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A review on indoles derivatives

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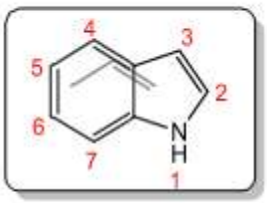
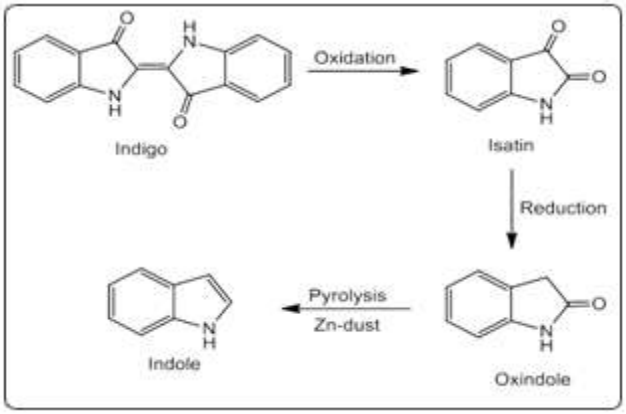
ABSTRACT
Indoles, both naturally occurring and synthetic, exhibit wide-ranging biological activity. Unusual and complex molecular architectures occur among their natural derivatives. As a result, this important ring system continues to attract attention from the international chemical community, and new methodologies for the construction of this ever relevant heteroaromatic ring continue to be developed. Unfortunately, many methods frequently start from ortho-substituted anilines, thereby greatly restricting the availability of starting materials. A more general approach would start from a mono-functionalized arene such as aniline or halo benzene, followed by cyclization with C–C or C–N bond formation to an unactivated C–H bond. Such methods are the subject of this perspective. Indole derivatives possess various biological activities, i.e., antiviral, anti-inflammatory, anticancer, HIV, antioxidant, antimicrobial, antitubercular, antidiabetic, antimalarial, anticholinesterase activities, etc. which created interest among researchers to synthesize a variety of indole derivatives.[5]

Keywords: Indole, Antiviral, Anti-inflammatory, Anticancer, Anti-HIV, Antioxidant, Antimicrobial, Ant tubercular, ant diabetic, Antimalarial, Anticholinesterase activities.

INTRODUCTION:-

- Indole is a benzo[b]pyrrole formed by the fusion of benzene ring to the 2,3 positions of pyrrole nucleus.
- The word "Indole" is derived from the word India, as the heterocycle was first isolated from a blue dye "Indigo" produced in India during sixteenth century.
- In 1886, Adolf Baeyer isolated Indole by the pyrolysis of oxindole with Zn dust. Oxindole was originally obtained by the reduction of isatin, which in turn was isolated by the oxidation of Indigo.
- Commercially indole is produced from coal tar





Indole is the most widely distributed heterocyle
Indole nucleus is an integral part of thousands of naturally occurring alkaloids, drugs and other compounds. [1]

Indole is also known as benzopyrrole which contains benzenoid nucleus and has 10 π-electrons (two from lone pair on nitrogen and double bonds provide eight electrons) which makes them aromatic in nature. Similar to the benzene ring, electrophilic substitution occurs readily on indole due to excessive π electrons delocalization [2]

Indole is an important heterocyclic system that provides the skeleton to lysergic acid diethylamide (LSD), strychnine, and alkaloid obtained from plants. Physically, they are crystalline colourless in nature with specific odours. The addition of the indole nucleus to medicinal compounds that is biologically active pharmacophore made it an important heterocyclic

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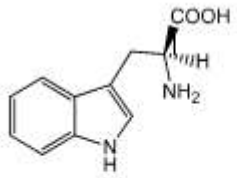
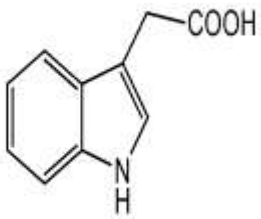
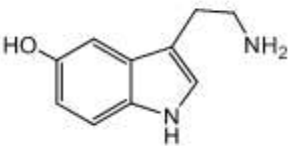
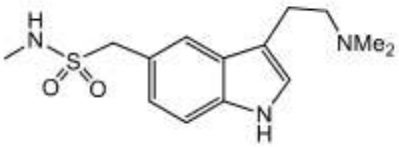
compound having broad-spectrum biological activities.[3]Due to this, researchers took interest to synthesize various scaffolds of indole for screening different pharmacological activities. Various natural compounds contain indole as parent nucleus for example tryptophan. Indole-3-acetic acid is a plant hormone produced by the degradation of tryptophan in higher plants. Derivatives of indole are of wide interest because of their diverse biological and clinical applications. Here, we have tried to summarize the important pharmacological activity of indole derivatives.[4]





Tryptophan: Amino acid Indol-3-ylacetic acid: Plant growth harmone





Serotonin: Neurotransmitter
Sumatriptan: Medicine for migraine

Synthesis:-

1]Fisherindole synthesis:

The**Fischerindolesynthesis**isachemicalreactionthat producesthearomaticheterocycleindolefroma(substituted)phenylhydrazineandanaldehydeorketoneunder acidic conditions.[1][2]Thereactionwasdiscoveredin1883by EmilFischer.Todayantimigrainedrugsofthetriptancl assareoftensynthesizedbythismethod.

Fischerindolesynthesis	
Namedafter	HermannEmilFischer
Reactiontype	Ringformingreaction
Identifiers	
OrganicChemistryPortal	fischer-indole-synthesis(https://www.organic-chemistry.org/namedreactions/fischer-indole-synthesis.shtm)

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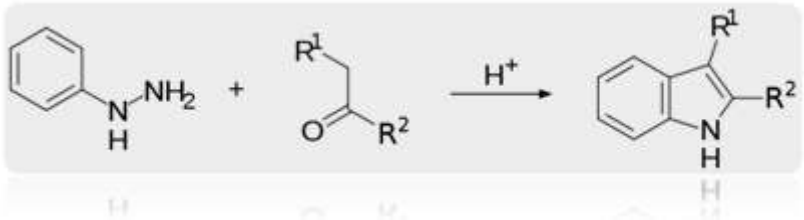
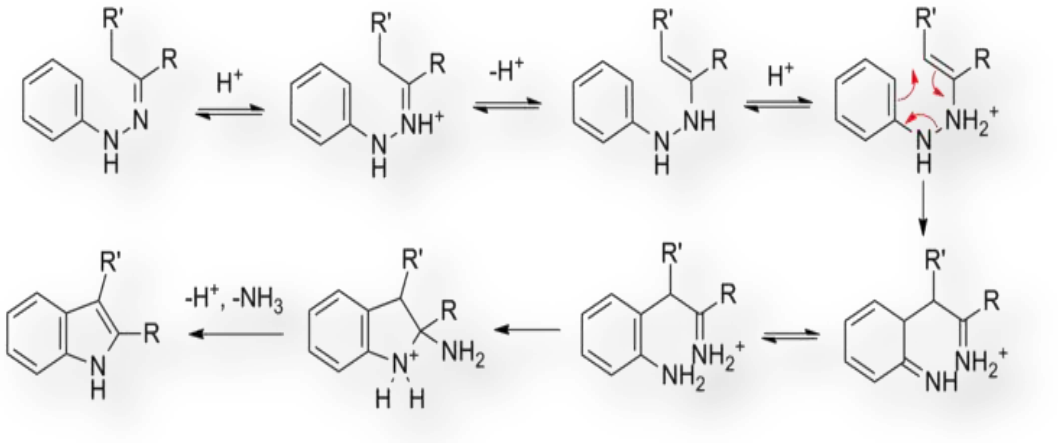
RSContologyID	RXNO:0000064 (https://www.ebi.ac.uk/ols/ontologies/rxno/terms?iri=http%3A%2F%2Fpurl.obolibrary.org%2Fobo%2FRXNO_0000064)

Thisreactioncanbecatalyzedby Brønstedacidssuchas HCl, H_2SO_4, polyphosphoricacidand p-toluenesulfonicacidor Lewisacidssuchasborontrifluoride, zincchloride, ironchloride, and aluminiumchloride.[6,7]

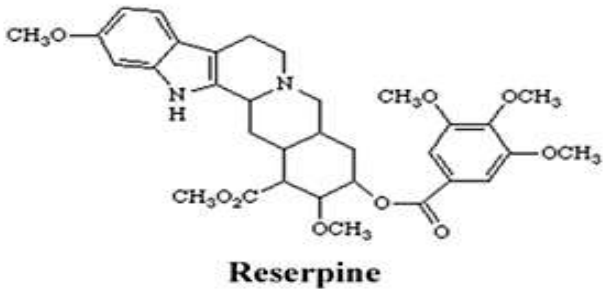


Reaction Mechanism:
The reaction of a (substituted) phenylhydrazinewith a carbonyl (aldehyde or ketone) initiallyformsaphenylhydrazonewhichisomerizestothe respectiveenamine(or'ene-hydrazine').After protonation,acyclic[3,3]-sigmatropicrearrangementoccursproducinganimine. Theresultingimineformsacyclicaminoacetal(oramin al),whichunderacidcatalysiseliminates NH_3, resultingintheenergeticallyfavorablearomaticindole.



Isotopiclabellingstudiesshowthatthearylnitrogen(N1)ofthestartingphenyl hydrazineisincorporatedintotheresultingindole.[8,9]

Reserpine



Reserpine

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Reserpine is a drug that is used for the treatment of high blood pressure, usually in combination with a thiazide diuretic or vasodilator.[10] Large clinical trials have shown that combined treatment with reserpine plus a thiazide diuretic reduces mortality of people with hypertension. Although the use of reserpine as a solo drug has declined since it was first approved by the FDA in 1955,[11] the combined use of reserpine and a thiazide diuretic or vasodilator is still recommended in patients who do not achieve adequate lowering of blood pressure with first-line drug treatment alone.[12,13,14] The reserpine-hydrochlorothiazide combo pill was the 17th most commonly prescribed of the 43 combination antihypertensive pills available In 2012.[15]

Medicinaluses:

Reserpine is recommended as an alternative drug for treating hypertension by the JNC 8.[16] A 2016 Cochrane review found reserpine to be as effective as other first-line antihypertensivedrugs for lowering of blood pressure.[17] The reserpine-thiazide diuretic combination is one of the few drug treatments shown to reduce mortality in randomized controlled trials: The Hypertension Detection and Follow-up Program,[18] the Veterans Administration Cooperative Study Group in Anti-hypertensive Agents.[19] and the Systolic Hypertension in the Elderly Program.[20] Moreover, reserpine was included as a secondary antihypertensive option forpatients who did not achieve blood pressure lowering targets in the ALLHAT study.[21]

It was previously used to treat symptoms of dyskinesia in patients with Huntington's disease[22] but alternative medications are preferred today.[23]

The daily dose of reserpine in antihypertensive treatment is as low as 0.05 to 0.25 mg. The use of reserpine as an antipsychotic drug had been nearly completely abandoned, but more recently it made a comeback as adjunctive treatment, in combination with other antipsychotics, so that more refractory patients get dopamine blockade from the other antipsychotic, and dopamine depletion from reserpine. Doses for this kind of adjunctive goal can be kept low resulting in better tolerability. Originally, doses of 0.5 mg to 40 mg daily were used to treat psychotic diseases. Doses in excess of 3 mg daily often required use of an anticholinergic drug to combat excessive cholinergic activity in many parts of the body as well as Parkinsonism. For adjunctive treatment, doses are typically kept at or below 0.25 mg twice a day.

Veterinary

Reserpine is used as a long-acting tranquilizer to subdue excitable or difficult horses and has been used illicitly for the sedation of show horses, for-sale horses, and in other circumstances where a "quieter horse might be desired.[24]

Antibacterial effects

Reserpine inhibits formation of biofilms by Staphylococcus aurous and inhibits the metabolic activity of bacteria present in biofilms.[25]

Adverse effects

At doses of less than 0.2 mg/day, reserpine has few adverse effects, the most common of which is nasal congestion.[26]Reserpine can cause: nasal congestion, nausea, vomiting, weight gain, gastric intolerance, gastric ulceration (due to increased cholinergic activity in gastric tissue and impaired mucosal quality), stomach cramps and diarrhea. The drug causes hypotension and bradycardia and may worsen asthma. Congested nose and erectile dysfunction are other consequences of alpha- blockade. [27] Central nervous system effects at higher doses (0.5 mg or higher) include drowsiness, dizziness, nightmares, Parkinsonism, general weakness and fatigue. [28] High dose studies in rodents found reserpine to cause fibro adenoma of the breast and malignant tumors of the seminal vesicles among others. Early suggestions that reserpine causes breast cancer in women (risk approximately doubled) were not confirmed. It may also cause hyperprolactinemia. [27] Reserpine passes into breast milk and is harmful to breast-fed infants, and should therefore be avoided during breastfeeding if possible. [29] It may produce an excessive decline in blood pressure at doses needed for treatment of anxiety, depression, or psychosis. [30]

Mechanism of Action

Reserpine irreversibly blocks the H + -coupled vesicular monoamine transporters, VMAT1 and VMAT2. VMAT1 is mostly expressed in neuroendocrine cells. VMAT2 is mostly expressed in neurons. Thus, it is the blockade of neuronal VMAT2 by reserpine that inhibits uptake and reduces stores of the monoamine neurotransmitters norepinephrine, dopamine, serotonin and histamine in the synaptic vesicles of neurons. [31] VMAT2 normally transports free intracellular norepinephrine, serotonin, and dopamine in the presynaptic nerve terminal into presynaptic vesicles for subsequent

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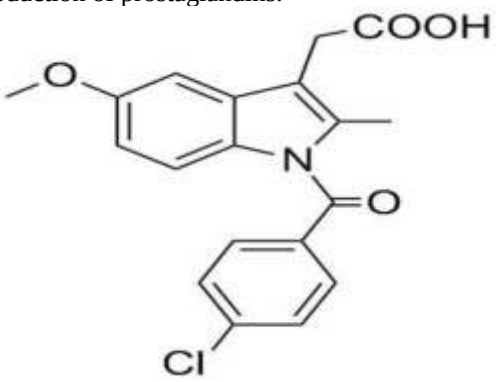
release into the synaptic cleft ("exocytosis"). Unprotected neurotransmitters are metabolized by MAO (as well as by COMT), attached to the outer membrane of the mitochondria in the cytosol of the axon terminals, and consequently never excite the post-synaptic cell. Thus, reserpine increases removal of monoamine neurotransmitters from neurons, decreasing the size of the neurotransmitter pools, and thereby decreasing the amplitude of neurotransmitter release. [32] As it may take the body days to weeks to replenish the depleted VMATs, reserpine's effects are long-lasting. [33]

Biosynthetic pathway

Reserpine is one of dozens of indole alkaloids isolated from the plant Rauvolfiaserpentinan[34] in the Rauvolfia plant, tryptophan is the starting material in the biosynthetic pathway of reserpine, and is converted to tryptamine by tryptophan decarboxylase enzyme. Tryptamine is combined with secologenin in the presence of strictosidine syntheses enzyme and yields strictosidine Various enzymatic conversion reactions lead to the synthesis of reserpine from strictasidine.[35]

Indomethacin

Indomethacin, also known as indomethacin, is a nonsteroidal anti-inflammatory drug (NSAID) commonly used as a prescription medication to reduce fever, pain, stiffness, and swelling from inflammation. It works by inhibiting the production of prostaglandins, endogenous signaling molecules known to cause these symptoms. It does this by inhibiting cyclooxygenase, an enzyme that catalyzes the production of prostaglandins.[36,37]



It was patented in 1961 and approved for medical use in 1963.[38,39] it is on the World Health Organization's List of Essential Medicines. [40]It is marketed under more than twelve different trade names.[41] In 2017, it was the 291st most commonly prescribed medication in the United States, with more than one million prescriptions.[42,43]

Medical Uses:

As an NSAID, indomethacin is an analgesic, anti-inflammatory, and antipyretic Clinical indications for indomethacin include:

Joint diseases

- Rheumatoid arthritis[44]
- ankylosingspondylitis[44]

osteoarthritis [44]

- Gouty arthritis [44]
- Acute painful shoulder bursitis or tendinitis [44] Headaches
- Trigeminal autonomic cephalgias[45]

• Paroxysmal hemicrania [45]
• Chronic paroxysmal hemicranial[45]

- Episodic paroxysmal hemicranial[45]

• Hemicrania continual [45]

- Valsalva-induced headaches [45]
- Primary cough headachell[45]

• Primary exertionalheadachell[45]
• Primary headache associated with sexual activity (preorgasmic and orgasmicy)[45]
• Primary stabbing headache (jabs and jolts syndrome)[45]

- Hypnicheadache[45]

Others

- Patent ductusarteriosus

Contraindication

Concurrent peptic ulcer, or history of ulcer disease Allergy to indometacin, aspirin, or other NSAIDS
• Roux-en-Y gastric bypass and gastric sleeve Patients with nasal polyps reacting with an angioedema to other NSAIDs
• Children under 2 years of age (with the exception of neonates with patent ductusarteriosus)
• Severe pre-existing renal and liver damage Caution: pre-existing bone marrow damage (frequent blood cell counts are indicated)
• Caution: bleeding tendencies of unknown origin (indometacin inhibits platelet aggregation)

- Caution: Parkinson's disease, epilepsy, psychotic disorders (indometacin may worsen these conditions)[46]

Concurrent with potassium sparing diuretics
• Patients who have a patent ductusarteriosus dependent heart defect (such as transposition of the great vessels)
• Significant hypertension (high blood pressure)
• Concomitant administration of lithium salts (such as lithium carbonate)

Adverse effects

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In general, adverse effects seen with indometacin are similar to all other NSAIDs. For instance, indometacin inhibits both cyclooxygenase-1 and cyclooxygenase-2, which then inhibits the production of prostaglandins in the stomach and intestines responsible for maintaining the mucous lining of the gastrointestinal tract. Indometacin, therefore, like other non-selective COX Inhibitors, can cause peptic ulcers. These ulcers can result in serious bleeding or perforation, requiring hospitalization of the patient.

To reduce the possibility of peptic ulcers, indomethacin should be prescribed at the lowest dosage needed to achieve a therapeutic effect, usually between 50 and 200 mg/day. It should always be taken with food. Nearly all patients benefit from an ulcer protective drug (e.g. highly dosed antacids, ranitidine 150 mg at bedtime, or omeprazole 20 mg at bedtime). Other common gastrointestinal complaints, including dyspepsia, heartburn and mild diarrhoea are less serious and rarely require discontinuation of indomethacin.

Many NSAIDs, but particularly indomethacin, cause lithium retention by reducing its excretion by the kidneys. Thus indomethacin users have an elevated risk of lithium toxicity. For patients taking Lithium (e.g. for treatment of depression or bipolar disorder), less toxic NSAIDs such as sulindac or aspirin are preferred

All NSAIDs, including indometacin, also increase plasma renin activity and aldosterone levels, and increase sodium and potassium retention. Vasopressin activity is also enhanced. Together these may lead to

Edema (swelling due to fluid retention)
Hyperkalemia (high potassium levels)[47]
Hypernatremia (high sodium levels)
Hypertension

Elevations of serum creatinine and more serious renal damage such as acute kidney failure, chronic nephritis and nephrotic syndrome, are also possible. These conditions also often begin with edema and high potassium levels in the blood.

Paradoxically yet uncommonly, indometacin can cause headache (10 to 20%), sometimes with vertigo and dizziness, hearing loss, tinnitus, blurred vision (with or without retinal damage). There are unsubstantiated reports of worsening Parkinson's disease, epilepsy, and psychiatric disorders. Cases of life-threatening shock (including angioedema, sweating, severe hypotension and tachycardia as well as acute bronchospasm), severe or lethal hepatitis and severe bone marrow damage have all been reported. Skin reactions and photosensitivity are also possible side effects.

The frequency and severity of side effects and the availability of better tolerated alternatives make indometacin today a drug of second choice. Its use in acute gout attacks and in dysmenorrhea is well-established because in these indications the duration of treatment is limited to a few days only, therefore serious side effects are not likely to occur.

People should undergo regular physical examination to detect edema and signs of central nervous side effects. Blood pressure checks will reveal development of hypertension. Periodic serum electrolyte (sodium, potassium, chloride) measurements, complete blood cell counts and assessment of liver enzymes as well as of creatinine (renal function) should be performed. This is particularly important if Indometacin is given together with an ACE inhibitor or with potassium-sparing diuretics, because these combinations can lead to hyperkalemia and/or serious kidney failure. No examinations are necessary if only the topical preparations (spray or gel) are applied. Rare cases have shown that use of this medication by pregnant women can have an effect on the fetal heart, possibly resulting in fetal death via premature closing of the Ductusarteriosus.[48]

In October 2020, the U.S. Food and Drug Administration (FDA) required the drug label to be updated for all nonsteroidal anti-inflammatory medications to describe the risk of kidney problems in unborn babies that result in low amniotic fluid.[49,50] They recommend avoiding NSAIDS in pregnant women at 20 weeks or later in pregnancy.[49,50]

Mechanism of action:

Indometacin, a non-steroidal anti-inflammatory drug (NSAID), has similar mode of action when compared to other drugs in this group. It is a nonselective inhibitor of cyclooxygenase (COX) 1 and 2, the enzymes that participate in prostaglandin synthesis from arachidonic acid. Prostaglandins are hormone-like molecules normally found in the body, where they have a wide variety of effects, some of which lead to pain, fever, and inflammation. By inhibiting the synthesis of prostaglandins, indometacin can reduce pain, fever, and inflammation. Indometacin mechanism of action, along with several other NSAIDs that inhibit COX, was described in 1971.[51]

Additionally, indometacin has recently been found to be a positive allosteric modulator

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(PAM) of the CB, cannabinoid receptor. By enhancing the binding and signalling of endogenous cannabinoids such as anandamide, PAMs may elicit increased cannabinergic signalling in a tissue specific manner, reducing the incidence of problematic side effects such as psychoactivity while maintaining some antinociceptive activity.[52]

Besides, indometacin has logarithmic acid dissociation constant pKa of 3 to 4.5. Since the physiologic body pH is well above the pKa range of indometacin, most of the indometacin molecules will be dissociated into ionized form, leaving very little un-ionized form of indometacin to cross a cell membrane. If the pH gradient across a cell membrane is high, most of the indometacin molecules will be trapped in one side of the membrane with higher pH. This phenomenon is called "ion trapping" The phenomenon of ion trapping is particularly prominent in the stomach as pH at the stomach mucosa layer is extremely acidic, while the parietal cellu are more alkaline. Therefore, indometacin are trapped inside the parietal cells in ionized form damaging the stomach cells, causing stomach imitation. This stomach imitation can reduce if the stomach acid pH is reduced

Indometacin's role in treating certain headaches is unique compared to other NSAIDS. In addition to the class effect of COX inhibition, there is evidence that indometacin has the ability to reduce cerebral blood flow not only through modulation of nitric oxide pathways but also via Intracranial precapillary vasoconstriction.[53]Indometacin property of reducing cerebral blood flow is useful in treating raised intracranial pressure. A case report has shown that an intravenous bolus dose of indometacin given with 2 hours of continuous infusion is able to reduce intracranial pressure by 37% in 10 to 15 minutes and increases cerebral perfusion pressure by 30% at the same time This reduction in cerebral pressure may be responsible for the remarkable efficacy in a group of headaches that is referred to as Indometacin-responsive headaches", such as idiopathic stabbing headache, chronic paroxysmal hemicranial, and exertional headaches.[54] on the other hand, the activation of superior salivary nucleus in the brainstem is used to stimulate the trigeminal autonomic reflex arc, causing a type of headache called trigeminal autonomic cephalgia. Indometacin inhibits the superior salvatory nucleus, thus relieving this type of headache.

Prostaglandins also cause uterine contractions in pregnant women. Indometacinis an effective tocolytic agent.[55] able to delay premature labor by reducing uterine contractions through inhibition of prostaglandin synthesis in the uterus and possibly through calcium channel blockade Indometacin readily crosses the placenta and can reduce fetal urine production to treat polyhydramnios. It does so by reducing renal blood flow and increasing renal vascular resistance, possibly by enhancing the effects of vasopressin on the fetal kidneys.

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