

Subatomic Medicine and the Atomic Theory of Disease

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Abstract

This review discusses the history of the discovery of subatomic particles, our current understanding of these particles and their use in medical technology and therapy and how these combine to propose an atomic theory of disease in which alterations in the subatomic particles are the root causes of disease. A better understanding of the anatomy of the atom itself could bring about new treatments for diseases and better outcomes. As we move towards the ideal of personalized genomic medicine, a bridge between scientific and clinical knowledge is needed to link the influence of subatomic particles with an individual's disease process.

Keywords: Electrons; Hadron; Subatomic particles; X-ray computed tomography scan; Single photon emission computed tomography; Positron emission tomography

Introduction

The realm of scientific knowledge, particularly within the field of medicine, now evolves at such a rapid rate that new technologies are increasingly available. However, not all find practical application in the medical arena, while others become far more important than originally anticipated. For example, the field of nuclear medicine was initially met with resistance and reluctance as physicians were dubious of its potential real world applications. Norman Holter, a physicist-chemist-engineer, parleyed experience with nuclear weapons testing in the South Pacific of the 1950s to be among the vanguard of this emerging science, finding the first national organization dedicated to this field of medicine [1]. Today, nuclear medicine is an integral part of modern medicine, allowing imaging of pathophysiologic conditions such as tumors and treatment of malignancies.

Progress in our understanding of molecular biology and its implication in health and disease during the 20th and 21st centuries has been exponential with the discovery of protein signaling pathways and the development of targeted therapies, as well as the discovery of the structure of DNA and subsequent sequencing of the human genome and the development of personalized genomic medicine [2,3]. Built upon these advances, new discoveries are being made in varying fields from anatomic sciences to molecular biology; and when examined together, create an emerging atomic theory of disease. Beginning with John Dalton's atomic theory in the mid-19th century, and then the discovery of radioactive particles by Madame Curie, the physical sciences have given us insight into the structure of the basic atom. It is fascinating to note that while subatomic particles are currently used in the fields of cardiology, cardiovascular surgery, radiology and nuclear medicine for diagnoses and therapies, we have yet to determine the role of the atom and subatomic particles on health and disease. Therefore, in this review, we provide the history of the discovery of subatomic particles, our current understanding of these particles and their use in medical technology and therapy, followed by a proposal of an atomic theory of disease.

Background

The discovery of subatomic particles yields from a long and complicated scientific journey. The theory that matter is composed of indivisible particles called "atoms" was first proposed in 5th century B.C. by the ancient Greeks, especially Democritus. The idea, however, only

began to take hold in the scientific community during contemporary times in the 17th and 18th centuries when scientists used the atom to explain various observations in nature. Isaac Newton explained the expansion of gases as the rush of atoms into empty space, and John Dalton developed his atomic theory based upon several experiments analyzing the properties of gases (Figure 1). He proposed that elements are made up of atoms, that atoms could not be created or destroyed, that all atoms of any element are equal, that atoms of one element are different from atoms of a second element, and that atoms can be combined in whole number ratios to form compounds [4]. Scientists now understand that portions of Dalton's atomic theory have been found to be inaccurate, although the basic fundamentals of the theory continue to remain true.

Despite these scientific findings, the existence of atoms was doubted by many until the discovery of subatomic particles in the 20th century, ironically demonstrating that the atom was actually divisible [5]. A series of experiments led to the understanding that an atom consists

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|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|--|
| 1A | | | | | | | | | | | | | | | | | 8A | |
| H | | | | | | | | | | | | | | | | | He | |
| | 2A | | | | | | | | | | | 3A | 4A | 5A | 6A | 7A | | |
| Li | Be | | | | | | | | | | | B | C | N | O | F | Ne | |
| | | 8B | | | | | | | | | | | | | | | | |
| Na | Mg | 3B | 4B | 5B | 6B | 7B | 8 | 9 | 10 | 1B | 2B | Al | Si | P | S | Cl | Ar | |
| K | Ca | Sc | Ti | V | Cr | Mn | Fe | Co | Ni | Cu | Zn | Ga | Ge | As | Se | Br | Kr | |
| Rb | Sr | Y | Zr | Nb | Mo | Tc | Ru | Rh | Pd | Ag | Cd | In | Sn | Sb | Te | I | Xe | |
| Cs | Ba | La | Hf | Ta | W | Re | Os | Ir | Pt | Au | Hg | Tl | Pb | Bi | Po | At | Rn | |

Figure 1: Common elements occurring in the human body. The six most common, hydrogen, carbon, nitrogen, oxygen, phosphorous, and sulfur, are highlighted in red. Lesser elements (blue) and trace elements (green) are also indicated. (The Encyclopedia of Science).

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of a nucleus made up of positively charged protons and neutrally charged neutrons, surrounded by negatively charged electrons (Figure 2). Further experiments discovered even more particles in the family of these subatomic particles. Although many of these other particles exist, neutrons, protons, and electrons are the most stable particles and are therefore considered the basic particles of matter.

Electrons were discovered by Sir Joseph John Thomson in 1887 through his work on cathode rays, glass tubes through which electrons flow. He was able to determine that the rays have a negative charge, by the observation that they were deflected toward the positive charged plate and away from the negatively charged plate in the glass tube [6]. This new-found subatomic particle was not rightfully named until much later when George Johnstone Stoney proposed in 1894 that the unit of electricity should be named the electron [7].

The electron is the lightest elementary particle, and one of the few elementary particles that does not decay. In 1903 at his Silliman Lectures at Yale, Thomson suggested electrons are stuck in a matrix of positively charged matter. Approximately the same time in Tokyo, Hantaro Nagaoka proposed a different, but ultimately more correct model, in which the electrons revolve around a central positively-charged body, like the rings around the planet Saturn [5]. Only later when Niels Bohr described the dynamics of the electron, would Thomson's raisin plum pudding model finally be discredited.

As atoms are electrically neutral, the next challenge was to find what balanced the electrons' negative charge. The atomic nucleus containing this positive charge was discovered by Ernest Rutherford during the early 1900s. His experiments involved directing a beam of energetic particles toward a piece of gold foil and examining the scatter of the particles. He deduced that a positively charged nucleus sits at the center of an atom around which electrons revolve [8]. Concurrent with the development of Rutherford's nuclear model, Bohr developed the first quantum theory of the atom. He focused on the dynamics of the electron, and ultimately derived a formula that gave the wavelength of light emitted from electrons [9]. This formula could then be used to calculate the nuclear charge, which supplied the one missing component of Rutherford's picture of the atom [5]. Rutherford then named the positively charged particles at the center of the atom "protons". In order to result in a neutrally charged atom, it was deduced that the number of protons should equal the number of electrons.

With development of his atomic theory, John Dalton in the 19th century was able to describe the atomic weights of several elements,

with hydrogen being used as a reference molecule. With the knowledge of the existence of protons and electrons, it was expected that the mass of an atom should be equal to its electric charge. Instead, the mass was twice that of the electric charge, leading to the eventual discovery of the neutron in 1932 by James Chadwick [5]. He studied unique particles produced by beryllium when bombarded with alpha particles from the radioactive element polonium, which were similar in mass to protons but electrically neutral. However, he believed it was a composite of a proton and electron [10]. It is difficult to pinpoint exactly when the neutron was fully accepted as an elementary particle, although one inspiration was a more accurate measurement of the neutron mass by Chadwick and Maurice Goldhaber in 1934, proving that it was larger than the additive mass of a proton and electron [5]. Further studies examining nuclear forces eventually were able to prove that the neutron was an individual particle [11,12].

Knowledge of the presence of the neutron led to better understanding of isotopes, which had been first described in 1913 by Frederick Soddy. Soddy studied radioactive decay, and discovered that there were some products of decay had the same mass as others, despite being of a different element. He then surmised that some atoms of the same element could have different masses. J.J. Thomson, discoverer of the electron, also studied characteristics of neon, and confirmed Soddy's theory with the finding that some neon atoms had different atomic masses than others [13]. This finding contradicted one aspect of Dalton's theory in that not all atoms of an element are necessarily identical.

These discoveries evoked more provocative questions, and the search for elementary particles of matter, the basic building blocks, began. Particles that historically were considered without any subcomponents, such as neutrons and protons, are now known to be composite particles, consisting of one or more elementary particles (Table 1). Current atomic theory states that the only elementary particles of matter are quarks and leptons. Neutrons and protons are types of hadrons, which are composed of quarks; neutrons consist of 2 down quarks and 1 up quark, whereas protons consist of 2 up quarks and 1 down quark. Electrons, on the other hand, are leptons. The fundamental difference between hadrons and leptons are that hadrons are subject to strong nuclear forces while leptons are subject to weak nuclear and electromagnetic interaction [5].

With the discovery of photons, or particles of light, came the idea that subatomic particles could also be considered the same way. This led to the development of quantum theory, which describes the dual wave and particle properties of matter at the atomic and subatomic level, as opposed to classical physics, describing macroscopic objects. In order to help explain the interactions and observations of subatomic particles, more particles beyond the basics described above were conjectured and then proven.

Many of the discoveries of previously unknown subatomic particles were due to observations of astrophysics and cosmic rays, which involve very high energy collisions. For example, positrons were discovered in 1932 by Carl Anderson during the observation of tracks of cosmic ray particles. He noted that positrons curved about in a magnetic field as much as electron tracks, but in the opposite direction. It became clear that positrons are antielectrons, in that they have the same mass but opposite electric charge as electrons. Soon it was recognized that for each kind of particle there is also an antiparticle [5]. Muons and pions were discovered shortly afterwards in cosmic rays in 1937 and 1947, respectively. Fortuitously, a charged pion was discovered in a particle accelerator in 1948, marking the advent of particle physics, and opening

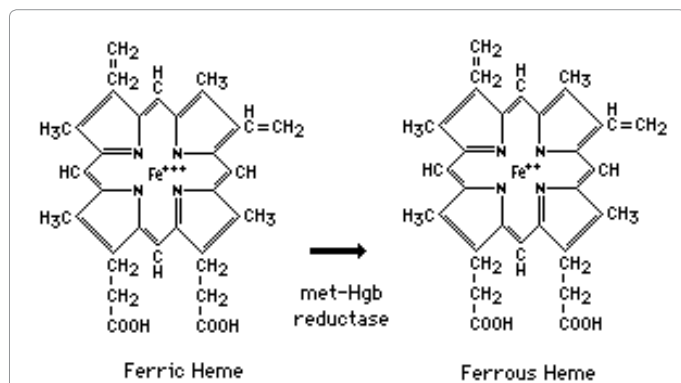


Figure 2: Methemoglobin indicated as Ferric Heme, is unable to bind oxygen because of the extra electron. It is reduced to hemoglobin, except in the case of overproduction or defective enzyme, thereby causing methemoglobinemia. (University of Virginia School of Medicine).

the door to the explosion of particle discovery [14]. Tau particles, W and Z particles, the Higgs bosons, strange particles, and more hadrons including ρ , ω , η , ϕ , Δ , Λ , Ξ , Ω have since been discovered in particle accelerators.

The quark model, stating that hadrons are composed of elementary quark particles, contributed to a great simplification and understanding of many of the known particles [14]. But, no scientist has been able to observe a quark in isolation. The birth of quantum chromodynamics was in 1973 and explained quarks in relation to a new particle, named gluons. This theory posits that a “glue” keeps quarks together inside the proton, neutron, and other hadrons through strong nuclear forces. Therefore, quarks, antiquarks, and gluons cannot be separated apart from other particles, and therefore, they cannot be directly observed. In addition, many of the particles that have been discovered have such short half-lives that they are very unstable and do not exist in ordinary matter. Interestingly, scientists now trust in the existence of quarks and gluons not through observation, but because the theories that rely on them continue to work [5].

Practical Applications

After over 100 years of discovery in the field of particle physics, only theories and models exist to describe particles and the forces involved in their interactions. Despite this, we have seen direct impacts from the use of subatomic particles on the field of medicine, beginning with the discovery of X-rays in 1895 by Wilhelm Roentgen. He realized that rays emitted from cathode ray tubes could pass through many solid objects, including human soft tissue though not bones, to excite nearby phosphorescent materials [15]. A few months later, Henri Becquerel discovered that some elements, especially uranium, have an innate radioactivity, itself able to phosphoresce after exposure to sunlight [15]. Marie Curie, fascinated by this idea, began her own studies based upon Becquerel’s work. She, along with her husband Pierre, developed techniques for isolating radioactive isotopes and understanding their properties, for which they won the Nobel Prize in Physics with Becquerel in 1903. With this work, they developed the hypothesis that radioactivity was an inherent property of the atoms in these elements, unaffected by external events [16]. In addition, the Curies discovered the elements radium and polonium, for which Marie won the Nobel Prize in Chemistry in 1911. Pierre, unfortunately, was not eligible for this award, as he had passed away a few years prior. Lastly,

the observations by the Curies of the effects of radioactive elements causing skin inflammation and other changes ultimately led to the field of radiation therapy [16].

Advancements in imaging technology afforded by particulate have dramatically influenced diagnostic accuracy and precision (Table 2). What once required an exploratory laparotomy by a surgeon now can be accomplished with an X-ray Computed Tomography (CT) scan. Though CT imaging was introduced in the 1970s, it is based on the X-ray science of the late 1800s. Using a single axis of rotation, three-dimensional images can be obtained from a large series of two-dimensional X-rays through ionizing radiation. This is compiled together with geometric processing to create a tomography or map of the inside of a human body and its parts. CT scanners now generate X-ray slice data from an X-ray source which rotates around the body, opposing scintillation system sensors based on photo diodes. An electron beam is deflected into a vacuum chamber, generating X-rays when the electrons hit the stationary body being imaged. Improvements in the design have now allowed dynamic cross sections of the body as the body slides through the X-ray circle, creating helical CTs, versus simple cross sections [17].

Magnetic resonance imaging offers another example of particulate science and medicine at its finest, offering precise illustrations of the soft tissue such that malignancies less than a centimeter in size can be identified. A magnetic field from a radio frequency transmitter changes the magnetic moments of hydrogen protons in the body to align with the direction of the field. Radiofrequency fields are then used to alter the alignment, causing nuclei to generate a rotating magnetic field itself which is detected by the scanner by varying degrees of proton decay. The specific rates of rotation within the body create a spatial three-dimensional image based on these varying rates of decay. Five tissue variables are measured which are used to construct these images: spin density, T1 and T2 relaxation times, and flow and spectral shifts. This non-ionizing radiation of the radiofrequencies eliminates the dangers inherent to ionizing radiation and is ideal for imaging tissues with many hydrogen nuclei and minimal density contrast [18].

Perhaps the area of most rapid growth in the application of subatomic science is the field of nuclear medicine, which uses radioactive decay to diagnose and treat various diseases. Diagnosis is based upon the physiology of the tissue or organ of interest, and the treatment relies on tracing the localized metabolism or on the uptake

| | |
|---------|--|
| Matter | Constituent of all physical objects, elementary particles are quarks and leptons |
| Quarks | Collectively form hadrons, possess intrinsic qualities of spin, charge, and mass |
| Leptons | Subject to weak nuclear and electromagnetic interactions, exist as electrons which combine with other particles, also exist as neutrinos |
| Hadrons | Subject to strong nuclear forces, two categories known as baryons and mesons |
| Mesons | A hadron composed of three quarks |
| Baryons | A hadron composed of one quark and one antiquark, exist as protons and neutrons |
| Nuclei | A composite of mesons and baryons |
| Atoms | Made up of nuclei and leptons |

Table 1: Elementary Particles of Matter.

| | Imaging | Therapy |
|-----------|--|--|
| MRI/3T | Images up to 2mm apart using radiofrequency transmitter | |
| PRRT | | Peptide and beta radiation for neuroendocrine tumors |
| CT | X-ray source, electron beam deflects into a vacuum chamber | Allows for detection of cancer before, during and after treatment |
| Proton | | Beam of energetic protons |
| Radiation | | X-rays, gamma rays and charged particles, external, internal or systemic |
| PET | Gamma rays, positron-emitting radionuclide, imaging metabolic activity | |
| SPECT | Gamma rays, radionuclide | |

Table 2: Use of Subatomic Particles in Imaging and Therapy.

of the radioactive particle by means of specific targets, such as receptors or antigens. Radionuclides are bound to a specific ligand, which then targets a particular part of the body or particular cells or molecule. These ligands are designed to be preferentially taken-up or localized in tissue during disease processes. Using Anger or gamma cameras, the emitted radiation is detected and enhanced physiological imaging is possible. Labeling of the radionuclide may be based on substitution (Iodine-131 for Iodine-127), direct isotope switch (Carbon-11 instead of Carbon-12), or attached to synthetic structure (Indium-111 bound to a chelator that is bound to intact antibody). Throughout the literature and current clinical practice, the most utilized radionuclides are technetium-99m (^{99m}Tc) and iodine-131 (^{131}I). The introduction of ^{131}I in 1941 by Saul Hertz was the heralded standard for tissue-specific thyroid radiotherapy followed over the years by the introduction of over 40 other radionuclide tracers [19]. In nuclear medicine, ^{99m}Tc remains the most widely used radionuclide, relied on for more than 70% of all procedures [20]. Introduction of new tracers is focused on their ability to localize in tissue of interest, pharmacokinetics, half-lives, and safety regulations [21].

Nuclear imaging is divided into three categories: planar or conventional scintigraphy, Single Photon Emission Computed Tomography (SPECT), and Positron Emission Tomography (PET). All three techniques rely on the detection of gamma radiation. The tracers used for scintigraphy and SPECT emit gamma radiation, which is directly measured. In contrast, PET tracers emit positrons, annihilating nearby electrons, which leads to the emission of two gamma photons on paths 180° apart, which are then detected. Scintigraphy and SPECT commonly use isotopes such as ^{99m}Tc , either attached to a ligand or known to independently localize to a particular organ system based on unique physiology or relative metabolic activity. A common example is the ^{99m}Tc -labeled bisphosphonate hydroxydiphosphonate (^{99m}Tc -HDP) to visualize bone metastases with increased osteoblastic activity. Importantly, scintigraphy is used to create planar two-dimensional images, while SPECT is able to capture multiple projections of the radionuclide decay using a rotating camera system and, through tomographic reconstruction, create three-dimensional images. PET imaging also creates three-dimensional images, but through coincidence emission detection of high-energy (511keV) photons is able to capture more information to localize radiation events, therefore providing higher resolution images than the single-photon SPECT. PET imaging commonly employs Fluorine-18, with the glucose analog, fluorodeoxyglucose (^{18}F -FDG), as well as other isotopes, like Carbon-11, Nitrogen-13 and Oxygen-15. Since the introduction of hybrid scanners in 1999 with SPECT/CT, followed in 2001 with PET/CT, nuclear medicine has been able to combine its functional imaging capabilities with current anatomical imaging technology of CT and MRI [22,23].

Medical oncologists rely on nuclear medicine to aid in the detection, diagnosis, staging, and surveillance of several cancers including lung, lymphoma, melanoma, breast, colorectal, esophageal, head and neck, pancreatic, ovarian, cervical, and thyroid cancers. For the majority of tumors, detection is through targeted radionuclides, such as ^{18}F -FDG, which enables the localization of neoplastic lesions with increased glucose metabolism. Another example is the localization and characterization of neuroendocrine tumors by means of the somatostatin analog octreotide, radiolabeled with Indium-111 (^{111}In -pentetreotide) or, more recently, with the positron emitter Gallium-68 (^{68}Ga -octreotide). For most tumors ^{18}F -FDG-PET imaging is the most commonly used modality. ^{18}F -FDG-PET imaging can depict the whole-body distribution of areas of increased metabolic activity, indicating

the relative underlying metabolic activity of a tumor. Over 90% of PET utilization is in the field of oncology, with cardiology and neuroscience at a distant 5% and 3%, respectively [24]. As reported by Gambhir et al., ^{18}F -FDG-PET imaging sensitivity and specificity in oncology are estimated at 84% (based on 18,402 patient studies) and 88% (based on 14,264 patient studies), respectively [25]. It has been shown that adding ^{18}F -FDG-PET imaging to conventional staging of cancer has altered the management of 13.7-36.5% patients [25]. Currently, exciting applications of PET and SPECT include the indirect visualization of gene expression using reporter probes that aid in the diagnosis as well as monitor the therapeutic treatment of the disease [26,27].

Additional applications of nuclear medicine are numerous. Endocrine studies of thyroid and parathyroid neoplasms, which helped pioneer the development of nuclear medicine, are still being used today. Cardiologists routinely acquire myocardial perfusion and ventricular function studies. Neurologists and neurosurgeons employ nuclear studies permitting neurological evaluations of dementia, brain tumors, and brain death. Skeletal imaging allowing detection of bone metastases, trauma, or osteomyelitis is increasingly available to all types of clinicians. Pulmonary studies, renograms, and tagged-white blood cell imaging have secured a place in the standard of care among specialists and primary care physicians alike. The uses of nuclear medicine continue to grow exponentially with modalities to image, diagnose, and treat disease.

Radiation oncology is another field of medicine utilizing ionizing particles to treat diseases. This field is versatile, and can be used in a number of situations. Most commonly, radiation therapy is used to treat malignant diseases, and can be used alone as treatment, or in concert with surgery or chemotherapy to provide for an augmented response. In addition, radiation therapy can be used to treat or prevent benign conditions that involve cell growth or inflammation, such as keloid scars or heterotopic ossification [28]. Fundamentally, high energy photon-based radiation therapy relies on subatomic double-strand DNA breaks that ultimately results in cancer mitotic cell-death [29]. Modern linear accelerators use magnets to accelerate electrons to high speed to collide with an extremely high density material, such as Tungsten, in order to generate bremsstrahlung. Bremsstrahlung is electromagnetic radiation produced by the deceleration of charged particle when deflected by another charged particle. This high energy x-ray is then collimated and modulated by modern devices with the help of computer-based inverse treatment algorithms in order to form therapeutic radiation. This is ultimately directed into a patient's tumor from multiple beam angles. Conceptually, high energy x-rays directly damages DNA or indirectly ionizes water molecules in the body to form free radicals, notably hydroxyl radicals, which in turns damages DNA. Single strand DNA damage can be repaired; however, double strand DNA damage results in mitotic cell-death [29]. Proton and carbon particle-based therapeutic radiation therapy is similar to photons except that protons and carbon ions are charged particles. However, because a proton has mass, it has unique physical characteristics, namely the Bragg peak, which is the energy loss of ionized radiation as it travels through tissue. Consequently, the Bragg Peak results in a precipitous drop off in physical dose that is calculated by the stopping power (MeV/cm) which is advantageous when the tumor is directly adjacent to a radiosensitive organ such as the spinal cord, rectum, or heart. However, the Relative Biological Effectiveness (RBE) of protons is similar to that of high energy x-rays at 1.1 [30]. Carbon-based therapy possesses the Bragg peak as well. In addition, its RBE is significantly higher than that of photons or protons at 2-3 [31]. Currently, there are three operational Carbon Ion Therapy centers in the world (2 in Japan and 1 in Europe).

From radiation exposure studies, it is known that radiation (photons, protons, neutrons, or ion beams) directly ionizes the atoms making up the DNA, modifying bases and causing double-strand breaks in the DNA, ultimately leading to defective products or cell death [32]. The probability of this type of damage is proportional to the absorbed dose. Radiation also works through indirect ionization, in which water is ionized, forming free radicals. Free radicals are atoms or molecules with unpaired electrons, which while important for cell signaling, can also react with DNA to cause significant damage called single strand break. A sum of two or more sub-lethal damages, not necessarily synchronous, and, therefore, with possible enzymatic repair in between, can ultimately lead to a lethal damage. Hence, the probability of this type of damage is proportional to the squared absorbed dose. Examples of free radicals include superoxide and the hydroxyl radical. Indirect ionization involving free radicals is more effective in an oxygen-rich environment, as studies have shown that tumor cells in a hypoxic environment are more resistant to radiation than in a normoxic environment [33].

This knowledge about radiation is used to our advantage to currently treat many types of cancers using external and internal radiation therapy. External therapy utilizes an outside source of radiation for local treatment, including, but not limited to, particle accelerators, reactor beams with neutron exposure, Stereotactic Body Radiotherapy (SBRT), Intensity Modulated Radiation Therapy (IMRT), and radiosurgery systems. SBRT is the culmination of improvements in imaging (PET, CT, MRI), tumor motion management (4-Dimensional CT, gating, tumor tracking), accuracy and precision of radiation delivery by modern linear accelerators, radiation treatment planning modeling systems, and image-guidance during radiation therapy. It is defined biologically by very high doses per session (extreme Hypofractionation) and limited number of treatment sessions (1-5) which translates to an extremely high Biological Equivalent Dose (BED) to the tumor [34]. A defining feature of SBRT is the utilizing of multiple beam angles (8-12) such that the normal tissue sees very little radiation, and the radiation is focused on the targeted tumor. This results in a steep dose-gradient of the tumor versus the normal tissue thus increasing the BED to the tumor while limiting the dose to critical structures. This has allowed for increased clinical tumor control, and reduced treatment-related toxicity [35]. Studies in stage I medically inoperable lung cancer have shown that delivery of 54-60 Gy in 3 fractions results in greater than 95% tumor control at 3-years with very acceptable treatment toxicities [36]. This is in contrast to conventional fractionated treatment course of 60 Gy in 30 fractions which historically resulted in local tumor control of only approximately 50% at best [35]. Similarly, in liver tumors, a recently published multi-institutional phase I/II liver SBRT study reported high local control rates (92% at 2 years), particularly with the most aggressive dose fractionations (60 Gy in 3 fractions) that translated to a high BED [37].

In contrast, internal therapy utilizes a source of radiation delivered inside the body, such as brachytherapy and nuclear medicine therapy. Internal therapy with radioisotopes, differently from conventional radiotherapy, exploits pathophysiological processes such as metabolic pathways, receptor or antigen binding. Classical examples are therapy with iodine-131 of relapsed/metastatic thyroid cancer, Radioimmunotherapy (RIT) with the anti-CD20 antibody ibritumomab-tiuxetan in non-Hodgkin's lymphomas and Peptide Receptor Radionuclide Therapy (PRRT) with radiolabeled somatostatin analogues ^{90}Y -octreotide or ^{177}Lu -octreotate [38,39]. PRRT with ^{90}Y -octreotide or ^{177}Lu -octreotate has been used to treat neuroendocrine tumors by exploiting the high-affinity binding of a radiolabeled octreotide to somatostatin receptors over-expressed

on the tumor cell surface, and the subsequent internalization of the peptide-receptor complex. The retention of the radioactivity into the lysosomes exposes the cell, and particularly the DNA material, to degradation [39]. Many classes of Non-Hodgkin's Lymphomas (NHL), indolent or aggressive, such as refractory/relapsing follicular NHL or diffuse large B-cell NHL, now can be treated with suitably radiolabeled monoclonal antibodies, such as in the radioimmunotherapy with anti-CD20 antibodies, either the ^{90}Y -labeled ibritumomab tiuxetan (Zevalin[®]) or the ^{131}I -labeled tositumomab (Bexxar[®]).

Additionally, localized prostate cancer is increasingly treated using high-dose proton therapy and brachytherapy [40]. Proton therapy is advantageous because the proton beam has a low chance of scattering, thus providing localized therapy with limited damage to surrounding structures.

Other subatomic particle technologies, such as alpha particle, show great promise for present and future applications, particularly when combined with more conventional chemotherapy [41]. New protocols utilizing systemically administered Ra-223 in bone metastases from hormone-refractory prostate cancer showed an increased progression-free survival in treated patients [42]. Presently alpha emitters are being experimented in many fields of nuclear medicine therapy, both in systemic and loco-regional applications [43].

Additional therapies utilizing energy on the electromagnetic spectrum including photons in lasers, microwave ablation, and radiofrequency therapy, are currently available to enhance patient care.

Despite the fact that radiation therapy is a local therapy, nearby tissues can be affected with treatment. For curative therapy, high radiation doses may unfortunately cause some side effects. Short-term effects include skin erythema or burning, but long-term effects may include fibrosis of tissue, damage to neighboring organs, or even the development of new cancers [44]. For palliative therapy, the main goal is to improve quality of life; therefore, the minimal amount of short-term effects is desired. Hence, radiation doses and overall treatment time may be lower in palliative cases [32]. Ideally, normal adjacent tissue that receives some radiation would be able to repair itself between doses in an attempt to limit toxicity; use of fractionation, which divides the total dose planned for a patient into smaller, more frequent doses, is based upon this idea [32]. Increased understanding of the effects of radiation therapy on an atomic level can lead to more specifically targeted therapies that limit these undesirable toxic manifestations.

In nuclear medicine, where the radioactivity is administered internally and is subsequently selectively accumulated at the desired site with a specific mechanism, the possible side effects may involve organs such as the bone marrow or the kidneys, depending on the implicated metabolic pathways.

Usually, knowledge of tolerance threshold doses of normal organs and tumoricidal doses, as well as dosimetric studies, help steering the course between the risk of unnecessary toxicity and of tumor undertreatment [45].

The Atomic Theory of Disease

The staggering advances in anatomy, physiology, and molecular biology over the past 600 years have led us to our current state in which the atom is now the anatomy of the 21st century. The next great advance in medicine will be bridging the subatomic, molecular and genomic levels by forming an atomic theory of disease, which states that alterations in the composition of subatomic particles are the root cause of disease. Tremendous discoveries are made each year in the field of

molecular biology and genomics as DNA and epigenetics continue to be the focus of an increasing number of biologists, chemists, physicists, and other scientists. The daily use of subatomic particles are gaining momentum in the diagnosis and treatment of disease, however the next step will be to demonstrate that the origin of disease emanates from diseased atoms with a pathologic distribution of subatomic particles resulting in pathophysiology at the molecular and cellular level.

The atomic theory of disease would include genetic differences at the atomic/subatomic level that are akin to Single Nucleotide Polymorphisms (SNPs), in which alleles for a gene differ on the exact nucleotide in a single location, which can change the ultimate protein structure. This can lead to subtle changes in function, or dramatic results which cause pathology [46]. We hypothesize that on a subatomic level, there could potentially be polymorphisms as well, in which there are subtle changes in the sea of subatomic particles. Isotopes, discovered 100 years ago, would fall into this category of subatomic polymorphism, as they differ in the number of neutrons present in the atom. Differences in other particles may not change the mass of the atom, but may alter some of the characteristics of the atom. As 99% of the body is composed of six elements (oxygen, carbon, hydrogen, nitrogen, calcium, and phosphorus) [47], polymorphisms would likely be found in these elements.

In terms of genomics and cell division, an atomic polymorphism in an element could change the nucleotide at a particular point in a gene. If the nucleotide does not change, it would be a synonymous genotype; in contrast, if the nucleotide changes, so does the genotype, causing a SNP and subsequently, a different allele. This would then account for basic human variations, as well as for disease processes that occur because of changes in these particles later in life.

A known example of a change in the subatomic milieu of an element leading to a disease process is that of methemoglobinemia, a disorder characterized by an overabundance of methemoglobin. Methemoglobin contains an oxidized form of iron (carrying an extra electron), as opposed to the reduced form in normal hemoglobin. This results in a shift in the oxygen-hemoglobin dissociation curve to the left, causing hypoxia. Methemoglobinemia can be congenital, due to a defect in an enzyme that normally reduces methemoglobin back to hemoglobin, or acquired, caused by breakdown products of drugs that can oxidize hemoglobin. While there less than 1% of methemoglobin normally present in human tissues, affecting local blood flow and inflammation through its effects on nitric oxide and heme, large quantities can lead to respiratory failure and death [48].

The subatomic composition of a molecule or atom can potentially be altered in two ways: externally or internally. Application of external energy such as exposure to radiation from an outside source, for example, the incidents at Chernobyl and Fukushima, could lead to instability of a nucleus, causing decay and a redistribution of subatomic particles within that nucleus. Internally, the direct incorporation of radioactive molecules or atoms into a system can affect the subatomic particles. Radiolabeled food containing a radioisotope such as dectan-90, would be metabolized, incorporated into our cells, and decay according to its half-life. This decay leads to emission of gamma radiation, which not only causes further damage to the cells, but may also create unstable isotope within the DNA that then goes on to replicate.

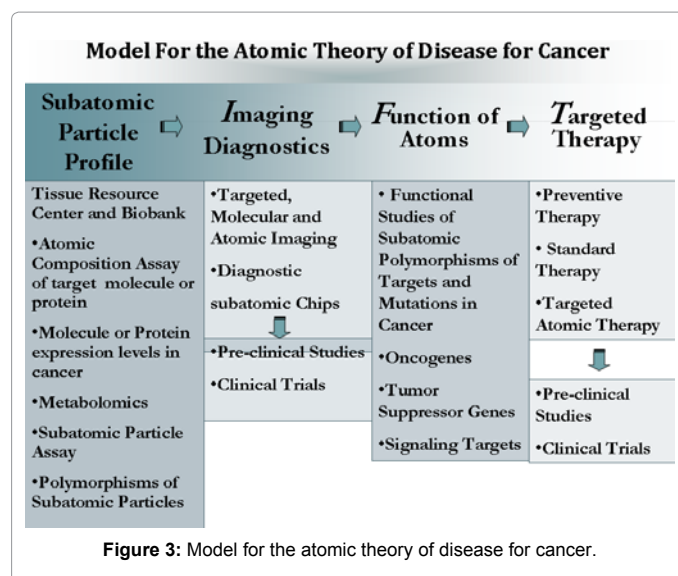
From a radiobiological point of view, the radiation damage, both on normal tissues and tumors, occurs primarily at a subatomic level, with the direct or indirect ionization of atoms of vital molecules, such as DNA, and then propagates, with a cascade, to the cell. The clinical

result will depend on the tissue characteristics, whether endowed with a high or a low turnover, on the uniformity of radiation distribution within the tissue, on the type of radiation used, e.g. the dose-rate, the fractionation and, on the other hand, the density of clonogenic stem cells, both in the tumor and the normal tissue. The final result will depend on the equilibrium between the damage inflicted to healthy and to tumor tissues. Hence, the duty of the nuclear medicine therapist has been compared to the journey of Odysseus, trying to steer a course between the two sea monsters [49].

Research laboratories, such as the European Organization for Nuclear Research (CERN) and United States Department of Energy Fermilab, employ particle accelerators to identify and describe subatomic particles and their behaviors. However, due to the instability of these particles, it is not possible to determine which precise isotopes will decay. Current techniques only measure isotopes after they have decayed and emitted radiation. Therefore, future research identifying isotopes in the body that will become unstable in the future and thus cause damage to DNA, would allow tremendous advancement in molecular medicine. Whether this research would involve significantly more sensitive gamma cameras, recording molecular vibrations, or new techniques using PET or SPECT, has yet to be determined.

We hope to be able to investigate our hypothesis in the near future (Figure 3). The key will be to develop an assay in order to assess for atomic polymorphisms and prove the existence of diseased atoms, such as the oxidized iron atom in methemoglobin. These diseased atoms will need to be proven to exist in disease-associated living tissues, such as bacteria, oncogenes, and cancer cells. They may also be found in disease-associated non-living tissues, such as carcinogens and foods. Our initial goal will be to assess for diseased atoms in the body's most common elements to identify where these are likely to occur. Nitric oxide (NO) is an ideal molecule to study, as it contains two of these elements. In the future, we then hope to study this phenomenon in diseased human cell lines, such as PANC-1, or oncogenes, such as Kras G12D [50].

Detection of diseased atoms may perhaps require the use of linear accelerators. Similar to the collaboration involved with the discovery of DNA's helical structure, the next great leap into the subatomic level of health and disease will likely require a concerted and synergistic effort by many types of scientists.



Conclusion

Our knowledge of the basic building blocks of matter is far from complete. Appropriate therapy requires a fundamental understanding of anatomy and that the atom represents the anatomy of the 21st century. We propose the atomic theory of disease in which alterations in the subatomic particles are the root cause of disease. By delving deeper into the anatomy of the atom itself, new ways will be found to treat diseases with better outcomes. As we move towards the ideal of personalized genomic medicine, a bridge between scientific and clinical knowledge is needed to link the influence of subatomic particles with an individual's disease process. It would truly herald the next step in understanding disease and mark our ascent to the world of personalized medicine.

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