediate institution of treatment as quickly as possible within the 3 h window has been understood by everyone involved. This has been achieved only by a process driven approach with little variation within institutions. Follow-up care of such patients who received IV-tPA is also heavily process driven. After administration of IV tPA, stroke order sets specify guidelines on permissible blood pressure ranges, the doses of drugs that can be used if it varies outside these parameters and other aspects of longer term care. By reducing variation this is a move towards six sigma [21].

Table 7.3 Action time limits for treatment of acute ischemic stroke

Treatment step	Time
Door to ED physician	≤10 min
Door to stroke team	≤15 min
Door to CT Brain initiation	≤25 min
Door to CT interpretation	≤45 min
Door to drug (≥80 % compliance)	≤60 min
Door to stroke unit	≤3 h

Adapted from [21]

But for everything else, there is very little developed process with great variation between patients and institutions. Hence the frequent refrain of the 12 h wait in the emergency room, the long wait between admission and getting something for pain and administration of other medicines. Apart from a few of these conditions described above, a diagnosis related process has not been developed. In the outpatient setting, these concepts are rarely applied, hence the long wait times between things happening. Performing a FTA can help understand the source of these variations. For one patient it maybe the delay in getting a room assigned and for the drugs to be delivered to the appropriate bed, for others it maybe delay in nursing receiving the care plan and orders. A systematic approach can pinpoint the delays and impose restrictions on each step of the process to prevent cascading of problems.

Checklists

Checklists are a simple, but very powerful variance reduction and safety tool which can be easily implemented. A checklist is a list of items or steps which need to be done for successful completion of a task. Dr. Atul Gawande's book the *Checklist Manifesto* is an excellent discussion and reference work on the subject [22]. A brief discussion and a few simple applications will be presented here. The interested reader is referred to the *Checklist Manifesto* for further information on the subject. Implicit forms of it have been discussed above as part of different variance reduction techniques. Checklists can be constructed for any diagnosis, procedure, or treatment to ensure safety standards are being met and nothing is omitted. Forms of it such as procedure "time outs": checking patient identity, side and sterile precautions prevent negligent medical errors from happening, especially in surgery. Checklists are commonly used in the airline industry to prevent accidents [22]. In Dr. Gawande's work, checklists are much more than mere verification of steps in a process, they are a great tool for teamwork and communication [22].

One field where checklists have made a systematic impact in day-to-day medical practice is Radiology. They help the radiologist avoid blind spots in imaging. A common scenario is when a scan is ordered for a particular part of the body looking for one particular thing such as an MRI scan of the brain looking for a brain tumor.

While focusing on the objective—in this instance the brain, it is easy to overlook secondary findings on the scan such as enlarged lymph nodes in the neck or a tumor of the salivary glands since these are small structures and not the focus of the primary study. MRI scans of the Lumbar spine for backache commonly get partial images of the kidneys uncovering cysts or tumors. Similarly, MRI Cervical Spine studies uncover thyroid abnormalities. To avoid such blinkers, radiologists use checklists to avoid missing such findings. A checklist constructed for brain imaging forces the radiologist to look at subtle findings in frequently overlooked parts of the scan [23]. This is in essence a process driven approach to each scan which is standard for a particular type of scan and a body region. The following example shows a successful application of this technique.

Case Example 7

MS is a 72-year-old female referred for evaluation of hip weakness. The main concern for the referring physician was whether this is due to statins. On examination, it was felt based on brisk reflexes in her knees that she may have spinal cord compression in the neck which was causing her symptoms. An MRI Cervical Spine was ordered which showed somewhat advanced arthritis in the cervical spine, however not enough to cause spinal cord compression. The radiologist working down her checklist did however note that a 1 cm swelling was partially visualized in the thyroid gland. The thyroid gland is partially visualized on MRI scans of the cervical spine. This was followed up with a dedicated thyroid ultrasound study with fine needle aspiration of the swelling which showed malignancy. The patient underwent thyroidectomy which confirmed the presence and total removal of the cancer. This was a purely serendipitous finding which was uncovered due to a disciplined, checklist driven approach adopted by the radiologist.

Checklists can ensure thoroughness in medication regimens for a particular diagnosis to reduce variation and meet standard of care. After debilitating illness such as a stroke when a patient returns to clinic after several months with a deluge of medical records, checklists ensure attention is not distracted from core objectives. If patient had an ischemic stroke, the checklist should include: (1) Blood Pressure control. (2) Antiplatelets (aspirin, clopidogrel, aspirin-extended release dipyridamole) or anticoagulation (low molecular weight heparins, warfarin, or dabigatran). (3) Statins. (4) Blood cholesterol <70 mg/dL. (5) Smoking cessation counseling. (6) Relevant lab work: PT/INR for patients on warfarin, cholesterol, liver function tests for patients on cholesterol reducing medications, HBA1c for diabetic stroke patients [19]. During the course of seeing patients, frequent omissions in these are found by simply using an ischemic stroke clinic visit checklist. Heart failure has a similar well-established set of checklists which have helped expand standard of care. Similar process driven approaches by anesthesiology have made anesthesia several times safer today than in the 1980s. Great successes have been reported using this tool in catheter related infections [24].

Checklists find great application in day-to-day diagnosis and treatment of neurological disorders in the outpatient setting.

Checklist 1

The following is an immunosuppression checklist that has been found to be very useful in day-to-day practice. This checklist screens for any obvious contraindication to immunosuppression with medications like prednisone, mycophenolate mofetil, methotrexate, or azathioprine. Detailed drug-specific FMEAs can then be applied if a patient is deemed appropriate for immunosuppression.

Immune Suppression Checklist

A. **Diagnosis**:
B. **Measurable Infection Screen**

   (a) **Tuberculosis**: **Quantiferon** **Tuberculin**
   (b) **HIV**
   (c) **Hepatitis Profile**
   (d) **Varicella Zoster** (**Shingles**)
   (e) **Herpetic Lesions**
   (f) **Active Urinary Tract Infections**
   (g) **Active Pneumonia**

C **Complete Blood Count**: **Hemoglobin** **WBC Count** **Differential**:
D. **Any Active Ongoing Infections**: **Yes** **No**
E. **History of frequent Pneumonias**, **Urinary Tract Infections**, **Diverticulitis**, **Colitis, or Sepsis**?
F. **Any Antibiotics/Antiviral/Antifungal/Cancer Treatments**: **Yes** **No**
G. **Any history of cancer**: **Yes** **No**: **Melanoma**: **Yes** **No**
H. **Expected Duration**:
I. **Immune suppression Intensity and Lifecycle**

Case Example 8

KA is a 77-year-old Indian male presenting with symptoms of neck weakness, double vision, and drooping of eyelids for the past several months. Physical examination revealed moderate pharyngeal weakness, fatigable ptosis, bilateral exotropia's and bifacial weakness. AchR and MUSK antibodies were negative. A single-fiber EMG confirmed a junctional disorder consistent with seronegative myasthenia gravis. Anti-Voltage-Gated Calcium Channel antibodies for Lambert Eaton Myasthenia Syndrome were negative. Prior to starting treatment with prednisone, the immunosuppression checklist was run which revealed the patient had an untreated positive PPD. Immunosuppression was deferred and patient referred to

Infectious Diseases for initiation of antituberculosis therapy. He failed therapy with Pyridostigmine. The contingency plan is to initiate plasmapheresis if symptoms worsen.

Case Example 9

MW is an 84-year-old Caucasian male presenting with symptoms of ptosis and diplopia. Symptoms were ongoing for several months. He was diagnosed with seronegative myasthenia gravis based on single-fiber EMG and negative antibody tests. Prior to initiating therapy with prednisone, the immunosuppression checklist demonstrated a positive PPD. A repeat PPD performed 2 weeks later by an infectious diseases specialist was also positive. The patient was placed on antituberculosis therapy successfully.

In Case Example 9, it is intuitive to think of tuberculosis given the high prevalence of tuberculosis among Asians. However, Case Example 10 represents a demographic with very low exposure to tuberculosis. MW had never been incarcerated or traveled to countries with high tuberculosis burden like India. This was discovered solely because of adherence to the immunosuppression checklist. Checklists help prevent unanticipated complications, usually errors of omission where a particular adverse event is considered so unlikely that it is omitted.

Case Example 10

DW is a 41-year-old female with Grave's disease, type 1 diabetes mellitus, breast cancer s/p resection, chemotherapy, and radiation 5 years ago presenting with ptosis and diplopia in addition to proptosis of the right eye from Grave's disease. The diagnosis was established by an abnormal single-fiber EMG. Given her brittle diabetes mellitus, she was considered a poor choice for steroids. It was anticipated that mycophenolate mofetil or azathioprine would be a better choice for her. On implementing the immunosuppression checklist, she was found to have a low WBC count of 2.9 K with a normal differential. The etiology of the leukopenia is unclear but it gives pause before starting MMF or Azathioprine since these drugs frequently cause leukopenia. Her prior history of breast cancer is also a relative red flag. A hematology workup is in progress to determine the cause of the leukopenia. In the interim, the patient is being treated with Pyridostigmine.

Checklist # 2: IVIG Checklist

During the course of treating autoimmune neurological disorders, complications from IVIG usage were seen not infrequently. The most concerning were cardiac events, especially chest pain, shortness of breath which usually turned out to be demand ischemia with mild elevation of cardiac enzymes. Given the relative

frequency of this and other complications, the frequent comorbidities (cardiac illness, diabetes mellitus, renal insufficiency) in these patients, an IVIG checklist was created to identify high-risk patients where considerable caution needs to be exercised before using IVIG or even alternatives considered.

IVIG Checklist

1. **Idiosyncratic**
   (a) **Allergies to Blood Products**
   (b) **Prior Transfusion Reactions**
2. **Hypertension**
   (a) **Normotensive**
   (b) **Controlled (140–160/<90)**
   (c) **Caution (160–180/<100)**
   (d) **Hold (>180/>100)**
3. **Cardiac**
   (a) **Normal**
   (b) **Stable Angina**
   (c) **Recent Angina (within 6 months)**
   (d) **Unstable Angina**
   (e) **Coronary Artery Disease**
   (f) **Myocardial Infarction (last 6 months)**
   (g) **Congestive Heart Failure**
   (h) **Demand Ischemia**
4. **Thrombotic Risk**
   (a) **None Deep venous Thrombosis Pulmonary Embolism Stroke**
5. **Renal Status**
   (a) **Normal**
   (b) **Mild Kidney Impairment**
   (c) **Severe Kidney Impairment**
6. **Ig A Deficiency**
   (a) **Yes**
   (b) **No**
7. **Clotting Disorder/Blood**
   (a) **Inherited: (Factor V Leiden, Prothrombin gene mutation, protein C, S deficiency, antithrombin III deficiency, MTHFR deficiency)**
   (b) **Acquired disorders: SLE, APLA syndrome, Lupus anticoagulant**
   (c) **Hemolysis**

Caution: **Allergies**, **prior transfusion reactions. Hypertension in caution range**, **add or increase antihypertensive medication doses**.

Extreme Caution: **Recent MI**, **Stable Angina**, **Demand Ischemia**.

Avoid: **Decompensated CHF**, **Unstable Angina, Ongoing thrombotic disorder**, **hemolysis**, **severe kidney impairment**, **IgA deficiency**.

Troubleshooting Checklists

In the aviation industry, checklists help identify a set of minimum basic responses to problems. Please see reference [22] for examples of aviation industry checklists. For the case of IVIG, based on observed mishaps, review of the literature, the following trouble shooting checklist was compiled to guide a basic initial minimum response to commonly experienced problems [25]. This checklist details specific mitigation responses to specific failure modes identified in the PSSA, FMEA of IVIG discussed in Chap. 4.

IVIG Complications Checklist

1. Headache, photosensitivity: Consider Aseptic Meningitis.
   (a) STOP/HOLD INFUSION.
   (b) MRI Brain/MRV (To rule out venous sinus thrombosis).
   (c) Meningitis: Fluids, rest, analgesics. Consider Lumbar Puncture.
2. Fatigue, Jaundice, Change in color of urine: Consider Hemolysis.
   (a) STOP INFUSION. ADMIT PATIENT.
   (b) IV FLUIDS.
   (c) Check CBC, CMP, Urine Hemoglobin, Serum Haptoglobulin, LDH, Reticulocyte Count.
   (d) Monitor for Hemolysis.
3. Shortness of breath: Consider Myocardial Infarction, Pulmonary Embolism.
   (a) STOP INFUSION. ADMIT PATIENT.
   (b) CT CHEST Pulmonary Embolism Protocol.
   (c) Lower extremity venous dopplers.
   (d) EKG. (Follow unstable angina, MI monitoring protocol), Telemetry.
   (e) Cardiac Enzymes (three sets, follow unstable angina, MI monitoring protocol).
   (f) Echocardiography.
4. Chest Pain: Consider Myocardial Infarction, Pulmonary Embolism.
   DO a, d, e, f as in 3 above.
5. Focal Deficits: Consider Stroke, Transient Ischemic Attack.
   (a) STOP INFUSION, ADMIT PATIENT.
   (b) STAT CTA Head and Neck for stroke.
   (c) FOLLOW INSTITUTIONAL STROKE PROTOCOL.

6. Muscle Aches, Cramps, Body pain.
   (a) Plenty of fluids.
   (b) Urinalysis, Check Creatine Kinase (CK) levels.
   (c) Observe.
7. Allergic Reaction/Itching/Hives.
   (a) Temporarily Stop Infusion.
   (b) IV Fluids.
   (c) Inj. Diphenhydramine 50 mg IV Stat. If severe combine with IV Dexamethasone 10 mg IV Stat or IV Methylprednisolone 50–100 mg IV Stat.
   (d) Anaphylactic Shock protocol (Epinephrine-pen if severe).

Conclusion

This chapter demonstrates the potential advantages in implementing a process driven approach to healthcare. Such an approach aligns healthcare processes with paradigms in high dependability industries like aerospace by borrowing systems engineering ideas and applying them to day-to-day healthcare. As shown above, the simple application of processes can prevent some of the wastage in medicine. The total estimated waste in the healthcare system is estimated at $765 billion dollars by a recent study done by the institute of medicine [24]. The split up of this waste is as follows: unnecessary services: $210 billion, inefficiently delivered services ($130 billion), excessive administrative costs: $190 billion, prices that are too high: $105 billion, Missed prevention opportunities: $55 billion and fraud: $75 billion [24]. Improving efficiency, reducing waste concept will be extended further in Chap. 9 where a powerful tool for implementing complex operations called microplanning will be presented.

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Chapter 8
Toyota Production System

Abstract This chapter introduces the reader to lean manufacturing principles. The life and work of W. Edwards Deming, Taiichi Ohno, and creation of Toyota Production System are discussed in detail. There is a detailed discussion of the salient principles of *Pull vs. Push*, avoiding waste, root cause analysis, the 5 why's principle, go and see for yourself (Genchi Genbutsu), Jidoka, and introduction to the principles of Kaizen. Case examples and application of these principles are presented.

Introduction to Lean Manufacturing

A powerful paradigm in manufacturing has been *Lean Thinking* which has been adopted systematically in many industries with generally good results [1–5]. Lean was pioneered by Toyota Motor Corporation (TMC); it is also referred to as the Toyota Production System (TPS) which is more a philosophy than a set of work practices. Its applications are so universal that it is applied in some form by every major manufacturer whether automobile or otherwise [1–5]. This section will emphasize more on the philosophy and processes behind lean and will avoid approaching it from a "slogan" viewpoint.

Lean has been adopted in healthcare administration to a great extent with many successes. It has started making in-roads into day-to-day bedside healthcare; however, it has not seen the widespread grass roots application among doctors, nurses, and pharmacists which will increase its impact. This section will present a brief overview of Lean followed by application of some important aspects of Lean which can improve dependability in healthcare.

Lean Thinking at its core seeks to eliminate waste and improve quality and reliability. The ideas were pioneered by W. Edwards Deming (1900–1993) and Taiichi Ohno (1912–1990). The work of these two remarkable individuals which started in Japan had the most profound impact on manufacturing across the world since the advent of the industrial revolution.

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The Teachings of W. Edwards Deming

W. Edwards Deming was born in Sioux City, IA. He earned his B.S. in engineering from the University of Wyoming in 1921 followed by M.S. and Ph.D. in mathematics and mathematical physics from the University of Colorado and Yale University in 1925 and 1928, respectively. In 1950, Dr. Deming was invited by the Japanese Union of Scientists and Engineers (JUSE), where he delivered a series of lectures entitled "Eight day course on Quality Control." This seminar had a very important impact on Japanese businesses which adopted his teaching to set benchmarks in quality which helped Japan dominate many industries, especially automobile in the years to come. Dr. Deming donated all the proceeds from the sale of transcripts of his lectures to JUSE. In recognition of his contributions, JUSE instituted the Deming Prize in his honor which is awarded annually to individuals and companies. The Deming Prize for Individuals is awarded to individuals who have made an outstanding contribution to the study of total quality management (TQM) or statistical methods related to TQM. The Deming Application Prize is awarded to companies for making achievements in quality by application of TQM in a designated year [1]. Dr. Deming popularized the Plan-Do-Check-Act cycle (discussed with examples in medical context later). A significant philosophy developed by Dr. Deming is the "Deming System of Profound Knowledge."

The "Deming System of Profound Knowledge" is as much a personal philosophy as an organizational one. It underscores the importance of individual development for organizational transformation and improvement. The individual seeks and attains a deeper understanding of events, life, and relationships with other people. This transformation leads to profound knowledge where the individual would set an example, be a good listener (but without compromise). The individual would continuously teach others and help others transition from current beliefs and practices towards the new ways of doing things without conflicts or guilt. With this transformation, the individual develops better judgment for his decisions and for the transformation of the organization [2]. Dr. Deming believed all managers must understand the "System of Profound Knowledge" which consists of four intertwined and inseparable parts [2]:

(a) Appreciation for a system: managers must have intimate knowledge of all processes involving a system such as production, relations with suppliers and customers.
(b) Knowledge of Variation: understand the nature and causes of variations in quality with understanding of statistical quality control techniques.
(c) Theory of Knowledge: understanding what is known about processes and what is unknown to develop hypothesis, gaining insight into data to be able to predict and further refine current state of knowledge and understanding, extending understanding by asking questions. "Without theory, experience has no meaning. Without theory, one has no questions to ask. Hence without theory, there is no learning."
(d) Psychology: understanding human behavior and interactions.

In *Out of the Crisis* [3], Dr. Deming advocated 14 principles as ideas for transforming American business.

1. Create purpose for improvement of products and services.
2. Being in a new economic age, western management must learn new responsibilities, measure up to the challenge, and demonstrate leadership for change.
3. Quality is important and must be built into the product in the first place. It should not be dependent on inspection.
4. Build relations with suppliers, moving towards a single supplier for any one item based on long-term relationships of mutual loyalty and trust. Such an approach minimizes total cost and does not create partnerships based on price tags.
5. Continuously improve the system of production and service with the end goals of improving quality and productivity. This would improve quality and constantly decrease costs.
6. Provide opportunities for continuous skill development by instituting training on the job.
7. Management should encourage leadership. Supervision of production workers and management should be to encourage everyone to do a better job instead of being adversarial.
8. Create an atmosphere without fear so that everyone can work effectively for the organization.
9. Integrate departments across the organization by breaking down barriers between them. Research and development, design, sales, and production must work together as a team to foresee and correct problems that maybe encountered during manufacturing or operation of the product or service.
10. A culture of leadership, ownership can achieve excellence. Slogans, artificial quotas, numerical goals create waste and adversarial relationships and should be eliminated.
11. The hourly worker should not be robbed of his right to pride of workmanship. The organization, including workers and their supervisors must be dedicated to excellence and quality.
12. Employees in management and engineering should also not be robbed of their right to pride of workmanship. For this to happen, abolish annual or merit rating and management by objectives.
13. Create programs for education and self-improvement.
14. Encourage everyone to work towards accomplishing the transformation. The transformation should be seen as everybody's responsibility and contribution.

The following sections will show that these principles are timeless.

Taiichi Ohno and the TPS

Taiichi Ohno is widely credited with being the creator of the TPS which is known as Lean manufacturing the world over. Taiicho Ohno, executive vice president at TMC was inspired by eliminating waste in the manufacturing process to improve efficiency, profitability, and productivity at Toyota. History has it that the inspiration for this system struck Mr. Ohno during a visit to a supermarket in the United States. When one product was sold, a replacement was ordered and placed on the shelf. Reordering and restocking therefore was highly driven by sales with customer demand driving what was being stocked and restocked on shelves. The Japanese word for waste is *muda*; TPS has at its heart the elimination of *muda*. It is interesting to define waste first so that its elimination can then be better understood [4]. Waste as identified by Mr. Ohno takes several forms—mistakes requiring reworking of finished goods, overproduction of goods with little market demand, steps in manufacture or services that do not add value and slow-down productivity, poor planning of steps in manufacturing which require expensive transport of unfinished goods from one step to the other slowing down the process, poor coordination of intermediate steps in manufacturing leading to downstream workers with little work since upstream processes have not completed in time. Finally, waste involves the delivery of goods or services which do not meet the customer's requirements or expectations [4]. The above represents the set of identifiable waste in manufacturing, where intermediate steps are well defined. Viewed from this perspective, the reader can only imagine the degree of waste in bureaucracies and healthcare systems. When viewed from this perspective, healthcare is riddled with *muda*. Detailing all types of *muda* in healthcare is beyond the scope of this book, but it includes errors in diagnosis and treatment, delays, duplication of effort, expensive laboratory tests and imaging which may not add value to the problem. The interested reader is referred to the work of James Womack, Daniel T. Jones, and Daniel Roos for a comprehensive review of the topic [4, 5].

While eliminating *muda* is the goal of lean manufacturing, how is this achieved in practice? The major ideas in lean manufacturing which have gone into folklore are the following [6]:

Just-in-Time

Just-in-time is synonymous with TPS. Each process manufactures exactly the same number of items which are used by the next process. This method eliminates manufacture of excessive numbers of intermediates or finished products, where there is no demand. It allows for great flexibility in manufacturing enabling the manufacturer to produce only the right amount of what is needed at the right time. This is the manufacturing equivalent of the supermarket principle observed by Mr. Taiichi Ohno in his visit to the United States. Conceptually, when a customer purchases a red color Toyota Camry in Dallas, TX, an instruction is sent to the

production line to build a replacement red Toyota Camry. Carried one step further, orders for component parts such as its engine, transmission; seats (depending on the trim) are placed further upstream in the process. Each step of the manufacturing process manufactures only a small number of parts to replace what was delivered at the end of the line to the customer.

Just-in-time facilitates the development of a "Pull" system. The customer's action of purchasing a product exerts a "Pull" on the manufacturing system leading to the manufacture of a replacement product. Manufacturing therefore is closely coupled to demand. This is the opposite of the "Push" system, where manufacture of goods or intermediates is performed independent of the level of utilization downstream leading to production or overproduction and inefficient application of resources [4–6]. Just-in-time requires close coordination and communication between manufacturing processes in the assembly line. A typical car today has an inventory of over 30,000 parts many of which are supplied from external vendors. Within the shop floor of the assembly line, a system called *kanban* is used to link different manufacturing units together. A *kanban* card is a card attached to a parts bin which contains information such as type of part, its quantity, and other information. When a part is removed from the bin, the associated *kanban* card is removed and sent upstream to the supplier indicating the part has been utilized. *Kanban* cards therefore carry information on what parts have been used and where they have been used so that the suppliers can manufacture exactly the same number of replacement parts and deliver it to the required location. The system today is completely electronic but the concept remains the same. This process is not just used by Toyota and its affiliates, but also by external vendors.

Jidoka

Loosely translated means "automation with a human touch." The origins of the *jidoka* system lie in the birth of the company itself. Sakichi Toyoda invented the self-powered loom with a built-in capability to stop production whenever thread breakage was detected. This enabled a machine to stop automatically when malfunction was discovered and prevented the manufacture of defective items. This allowed a single worker to be put in-charge of many looms which boosts productivity [6]. This has been refined and extended into the company's automobile manufacturing business. A single worker can monitor many different machines and processes assisted by modern computer aided visualization tools. When a problem is detected, the production process automatically shuts down to prevent defective parts from being manufactured. The malfunction itself is prominently displayed in production lines using monitors or flashing lights called *andon boards* which display information about the problem. (Effective data visualization therefore is a powerful tool in this system) When a worker discovers a problem with a particular process, he can pull an *andon* cord to stop the production line. The *jidoka* system therefore prevents defective parts from being passed down the assembly line, where they can become increasingly difficult to rectify.

Kaizen

The term *kaizen* refers to continuous incremental improvement. *Kaikaku* refers to radical improvement [5]. This requires deep understanding of processes and teamwork between workers and supervisors to refine processes towards gradual improvement. They require close collaborative relationships between workers and team managers and an atmosphere that fosters new ways of doing things and experimenting. Successful corporations devolve responsibility for limited experimentation for improving processes to the grassroots level of the production system. Workers and team managers collaboratively conceive new ways of completing a particular process and are allowed to experiment in a limited manner. Data (processing time, material usage, etc.) from the new method is compared to the old method. If there is significant improvement, the new method is adopted in a more widespread manner throughout the organization; otherwise, it is rejected to move onto the next new idea. *Kaizen* is intimately connected to the Plan-Do-Check-Act cycle which will be discussed further. Successful implementation of *kaizen* for any project therefore has teamwork, respect for coworkers implicitly built in.

The 5 Why's

Taiichi Ohno encouraged the 5 *Why's* principle which forms the basis of a very powerful investigative tool called *Root Cause Analysis*. He encouraged his staff to get to the root of every problem rather than solve the immediate problem on hand. The immediate problem is what is perceived, the deeper problems are the causes of what is perceived and the examiner has to probe deeper into the problem till he gets to the heart or *root cause* of the problem. In Mr. Ohno's words "The root cause of any problem is the key to a lasting solution." He encouraged the principle of *genchi genbutsu* ("go to the source and get the facts") which encourages managers to go to the shop floor and see the problem with their own eyes and understand the facts. A connected word in the lean lexicon is *Gemba* which means "the place" or "market," where the actual actions occur. When a problem arises in the *gemba*, managers should go there and understand the *genbutsu*. This is perhaps one reason for the success of Japanese automakers, while manufacturing problems are understood in reports and solutions proposed by managers in corporate offices in the west, the Japanese system encourages problems to be understood and solved on the shop floor. Taiichi Ohno stressed to his managers to see every problem as a *kaizen* opportunity. Once the root cause of the problem is understood, processes can be implemented to prevent their recurrence [7].

The following example of malfunction of a welding robot was used by Taiichi Ohno to explain the power of this principle. The first question relates to why did the robot stop? The answer is because a fuse was blown due to circuit overload.

The second question is why was the circuit overloaded? This was because there was insufficient lubrication in the bearings. This begs the question why did that happen? Because the oil pump on the robot was not circulating lubricating oil. Why was the oil pump not circulating enough oil? Because the pump's intake is clogged with metal shavings. Finally, why is the intake clogged with metal shavings? Because there is no filter on the pump. This is the root cause of the problem. The simplicity and power of this method can be readily appreciated from this example. What started as a fuse not working, a seemingly electrical problem can be sourced to the lack of a simple filter in the oil circulation system. A less detailed analysis which asked *Why* a fewer number of times would miss this solution. The *kaizen* opportunity here is the design of a filter for the oil circulation system which will prevent this problem from recurring [7].

Implicit in the 5 *Why's* or *root cause analysis* is the requirement for understanding the problem and making a correct formulation to attempt to get to the root cause and attempt a solution. Correct problem formulation is an essential requirement for application of this technique. Root cause analysis is an extremely powerful tool with immense applications in medicine. Of all the TPS principles which were described above, this is perhaps the most important for a physician since it can improve diagnostic accuracy considerably.

Taiichi Ohno's classic book *TPS*, *Beyond Large-Scale Production* is an invaluable textbook about these methods [8]. A criticism of lean has been the less-than-spectacular results when it was applied in the west in many industries. One reason for such a problem is possibly that many corporations attempted its implementation with slogans and catch phrases without encouraging the understanding of processes. Moving towards zero inventory does not necessarily mean successful implementation of TPS. Therefore, problem formulation and understanding of underlying processes is vital to successful application of lean or TPS. A crucial concept to understand is that *lean* is not a tool-kit, rather it is an operational philosophy which yields results in the appropriate context when applied with deep insight into processes.

Each of these is being applied successfully at medical centers in a piecemeal manner. The *andon* cord is being implemented as a powerful patient safety tool, where healthcare workers at any level of the hierarchy can pull the cord and stop a procedure if they feel there is a threat to patient safety. Therefore, it can promote the safety culture of an institution and prevent catastrophes such as the wrong side being operated, wrong patient being operated from happening. However eliminating waste has not become part of the operational culture of medical centers. Just-in-time helps with preventing over ordering of expensive, time-sensitive medical implants and medications which will need to be discarded if not used within a certain time frame. With respect to *jidoka*, the hospital of today resembles that of a 100 years ago in every respect without many robotic employees. Humanoid robots (incidentally the biggest developers of which are Honda and Toyota) could potentially in the coming years take over many low-level functions which are currently expensive and highly labor intensive—such as basic nursing functions, helping debilitated, elderly patients walk without falling. The most important, immediate tools from TPS which can be applied in everyday medical care are Root Cause

Analysis, *kaizen*, intelligent teamwork, and Plan-Do-Check-Act cycles. The application of just these three principles can have a significant impact on quality and dependability of healthcare.

Healthcare Application of Lean: A Personal Experience

Root Cause Analysis

Medicine is an imperfect science. For the same disease, there are myriad presentations and the challenge faced by the physician or examiner is to synthesize information gathered from history, examination, laboratory, and imaging data into a diagnosis which best explains the clinical condition. Root cause analysis, when applied in a disciplined manner and performed methodically in the form of asking the 5 *Why*'*s* has the following advantages:

(a) Prevents misdiagnosis caused by being distracted by abnormalities in data on initial testing.
(b) Encourage the examiner to explore underlying causes of what is immediately obvious and look for connections between symptoms or findings that appear diverse and unconnected.

This has been explored to a great extent in prior chapters with methods like fault tree analysis (FTA), graphical methods, byzantine generals problem to explore root causes of the problem. FTA helps perform the 5 *why*'*s* in a systematic manner and evaluate multiple etiologies. A few additional cases are presented in this section.

Case Example 1

RT is a 73-year-old male who was referred for evaluation of weakness. The major concern for the referring physicians was whether he had a form of myopathy. He himself was unable to narrate much of a history. From painstaking review of medical records and from bits of information he was able to provide, it appeared that he had been weak for a few years. The course was gradually progressive. He reported he had been well until he was seen for right hip pain. It looks like he received some right hip injections. Afterwards, he narrated he underwent preoperative cardiac evaluation for which he required stent placement. He reports his health going "downhill" since then. Following this, he developed a nonhealing ulcer of his left foot which caused him to be bedridden for almost a year. He was highly deconditioned after this and had started physical therapy at the nursing home. At the time of his current visit, he was making slow progress, where he could walk about 45–50 ft with a walker. Otherwise, he was mostly in a wheelchair. He found it difficult to raise his hands

above the head and comb his hair. He was on chronic prednisone therapy for unclear reasons, perhaps for suspected muscle inflammation. The referring physician suspected a primary muscle problem based on blood tests which showed an elevated creatine kinase (CK) level. He was being treated for a presumptive diagnosis of polymyositis. On review these were in the 300–400 range in the past (normal less than 180 u/l). He denied any muscle pains/aches or cramps. He had a long history of numbness in his feet for which he was diagnosed with "neuropathy," the cause of which was unclear. He denied any urinary or bowel incontinence. He had been on statins, the timing of which in relation to his current presentation was unclear.

On examination, indeed he was very weak and unable to get up from his wheelchair up into the examination table. Not only was he weak, he had profound sensory loss extending upto his knees on both legs. Reflexes were mildly decreased to normal in the arms and decreased in the legs. Physical examination revealed predominantly proximal weakness about the shoulder and hips with milder weakness more distally (about the knees and ankles) in the lower extremities. Plantars were up-going. The specific request from the referring provider was to perform an EMG, based on the results of which to perform a muscle biopsy to decide whether his muscle inflammation is getting better or not to adjust his steroid dose.

After considerable data distillation, the problem was summarized as a 73-year-old male with progressive weakness, mildly elevated CKs and numbness in the feet for many years. Physical examination showed proximal weakness, sensory loss in the legs, depressed tendon reflexes but abnormal up-going toes.

Question 1. *Why is the patient weak*? The first *Why* is probably better addressed as a *Where is the problem*? It is not immediately clear—the problem could be with nerves or muscles as suspected but muscle disease does not account for the numb feet or the abnormal plantar reflex. It could therefore be a problem with the spine. Therefore, the answer could be spine and nerves.

Question 2. *What could be the problem*? If it is a muscle disease, then it is likely muscle inflammation. Or it may be statin myopathy. This seems less likely. But his CK levels were elevated indicating muscle damage? Why should this be ignored when it is objective evidence of muscle damage?

Yes indeed they were, but the elevation was only mild and on review of records it was not lasting enough. They were high only for a few days. Therefore, even though the CK is abnormal, it is unlikely to indicate muscle disease is the *root cause* of his presentation. However, a severe spinal cord compression can cause severe weakness, numbness, and up-going plantars. Therefore, an MRI scan of the cervical spine was recommended as a first step and only if this was normal was it worth proceeding with nerve and muscle testing. The following images were obtained (Fig. 8.1).

The above MRI scan shows severe compression of the neck at C2 level which is extremely dangerous. The joint is unstable and any trivial trauma could potentially cause instant death from further severe compression of the high spinal cord and paralysis of breathing muscles or compression of the vital lower parts of the brain. This is the cause of the weakness, numbness, and abnormal reflexes. This would normally cause brisk reflexes but these could well be masked lower down by

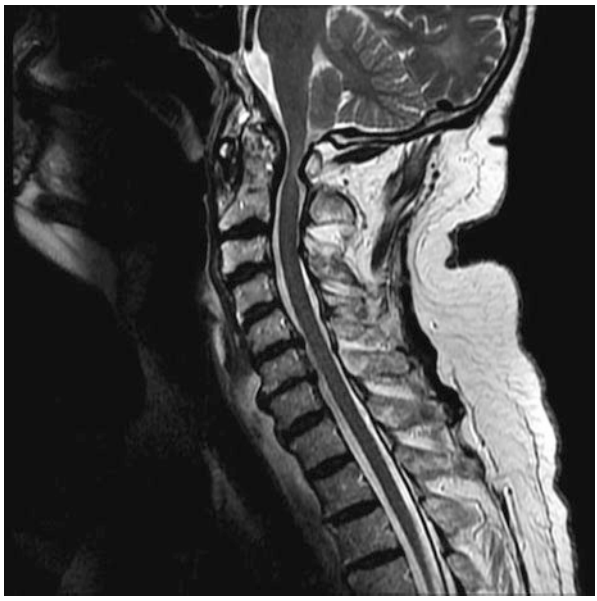

Fig. 8.1 Sagittal T2 weighted MRI scan of the neck showing severe compression of the spinal cord at the C2 level due to severe inflammatory arthritis of the cervical spine

coexisting neuropathy or radiculopathy. Additionally, the radiologist observed not just age-related arthritis but inflammation of the joint.

Question 3. *Why* is the joint inflamed?
This is a very unusual site for degenerative arthritis; therefore, inflammation is a more likely contributor to joint destruction than mechanical forces. The commonest cause of this is rheumatoid arthritis. Initial screening blood tests were sent for rheumatoid arthritis. Rheumatoid factor (RF) was negative; antinuclear antibody titers for lupus were positive in high titer suggesting an autoimmune condition. However, a negative screening test for RF does not exclude rheumatoid arthritis, newer blood tests, such as anti-CCP antibodies could be performed.

Question 4. *What* next?

(a) The neck was immobilized in a hard cervical collar to prevent further damage.
(b) Emergency consultation with a spine neurosurgeon was obtained for surgery to stabilize the spine.
(c) Spine precautions were instituted by calling the nursing home and all nurses and care givers made aware that they should not stretch the neck.
(d) Therefore, the root cause of the arthritis which caused compression of the spinal cord which caused the muscle weakness, numbness (attributed mistakenly to a generic neuropathy) is an inflammatory arthritis. This was discussed with the rheumatologist and further testing was pursued in this direction.

The above example shows how a methodical search process for the root cause of a problem can prevent the examiner from falling into the pitfalls of confounding

data (high CKs) and a disciplined quest leads to the correct solution. While the neurosurgical solution is the most essential and perhaps the most immediately obvious, going a step further and evaluating an autoimmune cause for the problem can prevent recurrence or other organ involvement.

Case Example 2

LK is an 84-year-old male with atrial fibrillation, congestive heart failure (CHF) s/p pacemaker placement with progressive decline in walking, balance, and falls for 8 months. CT Brain, CT myelogram, B12, Copper, immunofixation, ESR, CRP, paraneoplastic panel were all normal. Patient also had a tremor and over 6 months went from fully functional to a wheelchair. He was on multiple medications including Losartan/HCTZ, ASA, Clopidogrel, Amiodarone L-Thyroxine, Gabapentin, Fish Oil, and Sertraline.

On examination, he followed commands poorly, therefore the examination was limited. He had a poor attention span and seemed uninterested. Speech was normal without dysarthria or aphasia. Eye movements were normal. Motor examination revealed mild lower extremity proximal weakness which was 4 ± 5. He had normal strength distally. Sensory exam was grossly intact. He had an action tremor and mild cogwheel rigidity. Deep tendon reflexes were symmetric 3+ to the knees; 1+ at the ankles. Plantars were down going. On gait examination, he was unable to stand, with severe gait ataxia.

His care was fragmented across multiple medical centers in the region. He was seen by cardiologists at a nationally renowned center, neurological care was at another hospital and he was referred solely for the purpose of an EMG as part of work up of an ataxia. EMG findings are displayed in Table 8.1.

Given the additional demands placed on this EMG by the referring physician, root cause analysis was performed before the final report was finalized. A graphical model can be constructed to try to solve this problem. No one feature in this patient was pathognomonic; the combination of events had led to debility. The main decision nodes in the graphical framework are shown in Fig. 8.2.

Analysis was performed in the manner detailed in Chap. 5. Candidate hypothesis includes spinocerebellar ataxias (SCA), multiple systems atrophy (MSA), and drug toxicity. SCA seemed less likely due to late age of onset, rapid progression over 8 months. MSA was considered more likely, however prominent autonomic features which are a cardinal feature of this disease were lacking. Given the onset and rapid progression, mild features involving all the decision nodes, Amiodarone toxicity was considered a good candidate as the root cause of all these findings [9, 10].

Based on this root cause analysis, the following report was provided to the ordering clinician: “This is an abnormal study. There is electrophysiologic evidence of a moderate, length-dependent, sensorimotor demyelinating polyneuropathy. Conditions in the differential include drug-induced amiodarone vs. inflammatory

Table 8.1 NCS/EMG data for Case Example 2

Nerve and side	Latency (ms)	Distance	Amplitude	Velocity	F wave
Peroneal motor right					
Ankle	7.2 (<6.1 ms)	90 mm	1.7 (>2 mV)	39 m/s (>41 m/s)	68.6 ms (<56 ms)
Fib. head	15.4		1.2	40 m/s	
Pop fossa	17.9		1.1		
Tibial motor right					
Ankle	5.6 (<6.1 ms)	80 mm	2.4 (>3 mV)	38 m/s (>41 m/s)	66.5 ms (<58 ms)
Pop fossa	17.2		1.4		
Tibial motor left					
Ankle	5.6 (<6.1 ms)	80 mm	4.6 (>3 mV)	41 m/s (>41 m/s)	70.1 ms (<58 ms)
Pop fossa	17.2		3.5		
Ulnar motor right					
Wrist	3.4 (<3.5 ms)	80 mm	8.0 (>6 mV)		36.8 ms (<32 ms)
Below elbow	7.7		7.1	47 m/s (>49 m/s)	
Above elbow	10		6.3	43 m/s	
Ulnar sensory right	4.9 (<3.2 ms)	140 mm	5 (>10 μV)		
Sural sensory right	2.8	140 mm	12 (>6 μV)		
Muscle	*EMG findings*				
Tibialis anterior right	Absent spontaneous activity. Motor units show mild increase in amplitude and duration and polyphasia and mildly reduced recruitment				
Medial gastrocnemius right	Absent spontaneous activity. Motor units show moderate increase in amplitude and duration without polyphasia and mildly reduced recruitment				
Vastus lateralis right	Absent spontaneous activity. Motor units show mild increase in amplitude and duration with polyphasia and mildly reduced recruitment				
First dorsal interosseous right	Absent spontaneous activity. Motor units show mild increase in amplitude and duration without polyphasia and slightly reduced recruitment				
Triceps right	Absent spontaneous activity. Motor units show mild increase in amplitude and duration without polyphasia and normal recruitment				

Standard normal values are in brackets. There are only mild abnormalities showing mildly decreased motor amplitudes with mildly prolonged F waves (for patient's height) and chronic neurogenic changes

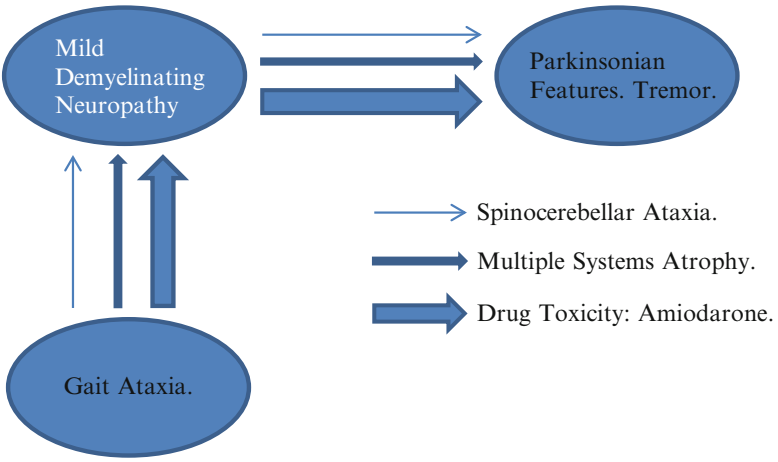

Fig. 8.2 Problem formulation in graphical form for Case Example 2

demyelinating neuropathies like CIDP. No electrophysiologic evidence of myopathy, motor neuron disease was demonstrated.

The referring clinician later performed an LP which showed a spinal fluid protein of 55 mg/dL without any cells, normal glucose. This finding was discussed with the cardiologist who substituted amiodarone with an alternate antiarrhythmic drug. In 3 months patient returned to independent walking. In 6 months patient returned to near normal and was reported to drive himself to his medical appointments.

Case Example 3

Mr. ALS is a 59-year-old male who was admitted to the hospital for altered mental status. At the time, his symptoms had presented over 2–3 weeks with progressive alteration of mentation manifested by prominent hallucinations, generalized jerking provoked by any loud stimulus in the room such as clapping of the hands (myoclonus), and violently kicking at night. He had a remote history of tonsillar cancer for which he had received chemotherapy and radiation to the neck. He was being treated for pneumonia at the time of this presentation. The main initial concern was for CNS infection or paraneoplastic syndrome. A spinal tap was performed for the same. Spinal fluid findings were unremarkable showing normal cells and protein. Viral PCRs for HSV, VZV, CMV, and EBV were negative. Cryptococcal antigen, bacterial cultures were negative. Initial cultures for tuberculosis were negative as well. The internal medicine service reported a good response to empirical treatment of community-acquired bacterial pneumonia. Therefore, the ongoing acute confusional state was difficult to explain. The working diagnosis was sepsis-induced encephalopathy; however, it was not felt to be an adequate

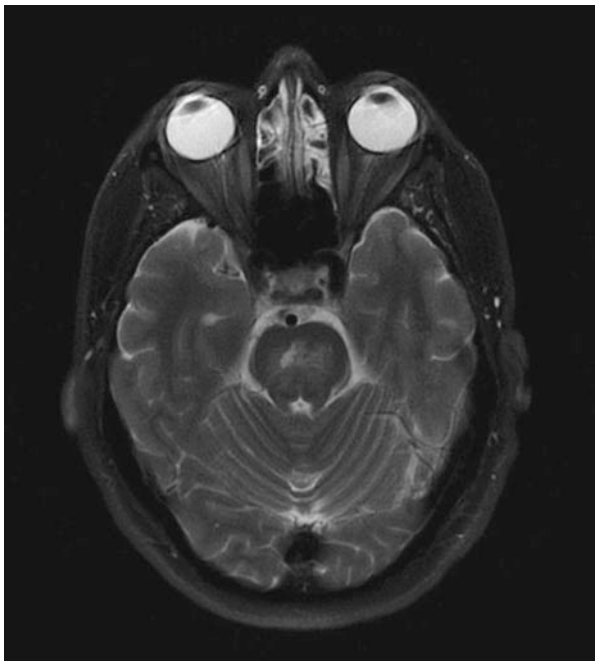

Fig. 8.3 MRI Brain: T2 weighted image showing abnormal signal in the pontine tegmentum

explanation given the progressive worsening of mental status in the face of excellent response of pneumonia to antibiotics. He had received high IV doses of Thiamine for possible Wernicke's encephalopathy. The bizarre behavior was very difficult to manage and prevented discharge from the hospital.

Root cause analysis was performed systematically on this problem. *Where* is the problem? The answer to that lies in picking the most important symptoms in the collage of what was being described as altered mental status—that Mr. ALS jerked violently in his sleep (implying he was acting out his dreams), had prominent visual hallucinations and startled easily. The intersection of all this is in the brainstem. The brainstem controls REM sleep and disconnects the body muscles from the brain during dreams to prevent acting out dreams. The prominent visual hallucinations, startling, and REM sleep problems all localized to the brainstem, especially the Pons as the source of the problem.

Based on this hypothesis an MRI Brain was requested. Figure 8.3 shows signal changes in the Pons obtained on the MRI Brain. The next question of *Why* is there a signal abnormality is answered by a process of imaging features and exclusion of infection and paraneoplastic phenomena. The most likely cause of this is postradiation scarring. Other causes such as brainstem infection, paraneoplastic disorder are considered low in the list of possibilities since CSF studies were benign. Therefore, root cause analysis reveals that the cause of the altered mental status is a constellation of excessive startle, visual hallucinations, REM sleep disorder all coming from a malfunction of the brainstem. The cause of the

brainstem malfunction is scarring from prior radiation therapy for cancer. Therefore, the root cause of the altered mental status is long-term consequences of radiation. This is not directly treatable; however, the altered mental status can be treated with Clonazepam which is excellent for treating REM behavior disorder. After the first dose of this medication given at bedtime, ALS woke normal and cured in the morning and was discharged home. On subsequent follow up visits in clinic, self-discontinuation of the medication by the patient led to repeated sleep problems with potential for injury to the spouse requiring institution of long-term therapy with clonazepam. At 2 years follow-up, he remains on a low stable dose of the drug.

Once the problem is solved using root cause analysis, subsequent sub-problems can be predicted and prevented. The next *Why* is better asked as a *What*, What else can happen due to radiation? The same disease mechanism can cause scarring of the carotid arteries years and even decades later and cause stroke. Therefore, the patient needs periodic monitoring of the carotid arteries using ultrasound and consideration should be given to aspirin, statins, or even stenting if and when narrowing of the carotids is severe.

Healthcare Applications of *Kanban* Cards

As described previously, *Kanban* cards are meant to facilitate close coordination and communication between different parts of the manufacturing process. While they are largely electronic at this time, the principle of summarizing vital information on a single sheet of paper has important applications in medicine to summarize the description of disease in a patient. *Kanban* cards have the following advantages:

- Progress Notes/Discharge Summaries can be extremely voluminous and tedious. They are meant to conform to diverse needs—regulatory, billing, legal which dilutes high value information. *Kanban* cards effectively summarize clinical information.
- Facilitate communication in fragmented care, especially involving multiple disciplines.
- Disease and patient specific, zero time and money investment.
- They reduce variation in diseases that lend themselves to standardization.

The following examples illustrate the principle for commonly encountered diseases in neurology.

Case Example 4

Myotonic dystrophy offers an excellent example for implementing *Kanban* cards. For a multi-system disease, the neurologist plays a central role in coordinating care. The disease involves multiple organ systems with the most important being heart,

System	Symptom	Testing	Frequency	Last Tested and Findings
Eyes	Cataracts	Eye Examination	Yearly	
Ears	Hearing Loss	Audiometry	With Symptoms	
Heart	**Arrhythmia**	**EKG**	**Yearly**	
Lungs	**Shortness of breath**	**Pulmonary Function Test**	**Yearly**	
Swallowing	Choking	Swallow Study, barium swallow.	With Symptoms	
Sleep Apnea	Sleep Apnea, snoring, daytime sleepiness.	Sleep Study	With Symptoms	
Hormones	Diabetes, cholesterol, Thyroid disease, sex hormones.	HBA1c, cholesterol, TSH, testosterone (in men)	Yearly	

Fig. 8.4 Myotonic dystrophy *Kanban* card. *Courtesy*: David Mayans, M.D.

diaphragms, diabetes mellitus, and cataracts. Well-coordinated care involves multiple specialties keeping track of their organ systems and coordinating care [11]. The following myotonic dystrophy information card shown in Fig. 8.4 helps patients coordinate their care and carry their information with them at all times.

Myotonic Dystrophy 1 Information Card

Myotonic Dystrophy Type 1

You have been diagnosed with myotonic dystrophy type 1. This is the most common muscular dystrophy. It is a genetic disease which means it is passed down families from one generation to the next. There is a 50 % chance that your children will inherit the disease. While this disease typically affects muscles, it affects the entire body. Myotonic Dystrophy can affect the heart, lungs, eyes, swallowing, and hormones. These need careful monitoring for timely diagnosis, treatment, and prevention of complications. Please read the other side of this card to see what tests may need to be performed. The most important are related to heart and lungs which are in bold.

Please visit http://mda.org/disease/myotonic-muscular-dystrophy/types/mmd1 for more information.

Case Example 5: Myasthenia Gravis Kanban *Card*

The myasthenia gravis *Kanban* card shown in Fig. 8.5 provides important actionable information about the type, severity, whether thymomatous or non-thymomatous, distribution of myasthenic weakness. It provides a running summary of the treatments that have been used for a particular patient and frequently encountered opportunistic infections that can complicate treatment.

Myasthenia Gravis Patient Information Card.

Name: **Date of Birth:** **Male/Female**

Year Diagnosed:

Diagnosis confirmed by: Serology Electrodiagnosis (rep stim or Single Fiber EMG)

Serology: Type (AchR Binding/Blocking/Modulating; MuSK Antibodies)

CT Chest: Thymoma Non Thymomatous.

Thymectomy, Month/Year: Pathology (Benign Thymoma, Hyperplasia, Thymic Carcinoma)

CLINICAL FEATURES.

Clinical Type: Ocular Facio/Bulbar Generalized Respiratory Involvement

Severity: Mild Moderate Severe Crisis

Rescue Therapies and date: IVIG Plasmapheresis. Rituximab

Medications and Date

Name	Start	Stop	Dose	Response	Adverse Events	Monitoring
Pyridostigmine			30/60/90			
Prednisone						See Steroid sheet.
Azathioprine						TPMT, CBC, LFT.
Mycophenolate Mofetil						CBC
Calcium/Vit D/Bisphosphonates						

Miscellaneous

Bone Scan: Date/Results

Killed Influenza Vaccine: Date.

Shingles/Genital Herpes: Date Recurrence:

Reproductive Counseling (Females)

Comments

Fig. 8.5 Myasthenia Gravis *Kanban* card. TPMT: Thiopurine methyltransferase level. Adapted from [12]

The Plan-Do-Study-Act Cycle

We will now discuss the next powerful idea from *lean*—the Plan-Do-Study-Act (PDSA) cycle. This goes by many different names and is common to *Six Sigma* discussed in Chap. 7. The roots of the idea were initially formulated by Walter Shewhart in the 1930s of the Bell Telephone Company. Dr. Deming became a great champion of this concept and referred to it as the "Shewhart cycle" which became popular in industry [13]. It is referred to as the Deming cycle, Shewhart cycle, and also Plan-Do-Check-Act cycle. The PDSA cycle is a quality improvement methodology which lends itself well to *kaizen*. It enables a limited test of a quality or process improvement initiative prior to its widespread adoption and permanent changes in the process. The classic cycle consists of the following four steps shown in Fig. 8.6 for effecting any change:

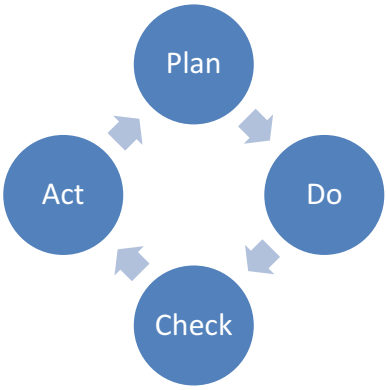

Fig. 8.6 The Plan-Do-Check-Act (PDCA) cycle

1. Plan—Plan the intervention that will likely improve the process, define objectives clearly, and institute metrics for the planned improvement which can be measured.
2. Do—Implement the planned change on a limited basis.
3. Study—The results of the plan and analyze data before and after instituting the change to study the results. Study why the method did or did not work and what can be learnt from failure.
4. Act—Based on the information gathered in the first three steps, act on the results. Adopt the change if it improved the process, else refine the plan and go through steps 1, 2, 3.

Repeated applications of the PDSA cycle leads to continuous refinement of processes and towards a better way of doing things. This lends itself to a very interesting question—is there a best way of doing things? Perhaps in the limit as the cycle is applied successfully an infinite number of times? Going back to the car example, is there one way to install a car seat? Yes. An optimal sequence of steps and intermediate process times can be derived by applications of the PDSA cycle for installing the front right seat of a Camry [14].

The PDSA cycle is in widespread use in hospitals and has made in-roads into healthcare systems. These tools are frequently adopted by hospital administration to improve processes such as scheduling, reducing wait times in hospitals. I will present this from a physician's perspective, where it is a very powerful tool which can be seen as the treatment arm of *lean*. As illustrated in the prior section, the 5 *Why's* are a powerful tool in assisting diagnosis. The Deming cycle can play such a guiding role in treatment and lends itself well to day-to-day application. The Plan-Do-Check-Act cycle was implemented as follows.

Case Example 6

The PDSA cycle was used successfully in the treatment of KLH (Case Example 4, Chap. 3) for the treatment of CNS Wegener's granulomatosis (currently called granulomatosis with polyangiitis or GPA). The detailed implementation was as follows:

Plan

(a) Start Steroids (IV pulse methylprednisolone 1,000 mg/day for 5 days followed by oral prednisone 60 mg/day) and Cyclophosphamide (Cytoxan).
(b) Metrics to determine improvement or worsening

1. MRI Brain to be performed in 2–3 months, same day as clinic visit to shorten lead times in decision making.
2. Repeat spinal tap in 3 months to see if inflammation is reduced in the spinal fluid.
3. Mental status and examination in clinic.

(c) Take appropriate precautions for side effects of both medications based on standard protocols.

Do

(a) Implement drug infusions
(b) Set up return appointments carefully coordinated with MRI Brain 2 h earlier to appointment.

Study

(a) MRI Brain after 2.5 months of treatment is shown in Fig. 8.7.

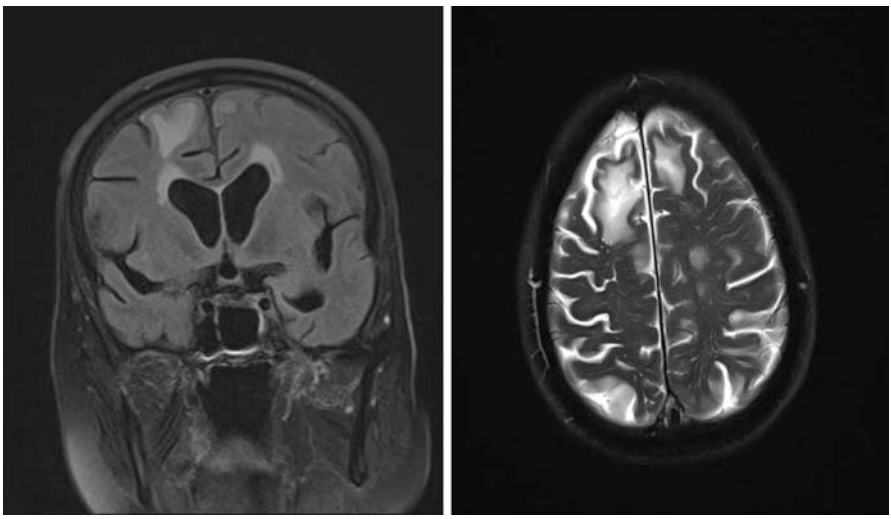

Fig. 8.7 The MRI is apparently worse, there are diverse signal changes denoting dead brain tissue and the ventricles are larger

(a) The clinic visit showed he was still confused, continued to have severe headaches. An unequivocal case for improvement could not be made to stay the course with more cycles of cyclophosphamide and prednisone.
(b) There was an odd mania with tangential, confused speech which maybe attributable to the side effects of high doses of prednisone. The second consideration was whether it could be the disease.

Based on the defined metrics, the treatment to date was felt to be partially effective. The causes of this were analyzed. On further focused review of medical databases, such treatment refractory cases similar to KLH were described even though prednisone and cyclophosphamide is the standard therapy for classic Wegener's granulomatosis. The subset of patients he belonged to were characterized by an overproduction of a class of antibodies called immunoglobulin G-4 or IgG-4 diseases. Most of the treatment-resistant cases described in the literature belonged to this subset and showed a better response to Rituximab. Rituximab is a very expensive drug as well and its use should be very judicious for cost and side-effect considerations. The current status was discussed with the rheumatologists who concurred with the above position. Therefore, one potential cause for failure was identified and a new PDSA cycle was initiated.

Plan

(a) Infuse Rituximab 375 mg/m^2 weekly for 4 weeks.
(b) Use same metrics for monitoring response.
(c) Reduce dose of prednisone to 40 mg to reduce steroid mania.

Do

(a) Infuse Rituximab and monitor for response in 3 months with MRI and clinic visit the same day.

Study
KLH was reviewed again 2–3 months later in the same manner as last time.

(a) Repeat MRI Brain showed same picture as last time without worsening.
(b) A repeat spinal tap showed CSF Protein 54 (down from 220 mg/dL), CSF white cells 4 (down from 187) and now in normal range.
(c) Following conclusions were drawn:

    1. The combination of prednisone and Rituximab has effected radiologic stabilization and spinal fluid normalization.
    2. Steroid mania and mental status are better.
    3. There is an unequivocal response to treatment.

Act

1. Continue to reduce dose of prednisone to reduce side effects which are proportional to dose.
2. Rituximab has been very effective and will be the drug of choice if there is exacerbation of the disease in future.

3. He continues to need close monitoring—clinic visit and perhaps less intensive radiologic monitoring in the weeks and months to come since treatment gains seemed well consolidated.

This method succeeded considerably and KLH attained a stable remission with remarkably improved headaches and mental status. The remission lasted 1 year and 4 months. He had recurrence of severe headaches at this time. The PDSA cycle was reinstituted with the knowledge gained from prior cycles. Retreatment with rituximab was instituted.

Further examples of PDSA cycles incorporated into a rigorous treatment plan will be discussed in Chap. 9.

Conclusion

The TPS revolutionized manufacturing in the second half of the last century. While its origins lay in Toyota's car plants, today it finds applications in innumerable industries around the world. These principles can be easily adapted and applied to the world of clinical medicine as shown by the numerous case examples. Additionally, many ideas discussed in other part of this book are closely related to TPS—fault trees, graphical methods, byzantine generals problem are merely different methods which can be effectively used to perform *root cause analysis*. The PDSA cycle has preliminary system safety assessment (PSSA) and failure modes and effects analysis implicitly built into it. In Chap. 9, all of these principles will be amalgamated into a *kaizen* project to make things better.

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Chapter 9
Reliance Implementation Methods Applied to a Kaizen Project

Abstract Reliance industries limited (RIL) owns and operates the world's largest Greenfield oil refinery complex in Jamnagar, India. While traditional oil refineries take between 6 and 8 years to build and operate, the Jamnagar refineries were built in record time in 3 years per phase. Reliance Industries uses a unique set of practices to prevent cost and time overruns and achieve project completion ahead of time. These hold unique opportunities which can be implemented in day-to-day clinical medicine. In this chapter, we describe the use of Reliance methods to transform the treatment of chronic inflammatory demyelinating polyneuropathy (CIDP). The Japanese word *Kaizen* stands for continuous improvement and was introduced in Chap. 8. This chapter implements a Kaizen project using Reliance methods for the treatment of CIDP to improve the limitations of traditional methods.

An Introduction to Reliance Industries Limited

Reliance Industries Limited (RIL), based in Mumbai, India, is ranked 99 in the Fortune 500 global list of the world's largest companies by revenue [1]. Reliance Industries was founded by Mr. Dhirubhai Ambani as a textile company and has since grown to become a large conglomerate with interests in petrochemicals, oil refining and exploration, retail, infrastructure, and life sciences. Reliance's entry into any business is transformative of that landscape; the company thrives on the challenge posed by an over-ambitious, mega scale project which has not been implemented anywhere in the world before. A study of all of Reliance's businesses is too vast to be covered in a book chapter; therefore this chapter borrows methods from RIL's crown jewel—Jamnagar Refineries, located in Jamnagar, in the western Indian state of Gujarat. RIL's Jamnagar refinery, built in two phases at a total capital cost of $16 billion, is the largest Greenfield refinery in the world with a refining capacity of approximately 1.3 million barrels per day. For the 2011–2012 period, RIL's refining business processed 67.6 million tons of crude with a capacity utilization rate of 109 % and exported $36 billion worth of refined products. RIL's gross refining margins (GRM) are among the highest in the world and stood at $9.5/barrel at the time of writing this chapter. *This chapter is limited to the study of a few extremely useful project implementation tools which are part of RIL's management methodologies for application in medicine and neurology*.

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Reliance Project Implementation Methods

Reliance blends a core management philosophy with a continuously refined business process which is common across a range of businesses. The following management methods were learnt from RIL and find valuable application in project implementation in clinical medicine. We explore concepts of Microplanning and Backwards Integration which have applications in clinical medicine.

Reliance "Microplanning"

At the heart of all successful Reliance projects lies a concept called "microplanning". Reliance performs highly detailed analysis of every project prior to implementation which requires an in-depth understanding of complexity, processes, resources, challenges, redundancies, and potential disruptions involved. Once such a detailed project plan is made which incorporates all these elements, unforeseen complications are few and time and cost overruns are naturally prevented. Falling behind schedule happens only when the project is not well planned into strictly controlled processes. Microplanning is conceptually very similar to the "Detailed Design" block in the systems engineering V shown in Fig. 7.1 of Chap. 7.

Microplanning is applied extensively by all employees across all Reliance businesses. At its heart, microplan involves setting a clear goal and establishing well-defined intermediate steps or *micro-milestones* leading to that goal. Each intermediate step is understood as a process which needs to be optimized both individually and in relation to all other processes that are connected to it. To the extent possible, intermediate processes required for the final goal are implemented in parallel to minimize overall process time. If any intermediate step of the process interferes with other processes, accommodations are made to both processes to minimize disruptions and interference. Once intermediate steps and processes are identified, processing times and costs for each intermediate step can be benchmarked. Once this is done, potential reconfigurations of the process sequence and stepwise innovation can be implemented. This enables accurate estimation of cost, time, implementation challenges, and prevents overruns since the original estimates have factored in all these elements. Microplanning is practiced not just with regard to projects implemented by Reliance employees but with vendors as well. This is partly why relationships with vendors are so close, so as to understand their capabilities, resources, limitations, and processes to accurately predict their success with the project. RIL's microplanning method involves making alternative plans and creating redundancies for any task to manage unforeseen complications. This is the management equivalent of *fault tolerance*.

Microplanning enables measurement since intermediate processes are well-defined which helps with forecasting and innovation, both for the project on hand and with the

global enterprise. Consider the following example of buying and installing a large prefabricated equipment for a particular refinery process (such as a boiler). Microplanning involves the following major steps and implementation:

1. Identify requirements and arrive at specifications. Identify manpower requirements, project ownership, and decision making responsibilities.
2. Identify supplier/technology partner.
3. Finalize orders—costs, delivery time frames.
4. Specify milestones for product development from vendor—fabrication, electrical/control system installation milestones, testing milestones.
5. Station Reliance employees at vendor fabrication facilities to monitor progress, understand technology, and provide close feedback to future operating group on equipment. Monitor progress and verify stated progress made by vendor.
6. Specify exact shipment times when product is ready to leave vendor's facilities.
7. Identify shipping requirements and book cargo space on large cargo carriers months in advance.
8. Identify loading/unloading requirements—the size, lift capacity of crane to unload cargo. Reserve lifting capacity for specific cargo based on exact arrival times from shipping company.
9. Obtain regulatory clearances to expedite customs.
10. Identify land transportation requirements—what road to take from the docks to the installation site which can handle such oversized cargo. Reserve appropriate trucks, loading/unloading cranes at required times.
11. Identify and train installation technicians at the onset—how to install the equipment correctly.
12. Identify and train technicians using simulators, product literature etc. for operation of the machinery.
13. Invest in special infrastructure this project will need such as site preparation, heavy lift cranes, trucks, power requirements, piping, and industrial automation systems.
14. Identify how this project and movement of such special oversized cargo would affect traffic and materials delivery for neighboring processes. For example, if a nearby worksite accessible only by the same road is involved in building a concrete structure on the same day as this cargo will be transported slowly by special movers which will block the road to the worksite, provide advance notice of potential disruption of their supply chain so that they have reserve construction materials (cement, steel, brick, etc.) to prevent disruption of that process.
15. At all levels of the process, invest in safety infrastructure for the equipment.
16. Based on above, identify the target completion date when the equipment will be functional and work backwards to set dates and times for intermediate milestones.

For the example above, microplanning therefore enables a solutions-based approach instead of just installing the equipment. It breaks an overall plan into small intermediate steps to visualize work flow with strict metrics between steps.

This ensures a process stays on track without cascading delays. The project is viewed not just from construction, installation perspectives, but it is integrated with training, safety, and specifications of remote processes which may be influenced by it. For the example above, if the equipment weighs 100 t, at the outset itself it enforces load requirements on the roads required for transporting this equipment and size and strength of the jetty for unloading this cargo. It enables a global view—how does this process interfere with others and what steps can be taken to minimize such disruptions or enhance synergies? Once these intermediate tasks are identified, costs and time frames can be accurately estimated and contingency planning—such as weather-related disruptions—performed. Paradoxically enough, a micro-view enables a holistic approach and possibly prevents expensive reengineering of linked processes.

Once the microplan is ready, processes with long lead times can be identified. In this case, the construction of the equipment itself is perhaps the rate determining step with the longest lead time from conception to delivery. Construction of the appropriate size jetty, road, heavy lift cranes, transportation trucks, electrical/piping requirements are others. This must, however, be done in parallel at the outset itself; otherwise implementation of the primary objective will be delayed. Personnel required for operation of the equipment must be hired, adequately trained well before delivery to enable error-free immediate operation once installation is complete. This too needs to be done in parallel, perhaps halfway along the way. This can be represented graphically as a flowchart for better data visualization, project management, and road map planning. Predicted dates for completion of intermediate milestones can be mapped onto the flowchart and the microplan shared with all members of the implementation team ranging from equipment vendors to construction personnel. Microplanning therefore requires close teamwork, high quality communication with all members of the project team, and with interrelated processes to be successful. Microplan is also related to checklists discussed in Chap. 7.

Since microplanning maps intermediate steps so well, it lends itself well to measurement and improvement in the form of *kaizen*. It enables targeted investments in process improvement and improving efficiency to be made. An example narrated by Reliance's master builder involves speeding up the time for hardening and drying concrete. The microplan for construction allocated 3 weeks for this step during phase 1. During phase 2, innovations in this step were identified in the form of additives which speed up drying time. This speeded up the process to 12 days instead of 21 days during the construction of phase 2 [2]. Construction microplans were then updated to reflect this development and adjust downstream processes to exploit this breakthrough.

A personal experience with microplanning would enhance appreciation of the utility of this principle. My visit to the Jamnagar refineries was implemented using a visit "microplan". The microplan was based on the following principles:

1. First identify the objectives of the book and the knowledge to be gained from Reliance. These were understood to be construction, operations, and management.

2. Identify the key personnel involved and contact them for the assistance they may be able to render. Email them the objectives of the book and request them for ideas and experience (such as microplanning, project integration) which may be useful. Request them to compile their ideas and contributions for a meeting.
3. Schedule appointments in Mumbai and Jamnagar with all relevant personnel.
4. Arrange a tour of the complex to appreciate the scale first hand.

During my visit to Jamnagar, I met executives from these departments and human resources together in the refinery conference room. The microplan was implemented in this manner because:

(a) I would not have to repeat myself and the book objectives to each executive I met, thus spending 15 min in introduction with each person. An opening statement addressed to all the executives together would suffice to introduce the subject.
(b) Repetition would be avoided—two people would not proceed to narrate the same thing.
(c) Ideas could be integrated between different operating groups. For example, construction and human resources involved great synergy since construction engineers described the great productivity they achieved from a motivated labor force due to progressive human resources management.
(d) Time would not be wasted in going from one office to the other in a vast refining complex.

The visit was planned down to the minute of departure from the refinery to arrive in time for our return flight back to Mumbai from the nearby town of Rajkot 130 km away. The microplan had made allowance for traffic disruptions should the highway be blocked by an accident on the way. This simple example shows how microplanning can be applied to any matter for efficient implementation.

Backwards Integration

Mr. Dhirubhai Ambani started his business in India manufacturing textiles under the Vimal brand name. Focusing on polyester-blended clothing, the business was a huge success with booming demand for durable, easy to maintain, affordable synthetic fabric. The hypothesis he posed was that since polyester is the main feedstock for the textile business, manufacturing polyester and integrating it with downstream textile manufacturing would have competitive advantages and synergies for both. For the new venture into raw material, the risk is mitigated to some extent by the captive market from the existing business thus hedging the venture to some extent. In short order, Reliance came to dominate manufacture of polyester and synthetic fabric in India and spawned a globally competitive petrochemical industry. Extending this concept backwards, since oil products are the feedstock for the petrochemical industry, Reliance expanded into the oil refining industry.

Finally, since the main cost of oil refining is crude oil itself, Reliance completed the process by entering the oil exploration business with successful crude oil and gas drilling in the KG-D6 field in India. This is called *backwards integration*, when a company progressively expands into earlier steps of its manufacturing chain.

Microplanning and backwards integration play extremely useful roles in clinical medicine as will be shown in the following sections. Following a visit to the Jamnagar Refineries, these were applied in great detail to day-to-day clinical neurology.

CIDP: The Traditional Way of Doing Things

Case Example 1

DS is a 53-year-old woman who presented to an outside hospital with rapidly progressive weakness and numbness which started in her feet and ascended to involve her arms in Feb–March 2012. Over the course of a few days, DS became quadriplegic and bedridden requiring assistance for everything from feeding to turning in bed. She was correctly diagnosed at the outside institution with acute inflammatory demyelinating polyneuropathy (AIDP), also called Guillain-Barré Syndrome. She was transferred for further treatment.

Following treatment with five sessions of plasmapheresis, she made the anticipated modest improvements followed by admission to inpatient rehabilitation. After spending 3–4 weeks in rehab, she developed recurrent symptoms which were felt to be related to her original GBS. She was treated again with plasmapheresis and discharged to rehab with the same degree of improvement. She was seen by the author another 4 weeks later with progressive deterioration, now a full 8 weeks from initial onset of symptoms. During the course of her illness, IVIG was attempted once, but it led to stroke-like symptoms which fortunately resolved after stopping infusion of the drug. This led to discovery of an asymptomatic right-sided carotid artery occlusion which made future use of IVIG risky because of its tendency to elevate the stroke risk.

The recurrent severe episodes had one interesting feature in common—while they involved all the limb muscles severely weakening the arms and legs, they never involved respiratory muscles or swallowing muscles. This is somewhat unusual for GBS since many people with severe illness will have some degree of respiratory and swallowing involvement. An alternative hypothesis was whether this was chronic inflammatory demyelinating polyneuropathy (CIDP), which has a similar profile but never involves the breathing or swallowing muscles. CIDP is steroid-responsive. Steroids form the third choice for treating CIDP along with plasmapheresis and IVIG [3].

After her third relapse, a tentative diagnosis of CIDP was made and treatment initiated with steroids concurrently with plasmapheresis. The lack of ocular, bulbar,

autonomic, ventilatory involvement despite quadriparesis favored CIDP over AIDP. Further she had experienced over 8 weeks of recurrent nerve problems. The hope was plasmapheresis would filter out the circulating antibodies and the steroids would suppress the immune system to stop their manufacture. DS had a good response to plasmapheresis and unlike the last two times, this time the response was sustained and better than she had experienced with plasmapheresis alone. DS was happily discharged to rehab in much better shape than she had ever been with an introduction to the new treatment plan which was to do long-term therapy with steroids for treatment of CIDP. Plasmapheresis would be reinitiated if there were any setbacks along the way and IVIG was rejected as being too risky due to the high stroke risk from the right carotid occlusion. The carotid occlusion was defined as a second problem and was treated according to standard guidelines with aspirin and atorvastatin 80 mg/day.

DS would spend 2 months in rehab before being seen in clinic. She had no relapses, continued to make steady progress with rapid progress to standing and walking with assistance and gross hand movements. The patient and physicians were delighted with this progress; the PLAN had worked and a slow taper of steroids was started to reduce side effects from prolonged high-dose steroid treatment. Weight gain, a frequent side effect of steroids was observed and patient counseled about "watching her diet". Bone loss and fracture of a vertebra were observed despite standard precautions (calcium, vitamin D); fortunately this did not need spine surgery or cause instability. She was also asked to follow-up closely with her primary care physician for "general medical conditions". Over the next 4 months, the dose of prednisone was tapered from 40 mg to 20 mg/day with durable benefit in her CIDP. She regained full strength in her proximal upper and lower extremity muscles, but continued to suffer from intrinsic hand muscle weakness and foot drops. Painful paresthesiae continued to require Gabapentin for pain relief.

In September 2012, a chance phone call to check on her well-being found her very confused and lethargic. An immediate evaluation in the emergency room led to discovery of severe dehydration, urinary tract infection, a blood sugar of 800 mg/dL (normal $<$150 mg/dL), and severe electrolyte abnormalities. Since these are all systemic side effects of steroids, the dose was reduced further since the nerves were 90 % back to normal in terms of strength and functionality and the side effects were greater than anticipated benefit. "Fault containment" was initiated with immediate assistance requested from orthopedics for a vertebral compression fracture and internal medicine endocrinology since controlling the blood glucose level was a significant challenge for the non-specialist. Given this plethora of complications, prednisone was tapered and discontinued over 3 weeks. Over the next 4 weeks, each side effect required the assistance of specialists—endocrine, orthopedics, and internal medicine across two medical centers.

Fortunately, 1 year later she returned to work full time, made a sustained, durable recovery and at the time of her last examination in May 2014 had no weakness. She continued to suffer from moderate painful paresthesias which were responsive to Gabapentin. We analyzed the complications she experienced.

She had heard the speech about reducing calories, checking sugars and blood pressures, but somehow it was never followed through and never implemented. It was lost somewhere in her transition from hospital to rehab to home. The physician stuck to the PLAN, which was how best to suppress the immune system for a durable response which would prevent worsening and prevent need for rescue therapy with plasmapheresis. The PLAN was successful, but the implementation was not. A careful analysis revealed that most of the side effects could have been prevented. The fact that she had a near cure from a relapsing remitting disease, however, presented a remarkable opportunity and begged the question—how can this be done better?

Kaizen: CIDP Treatment Implemented Using Reliance Microplanning

Following the experience with case Example 1, treatment of CIDP was implemented using Reliance microplanning. The following CIDP Microplan was defined and implemented.

1. Mission Objectives.
   1.1. Dependable treatment of CIDP (meeting all criteria for dependability).
   1.2. Establish specific Success and Failure objectives (see Fig. 9.1).
2. Diagnostic Confirmation.
   2.1. Confirm Clinical, CSF, and Nerve corroboration.
   2.2. Approach problem in Byzantine framework. (*See Chap.* 6)
3. Perform Preliminary System Safety Assessment (PSSA) followed by System Safety Assessment (SSA):

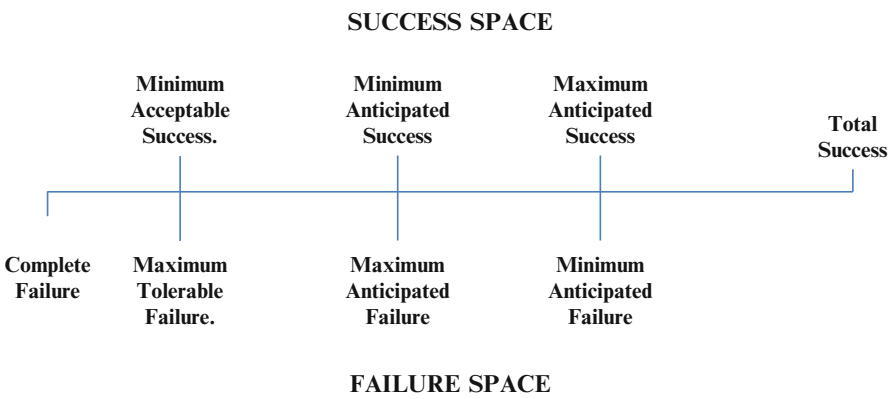

Fig. 9.1 Defining success and failure. *Source*: NASA [4]

3.1. Identify specific individual safety concerns and mitigation strategies. (*See Chap*. 2)
3.2. Implement "defense in depth" for identified risks.
3.3. The process includes FHA, FMEA, and mitigation strategies described in prior chapters.

4. Check Immunosuppression Checklist to identify risks prior to immunosuppression. (*See Chap*. 7)
5. Use Steroid and IV Methylprednisolone Failure Modes and Effects Analysis (FMEA). (*See Chap*. 4)
6. Use Steroid Nutrition Information. (*See Appendix*)
7. Implement Plan Do Study Act Cycles. (*See Chap*. 8)

7.1. Establish micromilestones.
7.2. Monitor implementation.
7.3. Perform shortfall analysis.

8. Collect data for continued improvement. (*See Chap*. 7)

The principles behind each of these steps have been discussed in detail in appropriate chapters referred to in the right column. A few additional aspects are discussed here. Step 1, establishing mission objectives, defining success, and failure is extremely important since this is a disease which is best treated in partnership with the patient. Figure 9.1 is a useful framework for defining success and failure borrowed from NASA.

For the case of CIDP, given its variable response to treatment, based on Fig. 9.1, the following success and failure conditions were defined to guide treatment (Table 9.1).

Defense in depth strategy (see Fig. 1.7, Chap. 1) was implemented for many aspects including blood pressure control (Table 9.2).

Case Examples of *Kaizen* Using the CIDP Microplan

Following the experience with patient DS in case Example 3.1, the following patients were treated using the CIDP microplan. It should be noted that the microplan was lacking step 6, steroid nutrition information sheet was not prepared and implemented till case Example 5.

Case Example 2

LM is a 66-year-old male who presents for evaluation of leg weakness and numbness. This started approximately 8 months ago, but progressed to the point that he could barely walk. Symptoms started with right hip pain for which he received two steroid injections. After the injections he noticed burning pain in his thighs.

Table 9.1 Defining success and failure conditions for treatment of CIDP

Success space	Failure space
Total success: Clinical remission with or without maintenance Rx. *Independent ambulation, little or no numbness and pain*	*Minimum anticipated failure*: Residual toe weakness, dropped great toe. Mild pain and numbness. Side effects: <10 lbs weight gain, cataract, osteopenia, hair loss
Maximum anticipated success: Ongoing Rx. Walk with three or four pronged cane. Distal weakness, AFO's, Mild to moderate pain not needing opioids, numbness	*Maximum anticipated failure*: Mild to moderate permanent foot drop, numbness, painful paresthesias. Side effects: Above, plus: HTN, >10 lbs weight gain, osteoporosis, moderate Diabetes mellitus
Minimum anticipated success: Ongoing Rx. Walk with walker. Moderate pain needing opioids, multiple pain medicines, severe numbness	*Maximum tolerable failure*: Able to stand with walker. Side effects: Above, plus Cushing Syndrome. Severe diabetes mellitus
Minimum acceptable success: Ongoing Rx. Unchanged strength. Moderate pain relief, severe numbness	*Complete failure: worsening hand symptoms*. Side effects: Above, plus Cushing Syndrome. Vertebral compression fractures. Severe diabetes mellitus. Other organ complications without benefit: example Stroke/DVT/PE from IVIG

Adapted from Fig. 9.1

Table 9.2 Defense in depth for management of blood pressure

Numerical range	Intervention
Nominal set limit: 150/90	No action needed
Allowable limit: 160/95	Monitor closely day of infusion. Provide prescription for Amlodipine 5 mg/day
Analysis limit: 170/100	Hold infusion. Start anti-hypertensive therapy: Lisinopril/HCTZ, Metoprolol
Safety limit: 180/110	As above, but send patient to ER/PCP for close monitoring

He then began developing difficulty with balance and walking. The legs started getting weak more recently. The burning pain worsened and progressed to involve both arms, torso, and worsened in his thighs. He denied any facial involvement. He had some mild problems with swallowing and feels like his voice isn't as strong as it was. He can't cough as strong as he could before. He had some constipation and urinary frequency. Past medical history includes hypertension, diabetes mellitus which are controlled with diet and exercise and low back pain. He was on Fentanyl patch for relief of pain.

On examination: Weight: 251.0 lbs. BP: 102/68, Pulse: 73. Mental status was normal. Cranial nerve examination was normal save gaze-evoked nystagmus. Motor examination revealed normal proximal upper extremity strength. The hand intrinsics showed moderate weakness being approximately 4/5 bilaterally. In the lower extremities, hip flexors were 4/5 bilaterally. There was considerable

weakness of dorsiflexion being 4-/5 bilaterally. Deep tendon reflexes were 1+ at bilateral biceps, brachioradialis, and absent elsewhere. Sensory exam revealed decreased sensation in stocking glove distribution to all modalities. Romberg was positive and routine gait was very unsteady and stooped forward. Patient needed a walker to stand and walk.

A nerve conduction/EMG was performed which showed the findings in Table 9.3.

Based on EMG findings in Table 9.3 (forearm conduction blocks involving the ulnar motor responses, slow conduction velocities, prolonged F waves), LM was diagnosed with CIDP. An MRI Brain was performed since he reported some swallowing difficulties and had nystagmus. This showed a large right-sided, vestibular schwannoma as an incidental finding. Since he had an intracranial mass, CSF studies were not performed. Supporting lab work showed ESR 17, CRP 0.6, normal CMP with glucose of 102 mg/dL, CBC: Hb 12.5 g/dL, WBC 6.6 and Plaletets: 178. TSH: 2.938; Serum and Urine Immunofixation were normal.

LM was treated using the CIDP Microplan, save the steroid nutrition sheet which had not been prepared at the time. The microplan yielded the following (Specific patient information is entered in italics):

1. **Mission Objectives**.

   1.1. Dependable treatment of CIDP (meeting all criteria for dependability).
   1.2. Establish specific Success and Failure objectives: **Success objectives**:

   (a) *The constant whole body pain was the most distressing aspect of his presentation. Therefore, the first mission objective was relief of pain.*
   (b) *Improve weakness in legs, ability to walk, and balance.*

   Failure Space:

   (a) *Worsening pain.*
   (b) *Worsening lower extremity weakness needing wheelchair confinement.*
   (c) *Worsening hand weakness.*

2. **Diagnostic Confirmation**.

   2.1. Confirm Clinical, CSF, and EMG Data.
   2.1: *Confirmed.*
   2.2 Approach problem in Byzantine framework. (*See Chap. 6*)
   2.2. *Problem was cast in a Byzantine generals framework for corroboration. Clinical, EMG data corroborate. CSF could not be obtained.*

3. **Perform Preliminary System Safety Assessment (PSSA), SSA**: (*See Chap. 2*)

   3.1 Identify specific individual safety concerns and mitigation strategies.
   3.1: *PSSA performed: The following risks were identified: borderline diabetes mellitus, borderline hypertension: Category: Minor.*
   3.2. Implement "defense in depth" for identified risks.

Table 9.3 NCS/EMG findings for case Example 2

Nerve and side	Latency (ms)	Distance	Amplitude (mV)	Velocity (m/s)	F waves (ms)
Peroneal and tibial motor (Right)	Absent				
Peroneal motor to Tib. Ant. (Right) Fibular Head	4.2	80 mm	1.4 (>2 mV)		
Popliteal Fossa	7.1		1.2	34 (>41 m/s)	
Median motor (Left) Wrist	5.0 (<4.4 ms)	70 mm	5.1 (>4 mV)		36.4 (<31 ms)
Elbow	10.3		4.8	47 (>49 m/s)	
Ulnar motor (Left) Wrist	4.0 (<3.5 ms)	70 mm	1.3 (>6 mV)		36.3 (<32 ms)
Below Elbow	10.4		0.3	32 (>49 m/s)	
Above Elbow	14.7		0.2	31	
Ulnar motor (Right) Wrist	4.0 (<3.5 ms)	70 mm	3.4 (>6 mV)		
Below Elbow	10.7		0.8	33 (>49 m/s)	41.1 (<32 ms)
Above Elbow	14.4		0.8	38	
Sural, ulnar sensory	Absent				
Median sensory (Left)	3.5 (<3.5 ms)		8 (μV) (<22 μV)		
Muscle and side	*EMG findings*				
Tib. Ant. (Right)	Profuse fibrillations and positive sharp waves. Motor units showed increased amplitude and duration, polyphasia with reduced recruitment				
Medial gastric (Right)	Moderate fibrillations and positive sharp waves. Motor units showed increased amplitude and duration, polyphasia with normal recruitment				
Vastus lateralis (Right)	Absent spontaneous activity. Motor units showed mildly increased amplitude, duration, polyphasia and normal recruitment				
Tensor Fasciae Latae (TFL), L5 paraspinal (Right)	Normal				
First Dorsal Interosseous (FDI) Right	Moderate fibrillations and positive sharp waves. Normal motor units with reduced recruitment				
Extensor Digitorum Communis (EDC), Triceps, Right	Normal				
T8 Paraspinals (Right)	Mild fibrillations and positive sharp waves				

Standard normative data are presented in brackets

3.2.1. *Defense in depth for hypertension implemented using Table 9.2.*
3.2.2. *Defense in depth for diabetes mellitus*: *Check blood glucose at home periodically. Request close follow-up with primary care physician.*

4. **Immunosuppression Checklist**. (*See Chap. 7*)

4.1 *No risks for immunosuppression identified.*

5. **Steroid and IV Methylprednisolone Failure modes and effects analysis** (**FMEA**). (*See Chap. 4*)

5.1. *Refer FMEA for IV Methylprednisolone, Chap. 2.*

6. **Steroid Nutrition Information**. (*See Appendix*)

6.1. *Not implemented at the time.*

7. **Implement Plan Do Study Act Cycles**. (*See Chap. 8*)

7.1. Establish micro-milestones.

7.1.1: *Greater than 90 % remission of pain in 4 weeks.*
7.1.2: Improved proximal strength in 8 weeks.
7.1.3: *Transition from Walker to 4 Pronged Cane in 3–4 months.*
7.1.4: *Onset of improvement in foot dorsiflexion/plantar flexion strength in 6 months.*
7.1.5: *Substantial improvement in dorsiflexion strength in 9 months.*
7.1.6: *Walk with simple cane or without support >90 % of time at 1 year.*
7.1.7: *Maintain durable remission.*

7.2. Plan Do Study Act Cycle interventions.
Plan

7.2.1: *Initial intervention*: *5 sessions of plasmapheresis concurrent with five doses of IV Methylprednisolone 1,000 mg/day* [5].
7.2.2: *Subsequent intervention*: *IV Methylprednisolone 1,000 mg Q Weekly for six doses* [5].

DO

7.2.3: *Plasmapheresis performed using temporary dialysis catheter.*
7.2.4: *IV Methylprednisolone infused after plasmapheresis to prevent removal during plasmapheresis. Subsequent doses infused at home through home health agency with blood pressure monitoring.*

Study

7.2.5: *Patient reviewed in clinic in 6 weeks after discharge after receiving several doses.*
7.2.6: *Subjective*: *Pain relief micro-milestone met. Patient had decreased the dose of fentanyl patch. Considerable improvement in proximal*

strength with improved ability to rise from sitting position. LM no longer needed a walker. He was ambulating with a 4 pronged cane.

7.2.7: *Blood pressure and blood glucose confirmed to be normal.*

Act

7.2.8: *Continue IV Methylprednisolone 1,000 mg/week for total of six more doses.*

7.3. Perform shortfall analysis.

7.3.1 *Micro-milestones were being met on time. No shortfall identified at the time of the first visit.*

The PDSA cycle was continued over subsequent visits using the same process detailed above. At his next return visit 2 months later, he was observed to have improved hand intrinsic muscle strength which were 4+/5 bilaterally. The right tibialis anterior showed 5− strength and the left 4+. At this visit, there was complete resolution of pain and patient discontinued Fentanyl. He continued to walk with a four pronged cane. In the Act step of the cycle, a decision was made to extend the treatments for a total of eight doses. The patient met micro-milestones and returned 3 months later. At this visit, the PDSA cycle showed the following shortfalls:

7.3.1: *Weight*: *296 lbs* (*gain of 45 lbs*), *2+ bilateral pitting edema.*

Patient admitted to being non-compliant with diet and relapsing to bad eating habits which had led to a similar weight gain in the past. He returned again another 3 months later. At this time, the PDSA cycle showed:

Plan

7.2.1: *IV Methylprednisolone infused weekly.*

7.2.2: *Reduce high calorie foods. Patient agreed to see nutritionist close to home.*

DO

7.2.3: *Home infusions, pulse, and blood pressure monitored during infusions.*

Study

7.2.4: *Normal upper extremity strength. Normal strength in tibialis anterior muscles. The right extensor halluces longus (EHL) showed 4+ strength, the left 2+. Deep tendon reflexes had started appearing: 2 + right biceps, 1+ left biceps, and 1+ bilateral brachioradialis. Absent elsewhere.*

Act

7.2.5: *Stop all treatments. Micro-milestones achieved.*

Shortfall Analysis

7.2.6: *Weight gain*: *80 lbs. Persistent 3+ pedal edema with stasis dermatitis.*

8. Collect data for continued improvement. (*See Chap.* 7)

8.1. The therapeutic approach was largely effective. The CIDP Microplan effectively met all mission objectives with substantially fewer side effects than the case of DS. The dose and duration of therapy needs to be refined.
8.2. Weight gain, pedal edema remain significant concerns.
8.3. HBA1c was confirmed to be stable at 5.4 % 6 months into treatment. Blood pressure remained stable. Therefore, diabetes mellitus and hypertension were not observed.

LM entered durable remission. He returned to clinic 10 months later. He walked independently without the need for a cane, had a normal examination, did not require any pain medications, and his extensor hallucis longus (EHL) muscles showed only trace weakness bilaterally. He continues to have 3+ pitting edema in his feet and has stasis dermatitis.

Case Example 3

RB is a 60-year-old diabetic male whose progressive weakness started several months ago. Six months ago he was in the hospital with pneumonia. It was a prolonged stay with empyema requiring surgery to remove the infection and chest tubes. After the surgery when he was at home he noticed weakness and pain in his legs. He developed progressive numbness in his legs. Over the summer he went from a cane to requiring a wheelchair for transportation. Subsequently, he developed weakness in his right arm and problems writing. He denied any problems with weight loss, swallowing, double vision, facial weakness, speech, or breathing. He also reports some aches and occasional twitching involving diffuse muscles at night. On examination, vitals: BP 139/75, Pulse 93, Weight 82.101 kg (181 lbs). Mental status and cranial nerves were normal. Physical examination showed normal strength proximally in bilateral upper extremities. The following muscles demonstrated considerable weakness: FDI was 3/5 on the right and 4+ on the left. The Abductor digiti minimi was 2 on the right and 4 on the left. The APB was 4 on the right and 5 on the left. In the lower extremities, hip flexors were 4/5 bilaterally, quadriceps and hamstrings showed 4/5 strength. The right tibialis anterior was 1/5 and the left 3/5. The medial gastrocnemius was 4/5 bilaterally. Deep tendon reflexes were 2+ in the upper extremities, absent at the knees and ankles. Plantars were down going bilaterally. Sensory examination revealed decreased pinprick, light

touch, and vibration below the knees and involving the fingers bilaterally. Patient was unable to stand due to weakness.

A nerve conduction/EMG was requested to evaluate for peripheral causes of severe weakness. The clinical differential diagnosis was critical illness neuropathy vs. CIDP vs. diabetic amyotrophy. The results are shown in Table 9.4. Systemic labs showed normal serum and urine immunofixation, baseline HBA1c of 8.8 %, absent ANA, CRP 7.7 (normal <10), ESR 21 (normal for age), TSH 1.655 (normal), and CK 614.

The EMG data shows patchy prolongation of latencies and absence of nerve responses which are concerning for an inflammatory neuropathy like CIDP. The following CIDP microplan was implemented (patient-specific information is entered in italics):

1. **Mission Objectives**.

   1.1. Dependable treatment of CIDP (meeting all criteria for dependability).
   1.2. Establish specific Success and Failure objectives: **Success objectives**:

   (a) *Improve weakness in legs*, *specifically ability to walk and balance*.

   Failure Space:

   (a) *Worsening lower extremity weakness needing wheelchair confinement*.
   (b) *Worsening hand weakness*.

2. **Diagnostic Confirmation**.

   2.1. Confirm Clinical, CSF, and EMG Data.
   2.2. Approach problem in Byzantine framework. (*See Chap*. 6)
   2.1 and 2.2 *Problem was cast in a Byzantine generals framework for corroboration. CSF studies showed protein of 45 mg/dl*, *normal cells. A clinical diagnosis of CIDP can be entertained with a high degree of certainty*.

3. **Perform Preliminary system safety assessment** (**PSSA**), **SSA**: (*See Chap*. 2)

   3.1 Identify specific individual safety concerns and mitigation strategies.
   3.1: *PSSA performed*: *The following risks were identified*: *diabetes mellitus*. *Category*: *Minor*.
   Patient also had a remote history of stroke.
   3.2 Implement "defense in depth" for identified risks.

   3.2.1. *Defense in depth for hypertension implemented using Table* 9.2.
   3.2.2. *Defense in depth for diabetes mellitus*: *Endocrine consult requested during planned hospitalization. Endocrinology recommended 35 units of Lantus insulin for general treatment of diabetes mellitus*, *to be increased to 45 units the night prior to IV methylprednisolone*

Table 9.4 NCS/EMG findings for case Example 3

Nerve and side	Latency (ms)	Distance	Amplitude (mV)	Velocity (m/s)	F waves (ms)
Peroneal (Right) Ankle	8.3 (<6.1 ms)	90 mm	0.7 (>2 mV)		
Fibular Head	18.0		0.4	30 (>41 m/s)	Absent (<56 ms)
Popliteal Fossa	20.5		0.4	37	
Tibial (Right) Ankle	6.2 (<6.1 ms)	80 mm	1.1 (>3 mV)		
Popliteal Fossa	18.9		0.8	31 (>41 m/s)	57.1 (<58 ms)
Median motor (Right) Wrist	8.0 (<4.4 ms)	70 mm	2.5 (>4 mV)		
Elbow	13.5		2.1	50 (>49 m/s)	Absent (<32 ms)
Ulnar motor (Right)	Absent	70 mm			
Ulnar motor (Left) Wrist	4.3 (<3.5 ms)	70 mm	7.7 (>6 mV)		
Below Elbow	8.8		6.7	42 (>41 m/s)	34.5 ms (<32 ms)
Above Elbow	18.9		6.1	50	
Sural, ulnar, median, sensory (Right)	Absent				
Radial sensory (Right)	2.1 (<2.2 ms)	100 mm	6 μV (>6 μV)		
Muscle and side	*EMG findings*				
Tibialis anterior (Right)	Moderate fibrillations and positive sharp waves. Absent motor units				
Medial gastrocnemius (Right)	Moderate fibrillations and positive sharp waves. Motor units showing increased amplitude, duration, and reduced recruitment				
Vastus lateralis (Right)	Moderate fibrillations and positive sharp waves. Motor units showing increased amplitude, duration, polyphasia, and slightly reduced recruitment				
Triceps (Right)	Absent fibrillations and positive sharp waves. Mix of normal and increased amplitude and duration motor units				
First dorsal interosseous (Right)	Moderate fibrillations and positive sharp waves. Motor units showing increased amplitude, duration, and markedly reduced recruitment				
Gluteus medius, L5 paraspinals, T10 paraspinals, EIP, Deltoid (Right)	Normal				

Standard normative data are in brackets

infusion. Additionally, Novolog 7 units three times daily prior to meals.

3.2.3 *Recurrent stroke risk as a consequence of treatment, especially IVIG was considered low.*

4. **Immunosuppression Checklist**. (*See Chap. 7*)

4.1. *No risks for immunosuppression identified.*

5. **Steroid and IV Methylprednisolone Failure modes and effects analysis (FMEA)**. (*See Chap. 4*)

5.1. *Refer FMEA for IV Methylprednisolone, Chap. 2.*

6. **Steroid Nutrition Information** (*See Appendix*)

6.1. *Not implemented at the time.*

7. **Implement Plan Do Study Act Cycles**. (*See Chap. 8*)

7.1. Establish micro-milestones.

7.1.1: *Improved proximal strength in 8 weeks.*
7.1.2: *Transition from wheelchair to walker in 2 months.*
7.1.3: *Transition from walker to 4 pronged cane between 3 and 4 months.*
7.1.4: *Onset of improvement in foot dorsiflexion/plantar flexion strength in 6 months.*
7.1.5: *Substantial improvement in dorsiflexion strength in 12 months.*
7.1.6: *Walk with simple cane or without support >90 % of time at 1 year and 3 months.*
7.1.7: *Maintain durable remission.*

7.2. Plan Do Study Act Cycle interventions.

Plan

7.2.1: *Initial intervention: IVIG 2 g/kg in five divided doses concurrent with five doses of IV Methylprednisolone 1,000 mg/day* [5].

DO

7.2.3: *IVIG and IV Methylprednisolone infused for first time as an inpatient.*
7.2.4: *Cardiac monitoring given potential for demand ischemia from IVIG and steroids.*
7.2.5: *Physical therapy as an inpatient.*
7.2.6: *Follow-up in clinic in 4–6 weeks.*

Study

7.2.5: *Patient reviewed in clinic 6 weeks after discharge.*
7.2.6: *Subjective*: *Able to stand and walk with the help of a walker which he had been unable to do previously.*
7.2.7: *As in-patient blood pressure rose up to 200/100 and blood glucose rose to a high of 657 mg/dl during one of the infusions. These were managed with defense in depth strategy with additional insulin and labetalol IV* (*in lieu of amlodipine since patient was inpatient*). *Patient remained stable without cardiac or neurological symptoms. As outpatient, sugars ranged from 100 to 350 mg/dl being closer to 100 mg/dl most of the time.*

Act

7.2.8: *A second round of IVIG and IV Methylprednisolone was planned 8 weeks after the first. Patient had considerable problem with access and transportation. He was encouraged to do the maximum over telephone and to return in 3 months.*

The PDSA cycle was repeated. The patient dropped out of follow-up due to transportation problems. He was specifically asked to come in for reevaluation which he did 5 months later. The following results were obtained:

DO

7.2.3: *IVIG 2 g/kg and IV Methylprednisolone 1,000 mg/day for 5 days infused as an outpatient since the initial infusion was well tolerated.*
7.2.4: *Monitor blood pressure and blood glucose as an outpatient.*
7.2.5: *Physical therapy as an outpatient.*
7.2.6: *Follow-up in clinic in 2 months.*

Study

7.2.5: *Subjective*: *Able to stand without support, walking confidently with a walker, sometimes with a cane.*
7.2.6: *Objective*: *Abductor Digiti Minimi*: *3 on the right and 5 on the left. APB showed 4+ on right and 5 on left. Hip flexors 5−/5, quadriceps 5/5, and hamstrings 5−/5 bilaterally. Tibialis Anterior 2+ on right and 3 on left. Medial gastrocnemius 4+/5 bilaterally. Reflexes showed return of knee jerk and absent ankle jerks.*
7.2.7: *Blood pressure was uncontrolled at 189/99. Blood glucose logs were reasonable and being monitored by PCP. 2+ pedal edema was observed. Weight was 203 lbs, gain of 20 lbs.*

Act

7.2.8: *Increase physical therapy and gait training to continue transition to ambulation with cane since he had improved strength in the lower extremities.*

7.2.9: *Request partnership with primary care physician for management of edema.*

7.2.10: *The absence of relapses suggests ongoing nerve inflammation has been curtailed. Therefore, reduce dose to IV Methylprednisolone 500 mg IV Q 2 weekly to consolidate therapy and prevent relapse.*

7.2.11: *Return in 3 months.*

The PDSA cycle was repeated and 3 months later at follow-up patient continued to be better, still using a walker for many activities for balance and a cane at other times. He was functionally independent, able to care for himself and mowing his yard without assistance. Objective physical examination remained very similar to the last one. Blood pressure continued to be high at 176/98, HBA1c was 7.7 %, better than the baseline of 8.8 % prior to treatment. He was encouraged to continue physical therapy and control of blood pressure with his primary care physician. Given his durable improvement, further treatment was deferred. He found it very difficult to come in for follow-up but promised to keep in touch over telephone.

RB was reviewed 8 months later. He was able to walk independently to a small extent and better with a cane. He had normal 5/5 strength in his left Abductor digiti minimi, the right was 4+/5. The left FDI was normal, the right continued to show severe weakness at 2+/5. He was able to perform all tasks with his hands and had returned to a normal lifestyle. APB was normal bilaterally. He had normal strength in the lower extremities save severe weakness in the right tibialis anterior which was 2/5 and the left was 4/4. The medial gastrocnemius was 5/5 bilaterally. His blood pressure continued to be high–180/90 mmHg; he reported better values at home and with his PCP. At this visit his HBA1c was 6.8 % and he had a total weight gain of 13 lbs.

7.3 **Perform shortfall analysis**.

7.3.1: *Standing, ambulation with walker micro-milestones were met on time. However, independent ambulation and percentage of time with cane micro-milestones had lagged behind.*

7.3.2: *Close follow-up, adequate control of blood pressure remained challenges which reduced the number of doses delivered.*

8. **Collect data for continued improvement**.

8.1. *Weight gain, pedal edema, blood pressure control need close attention and monitoring and are potentially persistent problems. Blood pressure can be expected to rise 20–30 mm systolic and 10 mm diastolic.*

8.2. *Blood glucose levels spike for 36–48 h after an infusion in most diabetics and require extra insulin, dietary restrictions, and fluids. After that period they are expected to return to baseline values.*

8.3. *Return of function in proximal muscles happens soon*; *distal muscles take much longer since re-innervation is likely length-dependent. It is possible that this process happens at a constant pace following initial control of the disease and does not need aggressive therapy in the absence of relapses.*

Case Example 4

BSB is a 69-year-old female with cirrhosis, s/p Transjugular Intrahepatic Portocaval Shunt (TIPS) procedure in September 2012, hypertension, rheumatoid arthritis, GERD, hypothyroidism who presented with bilateral upper and lower distal paresthesias as well as bilateral lower extremity weakness. The patient reported about 2 weeks ago that she began to notice tingling in her bilateral hands which she has not had before. It affects all of her fingers equally. She typically ambulates with a walker at home. Subsequently she began to note tingling in her feet as well as progressive bilateral lower extremity weakness which led to five falls. This has progressed to the point she is unable to stand. She denied any trouble with speech or swallowing, face numbness, dizziness, headache, blurry or double vision, urinary or fecal incontinence, or retention. She denied prior similar spells. She denied prodromal infectious symptoms such as fevers, chills, productive cough, diarrhea, or dysarthria. She denied any recent changes in her medications. She did receive a flu shot 3 months previously.

On exam, mental status, cranial nerves were normal. Strength testing was not reliable due to limited patient participation, but showed severe hip flexor weakness accompanied by poor strength in upper extremities as well. She was diffusely areflexic. Sensory examination was not reliable. Gait could not be tested since she was unable to stand due to weakness.

The patient had a cervical, thoracic, and lumbar spine MRI w/ and w/o Gad which showed advanced central canal stenosis at L2–L3. This could potentially explain the lower extremity symptoms; however, changes in the C spine were not severe enough to cause upper extremity symptoms. A nerve conduction/EMG was performed; the results are shown in Table 9.5.

Based on features of severely prolonged distal latencies, F waves (ulnar motor), absent sensory responses in the upper extremities, and spared sural sensory response, she was diagnosed with acute inflammatory demyelinating polyneuropathy (AIDP). She was treated with IVIG 2 g/kg in five divided doses with improvement in lower extremity strength and ability to stand and walk with the assistance of a walker.

She returned to clinic 4 weeks later with steady ongoing improvement. Over the next 1 month she could walk 200 ft. However, she thereafter experienced recurrence of symptoms with worsening lower extremity weakness and decreased ability to walk. She could walk only 10 ft and reported the numbness and tingling in the feet was returning. The recurrence of symptoms after 8 weeks raised concern for CIDP instead of AIDP which is potentially steroid-responsive. The following CIDP microplan was implemented.

Table 9.5 NCS/EMG findings for case Example 4

Nerve and side	Latency (ms)	Distance	Amplitude (mV)	Velocity (m/s)	F waves (ms)
Peroneal (Left) Ankle	12.6 (<6.1 ms)	90 mm	0.9 (>2 mV)		
Fibular Head	18.3		0.5	55 (>41 m/s)	Absent (<56 ms)
Popliteal Fossa	20.2		0.6	53	
Tibial (Left) Ankle	6.7 (<6.1 ms)	80 mm	1.4 (>3 mV)		
Popliteal Fossa	15.8		1.1	42 (>41 m/s)	50.8 ms (<58 ms)
Median motor (Right) Wrist	17.7 (<4.4 ms)	70 mm	1.3 (>4 mV)		
Elbow	23.3		1.4	43 (>49 m/s)	Absent (<32 ms)
Ulnar motor (Left) Wrist	6.3 (<3.5 ms)	70 mm	1.0 (>6 mV)		
Below Elbow	9.9		0.7	56 (>49 m/s)	
Above Elbow	12.8		0.7	40	41.4 ms (<32 ms)
Sural (Left)	2.7 (<4.2 ms)	140 mm	6 μV (>6 μV)		
Ulnar, median sensory (Left)	Absent				
Muscle and side	*EMG findings*				
FDI (Left)	Absent fibrillations and positive sharp waves. Mildly enlarged motor units with reduced recruitment				
Extensor Digitorum Communis (Left)	Moderate fibrillations and positive sharp waves. Normal motor units with markedly reduced recruitment				
Deltoid (Left), vastus lateralis (Left)	Normal				
Tibialis anterior (Left)	Absent fibrillations and positive sharp waves. Mix of normal and mildly enlarged motor units with normal recruitment				

Standard normative data is presented in brackets

1. **Mission Objectives**.

   1.1. Dependable treatment of CIDP (meeting all criteria for dependability).
   1.2. Establish specific Success and Failure objectives: **Success objectives**:

   (a) *Improve weakness in legs, specifically ability to walk and balance.*
   (b) *Improve numbness and tingling involving the hands and feet.*

Failure Space:

(a) *Worsening lower extremity weakness needing wheelchair confinement*.
(b) *Worsening hand weakness*.

2. **Diagnostic Confirmation**.

2.1. Confirm Clinical, CSF and EMG Data.
2.2. Approach problem in Byzantine framework. (*See Chap*. 6)
2.1 and 2.2 *Problem was cast in a Byzantine general's framework for corroboration. Based on demyelinating features on NCS/EMG, clinical presentation, progression over 8 weeks, a clinical diagnosis of CIDP can be entertained with a high degree of certainty*.

3. **Perform Preliminary system safety assessment** (**PSSA**), **SSA**: (*See Chap*. 2)

3.1. Identify specific individual safety concerns and mitigation strategies.
3.1: *PSSA performed*: *The following risks were identified*: *Hepatic disease and cirrhosis. Category*: *unclassified. It is difficult to predict impact on coagulation or precipitating liver failure. Therefore, this would require careful vigilance*.
3.2. Implement "defense in depth" for identified risks.

3.2.1. *Routine monitoring for steroid-induced diabetes, hypertension as potential side effect of therapy*.

4. **Immunosuppression Checklist**. (*See Chap*. 7)

4.1. *No risks for immunosuppression identified*.

5. **Steroid and IV Methylprednisolone Failure modes and effects analysis** (**FMEA**). (*See Chap*. 4)

5.1. *Refer FMEA for IV Methylprednisolone Chap*. 2.

6. **Steroid Nutrition Information**. (*See Appendix*)

6.1 *Not implemented at the time*.

7. **Implement Plan Do Study Act Cycles**. (*See Chap*. 8)

7.1. Establish micro-milestones.

7.1.1: *Improved proximal strength in 6 weeks*.
7.1.2: *Improved ability to ambulate with walker in 2 months*.
7.1.3: *Transition from walker to four-pronged cane between 3 and 4 months*.
7.1.4: *Walk with simple cane or without support >90 % of time at 9months*
7.1.5: *Reduce painful paresthesias by 90 % at 4 weeks*.
7.1.7: *Maintain durable remission*.

7.2. Plan Do Study Act Cycle interventions.

Plan

7.2.1: *Initial intervention*: *IV Methylprednisolone 1,000 mg/day for five doses* [5].
7.2.2: *If infusions are well tolerated, she would receive IV Methylprednisolone 1,000 mg Q Weekly for 6 weeks.*

DO

7.2.2: *IV Methylprednisolone as outpatient.*
7.2.3: *Physical therapy as outpatient.*
7.2.4: *Follow-up in clinic in 4 weeks.*
7.2.5: *A PICC line was needed since venous access was difficult.*

Study

7.2.6: *Patient reviewed in clinic 4 weeks later.*
7.2.7: *Subjective*: *Able to stand and walk with the help of a walker. She had regained ability to walk 80 ft.*
7.2.8: *Objective*: *Physical examination revealed Deltoids 4+/5 bilaterally but otherwise 5−/5 strength in upper and lower extremities. She remained diffusely areflexic.*
7.2.9: *Stable weight, blood pressure 158/60, normal blood glucose.*
7.2.10: *Pain objectives achieved. Adjunct pain relief to the patient's satisfaction was achieved with addition of Gabapentin 600 mg tid.*

Act

7.2.11: *Given steady improvement, reduce IV Methylprednisolone dose to 500 mg IV Q weekly for 6 weeks.*
7.2.12: *Return to clinic in 8 months.*

Following these actions, patient returned to clinic with normal strength and baseline ambulation prior to falling ill. She regained upper extremity reflexes; lower extremity reflexes remained absent. Her HBA1c was 5.6 % during therapy. Blood pressure remained at her baseline. She had a total weight gain of 24 lbs.

8. **Collect data for continued improvement**.

8.1. *A lower dose of IV Methylprednisolone 500 mg could be just as effective. BSB and two other patients reported less swelling in the ankles at this lower dose and the same degree of benefit as 1,000 mg.*
8.2. *Weight gain continues to be a pressing problem. Perhaps better nutrition guidance may help.*

Case Example 5

RH is a 63-year-old female who developed significant pain in both legs 6 months ago. She then noted increasing difficulty with walking up and down steps. Shortly afterwards she developed pins and needles and tingling in both legs, worse in the feet. She also experienced numbness below the knees bilaterally. The pain, numbness, and tingling were constant. Two months later she developed acute onset of left upper and lower facial droop. An MRI Brain performed at the time was normal. Around this time, she began experiencing significant leg weakness. The weakness made it difficult to walk without assistance. A month later she required a cane and then a walker to ambulate. She also reports significant fatigue which has been present for several months. At the time of her initial visit, she required a wheelchair most of the time.

An EMG done outside showed demyelinating features. A review of outside hospital records showed reference to CSF studies demonstrating elevated protein, the level itself was not available. Other lab work included B12, SPEP, HIV, HCV, RPR, immunofixation, folate, ANA, HBA1c, and ESR. All of these results were unremarkable. She was diagnosed with CIDP and was initiated on IVIG. She received three rounds of IVIG over the next 8 weeks. She did note mild improvement in symptoms after the first infusion. The primary benefit was in pain level. Unfortunately this was short lived and she regressed back to her original state over the course of several weeks. At the time of her clinic visit, she still experienced significant weakness, numbness, tingling. In the upper extremities, the numbness and tingling was in the fourth and fifth digits bilaterally and then progressed to the entirety of the hands. She still had significant weakness in both legs as well as both arms. She had difficulty in unscrewing a bottle cap and had given up her pastime of knitting. She denied any dyspnea, dysarthria, or vision changes. She also denied dysphagia or any prodromal infections or tick bites.

Physical examination revealed normal mental status, upper extremity strength. In the lower extremities she had 4/5 strength in her hip flexors, trace to 2/5 strength in tibialis anterior and medial gastrocnemius muscles. Sensory exam revealed loss of proprioception at the toes. She could barely stand at the time of her first visit. Prior to initiating treatment, a limited NCS/EMG was requested for confirmation which is shown in Table 9.6. Lab work for Lyme, Serum and Urine Immunofixation, ANA, SSA and SSB antibodies, CRP, ESR were all normal.

Based on her clinical presentation, NCS/EMG data, reportedly high CSF protein done outside, she was diagnosed with CIDP. The following CIDP microplan was implemented:

1. **Mission Objectives**.
    1.1. Dependable treatment of CIDP (meeting all criteria for dependability).
    1.2. Establish specific Success and Failure objectives: **Success objectives**:
        (a) *Improve weakness in legs, specifically ability to walk and balance.*
        (b) *Improve numbness and tingling involving the hands and feet.*

Table 9.6 NCS/EMG for case Example 5. RH

Nerve and side	Latency (ms)	Distance (mm)	Amplitude (mV)	Velocity (m/s)	F waves (ms)
Tibial (Right)	Absent	80			
Ulnar (Right) Wrist	3.2 ms (<3.5 ms)	70	6.6 mV (>6 mV)		
Below Elbow	7.0 ms		5.8 mV	48 m/s (>49 m/s)	40.3 ms (<32 ms)
Above Elbow	9.0 ms		6.1 mV	50 m/s	
Median motor (Right) Wrist	3.8 ms (<4.4 ms)	70	9.2 mV (>4 mV)		
Elbow	11.5 ms		6.2 mV	33 m/s (>49 m/s)	49.3 ms (<31 ms)
Sural, ulnar (Right)	Absent	140			
Median sensory (Right)	4.2 (<3.5 ms)	150	4 μV (>22 μV)		
Muscle and side		*EMG findings*			
FDI (Right)		Absent fibrillations and positive sharp waves. Normal motor units showing reduced recruitment			

Failure Space:

(a) *Worsening lower extremity weakness needing wheelchair confinement.*
(b) *Worsening hand weakness.*

2. **Diagnostic Confirmation**.

2.1. Confirm Clinical, CSF, and EMG Data.
2.2. Approach problem in Byzantine framework. (*See Chap.* 6)
2.1 and 2.2 *Problem was cast in a Byzantine generals framework for corroboration. Based on demyelinating features on NCS/EMG, clinical presentation, progression over 6 months, a clinical diagnosis of CIDP can be entertained with a high degree of certainty.*

3. **Perform Preliminary system safety assessment** (**PSSA**), **SSA**: (*See Chap.* 2)

3.1. Identify specific individual safety concerns and mitigation strategies.
3.1: *PSSA performed*: *No risks identified.*
3.2. Implement "defense in depth" for identified risks.

3.2.1. *Routine monitoring for steroid-induced diabetes, hypertension as potential side effect of therapy.*

4. **Immunosuppression Checklist**. (*See Chap.* 7)

4.1. *No risks for immunosuppression identified.*

5. **Steroid and IV Methylprednisolone Failure modes and effects analysis (FMEA).** (*See Chap.* 4)

   5.1. *Refer FMEA for IV Methylprednisolone, Chap.* 2.

6. **Steroid Nutrition Information** (*See Appendix*)

   6.1. *The Steroid nutrition sheet was discussed in detail with the patient. Patient showed a high degree of motivation and interest in cooperating with the nutritional recommendations.*

7. **Implement Plan Do Study Act Cycles.** (*See Chap.* 8)

   7.1. Establish micro-milestones.

   7.1.1: *Improved proximal strength in 6 weeks.*
   7.1.2: *Improved ability to ambulate with walker in 2 months.*
   7.1.3: *Transition from walker to four pronged cane between 3 and 4 months.*
   7.1.4: *Walk with simple cane or without support >90 % of time at 9months*
   7.1.5: *Reduce tingling painful paresthesias by 90 % at 4 weeks.*
   7.1.7: *Maintain durable remission.*

   7.2. Plan Do Study Act Cycle interventions.

   Plan

   7.2.1: *Initial intervention: IV Methylprednisolone 500 mg/day for five doses and plasmapheresis. IVIG was avoided since three rounds of infusions in the past did not yield tangible, durable benefits* [5].
   7.2.2: *Subsequently after discharge she was to receive IV Methylprednisolone 500 mg Q Weekly for four doses. The first dose was planned for 3 weeks after discharge.*

   DO

   7.2.2: *IV Methylprednisolone and plasmapheresis as inpatient.*
   7.2.3: *Physical therapy as inpatient. Plan for inpatient rehab after completion of therapy.*
   7.2.4: *Follow-up in clinic in 6–8 weeks.*
   7.2.5: *A temporary dialysis catheter was needed for plasmapheresis.*

   Study

   7.2.6: *Patient reviewed in clinic 6 weeks later.*
   7.2.7: *Subjective: Able to stand and walk with the help of a walker. She had made remarkable progress by the end of her hospital stay, therefore she was deemed "too good" for inpatient rehab.*
   7.2.8: *Objective: Normal upper extremity strength. In the lower extremities, she had normal 5/5 strength in hip flexors, quadriceps and 3/5 in medial gastrocnemius and tibialis anterior muscles. She had normal upper extremity reflexes and 1+ at the knees.*

7.2.9: *Stable weight with a 5 lbs weight gain. Blood pressure and glucose were normal.*
7.2.10: *Sensory symptoms relief objectives were completely achieved.*

Act

7.2.11: *Given steady improvement, reduce IV Methylprednisolone dose to 250 mg IV Q weekly for 4 weeks.*
7.2.12: *Return to clinic in 8 weeks.*

No shortfalls were identified. She was meeting micro-milestones ahead of projected times. She remained adherent to dietary recommendations detailed in Appendix 1. However, when she returned to clinic at the end of 8 weeks, she felt subjectively weaker and perhaps the disease was coming back. The PDSA cycle was repeated in the following manner:

Plan

7.2.1: *Resume IV Methylprednisolone 500 mg Q weekly for four doses.*

DO

7.2.2: *IV Methylprednisolone 500 mg Q Weekly as an outpatient.*
7.2.3: *Physical therapy as outpatient.*
7.2.4: *Follow-up in clinic in 8 weeks.*

Study

7.2.5: *Patient reviewed in clinic 8 weeks later.*
7.2.6: *Subjective*: *Able to stand and walk with the help of a cane. She was able to walk without assistance at home for short distances.*
7.2.7: *Objective*: *She continued to improve in weak muscles—the tibialis anterior and medial gastrocnemius were 4/5 in strength. Proximal lower extremity muscles showed normal strength. Deep tendon reflexes were normal to the knees and remained absent at the ankles.*
7.2.8: *Weight remained stable with a 5 lbs weight gain. Blood pressure and glucose were normal. HBA1c was 5.9 %.*

Act

7.2.11: *Given steady improvement, reduce IV Methylprednisolone dose to 500 mg IV Q 2 weekly for four doses.*
7.2.12: *Return to clinic in 8 weeks.*

At her subsequent return visit she had suffered a single mechanical fall, but continued to make steady progress otherwise. She had a 10 lbs weight gain which resulted from relaxing adherence to the steroid nutrition sheet over the holidays. Patient remained in durable remission. She was provided a prescription for physical therapy for gait and balance training and distal foot strengthening. Her dose of methylprednisolone was reduced further to IV methylprednisolone 500 mg Q 3 Weekly for three doses and then discontinued. Nine weeks after her last infusion

(and 1 year after her first clinic visit), she was seen in clinic. She was walking independently most of the time requiring a cane for support occasionally. Stubbing her foot from dropped toes was a problem which was circumvented to a large extent by ambulating with slippers or shoes which prevented the dropped great toe from triggering a fall. Physical examination showed normal strength everywhere save bilateral tibialis anterior muscles which were 4+/5 strength. Bilateral EHL and foot invertors continue to remain weak with trace strength in the former and 3/5 strength in the latter. She had a total of 18 lbs weight gain over 12 months of therapy, most of it in the latter half of treatment when she reduced adherence to the nutrition sheet when the dose of steroids was being reduced. She did not develop diabetes mellitus (HBA1c 5.5 %), hypertension, and had regained full function in her fingers. At this point, all mission objectives and durable remission were achieved and treatment discontinued.

8. **Collect data for continued improvement**.
   8.1. *A lower dose of IV Methylprednisolone 500 mg works well with lower weight gain and pedal edema.*
   8.2. *Weight gain can be mitigated to a great extent with adherence to the steroid nutrition sheet and lower doses of methylprednisolone.*
   8.3. *Total doses needed maybe lower as seen in this example.*

Conclusion

This chapter highlights continuous refinement. The long journey that started with case Example 1 was refined continuously through case Example 5. Knowledge from each experience was incorporated into subsequent cases with delightful outcomes. While there are many more cases with similar outcomes following this method, these were chosen because of verifiable follow-up information. The cost savings are enormous. In [6] the authors report their institutional cost of IV Methylprednisolone at $300 for a 1,000 mg dose. This compares to $235 per gram for IVIG. Therefore, the full dose for a 70 kg patient dosed at 2 g/kg would be $ 32,900 [6]. In the same article plasmapheresis is reported to cost $1,500 per exchange. Therefore, a series of 5 exchanges would be $7,500 [6]. Therefore, Reliance microplanning for CIDP can help achieve very high quality, durable outcomes at a fraction of the cost of traditional treatments. A great advantage with the microplan is it enables the patient and the physician to manage the entire disease lifecycle instead of piecemeal outcomes.

This method worked well with backwards integration of the clinic with inpatient care delivery. These were never seen in isolation, rather there was a seamless integration of the two forums of care delivery. These examples also show successful

examples of Disease Lifecycle Management. CIDP was not managed as a series of procedures like IVIG infusion or plasmapheresis, rather its treatment was divided into different phases of its lifecycle. An initial phase of aggressive immunomodulation was initiated with plasmapheresis or IVIG combined with steroid therapy. Subsequently, immunosuppression was consolidated with pulse methylprednisolone therapy. The emphasis then shifted towards mitigating side effects and facilitating re-innervation rather than ongoing immune suppression till there was complete recovery.

These examples show the advantages that lie in implementing Reliance microplanning and backwards integration. The reader will understand that the conceptual framework presented in section "Kaizen: CIDP Treatment Implemented Using Reliance Microplanning" has ubiquitous application. Similar paradigms and microplans can be developed for treatment of a whole range of medical and surgical disorders to improve quality and reduce variation.

Acknowledgments I am deeply grateful to the leadership and employees of Reliance Industries Limited (RIL) for their kindness in sharing their knowledge, experience, and wisdom with me.

Appendix 1: Steroid Nutrition Sheet . . . Contributed by Demera Hale, R.D. and Justin Hale, M.D.

Nutrition Tips When Taking Steroids

Steroids are often the cornerstone of treatment for a variety of disorders. However, patients taking steroids often say they feel hungrier than usual and often gain weight. Steroids can also cause fluid retention, increase blood pressure, increase blood sugar, and increase the risk of bone fractures. However, with wise nutritional choices, these unwanted side effects may be reduced significantly or even avoided; so patients can ultimately benefit from this very important treatment (Tables 9.7 and 9.8).

Choose Low-Calorie, Nutrient-Dense Foods

- Avoid foods that contain sugar in the ingredient list. Sugar is lurking in so many foods we eat, from ketchup to granola to orange chicken. The best way to avoid sugar is to not have it in the house.
- Also read the labels carefully for sugar in other forms, since the body treats them all the same. These include: high fructose corn syrup, corn syrup solids, rice syrup, organic dehydrated cane juice, dextrose, fruit juice concentrate, maltodextrin, turbinado sugar.

Table 9.7 Shopping list

	Recommended foods
Grains	Shredded wheat "Puffed" cereals Corn or 100 % whole wheat tortillas 100 % whole wheat pita bread Brown rice Quinoa 100 % whole wheat pasta
Vegetables	Fresh vegetables Frozen vegetables Canned vegetables with no added salt
Fruits	All fresh and frozen fruits
Milk and milk foods	Plain low-fat milk Natural cheese (Swiss, cheddar, Monterey jack) Plain low-fat Greek yogurt
Meat and other protein foods	Fresh fish, poultry, beef, and pork Water-packed tuna (rinse well with cold water in a strainer) Eggs Canned or dried beans with no added salt (rinse canned beans well with water) Unsalted nuts and seeds (sunflower, pumpkin)
Spices and seasonings	Herbs Mrs. Dash™ Frontier™ salt-free blends Fresh garlic or garlic powder Fresh onion or onion powder Ingredients for homemade no-salt-added salad dressings (see internet for recipes)
Main dishes	Ingredients for homemade casseroles made without added salt Ingredients for homemade soups with very-low-salt broth and no added salt Ingredients for homemade stews or chili without added salt
Snack foods	Fresh fruit Fresh vegetables Unsalted nuts and seeds Salt-free 100 % whole wheat crackers Unsalted popcorn

- Be aware of high-calorie beverages that are stripped of nutrients and fiber such as those found in sodas, sports drinks, and juice cocktails. Remember that 100 % juice is also a high-calorie beverage, since it is separated from the fiber that normally fills us up. Better to eat the grapes than drink the grape juice.
- Drink 8–9 cups of plain water daily.
- Limit foods that have been fried.
- Fill the refrigerator and pantry with nutritious staple foods such as whole fruits and vegetables, unprocessed lean meats (deli meats are highly processed and

Table 9.8 Example meal plan

Breakfast	1 cup spoon size shredded wheat 1 cup (½ on cereal, ½ to drink) 1 % low-fat milk Banana 1 oz walnuts
Morning snack	½ orange 1 hard boiled egg w/pepper
Lunch	Turkey sandwich: 2 oz turkey (low-fat, low-sodium deli meat) 1 slice low-salt 100 % whole wheat bread 1 tablespoon salt-free balsamic vinaigrette 1 tablespoon hummus 1 medium carrot, cut into sticks 1 small apple
Afternoon snack	1 slice low-salt 100 % whole wheat bread, toasted 1 tablespoon unsalted/sugar-free peanut butter
Dinner	2 cups macaroni and cheese (see recipe below) 1 cup green salad (romaine, green leaf, and butter lettuce) 1 tablespoon salt-free balsamic vinaigrette ½ cup steamed broccoli with a squeeze of lemon and dash of pepper
Evening snack	1 apple

loaded with salt), unsalted nuts and seeds, beans and legumes, and 100 % whole grain breads, rice and pastas.

- Half the plate or bowl should be loaded high with fresh fruits and vegetables, while the other half should be divided evenly between lean protein sources (such as poultry, fish, beans, legumes, or tofu), and 100 % whole grain products.
- Avoid fast food eating. But if you must, follow the plate model above. You will more than likely have to make special orders to ensure you are eating a healthy meal when eating out.

Choose Foods Low in Salt (Sodium)

- To avoid high blood pressure and swelling of the ankles, limit all foods that contain salt or sodium in the ingredient list.
- If you must eat a food that contains salt make sure that it has no more than 140 mg sodium per serving and eat only one serving. Besides the obvious potato chips, salt also lurks in deli meats, TV dinners, canned soups, and just about any fast food or sit-down restaurant entree.
- There are plenty of high flavor spices that can take the place of salt. Adding citrus, herbs, and salt-free spice mixes are just a few of the ways to add flavor to food without adding salt.
- Eat foods in their natural state. For example, serve corn on the cob instead of canned cream corn.

- Again, avoid fast food eating. But if you must, make sure to special order your food without added salt.
- And of course, do not add salt, soy sauce, or salt containing seasonings to foods.

Start a Vitamin Regimen

- Take a daily Multi-vitamin for your gender and age category.
- Take a daily Calcium and Vitamin D supplement for your age category.
- Take a daily Omega-3 supplement for your age category or eat at least once a week. Discuss with your doctor before starting omega-3.

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Chapter 10
Knowledge and Culture

> Do not walk in front of me, I may not follow. Do not walk behind me, I may not lead. Walk beside me and I will be your friend
>
> *Albert Camus*

Abstract This chapter presents the abstract philosophical principles behind the methods presented in prior chapters. The unique culture and philosophy of Branch Banking & Trust (BB&T) Corporation is studied and presented with applications to clinical medicine. The knowledge of the organization is increasingly recognized as the wealth of corporations and wealth of nations. With increasing complexity of products, knowledge and innovation are increasingly a collaborative effort. Organizations that are unable to collaborate and create fail to synergize their talents into creating great products or services. This chapter looks at the genesis of knowledge in organizations. Vision, mission, and values give birth to knowledge. Knowledge gives birth to processes. Knowledge development leads to development of an organization's identity and development of core competencies. This leads to a culture of excellence. Teamwork synergizes individual talents into a great product or service which is beyond the capability of any one individual alone. These principles are presented for forming a basis for successful outcomes in medicine. Case examples of poor outcomes from lack of teamwork and of immense success from successful teamwork are presented. Teamwork should not be seen as intellectual or professional altruism, but as a force and knowledge multiplication method. Features which guide successful teamwork are presented. The career of a physician goes through many seasons of evolution and development for which ongoing training, leadership, and development of strong institutional culture and loyalties are essential. Management concepts of mentorship, ownership, and collaborative responsibility are presented.

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Introduction

The prior chapters introduced methods and tools which improved dependability in diagnosis and treatment. This chapter is an exploration of the philosophical principles that evolved those methods and form the heart of enduring and iconic companies. These principles form the heart of the organization; they provide the abstract principles and basis for growth and evolution of the organization. In this chapter, we study the principles which helped BB&T Corporation, one of the leading banks in the United States successfully weather the recent financial crisis.

BB&T, headquartered in Winston Salem, North Carolina, with $176 billion in assets is the 12th largest bank in the United States [1]. BB&T has a footprint of over 1,800 centers in 12 states and Washington DC. BB&T provides consumer and commercial banking, securities brokerage, capital markets, asset management, mortgage and insurance products and services. A study of BB&T's resilience holds valuable lessons for how dependability, in the face of uncertainty and systemic risk, can be achieved. BB&T's strength lies in its core values—The BB&T Philosophy which is blended with a process-driven approach for managing day-to-day banking and developing employee potential. The origins of the BB&T philosophy lie in its history and development as a small North Carolina bank which grew because of a keen sense of dedication to its small business customers. BB&T's origins as a small state bank lending to farmers shaped its operating philosophy during its growth into a large regional bank. BB&T views its philosophy as a lighthouse guiding the bank in the changing tides of finance. The operating philosophy, whether at the abstract corporate level or at a local branch, is shaped by its moral sense of delivering a great fiduciary responsibility towards its customer. BB&T's methods have valuable lessons for synergizing and developing knowledge workers who form the core of many services-related fields such as medicine.

BB&T Philosophy

The heart and soul of BB&T is its philosophy, also termed its *core values*. This is ingrained in all employees at all levels of the organization. BB&T's refers to employees as "associates" in its management terminology. BB&T's values form the basis for all actions performed by all employees during the course of their duties. BB&T's guiding vision is to create the best financial institution possible, "to be the best of the best". This quest for excellence is perhaps the primordial factor maximizing human performance and lays the seeds for long-term growth and evolution. BB&T's approach to dependable finance is very *human*; by maximizing human potential, the bank's potential is maximized thus delivering shareholder and client value and dependability. These values are of course *long term*. The hierarchy and interaction of the core values are as shown in Fig. 10.1.

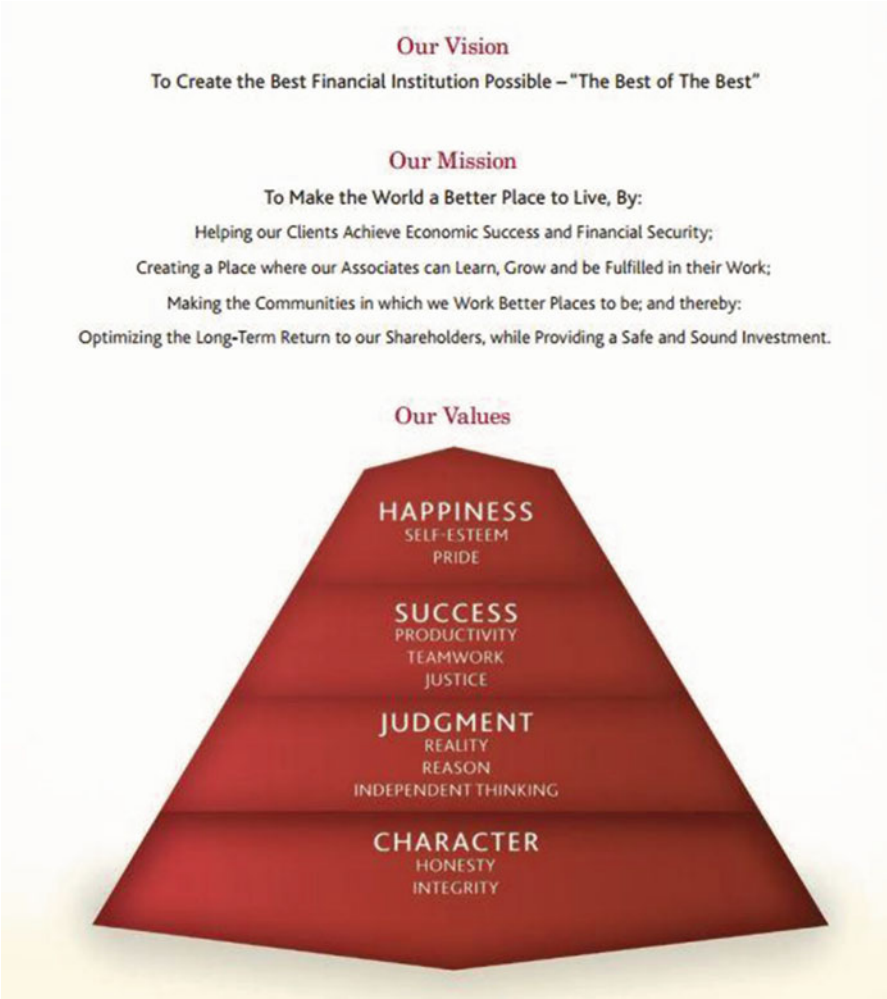

Fig. 10.1 BB&T values. *Source*: *Annual General Report. 2013*. Used by permission

BB&T's philosophy develops the associate and governs their actions to the highest moral, fiduciary, and intellectual standards. The customer is the focus of all bank activity, therefore he or she is the direct beneficiary of investments made in the associate. It follows therefore that to deliver the best of the best to the customer, the associate has to perform at peak capacity. Associate development by necessity is a long-term process and to travel this long journey, an employee needs two things, a core philosophy or set of *values* which acts as a moral and ethical compass and a method or *process* that delivers these values into tangible transactions. Therefore, an associate must be viewed as a long-term asset in whose growth and development lies the means to be the best of the best.

But firstly, what are *values*? They are hard to define since they vary so diversely with culture. The Oxford English Dictionary defines *values* as "beliefs about what is right and wrong and what is important in life" [2]. Values therefore establish standards for behavior and judgment. They provide guidance and clarity in uncertain times. They provide consistency in our actions. Actions guided by values therefore are least likely to stray from high ethical, moral, and legal standards. Therefore, once values are well established, conscientious actions follow. By consistent application, values proceed from our conscious to our sub-conscious behavior and actions. BB&T's core philosophy is composed of ten values which every associate is encouraged to internalize and apply consistently [3]. The stress on values comes from BB&T's belief that "ideas matter and an individual's character is of critical significance" [3]. In the following section, BB&T's ten values are listed followed by a brief discussion in the context of delivering dependability.

1. **Reality**
   The actions of all associates should be grounded in objective facts (reality-based) as opposed to being driven by subjective beliefs or perceptions. Decisions which are reality-based are less likely to go wrong and have negative consequences. Decisions should not be based on what associates "wish was so" or on ephemeral theories disconnected from reality [3]. It is important to realize that reality-based decision making does not constrain innovation. This leads to a deeper question of which objective facts are trustworthy and reliable. The barrage of conflicting economic data and volatility during the recent economic crisis makes reality-based decision making more challenging than it may appear on the surface. Associates are therefore encouraged to not merely accept and incorporate data into decision making, but also to examine its veracity closely. Reality-based decision making blends closely with critical analysis and error correction.
2. **Reason** (**Objectivity**)
   Clear thinking forms the basis for rational decision making based on objective facts. A mind that is grounded in reality should be capable of thinking clearly. Clear thinking requires rigorous intellectual discipline and is based on sound premises and logical thinking. Associates should be able to perform both inductive (from specific examples to general conclusions) or deductive (from general principles to specific problems) reasoning. The thought process should be guided by what is essential and have a clear mission and purpose [3]. An equally important virtue is to be able to continue to refine and clarify the reasoning process.
3. **Independent Thinking**
   Each associate is encouraged to think independently. Every person is therefore responsible for what they do and ownership of their ideas. Creativity is strongly encouraged and results only from independent thought. Each associate should assume responsibility for their actions and individual success or failure. Independent thinking is not contradictory to teamwork. It emphasizes that clear

thinking is an essential part of teamwork. Creativity and new ideas which result from independent thinking are essential for making things better [3]. New ideas are judged by their impact on the whole organization and how they contribute to the accomplishment of the mission. Independent thinking is an essential component of an employee's growth in the organization.

4. **Productivity**
   Wealth creation is at the heart of BB&T's business. Greater return on investment and improved productivity can happen only with rational allocation of capital through the lending and investment process in an efficient manner. Profitability is a measure of efficiency of an organization, which results from productivity. It follows therefore that to be the best of the best in the financial realm, all employees need to be the most productive. This is important for creating shareholder value and for contributions to society as a whole [3]. Striving for greater productivity inspires employees and organizations to innovate, whether by way of greater profits or lower costs. Lower costs lead to reduced waste in business processes. The idea behind this value is to inspire employees to turn their ideas into actions to improve economic well-being [3].
5. **Honesty**
   The highest standards of honesty and integrity are expected from all employees. This ideal is viewed as being consistent with reality [3]. This is important because conflict with reality is self-defeating. Being disconnected from reality leads to behavior and decision making which ignores objective facts leading to failure. Honesty blends with transparency which leads to institutional safety. It allows objective analysis of all outcomes, whether good or bad, and promotes understanding of failures which can be prevented in future. Honest failures from unforeseen circumstances should never be punished. It promotes free discussion of ideas. It encourages employees to assume responsibility for their thoughts and actions.
6. **Integrity**
   All employees are encouraged to behave consistent with principles. Being inconsistent with principles leads to long-term detriment. Principles must never be sacrificed under any circumstances. Violating principles, which may bring tempting returns in the short term, always leads to failure in the long term. The bank views itself as an organization with the highest integrity [3].
7. **Justice** (**Fairness**)
   The evaluations and rewards offered to individual employees should be objective and be based on their contributions towards accomplishing the goals of the institution and adhering to the institution's values. Such a system being reality-based and backed by objective facts is therefore inherently just. It therefore follows that those who contribute the most should also receive the most. A just, fair, reality-based approach is applied by managers towards their employees and vice versa. The idea is to prevent employee unhappiness which follows when employees perceive managers rewarding underperforming team members and underrewarding strong performers. High achieving, motivated employees would leave the institution if they perceive unfairness in their evaluation and

career advancement. This serves not just to deplete the institution of talent but also strengthens competitors. Rewards for superior performance encourages average performers to strive towards excellence, thus improving overall standards in the institution and fostering innovation. BB&T has an institutional culture of discriminating solely based on competency, performance, and character. Individual employees are judged solely based on their values, performance, and merits. BB&T's operational culture simultaneously rejects egalitarianism and collectivism [3].

8. **Pride**
   Pride is the happiness that is earned from living cherished values. Pride is a natural consequence of living a "strenuous life", one which is just, honest, independent in thought leading to great achievements (productivity). This form of pride must be distinguished from arrogance which is purely negative and undermines institutional excellence. Aristotle believed that "earned" pride (not arrogance) was the highest of virtues because it inspired all the others [3]. Striving for earned pride is therefore only a call to values-driven thought and action. Employees are encouraged to earn pride in their ideas and actions. Earned pride leads to strong loyalties to the institution, something which employees and customers would love to be associated with. Earned pride leads to high self-esteem.
9. **Self-Esteem (Self-Motivation)**
   Self-esteem stems from pride and accomplishment. It is the result of a job done well. It encourages employees to challenge themselves towards greater goals and develop ideas to achieve those goals. Self-esteem is closely allied with self-motivation. Self-motivation provides the energy for the quest for excellence. Guided by a strong work ethic, it leads to achievement. BB&T believes that what an employee receives from their work is proportionate to how much they contribute [3].
10. **Teamwork/Mutual Supportiveness**
    The day-to-day operation of a large bank with multiple services and lines of business is achieved by the collaborative, concerted efforts of its employees. Each employee contributes his independent thoughts and skills to the group of individuals that he is associated with to achieve these goals. Each employee must consistently act to achieve the agreed-upon objectives of the team. The need for team work stems from the evolution of the financial services industry into a complex system which requires diverse skills ranging from human resources management to risk management to financial modeling to be successful. As emphasized earlier, teamwork does not contradict independent thinking, it merely reinforces it in a more challenging context. Outstanding individuals can contribute more when they channel their talents and energies as members of a team and synergize each other' strengths [3].

The core values lie at the heart of all matters big and small at BB&T; they influence all aspects of operations. These values provide the framework for an employee's thoughts and actions during their growth at BB&T. The internalization

of these values tempers emotions which transform from reflexive feelings to a deeper understanding of thought and happiness. Emotions evolve in a manner where they reinforce best decisions and behavior towards long-term success and happiness. Beliefs inspire behaviors which lead to results [3].

While mission values are not unique to BB&T, translating them from abstract principles to day-to-day actions across thousands of employees is an important process. This is all the more important when a company grows by mergers and acquisitions, assimilating thousands of new employees in short periods of time who come from different organizations. A core philosophy therefore needs a *process* to spread these principles across the organization. BB&T achieves that through very innovative employee education programs which will be studied in subsequent sections.

The basis of BB&T's success is to understand the customer and to act only in the best interests of the customer. BB&T encourages all associates to understand the customer's needs, credit requirements, business processes, and best interests as the basis for all transactions [4].

BB&T University

BB&T University is the primary learning and development arm of BB&T. The main campus is located in Winston Salem with training centers across the bank's footprint. The main functions of the university are:

- Develop and administer the University Certification Program (UCP).
- Responsibility for learning administration through the learning management system (LMS).
- Operate the Leadership Development Program (LDP).
- Provide all merger training to newly acquired bank associates.
- Operate the BB&T Banking School at Wake Forest University.

The university operates on a "Demand-Pull" business model. Demand-Pull itself is discussed in detail in Chap. 8. Applied to banking operations, this refers to the fact that a business knowledge need is first identified ("demand") in the organization followed by course development to meet that need ("pull"). BB&T University is geared towards providing banking and financial industry knowledge for new employees who will serve as officers in the bank. The BB&T Banking School at Wake Forest University is geared towards existing bank employees who have shown exceptional performance but have a non-banking or finance background. This program helps such individuals gain domain knowledge in banking to lay the foundation for further career advancement at BB&T.

LDP is designed for training and mentoring new hires who are college graduates. Graduates of the LDP progress to solid careers at BB&T. They have served long, successful careers in the organization and form the vast majority of officers on the executive team of the bank. Class sizes vary depending on economic conditions and

hiring requirements, ranging from 120–150 individuals in economic boom years to 50–60 in more recent times. A great emphasis is placed on company culture and values throughout the program. The company core values are emphasized during all phases of the program. The course structure involves lectures from senior management, including the chairman. This allows new associates to come face to face with senior management, division heads, and understand company policies and management direction. There are two major training areas—business and corporate. The idea is to create knowledgeable employees who would fit into leadership roles within the organization in the years to come. Coursework includes finance, accounting, regulation, economics, and business administration. Training is divided into three phases.

Phase I introduces new associates to the company culture and philosophy. The aim is to internalize within them that BB&T is a values-driven organization. There is constant teaching and exposure of "vision/mission/values". Associates are able to determine during this phase if they fit in or not. This is also a great "self-awareness" phase. Associates learn to relate to one another and learn banking. They understand BB&T's positioning in the industry and their potential role in the organization. They learn different banking models. During this phase they learn the business and processes of a small community bank (BB&T's birth and roots). Progressively they learn the more complex range of products and services of a large bank. They learn to compare and contrast BB&T's operations with competitors. The topics during this phase are variable and include a talk and interactive session with the chairman. This phase typically lasts the first few months. Towards the end of this phase, associates are expected to be driven by the core values of the bank and get a sense of direction of where they fit in the organization. Phase I introduces associates to the basics of financial products and banking processes. Associates learn fundamental banking concepts such as credit analysis, financial analysis, and introduction to commercial underwriting. They learn to appraise loans and the underwriting process. This phase focuses on developing domain knowledge, understanding credit models, and building familiarity with different software used in banking. Associates learn to work in teams and tackle problems collaboratively. By the end of this phase, associates blend independent thinking and critical analysis with collaborative teamwork skills.

Phase II training becomes more specialized depending on the career interests of the associates. It is broadly classified into business and corporate. This phase usually lasts 3 months. Business associates go on to careers in commercial banking. This phase is very intensive since it expands considerably on skills acquired in phase I. By the end of phase II, business associates would have learnt all aspects of working in a community bank. The corporate trainees develop skills for roles in BB&T's core management and operations. Associates from this track go onto careers in human systems, regulations, audit, etc.

In Phase III, all associates come back together for a final review and undergo a series of formal end of program evaluations. All associates undergo a 90 day, 6 month, and end of program review. They are required to turn in papers and undergo formal testing in a bank simulator. The simulator exposes them to different

credit problems under different economic conditions and evaluates their responses. They are evaluated by a panel of senior managers from BB&T where they discuss and defend their actions in the simulations process. Upon successful completion, associates graduate and then undergo placement for their first job.

At the completion of their training, graduates are paired with their respective mentors. Every graduate is assigned a mentor for at least 2 years. Graduates with prestigious MBA degrees receive an additional 2 years of mentoring, for a total of 4 years. Mentoring is considered an extremely important aspect of career development at BB&T. Retention programs to prevent attrition of trained associates starts almost immediately following graduation. Past experience suggests that the greatest risk of attrition is during the 18–36 months period. There are many factors which account for this, two of the more important reasons are:

- Career disenchantment: During this period, stressors such as increased work responsibility or lack of fulfillment may play a role in seeking new career opportunities.
- Competing offers: BB&T's educational emphasis is well recognized in the banking industry. During the 18–36 month period, successful associates have built sufficient reputation to be approached for competing jobs in the financial services industry.

Mentoring plays a great role in mitigating attrition. Associates can communicate freely with a person outside their reporting lines and discuss perceived negatives (for example unsupportive boss, "work is not interesting" etc.) without fear of retribution. They can learn coping strategies from their mentors. Skill deficiencies can be addressed and goals for performance improvement can be formulated. In cases of major mismatches of an associate's aptitude and job responsibilities, mentors can help with transitions within the organization which can bring greater work satisfaction. Beyond the 5-year period, associate retention and satisfaction is much greater.

UCP refers to BB&T University's job-specific training process. Associates hired or promoted into a specific position are assigned the corresponding training curriculum (e.g., teller, retail lender, commercial lender, mortgage lender, etc.) to develop the skills necessary for discharging their job responsibilities. They are allotted 30 months to complete the program. The statistics confirm the benefits of investing in associate training and development. UCP graduates show consistently superior performance compared to their peers:

- Certified vs. non-certified Banking Service Officers
  - 40 % higher loan production
  - 68 % higher fee-based revenue
- Certified vs. non-certified Financial Center Leaders
  - 77 % higher loan production
  - 28 % higher net new transaction accounts

Most importantly, a statistical analysis comparing the UCP to associate retention has shown a strong positive correlation of +0.507 between the two. *Therefore, investments in associate education and career development have a positive impact on performance and retention*. Therefore, through BB&T University (including the LDP) and Banking school programs, the human systems division integrates recruitment, training, leadership development, and retention [5].

Section "From Values to Knowledge to Processes" will explore medical implementations of ideas borrowed from BB&T for patient care and physician training.

From Values to Knowledge to Processes

At the heart of successful organizations lie core values. Core values inspire an organizational mission and vision. This inspires the development of knowledge to deliver the mission objectives. The successful day-to-day translation of these objectives and delivery in the form of products and services requires the development of efficient processes. As the organization succeeds, it inspires new thought, development of new knowledge and newer processes on a bedrock of unchanging values (Fig. 10.2).

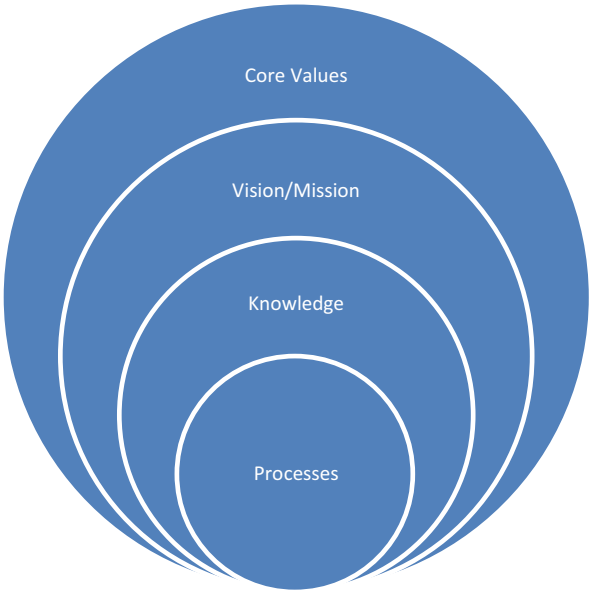

Fig. 10.2 The intertwined relationship between core values, organizational vision, mission, knowledge, and business processes of the organization

Knowledge Development in Medicine

Explicit and Implicit Knowledge

The knowledge of the organization takes many diverse forms. In their work *The Knowledge Creating Company*: *How Japanese Companies Create the Dynamics of Innovation*, Ikujiro Nonaka, and Hirotaka Takeuchi study the two types of knowledge that form the core of management decision making—implicit and explicit. Explicit knowledge is what is emphasized in western management; it is knowledge through rigor, deductive reasoning, formal education in the form of management degrees; found in articles, manuals, and databases and applied based on rules and guidelines. A vast majority of evidence-based medicine, professional guidelines come under this classification. Implicit knowledge is intuitive, based on individual insight and imagination which is not gained through formal education [6, 7]. Implicit knowledge forms the basis for new ideas and innovation. Successful companies create a background of core values, mission objectives, and a culture of learning that forms the milieu for development of explicit and implicit knowledge. This approach finds great application in medicine as well.

Core Competence

Core competence is an idea that dominated the business world in the 1990s based on an influential paper by management *gurus* C.K. Prahalad and Gary Hamel [6, 8]. During the last two decades, most western firms have shrunk their businesses into a few areas—defined by the concept of *core competence*. This has grown from exiting product manufacturing to technology development as well. For example, in the automobile industry, not only are vendors expected to supply parts conforming to a certain design, they are tasked with developing the technology as well. In its day-to-day application, core competence has come to mean defining a narrow range of products and services seen as the "core business" of a corporation and exiting anything that is seen as "non-core". During the same timeframe it was closely coupled with "outsourcing" whereby corporations, usually advised by management consultants, identified processes and services as core vs. non-core and divested the latter. This led many companies to exit entire business areas and shrink their portfolio of products and services.

The concept advocated by C.K. Prahalad and Gary Hamel, however, was *core competencies*. The two authors defined this as "the collective learning in the organization, especially how to co-ordinate diverse production skills and integrate multiple streams of knowledge". They envisioned the core competencies of an organization as the roots of a tree [6, 8]. These roots form an organization's core products which yield "end products", which are the goods or services delivered to the customer. Viewed this way, an automobile company should view its core

competency as engineering and product development. Perhaps finance, marketing are not its core competencies and can be safely outsourced to an outside vendor whose competencies lies in accounting, finance, and marketing, respectively. However, the design of engines, transmissions, brakes, and ongoing technology development in these areas are part of the firm's core competency of engineering. The end product is not the core competence of a corporation; it is merely a manifestation of its core competency. Core competency is abstract; core competence is a narrow physical manifestation of core competency.

Immunosuppression as a Core Competency

The conventional trend has been increasing knowledge fragmentation in the form of sub-specialization in medicine. The author's own sub-specialization in neurology lies in the field of EMG and neuromuscular medicine. The practice of neuromuscular medicine involves a host of autoimmune neurological disorders like myasthenia gravis, Guillain-Barré Syndrome (GBS), CIDP, and inflammatory myositis. While these conditions are neuromuscular, the treatment of these conditions over time led to increasing familiarity with immunosuppression. Over time, the author developed an interest (as a dilettante!) in "autoimmune clinical neurology" and Parkinson spectrum disorders as a core competency. Conversely, the author does not identify muscular dystrophy clinics or autonomic disorders which are within the realm of neuromuscular medicine as a core competency. The following examples illustrate successful application of this core competency to the organization's mission despite the applications being in an entirely different sub-specialty area. Case examples 1 and 2 are examples of core competency. Case example 3 is an example of implicit knowledge gained during the course of clinical work with valuable application in a completely different context a few years later.

Case Example 1

NG is a 35-year-old woman who initially presented with new right hemisphere onset seizures with secondary generalization. Patient was discharged on phenytoin and levetiracetam. She required readmission to the hospital 48 h later with multiple recurrent generalized tonic–clonic seizures. Additionally, the recurrent seizures were associated with progressive confusion, amnesia, encephalopathy, and decreasing level of consciousness. This was also associated with personality changes of hyper-religiosity, hyper-sexuality, and auditory hallucinations.

Over the subsequent 2–3 days, despite maximal doses of levetiracetam and phenytoin, the patient continued to have severely encephalopathic behavior and multiple electrographic seizures and three clinically evident seizures. The patient underwent several MRI Brain scans with and without Gad which were normal. Electroencephalography (EEG) studies revealed fronto-temporal onset secondarily generalized seizures. The maximum temperature was 100.2 °F. CSF studies

revealed 23 mononuclear WBC/hpf, RBC 91/hpf, protein 29 mg/dL, and glucose 74 mg/dL. Viral PCR's for HSV, CMV, EBV, and VZV were negative. CT Chest Abdomen and Pelvis with IV contrast did not reveal the presence of any tumors. Three weeks later, a paraneoplastic panel showed abnormal titers of Anti Voltage Gated Calcium Channel Antibodies (VGCC) P/Q and N type. Anti-NMDA receptor antibodies were negative [9].

In the interval that viral PCR's and paraneoplastic antibodies were pending, she was treated for presumed autoimmune limbic encephalitis. This was initially accomplished using IVIG 2 g/kg in five divided doses. After completion of IVIG infusions, there was improvement in the EEG with considerable reduction in seizure frequency. She was then started on Prednisone 80 mg/day which was then changed to 60 mg/day at the time of discharge. She was maintained on Levetiracetam 1,500 mg Bid, lacosamide 200 mg Bid, clonazepam, and zonisamide 200 mg QHS.

Successful long-term treatment of this patient required durable immunosuppression and secondary management of epilepsy. While this is a case of epilepsy which is well beyond the neuromuscular scope of practice of the author, the familiarity with immunosuppression necessitated contributing a lead role in the organization's responsibility to her long-term management. The epilepsy component was understood to be secondary. The principles of disease lifecycle management (DLM) were applied.

The patient and family were seen back in neuromuscular clinic for intermediate term care of epilepsy a few weeks after discharge. At the time of her follow-up visit, she demonstrated severe confusion, memory loss, and encephalopathy. Based on her initial response to IVIG, she was treated with a second round of infusions with 2 g/kg in four divided doses which was successfully tolerated. She was weaned off clonazepam and maintained on levetiracetam and zonisamide. She was continued on prednisone 60 mg/day with a very gradual taper down to 10 mg over 6 months. During this time, there was a gradual improvement in her mental status with steadily improving concentration, memory, and return to day-to-day function. A second line adjunct steroid sparing agent like azathioprine was strongly contemplated, but this was abandoned due to the patient becoming pregnant into the illness [9].

During the pregnancy and resolving autoimmune limbic encephalitis, her care was closely coordinated with her obstetrician. Zonisamide was weaned and discontinued and patient maintained on monotherapy with levetiracetam which is felt to be the safest in pregnancy. She was closely followed by her obstetrician and primary care physician for development of gestational diabetes mellitus given the continued need for prednisone in pregnancy (since azathioprine was not started). She remained seizure-free throughout pregnancy and puerperium with the dose of prednisone weaned to 5 mg/day. Over the next 1 year she regained her mental status with the ability to drive and resume her work as a healthcare provider in a nursing home. Three years later, she remains on prednisone 5 mg every other day and levetiracetam 1,000 mg twice daily with one breakthrough seizure experienced when she accidentally stopped both her medications. She went through one more pregnancy and delivered a second healthy baby between the second and third years of her illness.

Case Example 2 and 2.1

The following cases illustrate two examples of myasthenia gravis through which a better understanding of immunosuppression was gained as a core competency. The unusual severity of these cases was a very valuable learning experience which helped many other cases considerably.

Case Example 2

RW is 68 y/o male with new onset acetylcholine receptor-positive myasthenia gravis approximately 2 years ago. He presented as an inpatient with severe shortness of breath, mild ptosis, diplopia, moderate neck weakness, and mild proximal weakness. At his initial admission, he did not need rescue therapy. He was started on prednisone 60 mg/day and discharged; however, he had to rush to a nearby emergency room a few days later severely short of breath which required intubation. Following transfer, he was treated with IVIG initially. However, since there was no improvement 2 weeks later, plasmapheresis was initiated. He was restarted on prednisone after the fourth session of plasmapheresis and made a reasonable recovery to be successfully extubated. CT Chest did not reveal a Thymoma. He was discharged on prednisone 60 mg/day and pyridostigmine, but returned to clinic 4 weeks later severely short of breath with head drop and dysphagia. He was readmitted and treated with plasmapheresis and was continued on high-dose prednisone without improvement. He also underwent a thymectomy which showed a benign multiloculated cyst. At the end of five sessions of plasmapheresis since he continued to have severe bulbar weakness which was poorly responsive to multiple sessions of plasmapheresis, IVIG, and high dose prednisone, the decision was made to treat him with Rituximab 1,000 mg for two doses (off label) given 2 weeks apart. After discharge he was started on Mycophenolate Mofetil (MMF) 1,000 mg twice daily and maintained on a slow prednisone taper. Over the next 6 weeks he demonstrated steady improvement in strength with improvement in bulbar strength which enabled return to a normal diet from prolonged tube feeds and mechanically soft diets. He tolerated the MMF well which enabled a steady taper on prednisone down to 5 mg/day over the next 6 months. He has no symptoms from myasthenia gravis, leads a very active lifestyle, and save mild osteopenia does not have any other significant side effects from his ordeal.

Case Example 2.1

JBW is a 35 y/o female with MUSK (muscle-specific tyrosine kinase) antibody-positive myasthenia gravis. She presented with severe bulbar weakness and ventilatory failure in December 2010. She had an excellent response to IVIG and was discharged on Prednisone 20 mg/day. Follow-up care was difficult due to weight

gain from prednisone and continued smoking for many months with frequent bronchitis that complicated her respiratory function. She remained stable through 2011 on prednisone 10 mg/day but started experiencing difficult to treat crisis in 2012, some of which were exacerbated by family stress. This time, she had a modest response to IVIG. She was started in MMF 1,000 mg Bid as adjunct therapy since she had weight gain with prednisone and was poorly compliant with any short-term increase in steroid dose. A few months later, she started experiencing another round of decline which responded poorly to plasmapheresis. She was then treated with Rituximab 1,000 mg for two doses (off label) 2 weeks apart. Her MMF was increased to 1,250 mg Bid. She developed a mild neutrophilic persistent leukocytosis (WBC Count around 12,000) which was investigated by hematology and felt to be medication-related and benign. She declined steroids. Following treatment with Rituximab and maintenance with MMF 1,250 Bid, she developed steady improvement to the point of having no symptoms. She missed several follow-up appointments volitionally because of her asymptomatic status. Approximately 1 year ago, she stopped taking her MMF but remained in stable remission till recently when she started experiencing mild bulbar weakness when she called to resume treatment.

These cases present tough challenges presented by two types of myasthenia gravis—the classic AchR antibody-positive type and the MUSK antibody type. These patients did not respond to classic treatments such as prednisone and MMF. They did poorly with IVIG and plasmapheresis with persistent severe weakness involving bulbar and ventilatory muscles. The unusual course presented by these cases provided insights into prednisone unresponsive cases which require therapy with Rituximab. These cases also showed that once control is gained with Rituximab, remission can be maintained with MMF and low-dose prednisone and a prolonged remission can be expected. These insights were subsequently used with other difficult to treat conditions like stiff person syndrome.

Case Example 3

This case was encountered 2 years after case example 3 in Chap. 8. Implicit knowledge gained from that experience was applied to this case. SCT is a 44-year-old male who developed an upper respiratory tract infection followed by progressive weakness, numbness, and tingling involving his arms and legs. He presented to an outside hospital with rapidly progressing weakness, ventilatory failure requiring intubation, and mechanical ventilation. He was diagnosed at an outside hospital with GBS. He had prominent abnormalities with heart rate, blood pressure with frequent fainting spells from severe drop in blood pressure suggesting autonomic involvement. He was treated with IVIG and after extubation showed a profound, persistent alteration in mental status. He was transferred to our medical

center with concerns that the initial disorder was not GBS; rather it was Porphyria which can manifest with severe neuropathy and mental status changes.

Guillain-Barré classically affects only the peripheral nerves; behavioral abnormalities would be very rare in this condition. He had been empirically treated for porphyria without much improvement. Since he was many weeks out of his initial illness but nevertheless debilitated, blood and urine levels of porphyrins (the main abnormality in porphyria) would be expected to be normal, therefore not helpful. By then he had spent over 2 months in various hospitals. Spinal fluid examination showed albumino-cytological dissociation (CSF protein: 160 mg/dL without cells) but was normal otherwise. MRI Brain studies and serial continuous video EEGs were normal without evidence of seizures. CT Chest Abdomen and Pelvis was normal as well, excluding any obvious tumors.

On assuming care of this patient, there was an immediate sense of déjà vu from prior experience with case example 3 in Chap. 8. The same rigorous solution approach based on prior experience gained with Mr. ALS was applied. The generic-altered mental status was refined to make the following observations—he had prominent visual hallucinations, sleep problems, and was essentially acting out his dreams. The *Where* localized to the brainstem. The *why* was more difficult to answer. While porphyria can cause exactly the same symptoms, a repeat nerve conduction study confirmed demyelinating features and secondary axonal damage. Porphyria, on the other hand, is a primarily axonal motor neuropathy. Therefore, porphyria was not the preferred hypothesis but still nagging enough to preserve its place as the front runner.

The next *Why* asked if there is a link between GBS and brainstem malfunction? The answer is *yes*. Bickerstaff's encephalitis can cause brainstem involvement in GBS with decreased consciousness and visual hallucinations [10]. It is likely this represents a component of brainstem demyelination and inflammation. A more directed and refined literature search based on this problem formulation uncovered rare but similar presentations [11]. Autonomic dysfunction and high spinal fluid protein were the risk factors, all of which he had [11]. Antipsychotic medications recommended in these papers had already been tried with him and did not work at all. Based on prior experience with patient ALS in case example 3, Chap. 8, clonazepam was entertained as a potential solution. However, clonazepam should not be used in porphyria and belongs to the class of medicines which should be avoided in people with porphyria. After a lot of discussion with the family, clonazepam was started with almost immediate resolution of his symptoms. Over the next several weeks, results of autoantibody testing with paraneoplastic antibodies, anti-NMDA receptor antibodies returned negative. The patient made a successful recovery and regained complete ambulation and autonomic function over the next 6–8 months. He required clonazepam for several months after discharge for sleep and preventing visual hallucinations, but after complete clinical recovery this was eventually discontinued.

Complexity

Let us start with some trivia: Who invented the telephone? Alexander Graham Bell. Who invented the airplane? The Wright brothers. Who discovered penicillin? Sir Alexander Fleming. Who invented the jet engine? Sir Frank Whittle. Now extending this theme further—Who invented the Boeing 787 Dreamliner? Reference [12] provides valuable information on major suppliers for the Dreamliner. An exhaustive list of suppliers is beyond the scope of this chapter, but a cursory examination shows that the following competencies are involved: project management, design, materials, components, airframe systems, avionics, power systems, production, and testing [12]. Under the category of "structural components" alone, there are 28 major suppliers. The supply chain extends across dozens of countries, languages, and cultures. Similarly, answers to the same question are extremely difficult to find for everyday dependable technologies like cellular phones, trains, and automobiles.

Therefore, as complexity of products increases, it becomes extremely difficult to be the lone inventor. Successful, dependable, products require a harmonious integration of dozens of competencies, each of which is a successful blend of domain knowledge and manufacturing processes. While a single name can be the product leader or bring exceptional brilliance to a single great competency, it would be extremely difficult for that one person to provide knowledge and skills across an inventory list of millions of parts and services.

Therefore, the only way such great feats can be achieved is through teamwork. Single individuals originate ideas, which are converted into tangible products by a team effort consisting of work groups. Work groups collaborate to form divisions. Divisions amalgamate to form organizations. Sometimes a single organization draws different skills for the same product across different countries and languages. The European airplane manufacturer Airbus SAS is such an example; the entire effort is chiefly divided between France, Germany, the United Kingdom, and Spain and other countries of the world. The following lecture from Airbus' former Managing Director Jean Pierson delivered in 1991 emphasizes the existential need for teamwork [13]. "Airbus Industrie stands as a symbol of what Europe can accomplish when it combines its forces around a common project. Our products come in over 100 different colors—the colors of our customers around the world." Mr. Pierson saw Airbus not merely as an organization but as a powerful motivator for generating wealth, "the wealth that comes from skills retention, employment and career opportunities, import substitution, export earnings." He emphasized the multicultural spirit of Airbus which summed up the organization's guiding principles. "The determination of the partners to keep the damaging demons of intra-European rivalry at bay was a key factor in the success of Airbus Industrie. It is in the interests of Europe that this determination should prevail. If there could be one lesson. . .to be learned from the Airbus Industrie experience, it would be that co-operation is the key to prosperity and that there simply is room no more for narrow nationalistic endeavors [13]."

Therefore, for organizations to deliver complex, dependable products, highly talented individuals need to collaborate within and outside organizations, even countries or perish. Why not in medicine?

Healthcare is a unique industry. It demands the economics, costs, and outcomes of mass production; however, it is delivered by skilled craft workers. Great self-importance, massive egos, and disrespectful behavior are not merely condoned but sometimes encouraged as a virtue to burnish individual or departmental reputation. This discrepancy makes managing the human element a very important one for efficient healthcare delivery. Developing core values, knowledge, training and delivering dependable services in a teaching institution can be successfully done using BB&T's principles. The following sections will discuss some aspects of training, skill development, teamwork, and mentorship which were learnt from BB&T's core values and applied for the knowledge development of students, residents, and fellows with great results. We will start with teamwork first and address different aspects of training and skill development later.

Managing Complexity with Teamwork: Going Beyond Cliché

The practice of medicine in the new century is more complex than the old one. New understanding of diseases and new therapies have increased complexity to the extent that it is exceedingly difficult for one individual to meet the needs of many patients. As an example, consider a diabetic patient with renal failure who has a transplanted kidney, is on immune-suppressing medications presenting with worsening numbness of the feet. The possibilities in this situation are challenging—it could be a result of toxicity of drugs used for immune suppression after transplant vs. part of diabetic neuropathy or a new problem relating to infection or something else altogether. If the problem turns out to be medication toxicity from a commonly used transplant medicine called tacrolimus, the treatment involves careful coordination of medication changes between the nephrologists, transplant pharmacists, and neurologist who has to discern between these possibilities. A micro-plan can be created for this situation:

1. Neurologist provides evidence that nerve symptoms are due to transplant medication toxicity and not due to preexiting diabetes mellitus to the nephrologist and transplant pharmacist.
2. Transplant pharmacist adjusts dosing of tacrolimus or checks for interactions with other medications that may have precipitated the toxicity.
3. Nephrologist keeps a close eye to prevent organ rejection. If there is any worry of rejection, he institutes alternative measures to prevent the same.
4. The patient communicates back with the care team about any improvement or deterioration with the changes to medications.
5. Patient is reviewed in clinic in a reasonable time frame to confirm or reject the working diagnosis—usually 2–3 weeks.

6. Based on response, adjustments are made till the best possible outcome is achieved preventing neuropathy or worsening of neuropathy and preserving kidney function.

No single physician can manage this situation alone. This situation is seen frequently in different forms (sometimes it is altered behavior, seizures, or tremor from tacrolimus) and managed appropriately. This scenario details some of the key features of a successful team. Teamwork is discussed in a number of different management textbooks and workshops. It is highly promoted in slogans and exhortations, which implies it is a difficult occurrence in the natural environment. From the author's experience, in clinical medicine, a successful team has the following characteristics:

1. A team is inspired by core values, mission objectives to develop knowledge and provide service delivery. It centers on the patient. A team has a clear goal and purpose.
2. It is composed of team members and a team leader who share goals, responsibility, and ownership. The team leader may change depending on different phases of the problem.
3. The members of the team bring different skills. Each brings a domain expertise but has an understanding of the consequences of his actions on the other members. In applying the sum total of these skills in a coordinated, cooperative manner lies the ultimate goal.
4. There is interdisciplinary "overlap" between skills; in the example above the neurologist appreciates (a) the challenges faced by the nephrologist and transplant pharmacist and (b) is familiar to some extent with the transplant process and medications used for preventing rejection. He assists the two in trying to save a precious organ. The reverse is also true.
5. Each member of the team brings reality-based, objective, independent thinking and maximizes his skills and productivity.
6. There is clear understanding of individual roles and responsibilities.
7. There is clear communication in subjective and objective terms on intermediate milestones.
8. There is frequent review of where the team stands in relation to its ultimate goals. Shortfalls are addressed early to prevent a cascade of failure.
9. Success, failure, and responsibility are shared across all members. Blame is not assigned for failure, rather during review—how to prevent this in future or how to do it better are addressed.
10. All members of the team are equal with only mutual respect and collegiality between members.
11. There is total transparency and honesty between team members. Setbacks are openly shared and corrective actions solicited to prevent team failure.

A successful team develops processes to achieve its goals. Intermediate products and services are passed among different members of the team to carry the process forwards towards the ultimate goal. This requires successful hand-offs between

team members. A few successful teamwork examples will be presented here where these rules were met with superior outcomes. These will be followed with a few unsuccessful examples and why they failed.

Case Example 4

Continuing case example 4, EWS initially presented in Chap. 6 a patient who was initially evaluated for statin myopathy, but was determined to have paraneoplastic Lambert Eaton Myasthenic Syndrome (LEMS) based on EMG findings, CT Chest findings, and positive VGCC. Successful management of his condition required concerted, coordinated effort to deliver dependability. The following goals of care with responsible team members were created as shown in Fig. 10.3:

1. Establish the cell type of the tumor.
   (a) Cardiothoracic Surgeon.
   (b) Pathologist.

Fig. 10.3 Management of case example 4 from Chap. 6, a patient with paraneoplastic Lambert Eaton Myasthenic Syndrome (LEMS)

2. Aggressive treatment of Small Cell Lung Cancer using chemotherapy and radiation.
   (a) Medical Oncologist and supporting team (Nurses and medical assistants).
   (b) Radiation Oncologist and supporting team (Technologists, nurses, and medical assistants).
   (c) Pharmacist and supporting team (pharmacy technicians).
   (d) Tumor Coordinator.
3. Treatment of LEMS.
   (a) Neurologist.
   (b) Obtain and provide 3,4 diaminopyridine (3,4 DAP) according to research protocol. Periodic monitoring for side effects. Theresa Johnston Crews, RN; Dr. James Caress and Dr. Michael Cartwright.
4. Monitor for recurrence using CT scans and PET scans.
   (a) Radiologist and supporting team (technologists).
   (b) Nuclear Medicine and supporting team (technologists).
5. Supportive therapy.
   (a) Physical Therapists to help with physical debility.
   (b) Occupational therapists.
   (c) Nutritionist to maintain adequate nutrition through chemotherapy and radiation therapy.

Since EWS had become bedridden, from a neurological standpoint he was initially treated with IVIG to modulate the immune system for symptomatic relief. The only drug that is known to help is called 3,4 DAP which is available on compassionate use grounds from Jacobus pharmaceuticals. The approval and supply of this drug requires blood work monitoring and following an FDA protocol which had to be submitted before the drug could be supplied. This responsibility was assumed by my senior colleagues Dr. James Caress, Dr. Michael Cartwright, and ALS clinic coordinator Theresa Johnston Crews R.N. based on their experience with such protocols in the past. Jacobus pharmaceutical supplied 3,4 DAP free of charge for the patient. The dose was gradually increased up to 15 mg four times a day with significant improvement experienced by the patient. He did not develop any side effects but underwent periodic monitoring of blood counts, electrolytes, liver enzymes, EKG.

He was treated for the small cell lung cancer by his medical oncologist. He had a great response to chemotherapy. This was followed by radiation to the brain and spine according to standard protocols with excellent response. During one of his 3,4 DAP safety visits, he developed a deep venous thrombosis in his legs for which he was treated with lifelong anticoagulation. For most of this time, he was managed by his medical oncologist and radiation oncologist and recovered completely in terms of his LEMS. He stopped 3,4 DAP by himself around 1 year later since he no longer needed it. The median survival for extensive small cell lung cancer is 10 months; at

3 years, the patient is still alive and described himself to his oncologist as the "best he has felt" at the time of his last review visit.

This is an excellent example of teamwork exceeding the standard of care results. The team involved the ALS coordinator who obtained, managed, and followed up on 3,4 DAP for symptomatic relief. The long journey that started with the neurologist quickly involved many different specialists who later became the focus of care. The team leader quickly evolved to be the medical oncologist with supporting roles from the neurologist, cardiothoracic surgeon, pathologist, radiation oncologist, radiologist, and ALS clinic coordinator, Dr. Caress and Dr. Cartwright.

An effective care team was formed. The goal was clear—"Saving patient EWS". The initial team leader was the neurologist, but since the focus of the problem quickly evolved to managing lung cancer from weakness, leadership quickly shifted to the medical oncologist. The cardiothoracic surgeon and radiation oncologist provided supportive treatment for the goals directed by the medical oncologist since the treatment of small cell lung cancer is non-surgical. Each of these specialists has a different skill but lung cancer is a common area with overlapping expertise; each understands what the other is doing and what the challenges they are facing. Each appreciates his role in a wider problem and contributes to the larger picture.

Case Example 5

EDB is a 54 y/o male with acetylcholine receptor antibody-positive myasthenia gravis. His symptoms were mainly drooping of eyelids and double vision. He had some shortness of breath which was attributed to myasthenia gravis. He was otherwise strong. His co-morbidities were obesity, high blood pressure, obstructive sleep apnea, and borderline abnormal blood sugars. A chest X ray revealed low lung volumes, breathing tests showed a restrictive lung defect, and a decision needed to be made on treatment since the double vision was affecting his work as a machinist. On examination he had mild fluid accumulation in his lungs and feet. He additionally had sleep apnea, excessive daytime fatigue, and headaches. An initial trial of symptomatic treatment with pyridostigmine had been ineffective. There were two main concerns which needed to be addressed:

1. Improvement in ocular symptoms to enable him to work as a machinist.
2. The pulmonologist felt his shortness of breath was in most part due to diaphragmatic weakness from myasthenia gravis (and not obesity). He recommended treatment for the same.

The main dilemma with initiating treatment with steroids was worsening blood pressure, fluid retention, blood sugars, and further weight gain which would worsen sleep apnea and perhaps contribute to shortness of breath by worsening obesity. However, since it was getting progressively difficult for him to work and he was getting dyspneic easily, we agreed on a treatment trial with close monitoring to see if the myasthenia gravis component of his symptoms would improve. This patient

was seen during the author's earliest days as an attending physician before a lot of the elaborate theory for managing these patients using PSSA and failure modes and effects analysis (FMEA) was developed. This was done by establishing a team effort with a nutritionist, primary care physician, pulmonologist with the following goals and responsibilities:

Team Goals: 1. Improvement in ocular symptoms. 2. Improvement in shortness of breath if due to myasthenia. 3. Minimize side effects of steroid therapy.

(a) The nutritionist provides the diet recommendations to prevent worsening obesity.
(b) The primary care physician helps with monitoring and treating hypertension, blood sugars, cholesterol, fluid retention with diuretics to mitigate steroid side effects.
(c) The pulmonologist monitors his breathing, sleep apnea, checking the data on the CPAP machine to see if it is improving or worsening.
(d) The neurologist would monitor for neurologic improvement and decide changes in dosing with anticipated improvement. Since this was being initiated by a neurological condition the neurologist would be the team leader.

The team skills and competencies brought to bear on this patient are shown in Fig. 10.4.

This case predates the steroid information sheet and nutrition sheet, but a checklist of PPD to rule out tuberculosis, CT Chest, calcium, and vitamin D to prevent bone loss when on steroids, acid suppressing medications such as omeprazole were followed. He was started on prednisone 60 mg/day following the steroid checklist. The patient was reviewed 6 weeks later. He had actually lost 25 lb while on steroid treatment. His eyes were completely normal. Addition of a low dose of

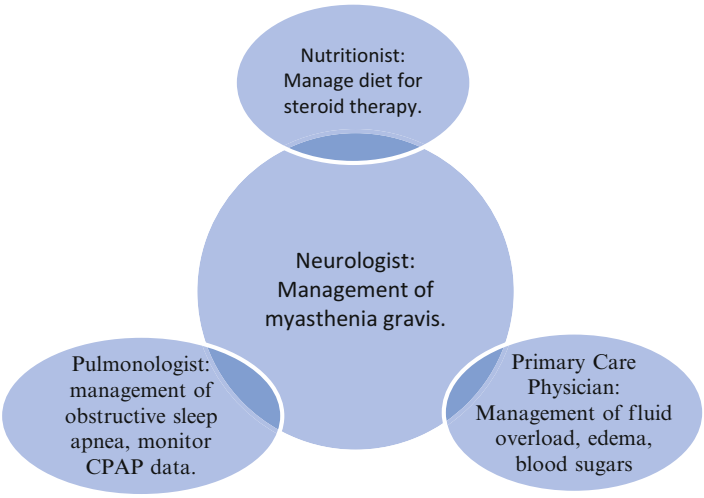

Fig. 10.4 Team skills involved in case example 5

diuretic, changing the dose of his blood pressure medications by his primary care physician, had prevented hypertension from getting worse. The pulmonologist noticed improving lung function and better sleep apnea requiring lower pressures on his CPAP settings. This team was established across two different hospitals and worked because of everything coming together, especially communication, mutual respect, and equality of team members.

These examples are more the exception than the rule. Unfortunately, hubris is all too common and it is difficult to form such fruitful teams. The next few cases illustrate the challenges which are seen all too commonly at most medical centers. Since this is a book about what works, these failures are presented in summary to highlight how a team effort fails when all the criteria described above are not met.

Failure of Complexity Management

The following examples show the failures that are all too common when successful teams cannot be formed.

Case Example 6

LGJ is a 40 y/o, overweight, diabetic female presenting with numbness, pain, and tingling in her feet. Symptoms had started at an unusually young age in the early 30s. She also had back pain and vague urinary symptoms ranging from urge incontinence to retention. Nerve studies over the years had at best shown minimal abnormalities with a diagnosis of diabetic polyneuropathy. Physical examination was normal save absent ankle jerks. A repeat NCS/EMG was ordered which showed the results in Table 10.1.

A review of the EMG findings shows only minimal abnormalities—the sural sensory response is 6 μV (normal > 6 μV). This is consistent with longstanding diabetes mellitus and can cause a painful neuropathy. However, given the severe back pain and urinary bladder symptoms an MRI Lumbar Spine was ordered looking for any congenital spine abnormalities or severe degenerative arthritis. The images are shown in Fig. 10.5.

The initial MRI Lumbar Spine was performed without contrast. The astute radiologist who read these images noticed unusually thickened nerve roots and called the author. He had never seen anything like this before, but based on imaging findings this could be either a form of Charcot Marie Tooth or it could be acquired, inflammatory as in CIDP. The genetic neuropathies are untreatable. If it is inflammatory, it would need treatment with steroids, IVIG, or plasmapheresis, each of which presented challenges in this patient given diabetes mellitus and obesity. The distinction between the two would be difficult by all simple methods, including a lumbar puncture looking at the spinal protein.

Table 10.1 NCS/EMG findings for case example 6

Nerve and side	Latency (ms)	Distance	Amplitude (mV)	Velocity (m/s)	F waves (ms)
Peroneal motor left Ankle	4.1 (<6.1)	90 mm	11.4 (>2)		
Fibular Head	9.0		10.8	51 (>41)	39.7 (<56)
Pop Fossa	10.3		10.5	63	
Tibial motor left Ankle	4.5 (<6.1)	80 mm	5.1 (>3)		
Pop Fossa	10.3		2.1	59 (>41)	59 (<58)
Sural sensory left	2.3 (<4.2)	140 mm	6 μV (>6 μV)		
Muscle and side	*EMG findings*				
Left tibialis anterior, medial gastrocnemius, vastus lateralis, long head of biceps femoris	Normal insertional activity, absent spontaneous activity. Normal motor units showing normal recruitment and fair activation				
Left L4/5 lumbar paraspinals	Normal				

Standard normative data are presented in brackets

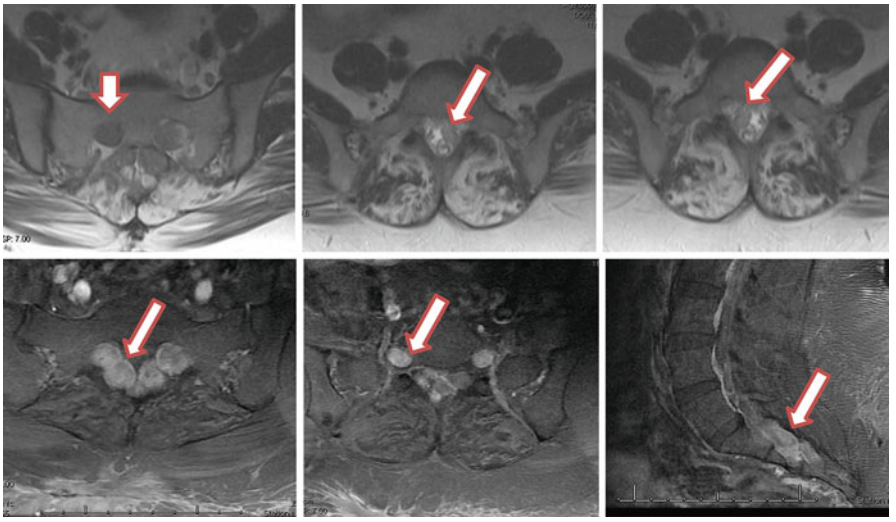

Fig. 10.5 MRI Lumbar Spine images for case example 6. *Top row*: T2-weighted images showing thickened nerve roots (*arrows*). *Bottom row*: subsequent gad-enhanced MRI Lumbar Spine showing avidly enhancing nerves indicated by *arrows*

The discrepancy between the MRI findings and EMG findings was most unusual. CIDP is diagnosed based on nerve conduction criteria, all of which were normal in this patient. CMT is also expected to show severely abnormal nerve conduction studies. Under these circumstances, performing a nerve biopsy of the sural nerve would be low yield, since the nerves were electrically near normal. A careful,

specific search of the literature was performed. A very similar case was reported in [14]. The diagnosis could be established by a nerve root biopsy since all the inflammation was in the nerve roots and not in the feet which is the traditional site for biopsy. Based on [14] an idea worth considering was decompression of the spine with concomitant nerve root biopsy which would allow more space for the swollen nerves to pass through, thus reducing compression on the inflamed nerve roots. This presented a reasonable plan which could potentially help this patient.

A request for a nerve root biopsy was rejected by the neurosurgeon. The neurosurgeon himself could not be directly approached, either by email, telephone, or for a meeting. All requests to his office, including faxing the prior case report, were handled by the nurse who felt frustrated she was in the middle of this and CIDP was not her job description. A request for an appointment was declined. If the patient had an MRI with contrast, then he might decide to see her; despite the patient living 4 h away and being a person of modest means, an integrated appointment (scan followed by clinic visit) would not be extended. If he felt he wanted to see the patient after the scan, he will offer an appointment. At no point could the author speak to the surgeon himself.

A referral was made to a top-tier university hospital in the same region. The patient took all her images, met the neurologist and neurosurgeon the same day based on the request and recommendation of the author. She carried the reprint of [14] which was reviewed by that institution. The neurologist and neurosurgeon established a team with the objective of establishing the diagnosis and performing spine decompression for symptomatic relief. A nerve root biopsy performed at the time of spine decompression confirmed the diagnosis of CIDP with post-operative relief of pain and tingling symptoms. Follow-up treatment included intermittent IVIG, steroids, and symptomatic treatments, all performed at the other institution. The economic benefits reaped by the other institution alone stand at several tens of thousands of dollars, the reputation cost cannot be measured since all the credit went to the second institution who helped her.

Applying the above rules, why did this fail? A team could not be formed. The surgeon did not understand the medical needs, refused to communicate except through his nurse who was not familiar with the demands of the disease and its treatment. He did not appreciate the limitations of the demands placed by him. Equality among team members was not met and the entire effort collapsed. A team could be formed at the other institution who bought their skills together in a coordinated manner and succeeded with consequent economic and reputation benefits.

Failed Management of Complexity: Case Example 7

SH is a 53-year-old female who unfortunately had her right leg amputated at the hip for treatment of Ewing's sarcoma as a teenager. For several years she had right hip pain which had been evaluated by several doctors, but it had been worsening causing her to come to the ER twice. She needed treatment with opioids twice

with temporary relief. Her referring physician wanted to know if anything could be done. She had numerous MRI scans to her lumbar spine, all of which were normal. Applying the rigorous process-driven approach to diagnosis, the main concern was whether she had a stump neuroma. This is an often painful tumor that grows in nerves or nerve stumps, sometimes many years after initial amputation or injury. An MRI Pelvis was requested for the same which showed a growth at the stump of the amputated leg concerning for a neuroma.

Surgical evaluation was requested but immediately rejected stating this should be managed medically. This was discussed with the patient who most kindly accepted. She was put on increasing doses of gabapentin and pregabalin, common drugs used to treat neuropathic pain with poor tolerance and worsening side effects. The pain worsened over the next few months. It was becoming increasingly obvious she may need surgery. Repeated requests for surgical evaluation were declined. A referral was made outside the institution to the surgical department of a top-tier university medical center where a specialist agreed to see her. A repeat MRI Pelvis was ordered which showed a much larger tumor than the prior one concerning for malignancy. This was immediately operated upon by surgeons at the second institution. The excised tissue was confirmed by the pathologist to be a malignant peripheral nerve sheath tumor (MPNST). The dollar cost is several thousand dollars; the reputation cost cannot be measured.

This too is an example of a failed team. A team could not be established because it was impossible to communicate needs and coordinate care. The surgeons did not appreciate the concerns of the physician, why surgery was requested—a rapidly enlarging swelling and severe pain causing frequent ER visits for the patient. The team failed at every level of the criteria needed for its smooth functioning. Hubris perhaps lies at the root of all failed teams.

Success and failure are self-reinforcing. The spirit of collaboration, respect for knowledge, and dedication to mission objectives inculcate respect in all concerned members of the team. One successful outcome lays the groundwork for future collaboration. Conversely, the damage from such failed teamwork is not merely specific to that incident but leads to future failure as well. Following these failed teams and inability to work on shared goals, multiple future surgical needs were addressed outside the institution to the nationally acclaimed institution. These sadly represent failed opportunities for the institution; however, a physician's greatest mission responsibility is to his patient.

Culture

At a deeper level, teamwork or the lack of one is closely linked to the culture of a particular profession or organization. While there are many definitions and perceptions of culture, a practical one is that advanced by Tom Tierney, author of *Aligning the Stars*. "A corporation's culture is what determines how people behave when they are not being watched" [6, 15]. Teamwork therefore results only from a culture

of contributing one's talents to problems or projects greater than oneself and a desire for continuous growth and learning. It is vital to the expansion of knowledge of an organization since all new ideas cannot be self-generated. Knowledge creation in organizations was studied extensively by Ikujiro Nonaka and Hirotaka Takeuchi [7]. The authors outlined a four stage process by which an organization develops knowledge: SECI which stands for socialization, externalization, combination/creation, and internalization. They termed an expression "Ba" to describe the meeting place of minds, which can be physical as in a lounge or coffee shop or can be mental where experiences are shared to expand knowledge and learning within an organization [6, 7].

Organizations which fail in teamwork therefore are generally unable to proceed beyond minimum complexity projects or first-order processes since they are unable to synergistically integrate diverse domain expertise in a coordinated manner. In the knowledge-driven economy, failure to innovate threatens survival. Therefore, teamwork and a culture of knowledge are essential for survival of knowledge-driven organizations.

Great teamwork blends into great customer service. The great customer service experienced by the customer at the end of the journey is a carrying forward of the great customer service at intermediate steps of the way. For example, the same nerve tests need to be elaborated differently for different physicians to ensure customer satisfaction. An EMG on a weak arm for an orthopedic surgeon after a traumatic injury to the nerve should address the level and severity of the nerve injury and whether any repair is taking place. This is important for surgical decision making. For more general applications, this information is perhaps redundant. For a rheumatologist treating a patient with steroids for muscle inflammation, information on whether the EMG shows less inflammation than the prior one suggesting effective treatment response is informative. Biopsy information also is important. Such a customer-focused team approach is essential in today's world for effective medical problem solving. Each professional must form a bridge to the next link in the chain of care.

Training and Skill Development

The training of medical students, residents, and fellows is a very well-researched area. This section will describe some key aspects learnt from industry, especially BB&T which was applied to selected trainees in neurology. The medical curriculum teaches inductive learning very similar to the FMEA methodology. Skill development can therefore be approached from two viewpoints—that of developing Decision Making Skills and Psychomotor skills. Being a physician and not a surgeon, the focus will be on the former. The author's teaching style generally involved discussing individual medical cases up until that point.

Using the BB&T model, a process-driven approach was adopted for training fellows. This prevents patchy knowledge development. A micro-plan for fellowship training was developed as follows:

1. Mission Objectives:
   (a) Broaden understanding of peripheral nerve, neuromuscular junction, and muscle diseases.
      (i) Develop diagnostic capabilities.
      (ii) Develop treatment skills.
   (b) Develop psychomotor skills necessary for performance of nerve conduction studies and EMG.
   (c) Secondary Objectives: Improve understanding, co-management of related fields in neurology—movement disorders, physical medicine, and rehabilitation and general neurology.
2. Clinic Approach
   (a) See the patient in 30 min to complete a thorough history, physical, review medical records, and most importantly develop a case formulation.
   (b) Develop a diagnosis and differential diagnosis prior to discussing the case with faculty. Use reasoning tools like FTA, Graphical methods, Byzantine framework, and any other formulation as appropriate.
   (c) The patient will be seen and examined together after initial discussion. All findings and diagnostic considerations will be reviewed.
   (d) Based on diagnosis, appropriate follow-up reading will be assigned. For example, if patient is felt to have LEMS, a review paper will be provided to broaden understanding.
   (e) At biweekly intervals, shortfalls in diagnosis and treatment from both faculty and trainees will be assessed and corrected.
3. Reading List (too numerous to list here, but an integral part of the training process).
   (a) The reading list would include review papers surveying disease at all levels of the peripheral nervous system—from anterior horn cell to nerve root to nerves to neuromuscular junction to muscle disorders.
   (b) Treatment of neuromuscular disorders, especially autoimmune disorders.

This approach reduced variations in what is taught and what is omitted to different postgraduate trainees. Everyone is provided with a reading list for inductive learning and case formulation sessions to develop deductive reasoning. Once satisfactory progress is made in this direction, treatment ability is developed in the trainee. The approach to EMG is similar, a brief reading list to understand theory and the spectrum of what is being sought by doing the test followed by a 3-month period of doing tests on patients to develop the skills for doing it independently. “Backwards integration” or “vertical integration” is heavily encouraged; the same

trainee is encouraged to take the train of thought forward—see the patient in clinic followed by do the EMG on the patient you have seen and finally integrate clinic and EMG together to see if the expected correct diagnosis was made or whether there is any shortfall. This approach also encouraged problem ownership—following a clinical problem from beginning to end in terms of diagnosis and treatment.

During the 1 year of training, skill development happens in four distinct phases shown in Fig. 10.6. This is very similar to the BB&T program.

During the initial phase, the trainee broadens his theoretical knowledge of neuromuscular disease. This involves reading review papers on commonly encountered clinical problems such as myasthenia gravis, GBS, CIDP, ALS, Inflammatory myopathies, and Muscular Dystrophies. There is a better understanding of molecular foundations, specific discriminating features of diseases, and options available for treatment. Concurrent with this phase is psychomotor skill development—how to perform nerve conduction studies and EMG accurately and efficiently. During this phase, there is a steady improvement in knowledge and skill from repeated clinical application and performance of procedures. This phase usually lasts up to 6 months. In phase III, independent diagnostic capabilities are consolidated and great progress is made in terms of planning treatment and mitigating side effects. In the last phase, great emphasis is placed on independent decision making and treatment planning. Patient ownership is greatly emphasized so that the patients seen in the capstone phase are essentially in the care of the trainee with the author playing only an advisory role.

The above approach leads to development of explicit and implicit knowledge over time. Shared knowledge, shared experience, shared values help the transformation from trainee to independent, rational, objective thinker. The explicit

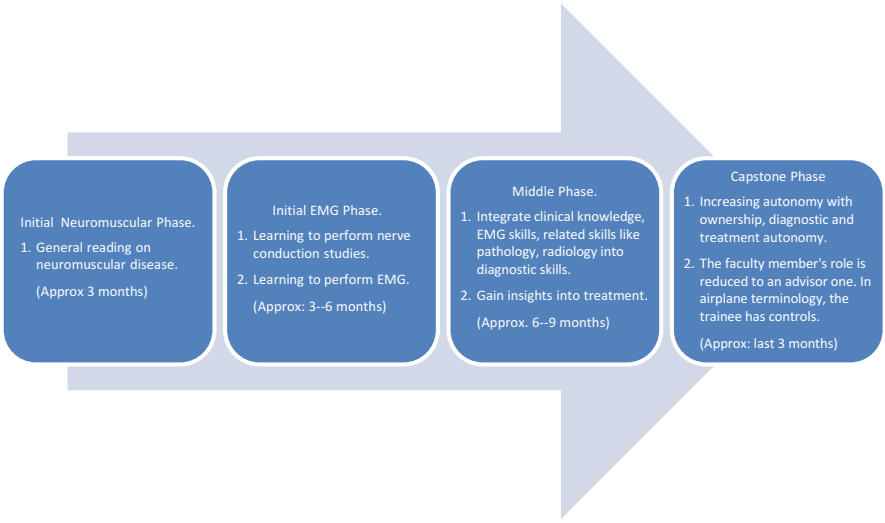

Fig. 10.6 The four distinct phases of subspecialty training

knowledge development approach shown above often leads to a great sense of problem ownership, cooperation, and respect between the trainees and the author. This approach was greatly successful at least 50 % of the time based on independent reviews and feedback provided to training directors. (The author contributes solely to clinical training.)

The end objective is to combine decision making skills and psychomotor skills into domain expertise, knowledge, and insight. This journey is completed to different extents with different trainees depending on their interests, goals, and objectives. For motivated trainees, once they attain sufficient training in nerve and muscle disorders, the journey is continued to build domain expertise in related areas such as movement disorders. Though a different subspecialty, it is a closely allied domain to nerve and muscle diseases. The trainee is able to see movement disorders (resulting from dysfunction of basal ganglia), nerve, and muscle disorders as his core competency. Finally, once domain expertise is achieved—such as in a specialty like neurology or nephrology, the journey extends further outwards to form bridges with other related domains. For example, domain expertise in brain tumors from a neurological perspective can connect seamlessly to more general medical oncology to understand the similarities and differences between the behavior of brain and lung tumors.

The training of technologists and therapists too can benefit considerably if viewed from the angle of core competency instead of being restricted to a single procedure or skill. Skilled technologists are at the heart of performing many tests (such as CT/MRI scans, EMG) and therapeutic procedures. Labor costs form a significant fraction of the cost of a procedure. There are significant advantages to developing technologists' skills along a competency rather than a procedure. This can integrate several services with a single technologist, making it much cheaper to offer a service and improving the margins. For example, EMG and EEG are different but related areas. Technologists skilled in both are a much more valuable asset to the institution since it helps integrate businesses and improve the bottom-line at a time when reimbursements for EMG are declining. The competency required for this is an understanding of electrical potentials and their measurements which are common to both areas. Technologists therefore can be trained with competency in neurophysiology and sleep medicine. Similarly, ultrasound imaging can be seen as a different competency which can be applied to different organ systems based on requirement—cardiac (echocardiography) and vascular (venous dopplers, carotid dopplers, etc.). Viewing an organization's skills in terms of competency helps integrate diverse products and services which reduces costs and improves bottom-lines considerably.

Medical training is closely allied with mentoring. Mentoring has been a tradition in all the professions: law, music, management, sports, and medicine. Mentoring becomes vital in any field where knowledge needs to be consolidated into judgment, application, and mere knowledge of facts alone will not do. Mentoring is most effective when the guiding professional has walked the same path before and understands the challenges the younger trainee is grappling with. Mentoring forms a most vital aspect of medical training; it helps the trainee go from student to

professional. For mentoring to be effective, the communication process is bidirectional, the senior guide learns something from it as much as the trainee does. It is best performed with a flat management structure, without hierarchy and continues for many years beyond graduation.

Philosophical Perspectives and Conclusion

A small diversion is in order here. Some of these topics have been analyzed down the ages by the greatest thinkers and philosophers of our time. Forms of it were encountered in prior chapters as the teachings of W. Edwards Deming, Taiichi Ohno. Where does knowledge arise is at the core of epistemology. Lectures are given in medical schools and universities all the time. How do these lectures pass into knowledge? Perhaps a look at how we perceive any sensation helps understand this. Our senses constantly perceive all manner of information, the light wind on our skin, the paint in the walls. Will Durant expresses it most poignantly: "Sensation is unorganized stimulus, perception is organized sensation, conception is organized perception, science is organized knowledge and wisdom is organized life. Each is a greater degree of order and sequence and unity [16]." The pursuit of greater order, harmony, and unity leads to greater insight, expertise, and knowledge which is the true wealth of organizations. Our journey has now come a full circle; the importance of the pursuit of knowledge was advanced by Baruch Spinoza in the 17th century and introduced in Chap. 1.

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