0

My name is Craig Thomas

Its my pleasure to welcome you to the NIHsPrinciples in Clinical Pharmacology course

Ive been asked to give the introduction toModule and as by extension the entire course

Before we begin with this introduction Ithink its worthy to say that youre all in a very fortunate position to be able to watchand learn from each individual lecturer in each of the modules

Youre going to get a wealth of informationabout the type of science that involves pharmacology and clinical pharmacology about the kindof data that is generated about how that data is used collectively to administer drugsto yield an optimal clinical benefit to patients

As this is the introduction to Module inthe course I think its imperative that we begin with some fairly straightforward definitionsof what pharmacology is

Pharmacology is the science of how drugs acton biological systems and how that system responds to the drug

A system is a fairly broad term

It can mean anything as complex as the humanbody which is a complex and integrated system

But it doesnt have to be such a complex systemto render any kind of pharmacological useful data

It can be something as simple as a cell lineor a protein that can be used to generate data that can be used by pharmacologists clinical pharmacologist and the practitioners of medicine to better optimize how a therapymight be used

Its important to realize that within eachof the lectures within each of the modules youre going to be learning about the kindof data that is generated in these various systems

Youre going to be learning about the detailsof how that data is generated how its used

to better define therapeutic use alone orin combination with other drugs

Clinical pharmacology is the applied versionof that

Its how all of that data can then be usedby physicians by veterinarians by pharmacists by scientists to better practice medicine

So both the basic research within pharmacologyand the more applied research within clinical pharmacology serves as the basis for the lecturesyoure going to hear throughout this course

So and basically this bullet point getsto that point

So doctors veterinarians pharmacists usethis knowledge to achieve optimal therapeutic outcomes through the appropriate preparationand dispensing of medicines

And thats important

So its not just how theyre given butits also how the drugs are prepared to before theyre given

So this is complex and throughout the courseyoure going to see the complexities laid out by the lecturers

Its important at least for me and I thinkfor a lot of people whom taught me and whom I respect in this field to bring this downto a core principle

At the heart of this is mechanism

Modern drug discovery is a mechanism drivenfield

And its important to realize that every therapeutic nearly all new experimental therapeutics and I would probably say all althoughI just cant prove that so Ill qualify with nearly all new experimental therapeutics havea defined mechanism

Sometimes more than one mechanism

And most have a companion diagnostic thatallow researchers to track the mechanistic engagement of that medicine within the complexsystems like the human body

And because we have a mechanistic rationaleor belief that we have a mechanistic rationale for why medicine should work within the humanbody to alleviate the effects of a specific

disease

And because we can often times track whetheror not that mechanism is engaged when a therapeutic is given to a human being because of thesereasons because of these realities clinical pharmacology has never been more importantin our ability to understand the benefit of a medicine and to tweak it to utilize itmore effectively

So really I want to restate that the lessonsyoure going to be learning throughout all of these modules are imperative to anybodywho wants to practice clinical pharmacology

This gets to the concept of seeing the forestseeing the trees

And this is not an easy thing to accomplishin any complex field: economics international relations and certainly pharmacology andclinical pharmacology there is the that battle between seeing the forest and alsoseeing the trees

Now what do we mean by the forest and whatdo we mean by the trees here in pharmacology and clinical pharmacology?

So the forest is the concept of visualizingunderstanding any medicine with a clinical benefit

So a large percentage of the population takesstatins to control their cholesterol certain types of cholesterol circulating cholesterolin the blood

And physicians can see that effect take placein an individual patient

And thats the forest

Thats seeing the benefit of a medicine

In the sense of a population we can see populationsof individuals take taking statins we can see the effect of how cholesterol certaintypes of cholesterol being lowered in a population

Thats the forest

But why do statins work?

Why does that specific medicine work?

Why does it effectively bring down cholesterollevels in an individual in a human being?

Thats the trees

The reason behind why these medicines work

Thats the more detailed oriented versionof seeing the trees

Now any scientist wishing to understandpractice and master clinical pharmacology

must be able to see both the forest and thetrees

And its important within the lectures andModule and all the others these are

designed to help students learn about both

Now within each lecture youre going to belearning specifics

Youre going to be learning about the trees

Now its important to keep in mind the forest

There are going to be individuals who arein medical school watching this course

Youre going to be people who are eventuallygoing to be visualizing the forest

Its imperative that you also understand thebasics the trees that the real details

the kind of data that pharmacology andclinical pharmacology yields

And thats the kind of data youre going tobe learning about in each one of these lectures

So lets consider some of the core principles

Foremost identifying and developing an experimentaldrug with a defined mechanismofaction is

often times the first step in developing anew therapy

This is drug discovery

This is where were going to be starting witha lot of these lectures

As a matter of fact all of module six delvesinto drug discovery and development

Within that module youre going to be learninga lot of how scientists and pharmaceutical

companies academic labs begin the processof developing a new drug

Almost exclusively that process begins withdefining a specific mechanismofaction

So a and these scientists and theseare high level practitioners of this type

of science that do this and do this well theyregoing to be looking for a drug a small molecule a biologic which inhibits and enzymeor activates a receptor

Thats the defined mechanismofaction

And the theories behind why inhibiting thatenzyme or activating that receptor might alleviate the symptoms or causes of a disease is thecommon first step that most drug discovery efforts take place

And thats when data what would probably bereferred to as pharmacological data thats when that data starts to get generated

And youre hear about a lot that early datain the module six drug discovery lectures

Within that within that mechanismofaction thats when we start to track these types of data

And we try to anticipate before we even getstarted what are the potential consequences of that mechanismofaction of inhibitingthat enzyme in a disease cell in tissues in the system at large

Because its within that anticipated consequencesof inhibiting that enzyme or activating that receptor that lay the groundwork for the potentialefficacy of a future drug

Now we also try to understand and anticipatethe consequences of inhibiting that enzyme or activating that receptor the anticipatethe consequences of the mechanismofaction of that drug or future drug on healthy cellson healthy tissues on the system at large

Because its often times that mechanismofactionworking systemically that creates the doselimiting toxicities that will define how much of adrug can be given to an individual patient the potential toxicology

So beyond that we have a handful of mechanismofactionsthat we know cant be tolerated by healthy cells by the tissues by the systems

These are mechanismofactions thatve learnedthrough trial and error hard fought lessons

Lessons that doomed many drugs

These if we if we have an offtargetevent in one of those mechanisms we know that that molecules or that potentialdrug is probably not going to survive the development phase of a drug

So these are known toxicities

Common examples include the hERG channel

This in an ion channel that governs certainelements of the human heartbeat

And we know that we cant inhibit or modulatethat particular ion channel in any relevant way and still have a therapy that would beof use with zero toxicology or zero toxicity

So there are hard fought lessons on knowmechanismsofaction

These are dozens if not almost a hundredknown mechanismofactions that we know that a future medicine cant have as an offtargeteffect

So we have all of these concepts the anticipatedconsequences good positive consequences of the mechanismofaction that were interestedin which would yield a potential efficacy in a patient

The potential that that mechanismofactionmight also have toxicity and then known toxicities

All of these are going to be the kind of datathat surround the question of mechanismofaction for a future therapy and the kind of datathat pharmacologists and clinical pharmacologists rely upon to then utilize a future medicinein a disease population

And its important to state that all of thesemechanismofaction related outcomes are concentration dependent

So we might need a concentration level toyield that efficacy but we cant achieve a certain concentration level of that drugin that human before it creates a toxicity

Within that dose window that achieves thedesired mechanismofaction related effect but not the toxicity thats the criticalelement that defines the therapeutic index of that therapy

The scale and timing of that mechanismofactionrelated event so the drugs effect in the

body its anticipated mechanistically definedeffect in the body this is critical

So when you provide a drug to a human bodyits not there forever

And its not there at a constant concentration

Youre going to see lectures on pharmacokineticsthat define how the different pharmacokinetic principles of a drug define how it longits there what kind of concentration it achieves

And not only what kind of a concentrationit achieves in the blood where were able to track it but whether or not that drugsystemically distributes to all the tissues of the body

Does it go to the brain?

These are all things that we design withinour drugs

These are all things we that we can trackwithin different systems animal systems or even in the human body

And its important to understand that thescale of that mechanismpfaction the level of inhibiting it plays a real role

So what percent of that mechanismofactionin the disease cells in the disease tissue in the system at large is needed to achievean effect and a positive effect for that patient population?

Is 0 percent enough?

Do we need to achieve 90 percent inhibitionof that enzyme or activation of that receptor to achieve a benefit for that medicine?

These are things that need to be thought aboutthat pharmacological data and clinical pharmacology data will provide evidence of

Because thats going to affect how eventuallywe dose that drug into patients

Not only that we need to know about the levelof effect on these offtarget actions that define whether or not this drug is going tobe safe for the human being

So again 0 percent inhibition?

Could we tolerate a certain amount of inhibitionof the hERG channel?

Perhaps but these are the kind of questionsthat the teams that are developing a drug need to ask themselves

How long can a mechanismofaction or theofftarget actions be tolerated in a system?

And how long does it need to be in place forit to be efficacious?

Drugs again small molecules in particularrarely are there for days or weeks

Some biologics can be but its importantthat we recognize or understand that the duration for the drug in the human body and the durationfor which its affecting that mechanismofaction the inhibition of that enzyme plays a realrole in how were going to define how useful the drug is and when its dosed the schedulethat its dosed upon thats all things that need to be understood and are part ofthe core principles of pharmacology and clinical pharmacology

So its important that you understand asyou as you listen to the lectures and all of the modules that this is not just a binaryonoff system

The presence and actions of a drug and itsmechanism are transient

Theyre defined by the exposure of that drugthe pharmacokinetically defined exposure of that drug and the activity of that drug thepharmacodynamics

And youre going to learn a lot about pharmacokineticsin modules two and three

Youre going to learn a lot about pharmacodynamicsin modules five in the lectures in module five

So continuing on with the core principles youre going to be learning a lot about these particular its of data

Its always important for you to keep thehuman element in the back of your mind

Different patient populations will have uniqueneeds

We treat pediatric patient populations differentthan we treat adult populations different

than we treat geriatric populations

They will all have different abilities todeal with certain levels of toxicity of a drug

Theyre going to have different metabolisms

Theyve defined how quickly a drug is absorbedor eliminated form the body

All of these things are things that you keepin the back of your mind as youre listening to these modules

But furthermore as you become a practicingscientist within this space dont begin one of these programs without asking yourselfwhat is the anticipated population?

If its a geriatric population you have toconsider the metabolic and patientderived demands of that population and its goingto have a lot of effects on the ideal type of drug that youre going to be developing

Different indications will have unique tolerances

For instance cancer therapies we will arebroadly considered to allow a lot more toxicity than therapies that we would use to chronicallytreat anxiety

Individuals who are up against a very difficultcancer diagnosis might be more willing and typically are more willing to deal withtherapies which cause higher level of adverse effects

Whereas somebody dealing with a mild levelof anxiety simply doesnt want to be dealing with a very toxic therapeutic regiment

The growing field of pharmacogenomics thisis basically how a patients genome is going to influence the choice of therapy and theoutcome of a particular therapy

This is a rapidly developing field

Youre lucky that there are in fact specificset of lectures within modules four and within modules seven that deal with these particularaspects in this burgeoning scientific field

Its remarkable that we have as much knowledgeas we do today about a human beings individual

genome

And were learning more about what that meansfor how an individuals genomic disposition affects how specific therapies may or maynot work

Ultimately the goal of all of this ultimatelythe goal of teams of scientists whether theyre medicinal chemists or pharmacologistsor clinical pharmacologist or practitioners of medicine the goal is to use this typedata to help doctors treat the patient rather than disease

Were learning more and more that individualtherapies are probably going to be the future of medicine

And a lot of the lessons youre going to belearning within each of the modules each of the lectures is designed to help you understandhow a specific medicine how the data that is broadly characterized as pharmacologicaldata or clinical pharmacological data can then be used to define a therapy course forthe person the patient the individual not broadly the disease

So clinical pharmacology will play a criticalrole in making this a reality

As I stated at the beginning of the coursethis is complex

And I made a point to say very very complex

And it is

I dont want that to be a daunting element

It shouldnt be a dauting element to anybodylistening to these lectures

This complexity in not insurmountable

Individuals do it all the time

They learn about these individual data sets the types of data

They become expert practitioners in pharmacokineticsor pharmacodynamics

They become experts in medicinal chemistryor molecular biology cellular biology

They become expert practitioners of experimentalmedicine

Because even though this is complex itsnot insurmountably complex

But its important that we embrace that complexity

Complexitys not a vice

Complexity is defined by the fact that humansare complex

Understanding the principles of clinical pharmacologyallows you to appreciate that the reasons behind success and failure can be narrow

Perhaps the drug was not dosed at the rightschedule or dose

So it can be a razor thin margin of errorthat defines success or failure for an individual therapy

Often times this is not clear

But as we develop the core principles of pharmacologyand clinical pharmacology were getting a better grasp of whats going to define successor failure for an individual therapy

Drug discovery pharmacology clinical pharmacologyand clinical practice as a result are team sports

No one individual or if they if oneindividual can learn all of this and be an expert practitioner of all of it thats prettyrare

As a result its usually teams that are ableto accomplish this

Oftentimes thats within private industryin biotechs and pharmas

A lot of government and really strong academiccenters can do this as well

But oftentimes not oftentimes almostalways Im going to go so far as to say always this is a discipline that is definedby teams of scientists coming together to develop a therapy

And its allowing the individuals who areexperts in one element of it to be driving the project when its at that stage

Allowing solid professionals to do that work

Thats where success comes from

When teams of experts come together with acommon purpose

And its important to state success or failureis oftentimes defined by application of best practices in all domains all the way fromtarget validation through the clinical application and advanced phase three clinical trials bestpractices and having individuals who are very experienced and knowledgeable when in eachelement of this process

Really that is going to define whether atherapys development achieves success

And as I stated although this is complexits not insurmountable

Last year in 0 the FDA approved 9 drugs giving hope to patients with complicated diseases ranging from cystic fibrosis to migraines

Each of these therapies is a testament tothe hard work of professionals who like you started off by learning the principles laidout in this course

So really youre at a terrific positionto youre at the beginning of an exciting adventure leaning all of these lessons thatare laid out in the courses modules and lectures coming forward

Thats the thats the extent of my introductionto these lectures

I hope that I know youre going to findthem all to be stimulating

Theyre all going to be of broad interestto all of you

Some of them are going to be of specific interestto several of you who are interested in developing and learning about pharmacokinetics pharmacodynamicsdrug discovery and clinical practice

Embrace these lectures

Take watch them rewatch them and allowthem to stimulate your interest more so that it already is

Thanks for you time

Enjoy all thats to come