As I'm going to argue repeatedly today, biology has become a science over the last 50 years. And, as a consequence, we can talk about some basic principles. We can talk about some laws and then begin to apply them to very interesting biological problems.

And so our general strategy this semester, as it has been in the past, is to spend roughly the first half of the semester talking about the basic laws and rules that govern all forms of biological life on this planet. And you can see some of the specific kinds of problems, including the problem of cancer, how cancer cells begin to grow abnormally, how viruses proliferate, how the immune system functions, how the nervous system functions, stem cells and how they work and their impact on modern biology, molecular medicine, and finally perhaps the future of biology and even certain aspects of evolution. The fact of the matter is that we now understand lots of these things in ways that were inconceivable 50 years ago. And now we could begin to talk about things that 50 years ago people could not have dreamt of. When I took this course, and I did take it in 1961, we didn't know about 80% of what we now know. You cannot say that about mechanics in physics, you cannot say that about circuit theory in electronics, and you cannot say that, obviously, about chemistry.

And I'm mentioning that to you simply because this field has changed enormously over the ensuing four decades. I won't tell you what grade I got in 7. 1 because if I would, and you might pry it out of me later in the semester, you probably would never show up again in lecture.

But in any case, please know that this has been an area of enormous ferment. And the reason it's been in such enormous ferment is of the discovery in 1953 by Watson and Crick of the structure of the DNA double helix. Last year I said that we were so close to this discovery that both Watson and Crick are alive and with us and metabolically active, and more than 50 years, well, exactly 50 years after the discovery. Sadly, several months ago one of the two characters, Francis Crick died well into his eighties, and so he is no longer with us. But I want to impress on you the notion that 200 years from now, we will talk about Watson and Crick the same way that people talk about Isaac Newton in terms of physics. And that will be so because we are only beginning to perceive the ramifications of this enormous revolution that was triggered by their discovery. That is the field of molecular biology and genetics and biochemistry which has totally changed our perceptions of how life on Earth is actually organized.

Much of the biology to which you may have been exposed until now has been a highly descriptive science. That is you may have had courses in high school where you had to memorize the names of different organisms, where you had to understand how evolutionary phylogenies were organized, where you had to learn the names of different organelles, and that biology was, for you, a field of memorization. And one point we would like, hopefully successfully, to drive home this semester is the notion that biology has now achieved a logical and rational coherence that allows us to articulate a whole set of rules that explain how all life forms on this planet are

organized. It's no longer just a collection of jumbled facts. Indeed, if one masters these molecular and genetic principles, one can understand in principle a large number of processes that exist in the biosphere and begin to apply one's molecular biology to solving new problems in this arena.

One of the important ideas that we'll refer to repeatedly this semester is the fact that many of the biological attributes that we posses now were already developed a very long time ago early in the inception of life on this planet. So if we look at the history of Earth, here the history of Earth is given as 5 billion years, this is in thousands obviously. The Earth is probably not that old.

It's probably 4.5 or 4 or 3 billion years but, anyhow, that's when the planet first aggregated, as far as we know.

One believes that no life existed for perhaps the first half billion years, but after half a billion years, which is a lot of time to be sure, there already begins to be traces of life forms on the surface of this planet. And that, itself, is an extraordinary testimonial, a testimonial to how evolutionary processes occur. We don't know how many planets there are in the universe where similar things happened.

And we don't know whether the solution that were arrived at by other life systems in other places in the universe, which we may or may not ever discover, were the similar solutions to the ones that have been arrived at here.

It's clear, for example, that to the extent that Darwinian Evolution governs the development of life forms on this planet that is not an artifact of the Earth. Darwinian Evolution is a logic which is applicable to all life forms and all biosystems that may exist in the universe, even the ones we have not discovered.

However, there are specific solutions that were arrived at during the development of life on Earth which may be peculiar to Earth.

The structure of the DNA double helix.

The use of ribose in deoxyribose. The choice of amino acids to make proteins. And those specific solutions may not be universal.

Whether they're universal in the sense of existing in all life forms across the planet, the fact is that many of the biochemical and molecular solutions that are represented in our own cells today, these solutions, these problems were solved already 2 and 3 billion years ago. And once they were solved they were kept and conserved almost unchanged for the intervening 2 or 3 billion years. And that strong degree of conservation means that we can begin to figure out what these principles were early on in evolution of life on this planet and begin to apply them to all modern life forms.

From the point of view of evolution, almost all animals are identical in terms of their biochemistry and in terms of their physiology.

The molecular biology of all eukaryotic cells, that is all cells that have nuclei in them, is almost the same.

And, therefore, we're not going to focus much in this course this semester on specific species but rather focus on general principles that would allow us to understand the cells and the tissues and the physiological processes that are applicable to all species on the surface of the planet. Let's just look here and get us some perspective on this because, the fact of the matter is, is that multicellular life forms, like ourselves, we have, the average human being has roughly three or four or five times ten to the thirteenth cells in the body. That's an interesting figure.

The average human being goes through roughly ten to the sixteenth cell divisions in a lifetime, i.e. ten to the sixteenth times in your body there will be cells that divide, grow and divide.

Every day in your body there are roughly ten to the eleventh cells that grow and divide. Think of that, ten to the eleventh.

And you can divide that by the number of minutes in a day and come up with an astounding degree of cellular replication going on.

All of these processes can be traceable back to solutions that were arrived at very early in the evolution of life on this planet, perhaps 550, 600 million years ago when the first multicellular life forms began to evolve. Before that time, that is to say before 500 to 600 million years ago, there were single-cell organisms.

For example, many of them survive to this day. There were yeast-like organisms. And there were bacteria. And we make one large and major distinction between the two major life forms on the planet in terms of cells. One are the prokaryotic cells. And these are the cells of bacteria, I'll show you an image of them shortly, which lack nuclei.

And the eukaryotic cells which poses nuclei and indeed have a highly complex cytoplasm and overall cellular architecture.

We think that the prokaryotic life forms on this planet evolved first probably on the order of 3 billion years ago, maybe 3.

billion years ago, and that about 1. billion years ago cells evolved that contained nuclei. Again, I'll show them to you shortly. And these nucleated cells, the eukaryotes then existed in single-cell form for perhaps the next 700 or 800 million years until multi-cellular aggregates of eukaryotic cells first assembled to become the ancestors of the multi-cellular plants and the multi-cellular animals that exist on the surface of the Earth today. To put that in

perspective, our species has only been on the planet for about 150, 00 years. So we've all been here for that period of time.

And a 150,000 sounds like a long time, in one sense, but it's just Â“a blink in the eye of the LordÂ” as one says in terms of the history of life on this planet, and obviously the history of the universe which is somewhere between 13 and 15 billion years old.

You can begin to see that the appearance of humans represents a very small segment of the entire history of life on this planet.

And here you can roughly see the way that life has developed during this period of time from the fossil record. You see that many plants actually go back a reasonable length of time, but not more than maybe 300 or 400 million years. Here are the Metazoa.

And this represents -- Well, can you hear me? Wow, 614 came in handy.

OK. So if we talk about another major division, we talk about protozoa and metazoa. The suffix zoa refers to animals, as in a zoo. And the protozoa represents single-cell organisms.

The metazoa represent multi-cellular organisms. And we're going to be focusing largely on the biology of metazoan cells this semester, and we're going to be spending almost no time on plants.

It's not that plants aren't important. It's just that we don't have time to cover everything. And, indeed, the molecular biology that you learn this semester will ultimately enable you to understand much about the physiology of multi-cellular plants which happen to be called metaphyta, a term you may never hear again in your entire life after today. That reminds me, by the way, that both Dr. Lander and I sometimes use big words.

And people come up to me afterwards each semester each year and say Professor Weinberg, why don't you talk simple, why don't you talk the way we heard things in high school?

And please understand that if I use big words sometimes it's to broaden your vocabulary so you can learn big words.

One of the things you should be able, one of the big take-home lessons of this course should be that your vocabulary is expanded.

Not just your scientific vocabulary but your general working English vocabulary. Perhaps the biggest goal of this course, by the way, is not that you learn the names of all the organelles and cells but that you learn how to think in a scientific and rational way. Not just because of this course but that this course helps you to do so. And as such,

we don't place that much emphasis on memorization but to be able to think logically about scientific problems. Here we can begin to see the different kinds of metazoa, the animals. Here are the metaphyta and here are the protozoa, different words for all of these.

And here we see our own phylum, the chordates. And, again, keep in mind that this line right down here is about 550 to 600 million years ago, just to give you a time scale for what's been going on, on this planet.

One point we'll return to repeatedly throughout the semester is that all life forms on this planet are related to one another.

It's not as if life was invented multiple times on this planet and that there are multiple independent inventions to the extent that life arose more than once on this planet, and it may have. The other alternative or competing life forms were soon wiped out by our ancestors, our single-cellular ancestors 3 billion years ago.

And, therefore, everything that exists today on this planet represents the descendents of that successful group of cells that existed a very long time ago. Here we have all this family tree of the different metazoan forms that have been created by the florid hand of evolution. And we're not going to study those phylogenies simply because we want to understand principles that explain all of them.

Not just how this or that particular organism is able to digest its food or is able to reproduce. Here's another thing we're not going to talk about. We're not going to talk about complicated life forms. We're not going to talk very much, in fact hardly at all, about ecology. This is just one such thing, the way that a parasite is able to, a tapeworm is able to infect people.

This is, again, I'm showing you this not to say this is what we're going to talk about, we're not going to talk about that.

We're not going to talk about that. There's a wealth of detail that's known about the way life exists in the biosphere that we're simply going to turn our backs on by focusing on some basic principles.

We're also not going to talk about anatomy. Here in quick order are some of the anatomies you may have learned about in high school, and I'm giving them to you each with a three-second minute, a three-second showing to say we're not going to do all this.

And rather just to reinforce our focus, we're going to limit ourselves to a very finite part of the biosphere.

And here is one way of depicting the biosphere. It's obviously an arbitrary way of doing so but it's quite illustrative.

Here we start from molecules. And, in fact, we will occasionally go down to submolecular atoms. And here's the

next dimension of complexity, organelles. That is these specialized little organs within cells. We're going to focus on them as well. We're going to focus on cells. And when we start getting to tissues, we're going to start not talking so much about them.

And we're not going to talk about organisms and organs or entire organisms or higher complex ecological communities.

And the reason we're doing that is that for 40 years in this department, and increasingly in the rest of the world there is the acceptance of the notion that if we understand what goes on down here in these first three steps, we can understand almost everything else in principle.

Of course, in practice we may not be able to apply those principles to how an organism works or to how the human brain works yet.

Maybe we never will. But, in general, if one begins to understand these principles down here, one can understand much about how organismic embryologic develop occurs, one can understand a lot about a whole variety of disease processes, one can understand how one inherits disease susceptibilities, and one can understand why many organisms look the way they do, i.e. the process of developmental biology.

And so, keep in mind that if you came to hear about all of these things, we're going to let you down. That's not what this is going to be about. This also dictates the dimensions of the universe that we're going to talk about because we're going to limit ourselves to the very, very small and not to the microscopic. On some occasions we'll limit ourselves to items that are so small you cannot see them in the light microscope. On other occasions we may widen our gaze to look at things that are as large as a millimeter, but basically we're staying very, very small. Again, because we view, correctly or not, the fact that the big processes can be understood by delving into the molecular details of what happens invisibly and cannot be seen by most ways of visualizing things, including the light and often even the electron microscope. Keep in mind that 50 years ago we didn't know any of this, for all practical purposes, or very little of this. And keep in mind that we're so close to this revolution that we don't really understand its ramifications.

I imagine it will be another 50 years before we really begin to appreciate the fallout, the long-term consequences of this revolution in biology which began 51 years ago. And so you're part of that and you're going to experience it much more than my generation did.

And indeed one of the reasons why MIT decided about 10 or 12 years ago that every MIT undergraduate needed to have at least one semester of biology is that biology, in the same way as physics and chemistry and math, has become an integral part of every educated person's knowledge-base in terms of their ability to deal with the world

in a rational way. In terms of public policy, in terms of all kinds of ethical issues, they need to understand what's really going on. Many of the issues that one talks about today about bioethics are articulated by people who haven't the vaguest idea about what we're talking about this semester.

You will know much more than they will, and hopefully some time down the road, when you become more and more influential voices in society, you'll be able to contribute what you understood here, what you learned here to that discussion.

Right now much of bioethical discussion is fueled by people who haven't the vaguest idea what a ribosome or mitochondrion or even a gene is, and therefore is often a discussion of mutually shared ignorance which you can diffuse by learning some basics, by learning some of the essentials. Here is the complexity of the cell we're going to focus on largely this semester, which is to say the eukaryotic rather than the prokaryotic cell.

And this is just to give you a feeling for the overall dimensions of the cell and refer to many of the landmarks that will repeatedly be brought up during the course of this semester.

Here is the nucleus. The term karion comes from the Greek meaning a seed or a kernel. And the nucleus is what gives the eukaryotic cell its name. Within the nucleus, although not shown here, are the chromosomes which carry DNA.

You may have learned that a long time ago. Outside of the nucleus is this entire vast array of organelles that goes from the nuclear membrane, and I'm point to it right here, all the way out to the outside of the cell. The outside limiting membrane, the outer membrane of the cell is called the plasma membrane.

And between the nucleus and the plasma membrane there is an enormous amount of biological and biochemical activity taking place.

Here are, for example, the mitochondria. And the mitochondria, as one has learned, are the sources of energy production in the cell. And, therefore, we'll touch on them very briefly. This is an artist's conception of what a mitochondrion looks like. Almost always artists' conceptions of these things have only vague resemblance to the reality.

But, in any case, you can begin to get a feeling for what one thinks about their appearance. Here are mitochondria sliced open by the hand of the artist. And, interestingly, mitochondria have their own DNA in them. One now accepts the fact that mitochondria are the descendents of bacteria which insinuated themselves into the cytoplasms of larger cells, roughly 1.5 billion years ago, and began to do a specialized job which increasingly became the job of energy production within cells. To this day, mitochondria retain some vestigial attributes of the bacterial ancestors which initially colonized or parasitized the cytoplasm of the cell.

When I say parasitized, you might imagine that the mitochondria are taking advantage of the cell.

But, in fact, the mitochondria represent the essential sources of energy production in the cell. Without our mitochondria, as you might learn by taking cyanide, for example, you don't live for very many minutes. And the vestiges of bacterial origins of mitochondria are still apparent in the fact that mitochondria still have their own DNA molecule, their own chromosome. They still have their own ribosomes and protein synthetic apparatus, even though the vast majority of the proteins inside mitochondria are imported from the cytoplasm, i.e., these vestigial bacteria now rely on proteins made by the cell at large that are imported into the mitochondrion to supplement the small number of vestigial bacterial proteins which are still made here inside the mitochondrion and used for essential function in energy production. Here is the Golgi apparatus.

And the Golgi apparatus up here is used for the production of membranes.

As one will learn throughout the semester, the membranes of a cell are in constant flux and are being pulled in and remodeled and regenerated. The Golgi apparatus is very important for that.

Here's the rough endoplasmic reticulum. That's important for the synthesis of proteins which are going to be displayed on the surface of cells, you don't see them depicted here, or are going to be secreted into the extracellular space.

Here are the ribosomes, which I might have mentioned briefly before. And these ribosomes are the factories where proteins are made.

Again, we're going to talk a lot about them. And, finally, several other aspects, the cytoskeleton. The physical integrity, the architecture of the cell is maintained by a complex network of proteins which together are considered to be the cytoskeleton. And they enable the cell to have some rigidity, to resist tensile forces, and actually to move.

Cells can actually move from one place to the other.

They have motile properties. They're able to move from one location to another. The process of cell motility, if that's a word you'd like to learn.

Here is what a prokaryotic cell looks like by contrast.

And I just want to give you a feeling. First of all, it looks roughly like a mitochondrion that I discussed before. But you see that there is the absence of a nuclear membrane. There's the absence of the highly complex cytoarchitecture. Cyto always refers to cells.

There's the absence of the complex cytoarchitecture that one associates with eukaryotic cells. In fact, all that a bacterium has is this area in the middle. It's called the nucleoid, a term which you also will probably never hear in your lifetime.

And it represents simply an aggregate of the DNA of the chromosomes of the bacterium. And, in most bacteria, the DNA consists of only a single molecule of DNA which is responsible for carrying the genetic information of the bacteria. There's no membrane around this nucleoid. And outside of this area where the DNA is kept are largely ribosomes which are important for protein synthesis. There's a membrane on the outside of this called the plasma membrane, very similar to the plasma membrane of eukaryotic cells. And outside of that is a meshwork that's called the outer membrane, it's sometimes called the cell wall of the bacterium, which is simply there to impart structural rigidity to the bacterium making sure that it doesn't explode and holding it together. And then there are other versions of eukaryotic cells. Here's what a plant cell looks like.

And it's almost identical to the cells in our body, except for two major features. For one thing, it has chloroplasts in it which are also, one believes now, the vestiges of parasitic bacteria that invade into the cytoplasm of eukaryotic cells. So, in addition to mitochondria which are responsible for energy production in all eukaryotic cells, we have here the chloroplasts which are responsible for harvesting light and converting it into energy in plant cells. The rest of the cytoplasm of a plant cell looks pretty much the same.

One feature that I didn't really mention when I talked about an animal cell is in the middle of the nucleus, here you can see, is a structure called a nucleolus. And a nucleolus, or the nucleolus in the eukaryotic cell is responsible for making the large number of ribosomes which are exported from the nucleus into the cytoplasm. And, as I mentioned just before, the ribosomes are responsible for protein synthesis.

It turns out this is a major synthetic effort on the part of most cells. Cells, like our own, have between 5 and 10 million ribosomes in the cytoplasm. So it's an enormous amount of biomass in the cytoplasm whose sole function is to synthesize proteins.

As we will learn also, proteins that are synthesized by the ribosomes don't sit around forever. Some proteins have long lives.

Some proteins have lifetimes of 15 minutes before they're degraded, before they're turned over. One other distinction between our cells, that is the cells of metazoa and metaphyta, are the cell walls, analogous to the cell walls of bacteria, this green thing on the outside. As I said before, we do not have cell walls around our cells. And we will, as the semester goes on, go into more and more details about different aspects of this cytoarchitecture during the first half of the semester. Here, for example, is an artist's depiction of the endoplasmic reticulum.

Why it has such a complex name, I cannot tell you, but it does.

It's called the ER in the patois of the street. The ER.

And the endoplasmic reticulum is a series of membranes.

Keep in mind, not the only membrane in the cell is the plasma membrane.

Within the cytoplasm there are literally hundreds of membranes which are folded up in different ways.

Here you see them depicted. And one set of these membranes, often they're organized much like tubes, represents the membranes of the endoplasmic reticulum which either lacks ribosomes attached to it or has these ribosomes attached to it which cause this to be called the rough endoplasmic reticulum to refer to its rough structure which is created by the studding of ribosomes on the surface.

As we will learn, just trying to give you a feeling for the geography of what we're going to talk about this semester, these ribosomes on the surface of the endoplasmic reticulum are dedicated to the task of making highly specialized proteins which are either going to be dispatched to the surface of the cell where they will be displayed on the cell's surface or actually secreted into the extracellular space. Many of the proteins that are destined for our body are not kept within cells but are released into the extracellular space where they serve important functions, and so we're going to focus very much on them.

Here's actually what some of these things look like in the electron microscope to see whether we can either believe or fully discredit the imaginations of the artists. Here's the rough endoplasmic reticulum I showed you in schematic form before. And you can see why it's called rough. All these black dots are ribosomes attached on the outside. Here's the Golgi apparatus.

You see these vesicles indicated here. And a vesicle, just to use a new word, is simply a membranous bag.

And keep in mind, by the way, that we're not going to spend the semester with these highly descriptive discussions.

Our intent today is to get a lot of these descriptive discussions out of the way so that we can begin to talk in a common parlance about many of the parts, the molecular parts of cells and organisms.

Here is the mitochondrion which we saw depicted before.

It looks similar to, but not identical to the artist's description of that. And keep in mind that the mitochondrion in our cells, as I said before, are the descendents of parasitic bacteria. Here's the endoplasmic reticulum, and the way it

would look, as it does in certain parts of the cell when it doesn't have all of these ribosomes studded on the surface. The endoplasmic reticulum here is involved in making membranes.

The endoplasmic reticulum here is involved in the synthesis and export of proteins to the cell's surface and for secretion, as I mentioned before. Much of what we're going to talk about over the next days is going to be focused on the nucleus of the cell, that is on the chromosomes on the cell and on the material which is called chromatin which carries the genetic material.

So the term chromatin is used in biology to refer simply to the mixture of DNA and proteins, which together constitutes the chromosomes. So chromatin has within it DNA, it has protein, and it has a little bit of RNA in it.

And we're going to focus mostly on the DNA in the chromatin, because if we can begin to understand the way the DNA works and functions many other aspects will flow from that.

I mentioned the cell's surface, and I just want to impress on you the fact that the plasma membrane of a cell is much more complicated than was depicted in these drawings that I showed you just before.

If we had a way of visualizing the plasma membrane of a cell, we would discover that it's formed from lipids. We see such lipids there, phospholipids, many of them. We'll talk about them shortly. That the outside of the cell, there are many proteins, you see them here, which thread their way through the plasma membrane, have an extracellular and intracellular part.

And these transmembrane proteins, which reach from outside to inside, represent a very important way by which the cell senses its environment. This plasma membrane, as we'll return to, represents a very effective barrier to segregate what's inside the cell from what's outside of the cell to increase concentrations of certain biochemical entities.

But at the same time it creates a barrier to communication.

And one of the things that cells have had to solve over the last 700 to 800 million years is ways by which the exterior of the cell is able to send certain signals and transmit that information to the interior of the cell. At the same time, cells have had to use a number of different, invent a number of different proteins, some of them indicated here, which are able to transport materials from the outside of the cell into the cell, or visa versa. So the existence of the plasma membrane represents a boon to the cell in the sense that it's able to segregate what's on the inside from what's on the outside.

But it represents an impediment to communication which had to be solved, as well as an impediment to transport. And many of these transmembrane proteins are dedicated to solving those particular problems.

Here you see, once again an artist's depiction form, aspects of the cytoskeleton of the cell. And when we talk about the cytoskeleton we talk about this network of proteins which, as I said before, gives the cell rigidity.

Keep in mind that the prefix cyto or the suffix cyt refers always to cells. Allows the cell to have shape. And here you can see this network as depicted in one way, but here it's depicted actually much more dramatically. And here you begin to see the complexity of what exists inside the cell. Here are these proteins.

These are polymers of proteins called vimentin which are present in very many mesenchymal cells. Here are microtubules made from another kind of protein. Here are microfilaments, in this case made of the molecule actin. And if we looked at individual molecules of actin they would be invisible.

This is end-to-end polymerization of many actin molecules.

And we're looking here under the microscope from one end of the cell to the other end of the cell. And you can see how these molecules, they create stiffness, and they also enable the cell to contract and to move. Some people might think that the interior of the cell is just water with some molecules floating around them. But if you actually look at what's present in the cell, more than 50% of the volume is taken up by proteins.

It's not simply an aqueous solvent where everything moves around freely.

It's a very viscous slush, a mush. And it's quite difficult there for many cells to move around from one part of the cell to the other. Here you begin to get a feeling now for how the connection, which we'll reinforce shortly in great detail, between individual molecules and the cytoskeleton.

And here you see these actin fibers. I showed them to you just moments ago stretching from one end of the cell to the other.

And each of these little globules is a single actin monomer which polymerize end-to-end and then form multi-strand aggregates to create the actin cytoskeleton. Here's an intermediate filament and here's the microtubules that are formed, once again giving us this impression that the cell is actually highly organized and that that high degree of organization is able to give it some physical structure and shape and form. I think we're going to end today two minutes early. You probably won't object.