Historical development in the field of toxicology

Technology, Development

Historical Development in the Field of Toxicology And Mechanisms and Factors Responsible for the Entrance of Toxicants in the Human body and their Harmful Effects Jorge D. Rebolledo Columbia Southern University Abstract The purpose of this paper is to make a short historical reference in the field of Toxicology and how this area ofsciencehas develop starting from centuries ago until our present. It is also the intention of this paper to explain how the toxics enter our body, how they are absorbed and the mechanisms responsible for that. Introduction As stated by E.

Monosson, some define Toxicology as the study of toxic materials, including the clinical, industrial, economic, and legal problems associated with them. Although toxicology—as a formally recognized scientific discipline—is relatively new (with major developments in the mid-1900s), the science itself is thousands of years old. Consider the potential results of early trial and error experiences of hunter-gatherers for whom identifying a toxic plant or animal was a life or death situation. Some of the most poisonous substances known today are naturally produced chemicals including ricin from castor beans or tetrodotoxin from the puffer fish.

Early humankinds’ careful observations of such plants or animals with toxic characteristics as frogs, containing curare, were put to use not only for avoidance of toxic substances but for weaponry as well. Many naturally-derived poisons were likely used for hunting, as medicinal (the Egyptians were aware of many such toxic substances as lead, opium and hemlock as early as 1500 BCE). Use extended eventually to political poisonings as practiced, for example, by the early Greeks and Romans. With time, poisons became widely used and with great sophistication.

Notable poisoning victims include Socrates, Cleopatra, and Claudius. One of the more interesting stories resulting from a combination of both ancient history and current toxicological research, is the story of King Mithridates, king of Pontus (120-63 BC) who according to toxicology legend was so afraid that he might be a casualty of political poisoning, is said to have concocted a potion from a great number of herbs for his own consumption. It is believed he understood that by consuming small amounts of potential poisons, he might protect himself from any would-be poisoner.

That is, he believed in the effectiveness of hormesis. Apparently, his plans worked so well that he gained a name for himself as one so mighty he could not be killed. Unfortunately, it is said that when circumstances were such that he desired to kill himself, he was unable to do so by ingesting poison and had to be run through by a sword instead. Whether or not the story is true, it has led current day scientists to speculate upon the ingredients of his potion. It is believed that some herbs that he may have used, for example, St. Johns Wort could truly have contributed to detoxification of some other poisons.

Recent studies have demonstrated that St. Johns Wort (often used as an herbal remedy) can increase the metabolism or breakdown of certain drugs and chemicals. This early story of toxicology relates a very important concept—that all animals have some kind of intrinsic ability for detoxifying a number of naturally-occurring toxicants in small doses (so that, in some cases low doses of chemicals may pass through the body without causing

harm. From this we derive the concept of a chemical threshold), and that these processes can be altered by exposure to other chemicals.

The question remains as to how adept animals, including humans, are at detoxifying many of the newer industrial chemicals or mixtures of industrial or industrial and natural chemicals. Additionally, it is well known that in some cases, detoxification of chemicals can produce even more toxic compounds. Pre-Industrial Toxicology As declared by E. Monosson, as humans sought to better understand natural compounds that were both beneficial and harmful to them, there was very little if any clear understanding of the fundamental chemical nature of substances.

That is, there was no connection between the ‘ extract’ and ‘ essence’ of a poisonous plant or animal and any one particular chemical that might cause toxicity. In fact, an awareness of chemistry in its modern form did not occur until around the mid to late 1600s. Paracelsus, a physician from the sixteenth century and one of the early “ Fathers of Toxicology” believed that all matter was composed of three “ primary bodies” (sulfur, salt, and mercury). Yet, Paracelsus also coined the now famous maxim of the newly emerging discipline of toxicology: “ All substances are poisons, there is none which is not a poison.

The right dose differentiates a poison from a remedy. ” (Paracelsus, 1493-1541) This phrase and Paracelsus’ name are committed to memory by hundreds of new toxicology students each year and has become the ‘ motto’ of toxicology. Interestingly, if one takes Paracelsus at face value, it appears that in this quote he was referring to substances which served as potential

remedies but could be poisonous if taken in high enough concentrations. Most of us are aware of the fact that overdosing can turn remedies to poisons, even with such apparently innocuous drugs as aspirin and Tylenol.

Another branch on the toxicologyfamilytree that developed in the sixteenth century, along with the study of drugs and the use of chemicals in hunting and warfare, was occupational toxicology. As humans learned how to remove and exploit such materials as coal, and metals and other minerals, occupational exposures to these chemical substances (and chemicals produced incidentally) resulted. Scientists eventually recognized the linkages among illnesses and exposures to these compounds.

Some of the first reports of occupational illness, or diseases caused by activities related to specific occupations, can be found in literature from the mid- to late-1500s. Early occupational observations include the ill effects from lead mining and madness caused by mercury exposure (for example, the saying “ mad as a hatter” was attributed to the common use of mercury in the hat felting process). Later, in the 1700s, Bernardino Ramazzini is credited with bringing to light diseases of tradesmen, including silicosis in stone workers and lead poisoning.

In the late 1700s, Sir Percival Potts made one of the more famous observations in toxicology, linking an occupational exposure (in this case soot in chimney sweeps) to cancer of the scrotum. At this point we have discussed the pre-Industrial Revolution developments in toxicology, that were primarily devoted to the study of such naturally-occurring toxicants as the polyaromatic compounds contained in soot and heavy metals, and such

toxins as botulinum toxin produced by the bacterium Clostridium botulinum.

Toxicology and the Chemical and Industrial Revolution

The chemical/Industrial Revolution of the mid-19th century released many naturally-occurring chemicals into theenvironmentin unprecedented amounts. Also, it produced and released new substances unlike any that had existed in the natural world. With the production and use of these chemicals, and the need to protect humans from the toxic effects of industrial chemicals, toxicology eventually evolved to include its modern day branches: pharmacology, pesticide toxicology, general toxicology, and occupational toxicology.

Towards the mid-late 20th century, environmental toxicology was developed to specifically address the effects on both humans and wildlife of chemicals released into the environment. A notable difference among the branches of toxicology is that pharmacology, pesticides and even occupational toxicology primarily have focused on the effects of relatively high concentrations of single chemicals. This compares to the relatively low concentrations of several different chemicals or chemical mixtures that are relevant to environmental toxicology. The chemicals considered by the earlier branches of toxicology were, and are, a known quantity.

That is, the research was designed to address questions about specific, well-characterized chemicals, exposure conditions, and even concentration ranges rather than complex chemical mixtures. For example, pharmacologists might work with a particular active ingredient (e. g. , salicylic acid or aspirin), and be confident about the route of exposure (oral)

and the concentration or dose. This is seldom the case in environmental toxicology, and hazardous waste assessment and cleanup in particular, where chemicals often are present in mixtures, routes of exposure may vary (for example, from oral to dermal to inhalation).

Significantly, exposure concentrations prove difficult to determine. Mechanisms and Factors Responsible for the Entrance of Toxicants in the Human body and their Harmful Effects Absorption of toxicants Absorption is the process whereby toxicants gain entrance to the body. Ingested and inhaled materials, nonetheless, are considered outside the body until they cross the cellular barriers of the gastrointestinal tract or the respiratory system. To exert an effect on internal organs a toxicant must be absorbed, although such local toxicity as irritation, may occur.

Absorption varies greatly with specific chemicals and with the route of exposure. For skin, oral or respiratory exposure, the exposure dose (or, " outside" dose) is usually only a fraction of the absorbed dose (that is, the internal dose). For substances injected or implanted directly into the body, exposure dose is the same as the absorbed or internal dose. Several factors affect the likelihood that a foreign chemical or, xenobiotic, will be absorbed. According to E. Monosson, the most important are: • Route of exposure Concentration of the substance at the site of contact • Chemical and physical properties of the substance The relative roles of concentration and properties of the substance vary with the route of exposure. In some cases, a high percentage of a substance may not be absorbed from one route whereas a low amount may be absorbed via another route. For example,

very little DDT powder will penetrate the skin whereas a high percentage will be absorbed when it is swallowed. Due to such route-specific differences in absorption, xenobiotics are often ranked for hazard in accordance with the route of exposure.

A substance may be categorized as relatively non-toxic by one route and highly toxic via another route. The primary routes of exposure by which xenobiotics can gain entry into the body are: • Gastrointestinal tract: Key in environmental exposure tofoodand water contaminants and is the most important route for many pharmaceuticals. • Respiratory tract: Key in environmental and occupational exposure to aerial toxicants and some drugs that use this route (i. e. : inhalers). • Skin: Also an environmental and occupational exposure route.

A lot of medicines are applied to the skin directly. Other routes of exposure—used primarily for specific medical purposes—are: • Injections (IV, Subcutaneous, Intradermal, Intrathecal) basically used for medications. • Implants (Hormone patches) • Conjunctival instillations (Eye drops) • Suppositories For a toxic to enter the body (as well as move within, and leave the body) it must pass across cell membranes (cell walls). Cell membranes are formidable barriers and major body defenses that prevent foreign invaders or substances from gaining entry into body tissues.

Normally, cells in solid tissues (for example, skin or mucous membranes of the lung or intestine) are so tightly compacted that substances cannot pass between them. Entry, therefore, requires that the xenobiotic have some capability to penetrate cell membranes. Also, the substance must cross

several membranes in order to go from one area of the body to another. In essence, for a substance to move through one cell requires that it first move across the cell membrane into the cell, pass across the cell, and then cross the cell membrane again in order to leave the cell.

This is true whether the cells are in the skin, the lining of a blood vessel, or an internal organ (for example, the liver). In many cases, in order for a substance to reach its site of toxic action, it must pass through several membrane barriers. Cell membranes surround all body cells and are basically similar in structure. They consist of two layers of phospholipid molecules arranged like a “ sandwich” and also known as " phospholipid bilayer". Each phospholipid molecule consists of a phosphate head and a lipid tail. The phosphate head is polar so it is hydrophilic (attracted to water).

In contrast, the lipid tail is lipophilic (attracted to lipid-soluble substances). The two phospholipid layers are oriented on opposing sides of the membrane so that they are approximate mirror images of each other. The polar heads face outward and the lipid tails inward. The cell membrane is tightly packed with these phospholipid molecules—interspersed with various proteins and cholesterol molecules. Some proteins p across the entire membrane providing for the formation of aqueous channels or pores. Some toxicants move across a membrane barrier with relative ease while others find it difficult or impossible.

Those that can cross the membrane, do so by one of two general methods: either passive transfer or facilitated transport. Passive transfer consists of simple diffusion (or osmotic filtration) and is " passive" in that there is no

requirement for cellular energy or assistance. Some toxicants cannot simply diffuse across the membrane. They require assistance that is facilitated by specialized transport mechanisms. The primary types of specialized transport mechanisms are: • Facilitated diffusion • Active transport • Endocytosis (phagocytosis and pinocytosis). Passive transfer is the most common way that xenobiotics cross cell membranes.

Two factors determine the rate of passive transfer: • Differences in concentrations of the substance on opposite sides of the membrane (substance moves from a region of high concentration to one having a lower concentration. Diffusion will continue until the concentration is equal on both sides of the membrane); and • Ability of the substance to move either through the small pores in the membrane or through the lipophilic interior of the membrane. Properties of the chemical substance that affect its ability for passive transfer are: • Lipid solubility Molecular size • Degree of ionization (that is, the electrical charge of an atom) Substances with high lipid solubility readily diffuse through the phospholipid membrane. Small water-soluble molecules can pass across a membrane through the aqueous pores, along with normal intracellular water flow. Large water-soluble molecules usually cannot make it through the small pores, although some may diffuse through the lipid portion of the membrane, but at a slow rate. In general, highly ionized chemicals have low lipid solubility and pass with difficulty through the lipid membrane.

Most aqueous pores are about 4 angstrom (A) in size and allow chemicals of molecular weight 100-200 to pass through. Exceptions are membranes of

capillaries and kidney glomeruli that have relatively large pores (about 40A) that allow molecules up to a molecular weight of about 50, 000 (molecules slightly smaller than albumen which has a molecular weight of 60, 000) to pass through. Facilitated diffusion is similar to simple diffusion in that it does not require energy and follows a concentration gradient. The difference is that it is a carrier-mediated transport mechanism.

The results are similar to passive transport but faster and capable of moving larger molecules that have difficulty diffusing through the membrane without a carrier. Examples are the transport of sugar and amino acids into red blood cells (RBCs), and into the central nervous system (CNS). Some substances are unable to move with diffusion, unable to dissolve in the lipid layer, and are too large to pass through the aqueous channels. For some of these substances, active transport processes exist in which movement through the membrane may be against the concentration gradient: they move from low to higher concentrations.

Cellular energy from adenosine triphosphate (ADP) is required in order to accomplish this. The transported substance can move from one side of the membrane to the other side by this energy process. Active transport is important in the transport of xenobiotics into the liver, kidney, and central nervous system and for maintenance of electrolyte and nutrient balance. Many large molecules and particles cannot enter cells via passive or active mechanisms. However, some may enter, by a process known as endocytosis. In endocytosis, the cell surrounds the substance with a section of its cell wall.

This engulfed substance and section of membrane then separates from the membrane and moves into the interior of the cell. The two main forms of endocytosis are phagocytosis and pinocytosis. In phagocytosis (cell eating), large particles suspended in the extracellular fluid are engulfed and either transported into cells or are destroyed within the cell. This is a very important process for lung phagocytes and certain liver and spleen cells. Pinocytosis (cell drinking) is a similar process but involves the engulfing of liquids or very small particles that are in suspension within the extracellular fluid.

Gastrointestinal Tract The gastrointestinal tract (GI tract, the major portion of the alimentary canal) can be viewed as a tube going through the body. Its contents are considered exterior to the body until absorbed. Salivary glands, the liver, and the pancreas are considered accessory glands of the GI tract as they have ducts entering the GI tract and secrete enzymes and other substances. For foreign substances to enter the body, they must pass through the gastrointestinal mucosa, crossing several membranes before entering the blood stream.

Substances must be absorbed from the gastrointestinal tract in order to exert a systemic toxic effect, although local gastrointestinal damage may occur. Absorption can occur at any place along the entire gastrointestinal tract. However, the degree of absorption is strongly site dependent. Three main factors affect absorption within the various sites of the gastrointestinal tract: • Type of cells at the specific site • Period of time that the substance remains at the site • pH of stomach or intestinal contents at the site.

Under normal conditions, xenobiotics are poorly absorbed within the mouth and esophagus, due mainly to the very short time that a substance resides within these portions of the gastrointestinal tract. There are some notable exceptions. For example, nicotine readily penetrates the mouth mucosa. Also, nitroglycerin is placed under the tongue (sublingual) for immediate absorption and treatment of heart conditions. The sublingual mucosa under the tongue and in some other areas of the mouth is thin and highly vascularized so that some substances will be rapidly absorbed.

The stomach, having high acidity (pH 1-3), is a significant site for absorption of weak organic acids, which exist in a diffusible, nonionized and lipid-soluble form. In contrast, weak bases will be highly ionized and therefore are absorbed poorly. Chemically, the acidic stomach may break down some substances. For this reason those substances must be administered in gelatin capsules or coated tablets, that can pass through the acidic stomach into the intestine before they dissolve and release their contents. Another determinant that affects the amount of a substance that will be absorbed in the stomach is the presence of food.

Food ingested at the same time as the xenobiotic may result in a considerable difference in absorption of the xenobiotic. For example, the LD50 for Dimethline (a respiratory stimulant) in rats is 30 mg/kg (or 30 parts per million) when ingested along with food, but only 12 mg/kg when it is administered to fasting rats. The greatest absorption of chemicals, as with nutrients, takes place in the intestine, particularly in the small intestine (see Figure 9). The intestine has a large surface area consisting of outward

projections of the thin (one-cell thick) mucosa into the lumen of the intestine (the villi).

This large surface area facilitates diffusion of substances across the cell membranes of the intestinal mucosa. Since the intestinal pH is near neutral (pH 5-8), both weak bases and weak acids are nonionized and are usually readily absorbed by passive diffusion. Lipid soluble, small molecules effectively enter the body from the intestine by passive diffusion. In addition to passive diffusion, facilitated and active transport mechanisms exist to move certain substances across the intestinal cells into the body, including such essential nutrients as glucose, amino acids and calcium.

Also, strong acids, strong bases, large molecules, and metals (and some important toxins) are transported by these mechanisms. For example, lead, thallium, and paraquat (herbicide) are toxicants that are transported across the intestinal wall by active transport systems. The high degree of absorption of ingested xenobiotics is also due to the slow movement of substances through the intestinal tract. This slow passage increases the length of time that a compound is available for absorption at the intestinal membrane barrier. Intestinal microflora and gastrointestinal enzymes can affect the toxicity of ingested substances.

Some ingested substances may be only poorly absorbed but they may be biotransformed within the gastrointestinal tract. In some cases, their biotransformed products may be absorbed and be more toxic than the ingested substance. An important example is the formation of carcinogenic nitrosamines from non-carcinogenic amines by intestinal flora. Very little

absorption takes place in the colon and rectum. As a general rule, if a xenobiotic has not been absorbed after passing through the stomach or small intestine, very little further absorption will occur.

However, there are some exceptions, as some medicines may be administered as rectal suppositories with significant absorption. An example, is Anusol (hydrocortisone preparation) used for treatment of local inflammation which is partially absorbed (about 25%). Respiratory Tract Many environmental and occupational agents as well as some pharmaceuticals are inhaled and enter the respiratory tract. Absorption can occur at any place within the upper respiratory tract. However, the amount of a particular xenobiotic that can be absorbed at a specific location is highly dependent upon its physical form and solubility.

There are three basic regions to the respiratory tract: • Nasopharyngeal region • Tracheobronchial region • Pulmonary region By far the most important site for absorption is the pulmonary region consisting of the very small airways (bronchioles) and the alveolar sacs of the lung. The alveolar region has a very large surface area (about 50 times that of the skin). In addition, the alveoli consist of only a single layer of cells with very thin membranes that separate the inhaled air from the blood stream. Oxygen, carbon dioxide and other gases pass readily through this membrane.

In contrast to absorption via the gastrointestinal tract or through the skin, gases and particles, which are water-soluble (and thus blood soluble), will be absorbed more efficiently from the lung alveoli. Water-soluble gases and liquid aerosols can pass through the alveolar cell membrane by simple

passive diffusion. In addition to solubility, the ability to be absorbed is highly dependent on the physical form of the agent (that is, whether the agent is a gas/vapor or a particle). The physical form determines penetration into the deep lung.

A gas or vapor can be inhaled deep into the lung and if it has high solubility in the blood, it is almost completely absorbed in one respiration. Absorption through the alveolar membrane is by passive diffusion, following the concentration gradient. As the agent dissolves in the circulating blood, it is taken away so that the amount that is absorbed and enters the body may be quite large. The only way to increase the amount absorbed is to increase the rate and depth of breathing. This is known as ventilation-limitation.

For blood-soluble gases, equilibrium between the concentration of the agent in the inhaled air and that in the blood is difficult to achieve. Inhaled gases or vapors, which have poor solubility in the blood, have quite limited capacity for absorption. The reason for this is that the blood can become quickly saturated. Once saturated, blood will not be able to accept the gas and it will remain in the inhaled air and then exhaled. The only way to increase absorption would be to increase the rate of blood supply to the lung.

This is known as flow-limitation. Equilibrium between blood and the air is reached more quickly for relatively insoluble gases than for soluble gases. The absorption of airborne particles is usually quite different from that of gases or vapors. The absorption of solid particles, regardless of solubility, is dependent upon particle size. Large particles (> 5 µM) are generally deposited in the nasopharyngeal region ((head airways region) with little

absorption. Particles 2-5 µM can penetrate into the tracheobronchial region. Very small particles (