todays lecture will be given by dr john

clinical pharmacology and vice chairman

of experimental therapeutics at

childrens national medical center

john is trained in pediatrics in

neonatal medicine and holds a phd in

clinical pharmacology

prior to joining childrens national

john worked at the sofia childrens

hospital from 9 to 00

currently john is supports several

programs in pediatric clinical

pharmacology and divides his time

between washington baltimore rotterdam

and basel

john has published over 0

peerreviewed papers in the field of

neonatal and pediatric clinical

pharmacology and is currently the

president of the american college of

clinical pharmacology we know you will

enjoy todays lecture

hi my name is john vandenanker im a

pediatrician neonatologist

and i would like to

the coming hour to talk about

developmental and pediatric pharmacology

to let you understand

how children are different from adults

so this slide what you can see is a busy

slide but im going to walk you through

it because its important to realize

when we give medications to adults but

also children

we talk about pharmacokinetics in other

words you give a drug to a patient

and whats going to happen with the

drugs in other words what the individual

will do to get rid of the medication

then we have pharmacodynamics you have

medication to a patient for a purpose

the patient has pain so what you want to

reach is pain relief so pharmacodynamics

is actually everything the drug is doing

to the human body

most of the time of course you give

medications to patients who have a

disease

and the disease might change the

pharmacokinetics

and the pharmacodynamics of medications

in the long run we have two goals we

want to see an effective medication

with no or minimal side effects

and that has to do with the clinical

outcomes

a chance to go back in history is always

i think very important and this is a

picture showing you the historical drug

development in children

you see here in the middle cops babys

friend its against colic

diarrhea cholera and teething and it

contains percent alcohol and quite

some morphine

in the same time period there was also

tots teething cordial what you cant

read probably a bit on the lower part of

the slide treats

satisfies the baby

pleases the mother gives rest to both

very noble goals but her issue was that

the rest to both meant for the children

death

another historical development was

sulfanilamide

in many years ago

we had problems with the appropriate

formulations

in 0 yes now we still have problems

with the right formulations for children

on the left side of the of the of the

picture you see sulfonylamide a very

good antibacterial agent

but there was nothing available for

children

a very smart chemist then decided to add

diteline glycol to the to the medication

to make it an elixir

clearly the drip was still very good but

the elixir killed both adults and

children because its the same material

you will put in your car in the winter

to prevent it from freezing

on the right side is chloramphenicol

still used in many many parts of the

world to treat severe infections

and this was also given to newborn

babies but without thinking that perhaps

newborn babies have a different way of

handling medication

what happened these kids were indeed

less able to handle the medication they

got cardiovascular collapse and they
died and the whole issue was of course
that these misadventures in children
led to the creation of the food and drug
administration that helps a lot adults
like us but still not that much children
so when we think about children these
are just two pictures of critically ill
infants
on the left side you see a child with a
congenital intestinal obstruction in
other words the baby needs surgery
otherwise theres going to be big pain
and also big problems for the child to
survive
the other child on the right side is a
little bit older and got a severe
infection and if you look very well the
right leg and the left leg theyre very
much compromised in the long run the
baby survived the infection but lost
both legs because of the disease
major things
other things were treating nowadays are
these many small babies
born instead of after 0 weeks that is a

normal age this born after weeks

and you can see the size the hand of the

mother is there a baby with a weight of

00 grams

so huge differences in weight in these

children and clearly also

huge differences in what kind of

medication they need

so when we then think about determinants

of drug response in infants

the red bar makes it very clear its

growth and development

why is it important because you have a

moving target continuously

and when you hit the moving target and

the wrong moment can have lifelong

consequences so the responsibility of

treating patients young patients with

medication is quite large

the lower part of the slide shows you

the what happens with the medication but

ill come back on that in my

presentation with real practical

examples to make you all enthusiastic

about pharmacology in children

in addition to normal growth and

development i mentioned earlier disease

already of course we dont treat healthy

individuals we treat patients with

diseases

and diseases have an impact on growth

and development

environment is important think about

babies fat formula or breastfeeding it

will change their life forever because

the intestinal metabolism is completely

different not only in the newborn but

even in you today

then finally ive also in my

presentation

give some information about genetics

because nowadays we are 0 years or more

already after the position after the

genomic area was discovered but then

children be quite far behind but i give

you some real clinical examples that

its important in children too

so what is the challenge of being

working in pediatric clinical

pharmacology

its to determine the sources of

variability

and this shows you the two main players

the key players on the left side

ontogeny or developmental changes

on the right side pharmacogenetics

and the right picture shows you actually

girls of years of age

and without much imagination you can see

some of these girls are still girls and

some of these girls of twelves are

turning into young ladies so when you

think about doing drug medications with

medic drug medica

direct research in children

just looking at age is not the right way

to do it you need to look really at the

developmental stage of these individuals

critical role of pharmacokinetics and

pharmacotherapy why is it in children

still so important in adults we dont

want to hear about it anymore its

because the combination of absorption

distribution metabolism and elimination

will dictate the exposure to the

medication and that will dictate those

we want to use

lets start with absorption

many many factors play a role in in oral

drug absorption and again im not having

no time to go to all these issues here

but

splenic blood flow is important guessing

ph

intestinal drug metabolism intestinal

surface area

intestinal drug transport microbial

colonization intestinal motility

gestic emptying time and biliary

function in addition to that also

biopharmaceutical interactions will play

a role

today i only want to give you two

examples one about gastric ph changes

and also about guessing emptying time

changes

so this is a slight showing on the

yaxis

adult activity

on the xaxis

gastric acid production pepsin

production and guest in production but

for today id like you to focus only on

the first part thats the guessic acid

production and what you can see here

clearly when you go from birth on the

left side of the slide to adulthood

there are changes in gastric acid

production and in the long run

it will be an increasing capacity is it

important to know for you yes its

important because the next slide will

show you that when you give order

medication and you dont realize that

this is the difference in gastric ph

things will change this is a all the old

slides from 9

so also for young people who listen to

the presentation never think that before

90 not important things were published

so its very worthwhile to look at these

things

so on the yaxis we see penicillin

concentration

on the xaxis the hours after the oral

administration of one dose

and what you can appreciate here is that

preterm neonates

and fulton neonates the both

the blue and the pink lines still have

capacity to absorb the medication

after oral administration but as soon in

yellow and in blue

you get older than two years of weeks of

age the problem will appear that you

dont observe it anymore

this is important to know because when

you treat patients with auto medications

and you dont realize this some of them

will be treated some dont and when they

dont improve you dont know where its

coming from

changes in gastric emptying time this is

a busy step but ill walk you through

this one on the yaxis the percentage of

the meal

on the xaxis different porsche nato

ages and this looked at 0minute gastic

retention in other words you give a

feeling to a child and 0 minutes later

you check how much is still in the

stomach

the or the light bars are preterm

infants the dark bars full fullterm

infants i like to focus today only on

preterm infants

between and hours of life

0 of the meal is still in the stomach

when you look at to 0 hours only 0

so in just a couple of days preterm

infants even are able to move the bowel

easier get easier the gastric emptying

done and when you think about

medications they need to be absorbed so

giving it in the first hours of life

will have a different impact than later

on

i give you an example of this one too to

make you sure make sure to you that you

you dont think thats just theory so

this was a study done some years ago

looking at scissor pride a medication

that was used for gaster reciprocal

reflux

and i made only for you clear what you

need to look at is the yellow part tmex

in other words the time you reach the

maximum concentration three different

groups postconceptional aidswise

children between and weeks

of these

children be and weeks of these

and then kids between and weeks

and what you can see here is that

younger kids have a longer tmax than

older kids indicating indeed that also

in addition to the gastic emptying time

also the intestinal

transport is changing important to

realize when you use medications orally

then we have other ways of giving

medications extra oral drug absorption

of course many many factors play a role

there too like regional blood flow

temperature diffusional surface area

hydration tissue binding sites local ph

and drug vehicle interactions and

finally barrier thickness i give you

just an example of barrier thickness to

remember this much easier

this slide shows you developmental

changes in thin skin thickness

on the left side of the softer of the

picture you see a child born after a

gestation age of weeks as i mentioned

earlier normal is 0 so this child is

born more than three months early and

this skin is looked after as the first

day after life postnatal h is written

there one day

you can see theres hardly any stratum

corneum in other words you put something

on the skin it goes immediately into the

system of the baby the same baby two

weeks later has developed a beautiful

stratum corneum in other words when you

put something on the skin there nothing

goes through or very limited and that

skin is comparable with the third

picture a child born on time in the

first day of life so something magical

happens as soon as you get born

the maturation is much faster so a child

born three months early

two weeks later already has the same

skin as a child who has been staying

three months longer in the in utero so i

think thats important for clinical

practice

so distribution is the next

factor and what you can see here on this

slide is the impact on development on

drug distribution on the yaxis the

percentages on the xaxis from birth to

0 years of age

the green line shows you the changes in

total body water the red line is the

changes in extracellular water and the

dotted line that changes in body fat we

know more details nowadays so this slide

shows you

in orange extracellular water

compartments

in green interstellar cellular water

compartments in gray protein and in a

blue fat

and from top is premature babies then

then full term babies and then we go on

from four months to adulthood and what

you can see in this slide is when you

premature born and you take together

extracellular water and intracellular

water that almost 90 percent nine zero

percent of the newborn baby is water

you can compare it with a jellyfish so

to say and when you get into adulthood

much more compartment is going to be fed

and other

issues and you can depending on how

heavy the threat compartment is you can

compare these individuals with calamares

thats to remember easy the differences

in these body composition is this

important yes it is i just give you one

example amikacin is a drug that is used

many times its like gentamicin or

tobramycin and its an antibiotic

and already in 99

jeanpaul londres published this paper

and i want you only to look at the bold

part the volume of distribution remember

the orange bars i just showed you so

when youre less than weeks gestation

your volume of imication is 0 liters

per kilogram and when you term its 0

liters per kilogram and what is

important to realize here is that indeed

what we saw with the orange bars is

reflected it may give medications to

children why is this so important

because the next slide shows you but

gentamicin so the brother or sister of

immunication that when you want to reach

an appropriate peak level you need to

give more of the medication to the

younger children and this shows you that

99 was a former slide showing that it

takes 0 years or more to change

clinical practice

because between brackets and under the

dose milligrams per kilogram you see

still to whether the child was

less than 9 weeks 0 to weeks more

than weeks in the first week of life

in the first days of life it didnt

matter

so finally in 00 we doubled the dose

based on the information that was

already available in 99 imported to

realize that not only translational

research is going from laboratory to

patients but also if we discover things

in patients how do we convince our

colleagues to listen to that

so then we go to metabolism

metabolism we always have been told that

it is primarily delivered thats correct

but there are also other sides of drug

metabolism

the brain metabolizes the lung

metabolizes the skin does it and the

most important other

organ that does this kind of work is the

gut

so for certain enzymes the gut has 0

percent of the activity so please

remember when you go home today that

liver is important but gut is at least

as important for metabolism

so what do we know about drug

biotransformation when i give a drug to

a patient there is a phase one step

determined by cytogram p0s and other

enzymes that results in a metabolite

that sometimes can get excreted but most

of the time for most medications we need

the phase two step

the gts the energy energies the st for

sulfur transferases and why are these

enzymes there because then you have a

metabolite that can be excreted by the

kidney so it comes to the urine

crucial to remember that whatever age

you have its important to have

proper working kidneys especially when

youre younger than two years of age

its crucial you can have a perfect

liver a perfect intestine a perfect

brain if your kidneys dont work you can

get rid of the medications

so what do we know about it this is a

picture showing the developmental

changes of one of the enzymes a

important because it is involved in

metabolism of 0 or more medications

this is published in the in 99 and i

want you to remember that because the

next slide will show you the more modern

ideas about it in general on the yaxis

again percentage of adult value on the

xaxis i like you only to look again

about the activity and what you can see

on from the left to right is the fetus

less than 0 weeks a feet is more than

0 weeks than children born dying in the

first day of life

and then babies dying in the first week

of life what you can see here is

changing capacity of metabolizing these

enzymes this is all done with microsomal

work in the children who passed away

this is 00 ron heinz who is the coop

the main author of this paper dedicated

of his

career on deciphering this and its

important it shows

human hepatic drug metabolizing enzymes

ontogeny and he just he decided to

divide them in three classes class one

two and three

in class one im only mentioning one

cytogram three a the second

in a row there thats one thats

important to fetuses

class two sc9

important for proton pump inhibitors i

come back at and the end of my

presentation in the genetic part about

cytochrome c9 then class

many many enzymes are by far the largest

class having both cytograms but also

parts of the phase enzymes and why did

he decided to do this

on the yaxis here you can see the

drugmetabolizing enzyme activity on the

xaxis four different groups

children with the gestation is between

0 and weeks

children between and 0 weeks

children with a postnatal age between

zero and six months and children with

the postnatal age between six months and

years and what you can appreciate

here for class is that there is more

activity in utero than after being born

then class two you can see it as some

variation in the different time frames

but no big relationship whereas then in

class three again the largest theres

hardly any activity before youre born

and after being born it became becomes

very active

of course all these differences in

enzyme activity were not designed this

way for us but were using that

knowledge now to really look at how we

can handle medications better

clearly we always need to translate what

is found in microsomes to real life and

this shows you on the yaxis the

clearance of midazolam used for sedation

in adults and children and on the xaxis

birth weight and what you can see here

is when you get the larger the clearance

will go up but you also can see here is

that theres a huge variation in the

different weight categories why do i

show the slide is because when you work

in your unit think about these things

you give the medication to children we

dont know much about these sit together

with pharmacists with geneticists with

parents and talk how you can get

information out of the medication youre

already giving to patients and this is

just an example we know that medes

limits me metabolized to one hydroxyl

midazolam

and four hydroxyumidazolam

one hydroxydust lamb by three a four

hydroxyl by a and a so when you just

design a study

and you you also take the effort to look

at the metabolites you will learn so

much about the developmental changes in

these enzymes and i mentioned earlier

a is important for 0 or 0

medications

another example is scissor pride a

medication used earlier said already for

reflux

and this is also a is the most

important

enzyme to metabolize scissor pride to

narcissist so we did a study

in the network again that did a single

dose kinetic study in newborn babies and

young infants

you remember this slide because i showed

you earlier tmax when i talked about

the changes in oral

ch in caster emptying and then i would

like you to look at the lower part of

the slide clearance so when the

microsomal work is correct we like to

see that theres also work in real life

and what you can see here is that

clearance is 0 for the youngest

children

0 for the children in between and

0 for the oldest so indeed for

cytochrome a it seems to be that the

work done

by ron hines is reflected in real

clinical life

not always so easy this is an example

does to make you aware that if youre

going to use medicines in

children study them because without

study them you can make major mistake

this is a drug called lean assolit its

a drug used when you have vancomycin

resistant bacteria in other words

theres nothing available anymore to

save your pa save the patient

so youre going to use this medication

without this study and im going to

underline now the importance you can see

that adults have a clearance of the drug

of 0 liter per kilogram children 0

and infants point in other words

intuitive you would think that children

always have less activity less clearance

in this case its the other way around

infants have a much higher clearance

think about this drug its against

bacteria

so when you wouldnt know this it would

give the same dose or a lower dose

intuitively than in adults these

patients will all die because you dont

give enough

and we would say that drug is not

working in children so this studies are

crucial i give you two more slides to

even show you how weird this medication

behaves

this slide shows you on the yaxis the

clearance of the medication on the

xaxis again the postconceptional age

and there are four groups open circles

are preterm infants less than eight

days of life

open triangles are the term infants

less than eight days of life and then we

have the closed circles

at the same preterm infants after the

first week of life

and the close triangles the full term

infants after their first week of life

and what you see in this slide already

is that clearly in the first week of

life its all lower but after the first

week of life it doesnt really matter

that much in the next slide give you

more details

clearance again on the yaxis of the

same medication

on the xaxis not postconceptional age

but postnatal age in days

and what you can see here indeed its

lower in the first week of life but

after the first week of life it doesnt

matter if youre born four months early

or on time you have the same clearing

capacity we really dont understand

still now why this is but without doing

the studies we would dose completely

wrong and now the dosing advice we have

for this medication works perfectly for

both adults and young premature infants

so you can see the rapid changes in this

patient

the other factors that play a role in

metabolism herbal medicine that depends

where you are in the world if hormone

medicines are used by parents or parents

giving herbal medicines to their

children

not many of us are asking about it

important to do though because it has a

lot of potential impact on how you

handle medications that you prescribe

disease i come back on that later in my

presentation

drugs there of course when you take one

medication or you give one medication to

your patient theres no more

interactions as soon as you add another

medication to that there will be

interactions and if you add to the third

or the fourth youre asking for problems

that you dont ask for problems you need

the drugs to treat your patients but you

need to be aware of that then genetics

come back on later hi show and then

nutrition is there showing this nice

grapefruit juice on the right side

and the issue is that when you have

medication on board and you take

grapefruit juice thinking its healthy

it potentially can kill you not because

grapefruit juice is bad no but it

inhibits

a lot of these enzymes that i talked

about earlier and they have medications

depending on these same enzymes you

suddenly get with the same dose much

higher concentrations that can lead to

horrible side effects

im going to give you now the example

about the disease

when you think about inflammation and
drug metabolism we know more and more
and more so whats inflammation can also
be infection can be trauma can be
surgery can be cancer we know all these
factors result in increases in
proinflammatory cytokines
that will result in a decrease of the
cytograms in other words make the link
you have infection going on of
inflammation going on
and your metabolism capacity goes down
in other words what happens is like
eating the grapefruit juice
the exposure of the same dose will go up
and the chances of side effects is
dramatically going up too this is
something not many of us think about
when in the intensive care and you get
medication against pain or to sedate you
were not thinking quickly to get only
0 percent of that medication if there
is infection
so when the hypotension that we link to
the infection persists we need to start
thinking that it might be because of

overdosing of our medications

so cytokine a we mentioned it earlier

i showed you this slide from huron heinz

and also from earlier but this is also

important again as i showed you before

for me dazzling

in in adult medicine midazolam clearance

is already used for tree activity

in patients at the intensive care just

to measure how strong the metabolism is

thats published in 00 and children we

always leave it later but i give you the

most recent data that was just published

in 0

this slide shows you the impact

information on the yaxis you see the

predicted clearance of midazolam

about the on the right part of the slide

which you can see is the crp and crp

states for c reactive protein a measure

of the severity of information

0 is the lower severity in this case

normally you and i will have less than

one

is more information and 00 is severe

and what you can appreciate from this

slide is that of course based on body

weight also but when youre going to get

more inflammation the cleaning capacity

goes down

and of course i showed you before that

getting older getting higher body

weights increases it so theres a

delicate balance between increase based

on maturation but then a dramatic

decrease based on being ill with an

infection theres more to come

because also when you get sick not only

you get more information but some of

your organs dont work like your liver

or your intestine or your kidneys and we

know that if you look at this slide

again we i showed you the topper part

earlier but then you look at the lower

part organ failure one organ failure two

organ failure three organ failure more

than three you see that the clearing

capacity even goes further down so these

patients are going to be hardly having

any capacity to metabolize their

medications

so when we combine this

its not that we talk about five percent

changes not just getting ill severely

ill

results in major changes this is minus

percent in the different lines that

are put there and you can see clearly

that sometimes it goes rapidly down

every time and hardly any capacity is

left so we really had to start that this

just published last year most of us

dont know that yet and im sure many in

the room wont know but now you know

start thinking about it when your

patients are very ill

so to summarize the a mediated

clearance of midazolam in children is

dependent on three parameters maturation

will make it more quick so you have more

capacity but when you have information

or organ failure it will change and this

is mideslam as an example but of course

it has implications for all the other a

substrates something to really take home

today

so then elimination the next step of

course this is a slide showing you the

maturation of renal function from on the

xaxis the first two days of life till

years of age

and this is an old slide again but that

shows you the changes in kidney weight

the changes in grammar filtration rate

in red the changes in kidney length in

blue and the changes in renal plasma

flow in yellow and you can see their

changes are there some are more dramatic

than others but from this slide you

dont appreciate how quickly the changes

are in the first month of life and the

distalite makes you that more aware

what you can see here on the yaxis the

gromial filtration rate so in other

words renal function

and on the xaxis kids between one and

two days of age eight to nine days of

age and fifteen and sixteen days of age

i want you only to look at the at the

green bars because these are the term

infants

so on the first days of life its 0 a

week later its 0 a week later its 0

so

when you think about newborn babies

being defined as being the same in the

first days of life this slide shows

you that they dramatically change in

their renal cleaning capacity

so when you treat a baby in the first

days of life for an infection and you

dose

an antibiotic a bit a certain dose

then you have to realize

that you might overdose the same baby

gets ill two weeks later and you want to

use the same dose because its still the

same newborn

surely youre going to underdose because

the baby has more than twice the

capacity to get rid of the medication

important to realize

this is just an example showing that for

a drug called ceftazidim theres other

antibiotic treatment and the yaxis is a

total body clearance on the xaxis of

gestational age of patients and this was

all studied on day three of life that is

dramatic increasing capacity in these

children throughout gestational ages the

longer they stay in utero the higher the

capacity when theyre born

coming back on that slide i showed you

earlier i make bald to the dose bit

against per kilogram if you surely

remember the major step from to

between 00 and 00

of course when we go up with dosing to

reach a good peak level and to kill

bacteria and i just showed you now the

arena

impairment we have to realize that also

the dosing interval needs to change

otherwise youre getting the toxicity

so between brackets on the bolted part

that was what we did in 00

between

every day hours or three times a day

but when you give much more dose you

have to be going to probably once every

two days and now we think even sometimes

for the youngest children every three

days so we have to really think about

these things together you as clinicians

cant have this all alone you have to

work with a pharmacist with a

pharmacologist and other colleagues to

make this optimal for for your patients

so to summarize this part i think its i

have trying to show you that there are

differences in extravascular absorption

rate and extent

that altered body composition will

influence distribution i showed you this

bar the orange bar showing the yellow

jellyfish in the calamares

that there is a marked untouching or

development of drug metabolizing enzymes

and furthermore that is also dynamic

influence of developmental renal

function

not that slow as we saw in the past but

really rapidly already in newborn babies

so lets then go to the other part of my

presentation that will be not

taking that much time but i think its

important for you all to know that

genetics play a role even in the

youngest individuals

so what do we know about

pharmacogenetics realized that in 9

already by friedrich vogel a german

colleague he already defined it that the

study of the role of genetics and drug

response and that definition

0 years later is still very very valid

this is just some history no time to go

over it but realize that there are some

important milestones in the history of

pharmacogenomics

mandel lays down the principles of

heredity

and it took to 9 before michael

alkabaum in germany started to link all

this genetics with how people handle

medications and nowadays of course we

have the pcr we have all kind of

opportunities to do so so im going to

give you two examples of enzymes that we

know something about that are easy to

remember also for you and are important

cytokine p0 to d or not a by d

just when you think about em stands for

extensive metabolizers pm for poor

metabolizers so what happens

you give a medication thats a substrate

for d when youre extensive

metabolizer or wild type normal you will

make stable metabolites and you will

excrete this medication then your poor

metabolizer the same medication same

dose will result in accumulation because

you are a poor metabolizer so you will

make less metabolites and you excrete

less so these patients

act like having a functional overdose

not because you and i made the mistake

that happens too tenfold overdose but

this is because

the father and mother of your patient

didnt give the patient this material

and of course the parents didnt know

that and this is also all just to

remember that genetics plays an

important role

so what do we know about d we know

that in caucasians theres a bimodal

distribution i will show you that later

here also graphically

five to ten percent of caucasian

population is deficient so these people

dont have activity of d so we didnt

give a drug thats dependent on d they

cant get rid of it

and so these poor metabolizers or pms as
we call them have two inactive forms of
the gene
and these people are indeed at risk for
concentration dependent side effects
with normal dosing
and some drugs may not work so codeine
needs to be metabolized by d to get
morphine out of there and for traumadoll
its also to be metabolized by d to
make the ectometabolite so if you dont
have d you can give them a kilogram of
codeine or trauma its not going to work
so this is the bimodal distribution from
caucasians on the yaxis the number of
tested individuals on the xaxis zip to
d activity to the left is faster to the
rise is slower but you can see indeed
that there is this second hump on the
right side that makes the lower
metabolism we know a little bit more
nowadays and i will show you that in the
next slide what you need to realize is
that when you treat patients it depends
where you live but i live in washington
dc multirational multiethnical very

diverse population very interesting

wonderful to live

but you have to realize that if there is

a chinese person sitting across you who

wants medication that these people are

in general a little bit more slow than

the caucasians with the bimodal

distribution

and i dont have the slide with me but

when you look at african americans

theyre even more slow so we think about

the africanamerican patients with

sickle cell disease

how long have we been trying to treat a

bit codeine

they were always deemed to fail and of

course we started to blame them that the

coding was not what they dont morph in

they didnt get good treatment and this

knowledge helps with that

so we know more this is a lot of data

from from the europe but in this in

addition to extensive metabolizes and

permitability we have also intermediate

metabolizers and on the left side ultra

rapid metabolizers and im going to give

you an example why thats important

this is a case report already more more

than 0 years ago but i think very

illustrative launched paper is quite

well

respected like the new england journal

in the us

it was a fullterm healthy male infant

both parents were physicians and saw a

physician every day because they were

very nervous as the first child

on day seven of the birth there were

intermittent periods of difficulty in

breastfeeding that can mean everything

that can mean nothing on day the baby

had regained his birthday thats very

reassuring thats what you want between

day 0 and but then of course day

grey skin milk intake had fallen that

was very ominous and then a day later

the baby was found dead a horrible story

both parents

very very vigilant went to doctors and

this happened still so the autopsy was

done there was no abnormality and the

coroner was very active he was measuring

all kind of

trying to find reasons why the baby

passed away and what he found was very

high levels of morphine 0 nanoguns per

milliliter when you or i would have

elegans per milliliter we both people

stop breathing too

so normally its point two to two so

whats going on so they were worried

that the parents gave the patient

something

so then we go back to pharmacogenetic

coding i mentioned codeine is

metabolized by d in the liver to

morphine then morphine goes to the blood

vein barrier to the myopia receptor to

give pain relief

already a long time ago 99

in healthy volunteers

the studies were done to give codeine to

poor metabolizers that are white dots

and codeine to extensive metabolizers

and what you can appreciate here on the

yaxis is morphine concentration in the

xaxis time after the same dose of

codeine when youre poor metabolizer

theres hardly any morphine produced

fitting with a poor metabolism by

extensive metabolizer you make quite

some morphine between 0 and 0

so what is the conclusion of this case

this was happened mother had pain after

a very painful procedure during the

delivery she was prescribed codeine and

paracetamol by the canadian physicians

every hours or twice a day for two

weeks

to make a long story short

in this time we could do genotyping of

the mother so it was discovered that the

mother had a gene duplication so she was

not because the parents gave the patient

something to die from it was because the

mother had a genotype that made out of

the codeine so much morphine that the

baby got it through breastfeeding and

passed away and that reason

this case led to a big warning from the

fda

to not use these medications during

breastfeeding and actually most recently

this year and the year before the fda

actually banned codeine use in all

children

also because of the risk for

decreased breathing so i think very

illustrative that genetics genome is

very going to be important to help us

understand what happens in some horrible

cases then c9 had promised that also

its important and that the more recent

9

a very

observing physician saw unusual sedation

in a subject receiving this

anticonvulsant

and they discovered that it was indeed

based on genetics

a mutation that was only affecting two

to five percent of caucasians

but twenty to twentyfive percent of

asians and drugs involved are omeprazole

lonzoprazole pontropism diazepam and it

can have major consequences and im

going to give you just an example to

show that it is not as easy again as the

d this is a

picture showing you on the yaxis

elimination rate constant ke

on the top is faster on the bottom and

slower and on the xaxis its two c 9

activity score in other words linking

genetics to the phenotype of the patient

and when you have on the right side the

star star mutation thats the

highest activity you can get normally in

c9

and i put it there drug x because id

like you to focus till to the end of my

presentation

lack of association between c9

activity score and elimination rate

content something that surprises you

because

when you really increases c9

you count on also an increase in

clearing capacity in this case it didnt

work

then we go to drug y

same picture on the yaxis that showed

you the slower and faster again the

activity score on the xaxis and we look

now to the star its still a star one

thats normal but star you can see

there is an increasing

clearance of this medication that fits

much better better logical thinking

about c9 so whats the explanation

this is explanation you need to know the

drug very well so the left jerk is

omeprazole thats a protein one of the

first actually the first proton pump

inhibitor

this slide is busy but i want you only

to look at the red big red arrow and the

big blue arrow c9 is there but what

you can see in omeprazole that a is

also important so when c9 has been

changed the a is still able to

metabolize represent very well so

therefore there was no real effect

when you look at pontropozol the other

medication you can see that the ship

touching item is much more important so

when youre going to change that

genetically

then it has a big impact on how you

handle the medication so again showing

that no physician alone no pharmacist

alone can do this work you need to make

teams otherwise youre not going to

improve the care for your patients

so

tip of the iceberg i wanted to show you

today but we know a little bit but where

you realize we know a lot about drug

metabolizing enzymes but what is also

important is that we know a lot

about what we dont know so transporters

receptors the normal development of

these things we dont know yet that

needs to happen in the coming years and

most of you listening are much younger

than i am thats your future theres a

lot of work to be done dont think we

know everything we know a little bit

so in the long run the most important

thing is of course to have target

therapy even for the youngest

individuals and for that again and i

repeat myself several times you need

teams no one of you in the room can do

it alone no one of me my colleagues and

myself can do it alone its for its for

you cant forget it

so before im going to finish up i think

this is always important this is a

quote by paracelsus his name was much

longer as you can see but we all know

him with pyrocelsus

that all substances are poisons

there is none which is not a poison

the right dose differentiates a poison

from a remedy

id like to thank you very much for your

attention i think that

i hope i give you an idea that indeed

children are different from adults also

when you give them medications

and

i want also to tell you that if there

are any questions about the course

please contact the program coordinator

at the nih and they will have crash

answers to that but they also will be

able to reach me and it will be always

willing to support whatever questions

you will come up with and i hope this

helps you in your clinical practice for

many years to come