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Darkness has finally fallen over the enclosed courtyard cafe adjacent to the luxurious hotel. The cool breezes, fed by the chilly Mediterranean Sea, have displaced the high daytime temperature that is so unusual this early in the Summer. The flurry and hubbub of the busy mealtime hours are no longer in evidence. In the distance can be heard the faint clatter of dishes being washed, dried, and stacked for the next day's activities, and the muted conversation of the staff as they go about their final activities for the evening. The low murmur of two young lovers - a soldier and his fiance - are the only other sounds. It is quite dark. The only visible sources of light are provided by the quarter moon trying to peep through the holes in the clouds above, the faint electric bulbs that mark the perimeter of the brick wall, and the candles illuminating the two occupied tables - one holding the couple in the center of the tree-lined court yard and the other a dark-garbed figure surreptitiously ensconced in the far corner.

If one were to allow his eyes to adjust to the dim light, the figure would resolve into an upright gentleman, almost military and Prussian in bearing. However, the match with which he lights his Havana cigar reveals the bearded, bespectacled face of a kindly, late middle-aged man in repose. The gentleman is Paul Ehrlich. The year is 1910. The city is Montpellier, in the South of France.

It had been a tiring journey - a seemingly endless series of conferences and banquets to introduce his new chemotherapeutic agent Salvarsan to the medical opinion leaders of France. At each stop along the way he dealt with frustration and controversy. The endless arguments and nitpicking by his fellow physicians and researchers taxed his energy as he attempted to penetrate their long-held beliefs and convince them of the safety and superiority of his novel organic arsenical over the traditional inorganic bismuth and arsenic treatment of syphilis. Finally, at this last destination, he gratefully accepted the plaudits and support from the learned professors at this most ancient of medical facilities. They had the wisdom to accept, with open minds, the veracity of his data. Their intense interest in eliminating the therapeutic applications of such poisons as arsenic and bismuth stemmed from the experiences of a former staff member of theirs, Hans Sloane, who investigated the effects of arsenic overdosage on the famous actor Barton Booth, over two hundred years earlier.

Now the conference and banquet were over; the attendees had left to enjoy the companionship of their families and friends. Now, Dr. Ehrlich can enjoy, in solitary quietude, his final cigar and cognac before retiring. As the smoke of his exhalation rises to join the clouds above, Professor Ehrlich is able to now allow his thoughts to carry him back to the events of the day. He remembers again how he concluded his address with expressions of sincere gratitude to those who had made such a major impact on his efforts: Pasteur and Henle for laying the framework for the study of infectious diseases; his older cousin Carl Weigert who had introduced him to the organic dyes and their tissue-specificities and selective powers; his friend and mentor Robert Koch, the discoverer

of the etiology of tuberculosis who laid the foundation for many of the major developments in immunology; and to his good friend Hata for developing the critical test of cure - the rabbit model of syphilis, and his mentor Kitasato, a former colleague. But one man had to remain nameless, the one man that he wished to laud above all others, the man who had such a major influence on him and encouraged him in his thinking to such an extent that the world of medical research would be forever changed as a result.

As Professor Ehrlich closes his eyes, allowing the gentle bite of his fragrant beverage to impart its pleasant feel and taste, his consciousness flows back to a time in 1893 when he first met the man whose wisdom and encouragement gave him the needed impetus to carry out his mission which culminated in the development of a synthetic chemical agent remarkably capable of safely curing millions of sufferers of the dread disease syphilis. The scene is as clearly seen tonight as it had been those many years ago on a warm noon day in early summer.

"Herr Professor, may I share your table for lunch?" the tall man asked in perfect Hoch Deutsch, leavened with an unknown foreign accent. "I see that we are both in a hurry to get back to our researches, I to the chemical analyses of new coal tar derivatives and you to their medical application as dye substances. Perhaps, while we dine, you can tell me what new chemical breakthroughs are being made in Berlin."

"Of course you may share the table," replied the good doctor. "But how do you know so much about me, that I am from Berlin, that I am working on aniline dyes, and that I am in a hurry to return to my researches? Have you been spying on me?" he chuckled.

"No," retorted the former, as the tall, heavily bearded man seated himself and carefully arranged his napkin with long, acid stained fingers. "It is a habit of mine to define the occupation, character, habits, and geographic origin of people whom I see on the street, confront in business, or, in your case, have the honor to share a table with. It enhances the powers of observation and logical thought which are the hallmarks of a good scientist and immensely aid scientific enquiry."

Ehrlich continued his questioning with: "Would you please tell me, then, how you were able to know so much about me by using these powers of yours?"

"That is simple, once you have honed your powers by constant practice," replied the tall, bearded man. "I knew that you were a professor by the reverence shown to you by the students who follow your every step, as well as the shape of your beard, which announces both your status and your city of origin. Recognition of the latter is assisted by the gold emblem on your chain, inscribed from the most noted medical research institute in Berlin, the Charité, and the additional distinct emblem, only given as a very special award for meritorious service at the professorial level, granted by the Medical Faculty of Berlin University. That you are a physician is especially obvious, due to the unique coupling of the bear, the symbol of Berlin, and the caduceus, the symbol of medicine." After pausing, as if for effect, he took a bite of the bread that had finally arrived and a sip of the moderately priced table wine and continued with his recitation, as if lecturing a class of medical

students: "The rapid movements of your head and eyes, as you attempt to locate a waiter in this climate that features a more *laissez faire* attitude towards service, is evidence enough of your desire to eat more quickly than is customary in the South of France. This is fortified by the fact that although you are very correctly dressed, as befits your station, your clothes and shoes are rather large, indicating that you object to spending any time on trying them on, or no doubt, any other activities that are not of major importance to you. Also, your hurry and recent laboratory activities are clearly announced by the many multicolored dye stains on your fingers that have resisted your perfunctory attempts at scrubbing away elimination, and the mud on your shoes that could only have been attained by taking a path through the new construction that is the shortest route between the university and the hotel."

When the stranger had completed his erudite discourse, Ehrlich, in a voice signifying delight and respect, exclaimed "That is an outstanding exhibition! What else do you know from our brief meeting?"

"Very little, only that you are originally from Silesia, are married, and of the Jewish faith. Nothing further comes to mind at the moment."

"I am deeply impressed by your skill, and I would like to ask your indulgence to see how I could attempt, in some small way, to emulate your methods." Encouraged by the smiling nod from his taller companion, Ehrlich continued, "When I first saw you this morning at breakfast, from a short distance, and did not know that I was to have the pleasure of your company, I did make some observations about you. It is a habit of mine. When I noted how tall, thin, and energetic you were, I immediately suspected that you were an American. Your height, facial shape, and luxurious hair and beard are quite reminiscent of the photographs of the former American president Abraham Lincoln. Then, after hearing you speak, I thought that you were Swiss. Your ease in quickly shifting between French and German was something that I thought only citizens of that multinational land could accomplish. However, it now becomes obvious to me that such is not the case. Although it is clearly not your native tongue, you speak perfect Hoch Deutsch. Even the most erudite Swiss cannot disguise the fact that his native tongue is Suisse Deutsch, a very distinct dialect, indeed. Also, yesterday, when I drew closer to you, I could tell that your French is perfect Parisian. This would not be uncommon to an ethnocentric French speaking Swiss, or an upper class Parisian, but it is marvelous to find such a confluence in another. I do see by the scars on your fingers that you do enjoy the science of organic chemistry, and the stain on your beard signifies that you are a frequent pipe smoker, although you have not demonstrated that habit in public. The fact that you hide this aspect of your life could reveal that you may be discretely avoiding other activities so as to obfuscate your true identity. Certainly, your clothes are quite new and yet not French in cut or style. Also, unlike other gentlemen of your obvious breeding and professional standing, you wear no signs or symbols of honor, service, or even luxury. Yet you have appended to your watch chain a disk bearing the likeness of Queen Victoria. Is that a British coin?" He paused and continued in a less certain tone: "I am afraid that I have reached the limit of my abilities in this direction. As a scientist, I have trained myself never to theorize beyond that which I can prove by repeated experiment or observation. Could you please tell me what is your nationality and with whom I have

the pleasure of dining? It would appear that the staff at this facility has conspired to prolong our discussion. I doubt if we will ever be able to obtain anything else to eat besides bread and wine."

"I thoroughly agree with you in both respects. I appreciate both your burgeoning new-found skill in observation and deduction and your disinclination to reach a conclusion on the very little evidence of my persona that I have revealed to your senses. It is a capital mistake to theorize before you have all of the evidence. It biases the judgement. Please permit me to introduce myself," the taller man said. "Suffice it to say, at this moment, that my name is Mr. Sigerson, I am Norwegian, and before resuming my deductive activities, I went on a two-year pilgrimage of exploration. Perhaps you have read of my exploits in the newspaper."

"I am sorry that I do not usually follow the news as thoroughly as I should, so I have not read of you. I am a monomaniac, concentrating exclusively on my work. I believe that one must not fish in too many waters. That is the secret of my success. My name is Professor Paul Ehrlich, and I am currently continuing to research the specific staining affinities of coal tar dyes and am initiating studies in immunology at the Institute for Infectious Diseases in Berlin with Professor Robert Koch."

Ehrlich's table companion looked keenly into his eyes, obviously relishing the turn that their conversation had taken, and said: "I cannot agree more with your observation regarding selective intake of information. In fact, I believe that a man's brain is originally like a little empty attic, and you have to stock it with such furniture as you choose. A fool takes in all the lumber of every sort that he comes across, so that the knowledge which might be useful to him gets crowded out, or at best is jumbled up with a lot of other things, so that he has a difficulty in laying his hands upon it. Now the skillful workman is very careful indeed as to what he takes into his brain-attic. He will have nothing but the tools which may help him in doing his work, but of these he has a large assortment, and all in the most perfect order. It is a mistake to think that little room has elastic walls and can distend to any extent. Depend upon it there comes a time when for every addition of knowledge you forget something that you knew before. It is of the highest importance, therefore, not to have useless facts elbowing out the useful ones."

Ehrlich replied: "This has been a most illuminating conversation. Although I had originally been in a rush to return to my researches, there comes a time when discussion and reflection on the problem may provide more progress than any individual experiment. If you can spare the time, I would greatly appreciate your giving me your thought on a subject that has been foremost in my mind for many years."

"Yes, of course," he retorted. "I am certain that your researches must have the highest degree of significance, if someone of your obvious scholarly attainment considers them of such overwhelming import that he is willing to sacrifice even part of his noon time meal for them. However, I may have a visitor and I may need to leave your company very quickly. I hope that you will understand."

Ehrlich replied: "Of course. But I will be especially obliged for any attention and assistance that you can bring to bear on this subject. As I indicated, I have been obsessed with but one object since my

youth. When I visited my older cousin, the researcher Carl Weigert, he permitted me to observe cells through the microscope for the first time. I was amazed to note that not all of the cells were stained to the same extent. Some were deeply stained while others were barely visible. After meditating on this, I theorized that this phenomenon is connected with the selective relationships of choice between the stain and cells, manifested by the readiness with which the stain was absorbed. The differences in affinities explained why it was that only certain dyes would form linkages with specific cell elements. I have devoted my life's work to defining the mechanism responsible for the specific affinity of cells for various coal tar derived, chemically pure dyes."

Chuckling, Sigerson interjected: "I see by your fingers, that the human dermis has an affinity for every color of dye possible. You seem to have defined those conditions perfectly."

"Yes, that is indeed the case," Ehrlich replied "People are afraid to touch anything in my laboratory for fear of acquiring the same nonspecific stains. However, my thoughts on the specific affinity of different dyes, at lower concentrations, of course, have led me to espouse theories that have met with cool receptions from my peers. After many years of painstaking research, I have come to the conclusion that chemical compounds, such as dyes and drugs, have specific side chains that fit, as do keys in a lock, into specific receptors in bacterial and mammalian cells."

Sigerson removed his recently lighted cigar from his mouth and stated:" Such is the situation that I found myself in several years ago. Using a similar chain of logic, I was able to devise a reagent with which I can easily detect the presence of human hemoglobin in a solution of only one part in one million. When I presented this finding to the professors at the laboratory in which I was working, they refused to accept my premise nor my efforts as worthy of pursuing towards an academic degree. Seeing that I was to be thwarted by the narrow mindedness of academe, I left the laboratory and initiated an independent study of chemical phenomena."

After taking another sip of wine, Ehrlich replied: "The same fate befell me at my previous location. After many dialogues with the newly appointed director, I had no recourse but to do the same. I also set up a private laboratory, until Dr. Koch recruited me for collaboration in his facility. In my laboratory I investigated the relationship between dyes and nerve cells. Again, the same high degree of specificity. I was also able to demonstrate that methylene blue had a much higher affinity for malarial parasites than cells of the human organism. The veracity of my observations, the very specific affinity of dyes for various tissues and organisms, has been supported by my more recent studies with the very concentration dependent interaction of toxins and their antitoxins. Thus, we have at least two independent classes of chemical interactions that support my hypothesis."

Looking ever more keenly at his companion, Sigerson said: "Splendid! I have always thought that when you follow two separate chains of thought, as you have done with chemical dyes and antibodies, you will find some point of intersection which should approximate to the truth. Taking your theories to the ultimate conclusion, if you were to appropriately modify the side chains of the various coal tar derivatives, you would be able to synthesize compounds that could kill microbes such as sleeping sickness and syphilis without damaging the cells of the body."

Ehrlich excitedly replied, "Exactly my thoughts! It is very inspiring to find someone who follows my theories and reaches the same conclusions! I even have devised expressions to define the ideal relationship. Those compounds with a high attraction to parasites I refer to as having high parasitotropy and those with weak effect on mammalian cells as having low organotropy. The index of these two factors expresses the relative medical utility of such compounds. A compound that attacks invading cells such as bacteria, fungi, parasites, or even cancer cells could be classified as a chemotherapeutic agent. I will try to devise drugs that are highly selective for disease cells on one hand and inactive against those of the host on the other --- a Magic Bullet if you will."

"I commend you on your interests and the very fine work that you have done. I can only hope that you will be able, with the assistance of Dr. Koch, find a cure for the illness that afflicts the wife of my very best friend." Then, tearing off his false beard and wig, revealing a moderately short haircut and clean shaven face, the tall gentleman, known to Ehrlich only as Herr Sigerson, leaped over the table and quickly ran from the scene, leaving as his parting exclamation: "I must go quickly now! The game is afoot! If you value your life, do not under any circumstance tell anyone that you saw me." And then he was gone forever.

This conversation was forever etched into the consciousness of Professor Ehrlich. Long had he mused about the one man who, in his earliest struggles with the scientific establishment, both understood and encouraged him. Finally, he smiled. "Now I know, I know," he thought to himself as he glanced down at the two books that he had acquired to help him alleviate the long hours that he would be required to endure on the train back to Berlin. Their titles were: *Späte Rache* and *Das Zeichen der Vier*.

Some may think that this account is fanciful. There are some who would doubt the actual existence of either Sherlock Holmes or Paul Ehrlich, or even both. Regardless, there is no doubt that Dr. Ehrlich, through hard work, intelligence, and creativity brought forth a new science of chemotherapy which was destined to revolutionize, eventually, the strategies by which new drugs are discovered. Salvarsan, or generically arsphenamine, was in used from 1910 until penicillin replaced it over 30 years later. It was not until the late 1930s that another scientist followed in Ehrlich's footsteps and introduced the next class of antiinfectives, the sulfonamides. Both the inventors of the sulfonamides and the developers of the useful application of penicillin acknowledged the contribution that Paul Ehrlich's efforts had on theirs. The fundamental underpinning of all modern immunology and medicinal chemistry, especially the theory of receptors, all derive from the initial concept of Ehrlich's creative research.

Who is to say that Ehrlich's bent for deductive reasoning and meticulous observation did not stem partly from his love of the stories about Sherlock Holmes, as penned by Sir Arthur Conan Doyle, another creative physician of note? There have been numerous accounts of Ehrlich's obsession with the Sherlockian adventures. When Sir Arthur learned about this, he sent his picture, along with a signed note, to the world renowned scientist. Thus, the Writings may have had an impact on the world far beyond that which has been previously deduced.

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Further Reading:

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2. Moss, Robert A. "Sherlock Holmes, Paul Ehrlich, and Salvarsan" in *THE BAKER STREET JOURNAL* (NS), 44, (1994), 20.
3. O'Brien, James F. "What kind of chemist was Sherlock Holmes?" in *CHEMISTRY & INDUSTRY*, 7 June 1993, 394.

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