INTRODUCTION
Use of pesticides in India began in 1948 when DDT was imported for malaria control and BHC for low cost control. India started pesticide production with manufacturing plant for DDT and Benzene Hexachloride (BHC) in the year 1952 in 1958 was producing over 5000 metric tones of pesticides. Currently there are more than 2000 pesticides registered for use, and production has increased to approximately 8,500 metric tones. Rampant use of these chemicals has given rise to several short-term and long-term adverse health effects of these chemicals. The first report of poisoning due to pesticides in India came from Kerala in 1958 where, over 100 people died after consuming wheat flour contaminated with parathion\(^1\). The chemical used was ethyl parathion known as Folidol E 605 and introduced by Bayer. In the same year poisoning in Kerala caused death of 102 people. This was mainly due to careless handling and storage of wheat, subsequently several cases of human and animal poisoning were reported by Sethuraman, 1977 and Banerjee, 1979. The Bhopal gas leak in 1984 killing thousands of people was another major mishap\(^2,3,4\). Despite the fact that the consumption of pesticides in India is still very low, about 0.5 kg per Ha of pesticide against 6.60 and 12.0 per Ha in Korea and Japan respectively, there has been widespread contamination of food commodities with pesticides residue basically due to non-judicious use of pesticides. In India 51% of food commodities are contaminated with pesticides residues and out of these 20% have pesticide residue above maximal residue level values on a world wide basis. It has been observed that their long term, low –dose exposure are increasingly linked to human health effects such as immune-suppression, hormone disruption, reproductive abnormalities and cancer.

Currently the chlorinated pesticides are phasing out due to their non-biodegradable property and persistent toxicity. Most of the chlorinated pesticides leave residue in various living systems for prolonged periods of their life span and are presumely responsible for acute and chronic neurotoxicity\(^5\). Since the main use of pesticides are in the agriculture sector in India, it is the rural population particularly the farmers who are most affected due to indiscriminate and rampant use of pesticides to compact the various pests and insects to control/minimize the crop losses. India is presently the second largest manufacturer in Asia and ranks 12\(^{th}\) globally.
The agricultural workers, sprayers, formulators and applicators are exposed to occupational hazards of pesticides directly or indirectly. In developing countries such as India where users are often illiterate, ill-trained, ill-informed and lacking appropriate devices are at a risk of developing pesticide toxicity. The Poison Information Centre in National Institute of Occupational Health in Ahmedabad reported that organo phosphorous pesticides were responsible for the maximum number of poisoning (73%) among all agricultural chemicals. In a study of 190 patients of acute organo phosphorous pesticides poisoning messianic manifestations were recorded which included GIT, CNS and cardiac manifestations. Studies on 356 workers in 4 units manufacturing HCH revealed neurological symptoms (21%) with significant increase in liver related enzymes which were related to the intensity of exposure. Observations confined to health surveillance in male formulators engaged of production of various pesticides (Malathion, Methyl Parathion, DDT and Lindain) revealed several types of adverse effects and reproductive problems. In another study the thyroid functions of formulators exposed to a combination of pesticides in the organized sector was examined. Total T3 was suppressed significantly in formulators while a marginal decrease (7%) in T4 levels.

TSH levels were also elevated by 28%. These formulators had significantly low serum cholineesterase activity and high serum BHC content indicating appreciable exposure to their working environment showed significant changes in electro cardiograph indicating cardio toxic effect of methomyl, carbamate insecticides in cotton field workers. Assessment of urinary biomarkers (Di Alkyl Phosphates DAP) is a recent development in the field of pesticide toxicology and considered non-invasive and sensitive tool for early detection of organo phosphates in the exposed workers.

SPECIAL PATIENT PROBLEMS:

Children: In comparison to adults, children may be at greater risk from pesticide exposures due to growth and development factors. Consideration of fetal, infant, toddler or child characteristics is helpful in an exposure evaluation: physical location, breathing zones, oxygen consumption, food consumption, types of food consumed and normal behavioral development. Furthermore, transplacental absorption and breast milk possess additional routes of exposure. Although environmental (and, at times, occupational) exposure to pesticide of this work, the significant hazard for childrens is unintentional ingestion. Thus, it is very important to ask about pesticides used and stored in home, day care facility, school and play areas.

Agricultural workers: Data from California’s mandatory pesticide poisoning reporting system would imply annual national estimate 10,000-20,000 cases of farm workers poisoning however it is believed that these figures still represent serious underreporting due to the lack of medical access for many workers and misdiagnosis by some clinicians.
Nomenclature and Development of OP PESTICIDES:

MONOCROTOPHOS:
Commonly known as monocrotophos (BSI, E-ISO, (m) F-ISO, ESA, JMAF). Chemical name (IUPAC)dimethyl(E)-1-methyl-2-(methyl-2-carbamoyl) vinylphosphate3-dimethoxyphosphinoxyoxy-N-methylisocrotonamide3- (dimethoxyphosphinoxy)-N-methylisocrotonamide (C.A)(E)-dimethyl phosphate ester with(E)-3-hydroxy-N-methylcrotonamide(8Cl);Reg.No(6923-224)Formerly(919-44-8) monocrotophos(919-44-8)(Z)analogue;(2157-98-4)(E+Z)Compounds. OMS834; ENT27 129 introduced by Ciba AG (now Ciba-Geigy AG) as code no 1414(Ciba-Geigy AG), SD 9129’ (Shell; Trade marks’Apadrin’ (to kenoGard VT AB) ‘Azodrin (to shell), ‘Crotos’ (to siapa) Nuvacron (to Ciba-Geigy AG).

\[
\begin{align*}
\text{E-Isomer} & : & \text{H}_3\text{CO}-\text{P} \rightarrow \text{O}\text{C} \rightarrow \text{NH} \rightarrow \text{CH}_3 \\
\text{Z-Isomer} & : & \text{H}_3\text{CO}-\text{P} \rightarrow \text{O}\text{C} \rightarrow \text{NH} \rightarrow \text{CH}_3
\end{align*}
\]

Uses: It is a fast-acting insecticide with both systemic and contact action, used against a wide range of pests including mite, sucking insects, leaf-eating beetles, bollworms and other lepidopterous larvae on a variety of crops. Dosage rates against mites and sucking insects are 250-500g/ha and against lepidopterous larvae 500-1000g/ha. It persists for 7-14days.
**Toxicology:** Acute oral LD$_{50}$ for rats 14 mg tech/kg; for birds 1.0-6.5mg/kg, acute percutaneous LD$_{50}$ for rats 336mg/kg; non irritant to skin and eyes of rabbits. Inhalation LC$_{50}$ (4-h) for rats c.0.08mg/l air. In 2-y feeding trails NEL was estimated by WHO (JMPR 1972) as; for rats 0.5mg/kg diet (0.025mg/kg daily); for dogs 0.5 mg /kg diet (0.0125mg/kg daily). In a 30 d-trial with human volunteers a daily oral dose of 0.006 mg/kg was without effect LC 50(24-h) is; for rainbow trout 12 mg/l; for bluegill 23 mg/l. It is highly toxic to honeybees, LD$_{50}$ 0.033-0.084 mg/bee. ADI for man 0.0006mg/kg.

**PARATHION-METHYL:**
Commonly known as parathion-methyl (BSI,E-ISO,(m) F-ISO); methyl parathion (ESA,JMAF); metaphos(USSR). Chemical name (IUPAC) O, O- dimethyl O-4 – nitrophenyl phosphorothiate (C. A) O,O- dimethyl O-(4 –nitrophenyl ) phosphorothioate (9CI) ;O,O- dimethyl O,( p-nitrophenyl) phosphorothioate (8CI); Reg no( 298-00-0). OMS 213; ENT 17 292. It is insecticidal activity was described by G. Schrader ( Angew. Chem Monograph No; 52( 2 nd Ed) , 1952). Introduced by Bayer AG( DEP 814 412) as trade marks ‘Folidol-M’ ‘Metacide’ ‘ Bladan M’ ‘ Nitrox 80’.

![PARATHION-METHYL](image)

**Uses:** It is a non-systemic contact and stomach insecticide with some fumigant action. It is generally recommended at 15-25g a.i /100 l. it is non persistent.

**Toxicology:** acute oral LD$_{50}$ for male rats 14 mg /kg, for females 24mg/kg. Acute percutaneous LD$_{50}$ for rats 67mg/kg. In 2 –y feeding trails NEL for rats was 2mg/kg diet. LC$_{50}$ (96-h) is: for rainbow trout 2.7mg /l ; for golden orfe 6.9 mg /l ADI for man 0.02mg/kg.

**MALATHION:**
Commonly known as malathion ( BSI, E-ISO, ESA, BPC); maldison ( Austraila, New Zealand); malathion (JMAF); mercaptothion ( republic of south Africa) ; carbofos(USSR); exception ( federal Reblic of Germany). Chemical name (IUPAC) diethyl dimethoxyphosphinothioylthio)succinate; diethyl (dimethoxythiophosphorylthio) succinate S-1,2 bis ( ethoxycarbonyl) ethyl O,O – dimethyl phosphorothioate (C.A) diethyl (Dimethoxy phosphinothiyl) thio butanedioate (9CI); diethyl
mercaptosuccinate S-ester with O, O-dimethyl phosphorodithioate (8Cl); Reg No (121-75-5). OMS1; ENT 17 034. Introduced by American Cyanamid Co. (USP 2 578 652) as code no EI 4049 trademark ‘Cythion’ for deodorized grade other marks include ‘malathion’.

**Uses**: It is non-systemic insecticide and acaricide of low mammalian toxicity. It is generally non-phytotoxic but may damage cucumber, string bean and squash under glasshouse conditions. In addition to a wide range of agricultural and horticultural uses.

**Toxicology**: Acute oral LD$_{50}$ for rats 2800mg/kg. Acute percutaneous LD$_{50}$ (24-h) for rabbits 4100mg/kg. In 1.75-y trials rats receiving 100mg tech/kg diet showed normal weight gain. LC$_{50}$ (5-d) is; for bob white quail 3497mg/kg diet; for ring neck pheasant 4320 mg/kg diet (USDI Wild life Rep., 1972, no 152,p 36). LC$_{50}$(96-h) is; for bluegill 0.103mg/l; for large mouth bass 0.285mg /l (USDI Resource Pub 1980, No.157, p47) Topical toxicity for honey bees, LD$_{50}$ 710ng/bee. ADI for man 0.02mg/kg.

**MEVINOPHOS**

Commonly known as mevinophos (BSI, E-ISO, (m) F-ISO, ESA); the isomer present (E) and (Z) – or cis and Trans (with respect to carbon chain) should be stated. Chemical name (IUPAC) methyl 3-(Dimethoxyphosphinoxyloxy) but-2-enoate; methyl3 - (Dimethoxyphosphinyloxy) but-2enoate; 2-methoxycarbonyl- 1- methylvinylidimethyl phosphate. (C.A) methyl-3- (Dimethoxyphosphin) oxy-2-butenoate(9Cl);methyl3-hydroxycrotonate dimethyl phosphate ester( 8Cl); Reg no(26718-65-0), formerly (298-01-1) (E)- isomer; (338-45-4)( Z)-isomer(7786-34-7)( Z+E isomers). ENT 22 374. Its insecticidal properties were described by R.A Corey et al. (J. Econ Entomol., 1953, 45, 386). Introduced by Shell chemical co.USA. (USP 2 685 522) as code no ‘OS-2046; the trade mark ‘Phosdrin’ (shell). Apavinofos (kenogard VT AB).
Uses: It is a contact and systemic acaricide and insecticide with short residual activity. It is effective against beetles and mites at 200-300g/ha, caterpillars at 250-500g/ha, sap feeding insects at 125-250g/ha.

Toxicology: Acute oral LD₅₀ for rats 3-12 mg tech/kg for mice 7-18mg/kg for birds 0.75-7.0mg/kg. Acute percutaneous LD₅₀: for rats 4-90mg/kg; for rabbits 16-33 mg/kg. In 2-y feeding trials no effects was observed in rats receving 4mg/kg diet or dog 5mg/kg diet. LC₅₀ (48-h) for fish in range 0.02-31mg/I. It has little effect on wild life in practice because it is rapidly broken down to less toxic decomposition products. ADI for man 0.0015mg/kg.

PHOSPHAMIDON:
Commonly known as phosphamidon (the ratio of stereo isomers being stated) (BSI, E ISO, (m) F-ISO, ANSI, ESA); exception (Italy) Chemical name(IUPAC) 2-Chloro-2-diethylcarbamoyl-1-methylvinyl dimethyl phosphate; 2–chloro-3-dimethoxyphosphinoxyloxy-N-N- diethylbut-2 enamide(C.A) 2- chloro-3- ( diethylamino)-1-methyl-3-oxo-1-propenyl dimethyl phosphate(9Cl); Dimetyl phosphate ester with 2-chloro-N,N- diethyl-3-hydroxy crotoamide)(8Cl); Reg no(1317-21-6) (E)-+(Z) isomers ;( 23783-98-4) ( Z) isomers; (297-99-4) (E) isomer. OMS 1325;ENT 25 515. Its insecticidal properties were described by F. Bachmann&J. Meierhans( Bull Cent. Int. Antiparasit., 1956, Nov ,p.18) Introduced by Ciba AG( now Ciba-Geigy AG)( BEP 552 284; gbp 829 576) as code no ‘C’ 570 ; trade mark ‘Dimercon’.
**Uses:** Pure phosphomidon is a systemic insecticide which is rapidly absorbed by plants and has little contact action. It is effective against sap-feeding insects at 300-600g/ha and other pests including Chilo plejadellus, Diarrhea saccharalis and rice leaf beetles at 500-1000g/ha.

**Toxicology:** Acute oral LD50 of rats 17.4mg/kg. Acute percutaneous LD 50 for rats 374mg/kg; slight irritant to skin and eyes of rabbits. Acute inhalation LC50(4-h) for rats c. 0.18mg/l air. In 2-y feeding trials NEL was: for rats 1.25mg/kg daily; for dogs 0.1mg/kg daily. It is highly toxic to birds and honeybees. Temporary ADI for man 0.0005 mg/kg( until 1986).

**DICHLORVOS:**
Commonly known as dichlorvos (BSI, E-ISO,(m) F-ISO,BPC,ESA); DDVP(JMAF); dichlorfós (USSR); DDVF( former exception, USSR). Chemical name (IUPAC) 2,2 dichlorovinyl dimethyl phosphate(I). (C.A) 2,2-dichlorethenyl dimethyl phosphate(9Cl)(I) (8Cl); Reg no(62-73-7). Trival name DDVP. OMS14;ENT 20 738. Its insecticidal properties were described by Ciba AG( now Ciba-Geigy AG)( GBP 775 085) but an incorrect structure was given to the compound; it was later reported by A.M Martson et al. (J Agric. Food Chem., 1955,3,319) as an insecticidal impurity in Trichlorfon. Introduced by Ciba-Geigy AG shell chemical co., and Bayer AG( gbp 775 085 to Ciba-Geigy AG shell chemical co ., and Bayer AG( GBP 775 085 to Ciba-Geigy; USP 2 956 073 to shell) as code no 'Bayer 19 149' trade marks Apavap’ (to KenoGard VT AB) Dedevap (to Bayer) Nogos, Nuvan( both to Ciba-Geigy), Vapona (to shell for agronomic uses only).

![Chemical structure of Dichlorvos](image)

**Uses:** It is a contact and stomach-acting insecticide with fumigant and penetrant action. It is used as a household and public health fumigant especially against Diptera and mosquitoes; for the protection of stored products at 0.5-1.0g a.i/100m³; for crop protection against sucking and chewing insects at 300-1000g/ha.
**Toxicology:** Acute oral LD 50 for rats 56-108mg/kg. Acute percutaneous LD 50 for rats 75-210 mg/kg. In 90-d feeding trials receiving 1000mg/kg diet showed no intoxication. Inhalation LC50 (4-h): for mice >0.22mg/1 air; for rats 0.20mg/1air. LC 50(24-h) for bluegill is 1 mg/l. It is highly toxic to honeybees and toxic to birds. ADI for man 0.004 mg/kg.

**DICROTOPHOS:**

Commonly known as dicrotophos (BSI,E-ISO,F-ISO,ESA). Chemical name (IUPAC)(E)-2- dimethyl carbamoyl -1-methylvinyl dimethyl phosphate; 3-dimethyl phosphinoyloxy -N,N-dimethyl isocrotonamide; 3-dimethyl phosphinoyloxy-N,N-dimethyl isocrotonamide (C.A ). (E)-3- (dimethyl amino)-1-methyl11-3-oxo-1-propenyl dimethyl phosphate(9CI) Dimethyl phosphate ester with (E)-3-hydroxy-N,N-dimethylcrotonamide(8CI) Reg No (141-66-2) dicrotophos ;(18250-63-0) the (z) analogue (3735-78-3)(E+Z) compounds.OMS 253;ENT 24 482. its insecticide properties were described by R.A. Corey(J. Econ Entomol., 1965,58,112). Introduced by ciba AG( now Ciba-Geigy AG) and later by shell Chemical Co., USA(BEP 552 284; GBP 829,576 both to Ciba-Geigy;USP 2 956 073;3 068 268 both to shell) as code no ‘C-709’ (Ciba-Geigy) SD ‘3562’ (Shell); trade marks ‘Bidrin’ ( Shell). ‘Carbicron’’ Ektafos’( Ciba-Geigy) ‘Diapadrin’ (KenoGard VT AB).

![Chemical Structure of Dicrotophos](image)

**Uses:** Dicrotophos is a systemic insecticide and acarcide of moderate persistence. It is effective against sucking. Boring and chewing pests at dose rates of 300-600g a.i /ha and is recommended for use on coffee, cotton, rice and other crops.

**Toxicology:** Acute oral LD50 for rats 17-22mg/kg; for birds 1.2-12.5mg/kg. Acute percutaneous LD50 for rats ranges from 111-136mg/kg to 148- 181mg/kg, depending on the carrier and the conditions of the test; for rabbits 224mg/kg, slight transient to skin and eyes of rabbits. Inhalation LC50 (4-h)c. 0.09mg/1 air. In 2-y feeding trails NEL was: for rats 1.0mg /kg diet (0.05mg/kg daily); for dogs 1.6mg/kg diet (0.04mg/kg daily). NEL in a 3-generation reproduction study with rats was 2mg/kg daily. It is not neurotoxic to hens. LC50 (24-h) is: for mosquito fish 200mg/l; for harlequin fish 1000mg/l. it is very toxic to honeybees but because surface residues rapidly decline little effect is seen in practice.
**CHLORPYRIFOS:**

Commonly known as Chlorpyrifos (BSI, E-ISO, ANSI, ESA,BPC); chlorpyriphos(m) F-ISO, JMAF); Chlorpyrifos -ethyl(m) France). Chemical name(IUPAC) O,O- diethyl 0-3,5,6- trichloro-2-pyridyl phosphorothioate, (C.A) O,O diethyl O-(3,5,6- trichloro-2-pyridinyl )phosphorothioate(9Cl); O,O- diethyl O,(3,5,6- trichloro-2 pyridyl ) phosphorothioate(8Cl); Reg. No (2921-88-2). OMS 971; ENT 27 311. Its insecticidal properties were described by E.E Kenaga et al. (j. Econ. Entomol., 1965,58,1043). Introduced by Dow Chemical Co(USP 3 244 586) as code no. Dowco 179; trade marks 'Dursban'. 'Lorsban'.

![Chemical structure of Chlorpyrifos](image)

**Uses:** It has a broad range of insecticidal activity and is effective by contact, ingestion and vapour action, but is not systemic. Used for the control of flies, house hold pests, mosquitoes (larvae and adults) and of various crop pests in soil and on foliage; also used for control of ectoparasites on cattle and sheep.

**Toxicology:** Acute oral LD$_{50}$ for rats 135-163mg/kg; for guinea-pigs 500mg/kg; chickens 32mg/kg; for rabbits 1000-2000mg/kg. Acute percutaneous LD$_{50}$ (in solutions) for rabbits is c. 2000mg/kg. In 2-y feeding trials NEL based on blood plasma cholinesterase activity, was: for rats 0.03mg/kg daily; for dogs 0.01mg/kg daily. It is rapidly detoxified in rats dogs and their animal species LC$_{50}$(96-h) for rainbow trout is 0.003mg /l. ADI for man 0.01 mg/kg.
Route of Exposure of OP Pesticides in the Body:

Inhalation: Exposure of low-vapor concentrations may affect only the eye, nose, and airways. Miosis, visual disturbances, rhinorrhea and some degree of dyspnea develop within seconds to several minutes. After inhalation of high vapor concentrations, victims lose consciousness within one or two minutes and they have seizures, flaccid paralysis, and apnea.
**Eyes:** Miosis rapidly occurs after splash exposure or eye contact with vapor. Miosis may be accompanied by deep, aching eye pain, conjunctival irritation and visual disturbances. Dim vision may be because of constricted pupils or inhalation of cholinergic fibers of the retina or central nervous system. The mitotic pupil may improve vision, although a complaint of blurred vision is common\(^{18}\). Direct installation of dilute nerve agents in to the eye does not produce tissue damage\(^{19}\).

**Gastrointestinal:** The oral route of entry is important in accidental and intentional OP pesticides poisoning. Occupational accidental ingestion may occur in children. Oral ingestion may cause nausea and vomiting may occur. Abdominal pain and diarrhea together with a cholinergic syndrome, CNS and cardiovascular effects can produce moderate to severe OP poisoning.

**Dermal exposure:** The skin is the largest organ in the body and the major route of adsorption of pesticides. If the skin is sweaty, wet or there is a rash, sore cut or other skin problem, pesticides will be absorbed more rapidly then in greater amount, f pesticides are spilled or splashed on the skin and not removed immediately and thorough absorption will continue as long as they are in contact with the skin. Pesticides are absorbed from contaminated work clothing, and can enter the body by walking bare foot on treated surfaces. Children can absorb pesticides from contact with treated pets, lawn contaminated carpet, upholstery and other surfaces.

**Skin:** In dermal absorption, symptoms and signs usually manifest in about two to three hours. Initial local effects of liquid, which are seldom noticed, include muscular fasciculations and sweating at the contamination site. A large droplet may also cause gastrointestinal effects and complaints malaise and weakness. Droplets containing near lethal or lethal doses can cause loss of consciousness, seizures, flaccid paralysis and apnea.

**Dermal adsorption of Vapour:** Pesticide vapors can also be absorbed through the skin even though the primary route of absorption is the lungs. Dermal exposure is much greater than respiratory exposure in workers who handle pesticides and pesticide treated crops. Skin exposure accounted for more than 90% of total body burden in applicators spraying trees and ornamental shrubs.

Respirable particle size:
- \(>10 \mu\)- reach upper air ways.
- 5 to 10\(\mu\)- reach central bronchial pathways.
- 1 to 5\(\mu\) –peripheral bronchial pathways.
Breathing Rate: The input of OP pesticides in the lungs depends on the rate and frequency of breathing per minute. If there is an increased rate of breathing (hyperpnoea) then depending on the respirable particle size the amount of entry of pesticides is more and vice-versa.

Volume of Breathing (Ventilation): Similarly depending on ventilation (hyper or hypo ventilation) the entry of OP pesticides is more or less in the tracheo-bronchial tube.
Major factors influencing pesticide exposure and Absorption

- Type of formulation
- Rate of absorption into the body
- Duration of exposure
- Protective clothing and equipment
- Climate (Temperature, humidity)
- Work practices

Type of formulation: Chemical composition of organophosphorous pesticides.

Ratio of adsorption into the body: Different OP pesticide adsorbed by the body by different exposure.

Duration of exposure: The OP pesticides exposure is a time taken process by hours and days. It depends on quantity of chemical and utilization of Crops.

Protecting clothing (hand gloves, eye goggles): OP pesticide sprayers must wear hand gloves, clothes and eye spectacles and other required for protection from OP pesticide poisoning.

Climate environment: (Temperature, humidity): India is a tropical country and generally the farmers do the agriculture in hot and humid climate therer by entering there cutaneous exposure to the environment OP pesticides periodically spread for the protection of the crop.

Work protection: To avoid OP pesticide compounds from spraying area to house and handling is also avoid from house and food items. Take care about children’s and animals and birds.

Smoker’s habits: The smokers to clean their hands and to take food item. Smoking and pesticide spraying is also creating respiratory problem and cardiovascular effects.

Personal hygiene: In personal habits individuals to take care about OP pesticide utilization.
**Cholinergic Syndromes:** Parasympathetic stimulations or cholinergic syndromes are due to the acetylcholine accumulation at the nerve endings stimulating both muscarinic and nicotinic receptor. Muscarinic effects include increased bronchial secretion, excessive sweating, salivation and lacrimation, pinpoint pupils, bronchoconstriction, abdominal cramps (vomiting and diarrhea), increased urinary frequency, bradycardia, hypotension, and in severe intoxicated patients pulmonary edema may occur. Nicotinic effects comprise of tachycardia, hypertension, mydriasis, twitching and fasciculation of muscles, and in more severe cases, paralysis of diaphragm and respiratory muscles\textsuperscript{20,21}

**Cholinergic syndrome:** Cholinergic syndrome is called parasympathetic stimulation of cholinergic fibres due to the AchE accumulation at the nerve endings stimulating both muscarinic and nicotinic receptors.

**Muscarinic effects:**
1. Increased bronchial secretions
2. Excessive sweating
3. Excessive salivation and lacrimation
4. Pinpoint pupils (miosis)
5. Broncho constriction
6. abdominal cramps (Vomiting and diarrhea)
7. Increased urine frequency
8. cardiovascular effects (Bradycardia, hypertension)

**Nicotinic effects:** Tachycardia, hypertension, mydriasis, muscle twitching, tremors and abnormal Babinsky reflexes (dorsi flexion).

**CNS effects:** Headache, Dizziness, restlessness, anxiety, convulsions, coma, mental confusion.

**Central nervous system effects:** CNS effects include headache, dizziness, restlessness and anxiety, mental confusion, convulsions and coma.
**Cardiovascular effects:** Cardiovascular cholinesterase inhibition increases the vagal nerve influence on heart rate and the expected result is bradycardia. In a person who is accidentally poisoned however other factors, such as fear, hypoxia and ganglionic stimulation, may contribute to acceleration of heart rate. Some of the most commonly reported early symptoms include headache, nausea, dizziness, and hypersecretion, manifested by sweating, salivation, lacrimation, and rhinorrhea. Muscle twitching, weakness, tremor in coordination, vomiting, abdominal cramps, and diarrhea all signal worsening of the poisoned state. Miosis is often helpful diagnostic sign and the patient may report blurred and or dark vision. Anxiety and restlessness are prominent, as are a few reports of choreiform movements. Psychiatric symptoms including depression, memory loss, and confusion have been reported. Toxic psychosis manifested confusion or bizarre behavior, has been misdiagnosed as alcohol intoxication.

**Intermediate syndrome:** The intermediate syndrome consists of marked weakness of the proximal skeletal musculature (including the muscles of respiration) and cranial nerve palsies, which may occur one to four days after acute OP pesticide poisoning. This syndrome that was observed after certain organophosphate poisoning has not yet been reported after nerve agent poisoning. Intermediate syndrome is probably a consequence of cholinergic over activity at the neuromuscular junction and a connection has been made between the intermediate syndrome and OP induced myopathy.

Organophosphates whose breakdown is relatively slow, significant temporary storage in body fat may occur. Some organophosphates such as diazinon and methyl parathion have significant lipid solubility allowing fat storage with delayed toxicity due to late release. Delayed toxicity may also occur atypically with other organophosphates, specifically dichlorofenthion and demeton–methyl. Many organothiophosphates readily undergo conversion from thions (P=S) to oxons (P=O). Conversion occurs in the environment under the influences of oxygen and light, and in the body chiefly by the action of liver microsomes. Oxons are much more toxic than thions, but oxons break down more readily. Ultimately both thions and oxons are hydrolyzed at the ester linkage, yielding alkyl phosphates and leaving groups both which are of relatively low toxicity.

**OPIDN:** Organophosphates have caused a different kind of neurotoxicity consisting of damage to the afferent fibers of peripheral and central nerves and associated with inhibition of “neuropathy target esterase” (NTE). This delayed syndrome has been termed organophosphate-induced delayed neuropathy (OPIDN), and is manifested chiefly by weakness or paralysis and paresthesia of the extremities. OPIDN predominantly affects the legs and may persist for weeks to years.
OPIDN, an intermediate syndrome this syndrome occurs after resolution of the acute cholinergic crisis generally 24-96 hours after exposure. It is characterized by acute respiratory paresis and muscular weakness primarily in the facial, neck and proximal limb muscles. The most common compounds involved in this syndrome are methyl parathion, fenthion, and dimethoate. In organophosphate long stored Malathion which strongly inhibits the hepatic enzymes operative in Malathion degradation, thus enhancing its toxicity. Degradation of some compounds to trimethyl phosphate can cause restrictive lung disease.27
Clinical manifestations according to the route of exposure of OP Pesticides:

Organophosphorous pesticides are toxic because they inhibit the actions of an enzyme in nervous tissue called acetylcholinesterase (AchE) which in turn inactivates a "neurotransmitter" acetylcholine (Alchol).

Neurotransmitters are present in various parts of the nervous system to enable transmission of stimulation either between nerves and various organs.

The various acute systems of Organophosphorous pesticides can be explained by the various sites where acetylcholine is present as a neurotransmitter and where abnormally increased levels can disturb function.

Acetylcholine is also present in the junctions between nerves and the muscles and in some nerve-to-nerve connections (synapses) in the brain.

Organophosphate poison insects and mammals primarily by phosphorylation of the acetyl choline esterase (AChE) at nerve endings. The result is loss of available AChE so that the effector organ becomes over stimulated by the excess acetylcholine (ACh, the impulse-transmitting substance) in the nerve ending. The enzyme is critical to normal control of nerve impulse transmission from nerve fibers to smooth and skeletal muscle cells, glandular cells, and autonomic ganglia, as well as within the central nervous system (CNS). Some critical proportion of the tissue enzyme mass must be inactivated by phosphorylation before symptoms and signs of poisoning become manifest.

At sufficient dosage, Loss of enzyme function allows accumulation of Ach peripherally at cholinergic neuroeffector junctions (muscarinic effects), skeletal nerve-muscle junctions and autonomic ganglia (nicotinic effects), as well as centrally. At cholinergic nerve junctions with smooth muscle and gland cells, high Ach Concentration causes muscle contraction and secretion respectively. At skeletal muscle junctions, excess Ach may be excitatory (cause muscle twitching), but may also weaken or paralyze the cell by depolarizing the end-plate. In the CNS, high Ach concentrations cause sensory and behavioral disturbances, incoordiantion, depressed motor function, and respiratory depression. Increased pulmonary secretions coupled with respiratory failure are the usual causes of death from organophosphate poisoning. Recovery depends ultimately on generation of new enzyme in all critical tissues.
Organophosphates are efficiently absorbed by inhalation, ingestion, and skin penetration. There is considerable variation in the relative absorption by these various routes. For instance, the oral LD$_{50}$ of parathion in rats between 3-8mg/kg, which is quite toxic$^{28,29}$ and essentially equivalent to dermal absorption with an LD$_{50}$ on the other hand, the toxicity of phosalone is much lower from the dermal route than the oral route, with rat LD$_{50}$ of 1500mg/kg and 120mg/kg respectively$^{30}$. In general, the highly toxic agents are more likely to have dermal toxicity than the moderately toxic agents.

Organophosphorous pesticide poisoning depends on the rate at which the pesticide is absorbed, breakdown occurs chiefly by hydrolysis in the liver, rates of hydrolysis vary widely from one compound to another. In the case of certain organophosphates whose breakdown is relatively slow, significant temporary storage in the body fat may occur. Some organophosphates such as diazinon and methyl parathion have significant lipid solubility, allowing fat storage with delayed toxicity due to late release$^{31}$. Delayed toxicity may also occur atypically with other organophosphates, specifically dichlorofenthion and demeton-methyl$^{32}$. Many organophosphates readily undergo conversion from thions (P=S) to oxons (P=O). Conversion occurs in the environment under the influence of oxygen and light, and in the body chiefly by the action of liver microsomes. Oxons are much more toxic than thions, but more readily both thions and oxons are hydrolyzed at the ester linkage, yielding alkyl phosphates and leaving groups, both of which are relatively low toxicity. They are either excreted or further transformed in the body before excretion.

The distinction between the different chemical classes becomes important when the physician interprets tests from references laboratories. This can be especially important when the lab analyses for the parent compound (i.e chlorpyrifos in its thiophosphate form) instead of the metabolite form (chlorpyrifos will be completely metabolized to the oxon after the pass through the liver).

Within one or two days of initial organophosphate binding to AchE, some phosphorylated acetylcholinesterase enzyme can be de-phosphorylated (reactivated) by the oxime antidote pralidoxime. As time progresses, the enzyme phosphoryl bond is strengthened by loss of one alkyl group from the phosphoryl adduct, a process called aging. Pralidoxime reactivation is therefore no longer possible after a couple of days$^{33}$ although in some cases, improvement has still been seen with pralidoxime administration days after exposure$^{34}$. 
**OP pesticides poisoning causes a series of symptoms**

Initial symptoms (mild)

Nausea, headache, tiredness, giddiness, papillary constriction, blurred vision

↓

Worse (moderate)

Vomiting, abdominal pain, diarrhea, sweating, salivation

↓

Progressive worsening

Muscular twitching in the tongue and eyelids further progressive it leads tremors, convulsions and paralysis

↓

Finally to respiratory muscle, paralysis, convulsions and coma

In mild conditions increased salivation, contraction of pupil of eyes, lacrimation, nausea, headache, weakness of muscles and dizziness.

In moderate conditions excessive salivation, small pupil with visual disturbance lacrimation, sweating, vomiting, diarrhea, headache, and drowsiness weakness increased muscles tension disturbed gait, broncho constriction and bronchial hyper secretion. Breathlessness increased.

In severe conditions mild and moderate conditions increased and as well as depressed consciousness or coma. Reduced respiration, cyanosis, convulsions and cardiac failure:
### Symptoms and Signs of OP Poisoning

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased Salivation</td>
<td>Excessive salivation</td>
<td>Symptoms for mild and moderate</td>
</tr>
<tr>
<td>Contraction of pupil of eye (miosis)</td>
<td>Small pupil with visual disturbance</td>
<td>And moderate poisoning increased</td>
</tr>
<tr>
<td>Lacrimation (tears in eye)</td>
<td>Lacrimation</td>
<td>Plus:</td>
</tr>
<tr>
<td>Nausea</td>
<td>Sweating</td>
<td>Depressed</td>
</tr>
<tr>
<td>Headache</td>
<td>Vomiting, diarrhea</td>
<td>Consciousness or coma</td>
</tr>
<tr>
<td>Weakness( of muscles) or tremor</td>
<td>Headache, drowsiness</td>
<td>Reduced Respiration</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Weakness increased, muscles tremor, increased muscle tension</td>
<td>Cyanosis</td>
</tr>
<tr>
<td></td>
<td>Disturbed gait (ataxia)</td>
<td>Convulsions</td>
</tr>
<tr>
<td></td>
<td>Bronchoconstriction and bronchial hyper secretion</td>
<td>Cardiac Failure</td>
</tr>
<tr>
<td></td>
<td>Breathelessness increased</td>
<td></td>
</tr>
</tbody>
</table>

Severity of Organophosphorous pesticides based on AchE and BchE inhibition

<table>
<thead>
<tr>
<th>Grade</th>
<th>BchE Activity (%)</th>
<th>AchE Activity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>40-50</td>
<td>50-90</td>
</tr>
<tr>
<td>Moderate</td>
<td>10-40</td>
<td>10-50</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;10</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>
Organophosphorous pesticides generally well absorbed via the respiratory tract and the skin as well as the gastrointestinal tract.

All signs and symptoms are cholinergic in nature and affect muscarinic, nicotinic, and central nervous system receptors\textsuperscript{35}. The critical symptoms in management are the respiratory symptoms. Sufficient muscular fasciculation and weakness are often observed.

Bronchospasm and bronchorrhea can occur, producing tightness in the chest, wheezing, productive cough, and pulmonary edema. A life threatening severity of poisoning is signified by loss of consciousness, incontinence, convulsions, and respiratory depression. The primary cause of death is respiratory failure, and there usually is a secondary cardiovascular component. The classic cardiovascular sign is bradycardia which can progress to sinus arrest. Toxic myocardiopathy has been a prominent feature of some severe organophosphate poisonings.

Organophosphate pesticide poisoning—some of the most commonly reported early symptoms include headache, nausea, dizziness, and hyper secretion, the later of which is manifested by sweating, salivation, lacrimation and rhinorrhea, muscle twitching, weakness, tremor in coordination, vomiting, abdominal cramps and diarrhea all signal worsening of the poisoned state. Miosis is often a helpful diagnostic sign and the patient may report blurred and dark vision. Psychiatric symptoms including depression, memory loss have been reported. Toxic psychosis, manifested as confusion or bizarre behavior, has been misdiagnosed as alcohol intoxication.

Some of the typical cholinergic signs of bradycadia, muscular fasciculation lacrimation, and sweating were less common. Seizures (22%-25%) and mental status changes including lethargy and coma (54%-96%) were common\textsuperscript{36,37}. In comparison only 2-3% of adults present with seizures, other common presenting signs in children including flaccid muscle weakness, miosis and excessive salivation. In one study 80% of cases were transferred with the wrong preliminary Diagnosis\textsuperscript{36}. In a second study 88% of the parents initially denied any exposure history\textsuperscript{37}.
MECHANISM OF TOXIC SUBSTANCES ENTERING INTO THE BODY

Toxic substances normally enter the body through the lungs (inhalation), the skin (absorption), or the gastrointestinal tract (ingestion). This toxic substance enters the bloodstream it is partitioned into body tissues, where it may act on target organs or tissues. For various reasons including insolubility, some substances are not distributed through the body. Ultimately, toxic substances are eliminated from the bloodstream through accumulation in various sites in the body and through biotransformation and excretion. Sites of accumulation of toxic substances may or may not be the primary sites of toxic action.

Carbon monoxide reaches highest concentration in red blood cells, where it competes successfully with oxygen for binding sites in hemoglobin. It then causes widespread brain damage when these red blood cells fail to supply an adequate amount of oxygen to the brain. Lead, a potent toxic substance, is found in highest concentrations in bone but exerts its most serious effects on the brain. The liver and kidney are major sites of accumulation of toxic substances probably because of their large blood and their roles in eliminating toxic substances from the body. The body has a number of ways to detoxify foreign substances.

The liver is the principal organ involved in detoxification, but other organs such as kidney, the intestine and the lungs also play major roles. Every tissue has some capacity for detoxification.

Excretion of substances may undergo biotransformation, the biochemical process by which it is converted into new chemical compounds to which are often more easily excreted. This process usually changes lipophilic compounds to compounds which are more hydrophilic (water soluble) and therefore more easily excreted.

Toxic substances seem to act selectively on the various components of the nervous system, damaging the neuronal bodies (neuropathy), axons (axonopathy) and myelin sheaths (myelinopathy). A common type of structural change induced by toxic substances on axons is central-peripheral distal axonopathy (CPDA). Degeneration of this type usually begins at the end of the axon and proceeds toward the cell body hence it is often referred to as the “dying-back” process. Some organophosphorous insecticides can cause this type of damage.
Toxic substances often cause a slow degeneration of the nerve cell body or axon that may result in permanent neuronal damage. Acute carbon monoxide poisoning, can produce a delayed, progressive deterioration of portions of the nervous system that may lead to psychosis and death over a period of week.\textsuperscript{20}

Toxic chemicals can induce functional changes that involve modifications of motor and sensory activities, emotional states and integrative capabilities such as learning, and touch and pain sensation. These effects may be caused by destruction of the myelin sheath that surrounds neurons (a process known as demyelization), damage to the neuron itself, or damage to the neurotransmitter system. Sensory changes are often reported as numbness or a tingling sensation. Methyl mercury is one chemical that is extremely toxic to the visual, sensory, and motor system.

Organophosphates and carbamate insecticides can induce functional changes by inhibiting acetyl cholinesterase, an enzyme that breaks down the neurotransmitter acetylcholine. The functional changes include hyperactivity, neuromuscular paralysis, weakness, vomiting, diarrhea, and dizziness, with more severe cases exhibiting convulsions, coma or death. The onset and duration of symptoms depends on the inherent toxicity of the insecticide, the dose, the route of exposure, and preexisting health conditions. Some organophosphorous pesticides can produce delayed and persistent neuropathy by damaging neurons in the spinal cord and peripheral nervous system.

OPs and carbamates are all directly related to the dose and route of exposure which in turn determine the degree and rate of acetylcholinesterase.

The acute toxicity of nerve agents is due primarily to irreversible inactivation of AchE leading to an accumulation of toxic levels of acetyl choline.\textsuperscript{18} Like other OP compounds, these agents act by binding to a serine residue at the active site of a cholinesterase molecule, thus forming a phosphorylating protein that is inactive and incapable of breaking down acetylcholine. The resulting accumulation of toxic levels of acetylcholine at the synapse initially stimulates and then paralyses cholinergic synaptic transmission. Cholinergic synapses are found in the central nervous system (CNS), at the termination of somatic nerves, in the ganglionic synapses of autonomic nerves and at the Para synaptic nerve endings such as those in the sweat glands.
Toxic substances often affect the higher functions of the nervous system such as learning, memory, and mood. Exposure to inorganic lead to mental retardation in children. Behavioral changes may be the first indications of damage to the nervous system. An individual exposed to toxic substances may initially experience vague feelings of anxiety or nervousness. These feelings may progress to depression, difficulty in sleeping, memory loss, confusion, and loss of appetite or speech impairment. In severe cases a person may exhibit bizarre behavior, delirium, hallucinations, convulsions or even death.

It has been proposed that exposure to toxic substances may trigger biochemical events that may later contribute to the cause of certain neurological diseases such as Parkinson's disease, amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease) or Alzheimer's disease.

The developing nervous system is especially vulnerable to certain toxic substances. Its cells are actively growing, dividing, migrating and making synaptic connections, and the blood-brain barrier is not yet fully developed. During the first weeks of prenatal development, toxic substances may interrupt closure of neural tube, leading to such birth defects as spina bifida.

The dose of the toxic substances and nutritional deficiencies in the mother also influences the extent of damage Ex: Ethanol (alcohol), cocaine, antibiotics and steroids.

Diseases involving organs such as the kidney or liver can indirectly affect the nervous system, the build up of waste products in the blood stream due to kidney failure or diabetes.

Naturally occurring toxic substances such as tetratoxin (from the puffer fish) and saxitoxin (from the marine alga responsible for paralytic shellfish poisoning) block ion channels, initially is followed by difficulty in speaking and swallowing and by an inability to coordinate muscular movements.

**Actions on Neuronal structures:** Substances such as mercury and lead cause degeneration of the central nervous system. Intoxication by organic mercury, particularly in children, can cause degeneration of neurons in the cerebellum and can lead to tremors, difficulty in walking, visual impairment and even blindness.

The peripheral nervous system is particularly vulnerable to the effects of toxic substances because it lies outside the central nervous system which is partially protected by the blood-brain barrier.
A large number of neurotoxic substances can cause degeneration of glial cells and the myelin that these cells produce. Diphtheria toxin, for example, interferes with the cell bodies of myelin producing glial cells. Hexachlorophene interferes with the energy-producing mitochondria within glial cells. Perhexilline maleate, a drug used to treat the chest pain of angina pectoris, sometimes causes degeneration of myelin and leads to numbness in the hands and feet and muscle weakness.

Organophosphorous compounds Carbamate insecticides, and nerve gases act by inhibiting acetyl cholinesterase, the enzyme that inactivates the neurotransmitter acetylcholine. This results in a build up of acetylcholine and can lead to loss of appetite, anxiety, muscle twitching and paralysis.

Amphetamines stimulate the nervous system by causing the release of the neurotransmitter norepinephrine and dopamine from nerve cells. Cocaine affects both the release and reuptake by which neurotransmitters and their metabolites and recycled) of norepinephrine and dopamine. Both amphetamines and cocaine cause paranoia, hyperactivity and aggression as well as high blood pressure and abnormal heart rhythms.

The nervous system is supplied by an extensive system of blood vessels and capillaries. The brain needs large quantities of oxygen and nutrients and relies on an extensive circulatory system to supply needed substances and to remove toxic waste products. Lead damages capillaries in the brain and leads to the swelling characteristic of encephalopathy. Other metals (e.g. Cadmium, Thallium and Mercury) and organotins (e.g. trimethyltin) cause rupturing of vessels that can result in encephalopathy as well.

Organophosphates poison insects and mammals primarily by phosphorylation of the acetylcholinesterase (AChE) at nerve endings. The result is a loss of available AChE so that the effect organ becomes over stimulated by the excess acetylcholine (Ach the impulse-transmitting substance) in the nerve ending. The enzyme is critical to normal control of nerve impulse transmission from nerve fibers to smooth and skeletal muscle cells, glandular cells and autonomic ganglia as well as within the central nervous system (CNS).

Loss of enzyme function allows accumulation of AChE peripherally at cholinergic neuroeffector junctions (muscarinic effects), skeletal nerve-muscle junction, and autonomic ganglia (nicotinic effects), as well as centrally. At cholinergic nerve junctions with smooth muscle and gland cells high Ach concentration causes muscle junctions, excess Ach may excitatory (cause muscle twitching) by may also weaken or paralyze the cell by depolarizing the (endplate) in the CNS, high Ach concentrations cause sensory and behavioral disturbances, in coordination, depressed motor junction
and respiratory depression. Increased pulmonary secretions coupled with respiratory failure are the usual causes of death from organophosphate poisoning.

AchE synthesis within the mitochondria from choline in the presence of enzyme choline acetyl transferase (acetylase) in addition it requires acetyl co enzyme A, ATP and glucose with exception of choline all components required AchE for its function.

AchE once formed is temporally stored in minstic vesicles (synaptic vesicles) nerve impulses when reaches to presynaptic membrane it release AchE in to the synaptic cleft. AchE attach to nicotinic Ach receptors on motor and plate surface.

**Direct inhibitors of AchE:** They are effective without any further metabolic modification after adsorption in to the body. They cause symptoms and signs quickly during after experiment.
Ex: Dichlorovos

**Indirect inhibitors of AchE:** They need to be transformed in the body to be effective all OP pesticides that are those containing a P=S bond. These are not active inhibitors of AchE but require activation by oxidation of P=S to the P=O group. They induce symptoms and signs later and the effect a longer even after cessation of exposure.
Ex: Malathion, Parathion. Acetylcholine receptors:

The Acetylcholine receptors are present on all the autonomic post ganglonic neuronal membrane. These Acetylcholine receptors are mainly of two types.

Nicotinic receptors which are stimulated by low doses of the drug Nicotine and that is why they are called Nicotine receptors.

Acetylcholine receptors present on the membrane of smooth muscle, cardiac muscle and gland cells these are not stimulated by Nicotinic but are stimulated by the “Muscarinic” a Mushroom poison they are called therefore muscarinic receptors. These receptors are blocked by Atropine.
Advantages of Biomarkers: Dialkyl phosphates are non-toxic, do not inhibit AchE, rapidly excreted in urine, represent recent experiment which the part of 2 or 3 days experiment is very sensitive indicator to indicate body burden of the OP pesticides.

Biotransformation: Biotransformation is a chemical process by a toxic substance excretion is converted into a number of chemical compounds which are more easily excreted.

Organophosphorous pesticides also influence children at high risk from pesticide exposure high rates on metabolism why because they are having less mature immune system not able to protect them against pesticides. Children are this pesticide contents hand to mouth in behavioral effects. Children internal organs are not fully developed. Their excretory system may not be able to excrete these chemicals. Pesticide type may effect their development by blackening the absorption of nutrients necessary for their development.

Babinski sign Effect: This reflects it's positive if there is dorsi flexion of the great toe and abductions of small toe. Babinski sign effect is negative (not present) if there is plantar flexion of the great toe and also of the small toes.
**Nervous System:** The fundamental unit of the nervous system is the nerve cell or neuron. While neurons have many of the same structures found in every cell of the body, they are unique in that they have axons and dendrites, extensions of the neuron along which nerve impulses travel, and in that they synthesize and secrete neurotransmitters specialized chemical messengers that interact with receptors of other neurons in the communication process. The nervous system is anatomically separated into two major divisions: Central nervous system and the Peripheral nervous system. The central nervous system encompasses the brain and spinal cord, while the peripheral nervous system encompasses the nerves that travel to and from the spinal cord, sense organs, glands, blood vessels, and muscles.

The brain is composed of between 10 billion to 100 billion cells organized into vast networks of interacting axons and dendrites. The brain and spinal cord control vital functions of the body (including vision, hearing, speech, learning, memory and muscular movements) through these complex networks and through a wide variety of neurotransmitters.
Most of the central nervous system is partially protected by the blood-brain barrier, a layer of tightly exposed cells in blood vessel wall that allow some substances to pass from blood to neural tissue while keeping others out. The selective barrier protects much of the nervous system from substances that are either not necessary for metabolic function or that may be damaging. Smaller compounds and compounds that are soluble in lipids tend to cross the barrier more easily, while larger compounds and substances which are soluble in water may be kept out. In addition some compounds cross the barrier with the help of carrier proteins which bind specifically them.

The first signs of the nervous system are exhibited around the 10th to 14th day of fetal development, when a flat sheet of around 125,000 cells forms from the outer layer of the ball of undifferentiated embryonic cells. The sheet then rolls in to a tube, called the neural tube, which will eventually develop into the spinal cord and brain.

The neuron consists of the cell body and the dendrites and axons projecting from it. The neuronal membrane contains a complex system of pumps, receptors, and channels through which charged molecules (ions such as sodium, calcium and potassium) travel into and out of the cell.

The nervous system undergoes major changes with aging, at the tissue and cellular level, the aging process results in nerve cells loss, neurofibrillar tangles (abnormal accumulation of certain filamentous proteins, and neurotic plaques abnormal clusters of proteins and other substances near synapses). Aging is also accompanied by alterations in neurotransmitter concentration and the enzymes involved in the synthesis of these transmitters.

Certain nerve cells are specialized to respond to particular stimuli. Chemoreceptors in the mouth and nose send information about taste and smell to the brain. Cutaneous receptors in the skin are involved in the sensation of heat, cold and touch. Glial cells appear to perform functions which support neurons that function is supplying nutrition structural support and insulation. Certain glial cells produce myelin, a fatty substance that covers the axons of many neurons throughout the body and acts as insulation. Electrical information in the form of nerve impulses travels along the axons and dendrites of neurons. The impulses are generated by a rapidly changing flow of charged ions, primarily sodium and potassium, through channels in the nerve cells membrane. The insulating myelin sheath surrounding many nerves allows the electrical impulses (action potentials) to travel farther and faster than they otherwise could. Impulses generally travel away from the cell body of the neuron along axons and interact with the dendrites of other neurons. The point interaction between adjacent nerve cell is called synapse.
Synapse: The junction between the two neurons is called synapse. It is not anatomical continuation, but, it is only a physiological continuity between two nerve cells. Synapse is classified by two methods:

**Anatomical classification and Functional classification**

**Anatomical classification:** Axosomatic synapse: Axon of one neuron ends on soma (cell body) of another neuron.

**Axodendritic synapses:** Axon of one neuron terminates on dendrite of another neuron.

**A xoaxonic synapse:** Axon of one neuron terminates on axon of another neuron.
**Functional Classification:** On the basis of transmission of impulses, the synapse is classified in two categories.

1. Electrical synapse
2. Chemical synapse

**Electrical synapse:** The physiological continuity between the pre synaptic and the post synaptic neurons of electrical synapse is provided by the gap junction between the two neurons. So there is direct exchange of ions between the two neurons, because of this reason, the action potential reaching the pre synaptic terminal produces the potential change in the post synaptic neuron. The important feature of the electrical synapse is that the impulse is transmitted in either direction through the electrical synapse. The electrical synapse is commonly found in the nervous system. It is also seen in some tissues like that cardiac muscle fibers, smooth muscle fibers of intestine and epithelial cells of lens in the eye.

**Chemical synapse:** Chemical synapse is the junction between a nerve fiber and a muscle fiber or between two nerve fibers, through which the signals are transmitted by the release of chemical transmitter. In the chemical synapse, there is no continuity between the pre synaptic and post synaptic neurons because of the presence of a space called synaptic cleft between the two neurons. The action potential reaching the pre synaptic terminal causes release of neurotransmitter substances from the vesicles of this terminal. The neurotransmitter reaches the post synaptic neuron through synaptic cleft and causes the production of potential change.

Neurotransmitters stored in vesicles in the axon terminal are released by electrical impulses, travel across the synaptic cleft, and bind to receptors on adjacent nerve cells, triggering biochemical events that lead to electrical excitation or inhibition, information may also be transmitted from nerves to muscle fibers; in the case the point of interaction is called the neuromuscular junction.

**Neurotransmitters:** A neurotransmitter is a substance that should be synthesized and released from the presynaptic neuron, when stimulated by an appropriate stimulus.

Neurotransmitters are chemical messengers that can be subdivided into two categories:

The classical neurotransmitters and the neuropeptides. Classical neurotransmitters include serotonin, dopamine, acetylcholine, and norepinephrine; the neuropeptides include endorphin, enkephalin, substance P and vasopressin. Classical neurotransmitters are typically secreted by one neuron into the synaptic cleft, where they interact with receptors on the surface of the adjacent cell.
Neuropeptides, on the other hand, may act over long distances, traveling through the blood stream to receptors on other nerve cells or in other tissues. Binding of a transmitter to receptors triggers a series of biochemical events that ultimately affect the electrical activity, or excitability, of the neuron. Depending on the type of transmitter released and the type of receptors, the effect of the chemical interaction is either to inhibit or to stimulate the electrical activity of the adjacent cell.

The Chemical substance that acts as the mediator for the transmission of nerve impulse from one neuron to another neuron through a synapse is called the neurotransmitter. The chemical messengers which modify the synaptic transmission are generally called neurotransmitters\textsuperscript{46}.

\textbf{History:} Existence of neurotransmitter was first discovered by an Austrian scientist named Otto Loewi in 1921. He dreamt of an experiment which he did practically and came out with this discovery.

\textbf{Loewi Experiment:} He used two frogs for this experiment. The heart of frog A was with intact vagus nerve and was placed in a saline filled chamber. The heart of frog B was denervated and was kept in another saline filled chamber. Both the chambers were connected in such a way that the fluid from chamber of frog A could flow into the chamber of frog B\textsuperscript{47}.

When vagus nerve of frog A was electrically stimulated, slowing of heart rate was observed. After a short delay, the heart rate in frog B also was found to be slowing down. From this observation Loewi
speculated that some chemical substances must have been released from the vagus nerve of frog A, which was responsible for the slowing down of the heart rate in frog B. He named it as “Vagusstoff”. Later this chemical substance was considered as a neurotransmitter and called acetylcholine. Micro application of the substance to the postsynaptic membrane should mimic the effect of stimulation of pre synaptic neuron. Pharmacological agents should be able to modify the effect of synaptic neuron stimulation. Neurotransmitters are classified into amines, amino acids and polypeptides. Recently purines and nitric oxide gas are also considered as neurotransmitters.

**Acetylcholine**: It is synthesized from the reaction involving choline and acetate in the presence of enzyme choline acetyl transferase. Acetyl choline is the neurotransmitter, which is secreted from all the motor neurons that come out of the spinal cord. It is released in the ganglion of the autonomic nervous system and at the post ganglionic nerve endings of parasympathetic neurons and in some of the sympathetic post ganglionic neurons also (sweat glands, skeletal muscles), acetylcholine is secreted. The transmitter at the neuro muscular junction is acetyl choline. In addition to these, it also forms the transmitter in a number of pathways in the central nervous system. The inactivation of acetylcholine is catalyzed by acetylcholine esterase.

**Acetylcholine receptors**: There are two types of receptors present for acetylcholine known as muscarinic and nicotinic. The actions of acetylcholine on smooth muscle glands mimic the actions of muscarinic alkaloid and the actions are blocked by atropine. The actions on the autonomic ganglion mimic the effects of nicotine, which are not blocked by atropine. These nicotinic receptors are also present in the neurons of CNS and in neuro muscular junction. In the brain, both nicotinic and muscarinic receptors are acetylcholine is present.

**Nicotinic receptors**: Nicotinic acetylcholine receptors show the presence of 5 subunits around a channel in the cell membrane. There are two identical subunits to which acetylcholine binds, resulting in the configurationl change of the receptors. This leads to the opening of Na+ channel produce depolarization. This type of receptors seen in the ganglia and neuronal membrane. In the ganglia and neuromuscular junction, the receptor is arranged in a symmetrical fashion, where as in the neuron, it is arranged in pentagonal array. The nicotinic receptors at the neuromuscular junction can be blocked by the snake venom α-bangarotoxin and the nicotinic receptors present in the brain show no such blockade.
Cholinergic receptors

Types

Muscarinic : M₁, M₂ & M₃
Nicotinic : Nₘ & Nₙ

Distribution

M₁ : CNS (Cortex, hippocampus, corpus striatum)
M₂ : Heart
M₃ : Smooth muscle and Glands
Nₘ : Neuromuscular Junction
Nₙ : Autonomic Ganglia
Adrenal medulla : CNS

Mechanism of action

M₁ : IP₃/DAG
M₂ : Decrease in cAMP, K⁺ channel opening
M₃ : Increase in cytosolic Ca²⁺ through IP₃/DAG
Nₘ : Opening of cation channel (Na⁺, K⁺)
Nₙ : Opening of Na⁺, K⁺, Ca²⁺ channels

Antagonists: Atropine for all 3 types of muscarinic receptors
- Nₘ tubocurare
- α-Bungarotoxin
- Nₙ Hexamethonium

Muscarinic receptors: Muscarinic acetylcholine receptors are of 5 types encoded by five different genes. These receptors are coupled to G proteins or K⁺ channels or phospholipase C. In the brain M₁ receptors and more M₂ is concentrated in the heart. The smooth muscle contains both M₂ and M₄ types. The pancreatic islets and acinar tissue contain M₄ type. M₃ and M₄ receptors are present in the smooth muscle.
Effects of Parasympathetic stimulation:

<table>
<thead>
<tr>
<th>Organ</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>Decrease in rate, force and conduction (vagal inhibition) (Muscarinic)</td>
</tr>
<tr>
<td>Blood vessels</td>
<td>Vasodilatation, fall in blood pressure (muscarinic)</td>
</tr>
<tr>
<td>Bronchiole</td>
<td>Contraction of smooth muscle</td>
</tr>
<tr>
<td>Iris of eye</td>
<td>Miosis (muscarinic)</td>
</tr>
<tr>
<td>Ciliary muscle</td>
<td>Contraction</td>
</tr>
<tr>
<td>Lacrymal</td>
<td>Secretion (tears)</td>
</tr>
<tr>
<td>Salivary glands</td>
<td>Secretion</td>
</tr>
<tr>
<td>GI tract</td>
<td>Secretion of digestive juice, increased motility</td>
</tr>
<tr>
<td>Sphincter</td>
<td>Relaxation</td>
</tr>
<tr>
<td>Bladder</td>
<td>Contraction of detrusor muscle</td>
</tr>
<tr>
<td>Male genitalia</td>
<td>Erection (penis)</td>
</tr>
</tbody>
</table>

To consider one substance is neurotransmitter that substance contain

1. The substance must be found in a neuron.
2. It must be produced by a neuron
3. It must be released by a neuron
4. After release, it must act on a target area and produce some biological effect.
5. After the action, it must be inactivated.
Classification of Neurotransmitters:

Many substances of various chemicals nature are identified as neurotransmitters, depending upon their chemical nature.

**Neurotransmitters are classified in to three groups**

<table>
<thead>
<tr>
<th>Group</th>
<th>Name</th>
<th>Site of secretion</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amino acids</td>
<td>GABA</td>
<td>Cerebral Cortex, Cerebellum, Basal Ganglia, Retina and Spinal Cord.</td>
<td>Inhibitory</td>
</tr>
<tr>
<td></td>
<td>Glycine</td>
<td>Fore brain, Brain Stem, Spinal Cord and Retina</td>
<td>Inhibitory</td>
</tr>
<tr>
<td></td>
<td>Glutamate</td>
<td>Cerebral Cortex, Brain Stem and Cerebellum</td>
<td>Excitatory</td>
</tr>
<tr>
<td></td>
<td>Aspartate</td>
<td>Cerebellum, Spinal Cord and Retina</td>
<td></td>
</tr>
<tr>
<td>Amines</td>
<td>Noradrenline</td>
<td>Postganglionic, Adrenergic, Sympathetic Nerve Endings</td>
<td>Excitatory and Inhibitory</td>
</tr>
<tr>
<td></td>
<td>Adrenaline</td>
<td>Hypothalamus, Thalamus and Spinal Cord</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dopamine</td>
<td>Basal ganglia, Hypothalamus, Limbic System, Neocortex, Retina and Sympathetic Ganglia.</td>
<td>Inhibitory</td>
</tr>
<tr>
<td></td>
<td>Serotonin</td>
<td>Hypothalamus, Limbic System, Cerebellum, Spinal Cord, Retina, G.I Tract, Lungs and Platelets.</td>
<td>Inhibitory</td>
</tr>
<tr>
<td></td>
<td>Histamine</td>
<td>Hypothalamus, Cerebral Cortex, G I Tract, Mast Cells and Spinal Cord.</td>
<td>Excitatory</td>
</tr>
<tr>
<td>Others</td>
<td>Nitric Oxide</td>
<td>Many parts of CNS , Neuromuscular Junction and G.I Tract</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acetyl choline</td>
<td>Preganglionic parasympathetic nerve endings.</td>
<td>Excitatory</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post ganglionic parasympathetic nerve endings.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Preganglionic sympathetic endings</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Postganglionic sympathetic cholinergic nerve endings.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neuromuscular Junction, Cerebral Cortex, Hypothalamus, Basal Ganglia, Thalamus, Hippocampus and Amacrine cells of retina.</td>
<td></td>
</tr>
</tbody>
</table>
**Amino acids:** The neurotransmitters of this group are involved in fast synaptic transmission and are inhibitory and excitatory in action. GABA, glycine, glutamate (glutamic acid) and aspartate (aspartic acid) belong to this group.

**Amines:** Amines are the modified amino acids. The neurotransmitters of this group involve in slow synaptic transmission. These neurotransmitters are also inhibitory and excitatory in action. Noradrenaline, adrenaline, dopamine, serotonin and histamine belong to this group.

**Others:** Some neurotransmitters do not fit in to any of these categories. One such substance is acetylcholine. It is formed from the choline and acetyl co-enzyme A in the presence of the enzyme called choline acetyl transferase. Another substance included category is the soluble gas nitric oxide (NO).

**DEPENDING UPON FUNCTION:** The neurotransmitters cause excitations of post synaptic neuron while other cause inhibition. Thus the neurotransmitters are classified in to two types.

1. **Excitatory neurotransmitters**
2. **Inhibitory neurotransmitters**

1. **Excitatory neurotransmitters:** The excitatory neurotransmitters are responsible for the conduction of impulse from the presynaptic neuron to postsynaptic neuron. The neurotransmitters released from the presynaptic axon terminal do not cause development of action potential in the post synaptic neuron. Rather, it causes some change in the resting membrane potential—slight depolarization by the opening of sodium channels in the post synaptic membrane and the influx of sodium ions from ECF. The Slight depolarization is called excitatory post synaptic potential (EPSP). EPSP in turn causes development of action potential in the initial segment of the axon of the postsynaptic neuron. The common excitatory neurotransmitters are acetylcholine and nor adrenaline.
2. **Inhibitory Neurotransmitters:** The inhibitory neurotransmitter inhibits the conduction of impulse from the presynaptic neuron to the postsynaptic neuron. When it is released from the presynaptic axon terminal due to the arrival of action potential, it causes opening of potassium channels in the postsynaptic membrane and efflux of potassium ions. This leads to hyperpolarization which is called the inhibitory postsynaptic potential (IPSP). When IPSP is developed, the action potential is not generated in the postsynaptic neuron. The common inhibitory neurotransmitters are gamma amino butyric acid (GABA) and dopamine.

**TRANSPORT AND RELEASE OF NEUROTRANSMITTERS:**

The neurotransmitter is produced in the cell body of the neuron and is transported through the axon. At the axon terminal, the neurotransmitter is stored in small packets called vesicles. Under the influence of a stimulus, these vesicles open and release the neurotransmitter into the synaptic cleft. It binds to specific receptors on the surface of the postsynaptic cleft. It binds to specific receptors on the surface of the postsynaptic cell. The receptors are G proteins, protein kinase or ligand gated receptors.

**INACTIVATION OF NEUROTRANSMITTER:**

After the execution of the action, neurotransmitter is inactivated by four different mechanisms:

1. It diffuses out of synaptic cleft to the area where it has no action.
2. It is destroyed out of synaptic cleft to the area where it has no action.
3. It is destroyed or disintegrated by specific enzymes.
4. It is engulfed and removed by astrocytes (macrophages).
5. It is removed by reuptake process, i.e., the neurotransmitter is taken back into the axon terminal from where it was released.
ACETYL CHOLINE: Acetylcholine is a cholinergic neurotransmitter. It possesses excitatory function. Acetylcholine is the transmitter substance at the neuromuscular junction. It is also released by the following nerve endings.

1. Preganglionic parasympathetic nerve
2. Postganglionic parasympathetic nerve
3. Preganglionic sympathetic nerve
4. Postganglionic sympathetic cholinergic nerve
5. Nerves supplying eccrine sweat glands
6. Sympathetic vasodilator nerves in skeletal muscle
7. Nerves in amacrine cells of retina
8. Many regions of brain

Acetylcholine is synthesized in axon terminals and stored inside the vesicles. It produces the excitatory function of synapse by opening the ligand gated sodium channels. Acetylcholine has very quick and potent action. It is also destroyed immediately after executing the action by the enzyme acetylcholinesterase. The enzyme is present in basal lamina of synaptic cleft.
**NORADRENALINE:**

It is the neurotransmitter in adrenergic nerve fibers. It is released in the following structures.

1. Postganglionic sympathetic nerve endings
2. Cerebral cortex
3. Hypothalamus
4. Basal ganglia
5. Locus ceruleus in pons
6. Spinal cord

In many places, noradrenaline is the excitatory chemical mediator and in very few places, it causes inhibition. It is believed to be involved in dreams, arousal and elevation of moods.
**DOPAMINE:**

Dopamine is secreted by nerve endings in the following areas:

1. Basal ganglia
2. Hypothalamus
3. Limbic system
4. Neocortex
5. Retina
6. Small intensely fluorescent cells in sympathetic ganglia

Dopamine possesses inhibitory action. The prolactin inhibitory hormone secreted by hypothalamus is considered by dopamine.

**SEROTONIN:**

Serotonin is otherwise known as 5-hydroxy tryptamine. It is synthesized from tryptophan by hydroxylation and decarboxylation. A large amount of serotonin (90%) is found in enterochromatin cells of GI tract. Small amount is found in platelets and nervous system. It is secreted in the following structures.

1. Hypothalamus
2. Limbic system
3. Cerebellum
4. Dorsal raphe nucleus of midbrain
5. Spinal cord
6. Retina
7. GI tract
8. Lungs
9. Platelets

It is an inhibitory substance. It inhibits impulses of pain sensation in posterior gray horn of spinal cord. It is supported to cause depression of mood and sleep. Serotonin causes vasoconstriction, platelet aggregation and smooth muscle contraction. It also controls food intake.
HISTAMINE: It is secreted in nerve endings of hypothalamus, limbic cortex and other parts of cerebral cortex. It is also secreted by gastric mucosa and mast cells. Histamine is an excitatory neurotransmitter. It is believed to play an important role in arousal mechanism.

GAMMA AMINO BUTYRIC ACID (GABA): GABA is an inhibitory neurotransmitter in synapses particularly in CNS. It is responsible for presynaptic inhibition. It is secreted by nerve endings in the following structures: 
1. Cerebral cortex 
2. Cerebellum 
3. Basal ganglia 
4. Spinal cord 
5. Retina 
GABA causes synaptic inhibition by opening potassium channels and chloride channels. Potassium come out of synapse and chloride enters in this leads to hyper polarization which is known as inhibitory post synaptic potential (IPSP).

SUBSTANCE P: Substance P is a neuropeptide that acts as a neurotransmitter and as a neuromodulator. Substance P is a polypeptide with 11 amino acids residues. It belongs to a family of 3 related peptides called neurokins or tachykinins. The other peptides of this family are neurokinin A and B which are not well known like substance P. Substance P is secreted by the nerve endings (first order neurons) of pain pathway in spinal cord. It is also found in many peripheral nerves, different parts of brain particularly hypothalamus, retina and intestine. It mediates pain sensation. It is a potent vasodilator in CNS. It is responsible for regulation of anxiety, stress, mood disorders, neurotoxicity, and nausea and vomiting.

NITRIC OXIDE: Nitric oxide (NO) is a neurotransmitter in the CNS. It is also the important neurotransmitter in the neuromuscular junctions between the inhibitory motor fibers of intrinsic nerve plexus and the smooth muscle fibers of GI tract. Nitric oxide acts as a mediator for the dilator effect of acetylcholine on small arteries. In the smooth muscle fibers of arterioles, nitric oxide activates the enzyme guanylyl cyclase, which in turn causes formation of cyclic guanosine monophosphate (cGMP) from GMP. The cGMP is a smooth muscle relaxant and it causes dilatation of arterioles. Thus nitric oxide indirectly causes dilation of arterioles.
The peculiarity of nitric oxide is that it is neither produced by the neuronal cells nor stored in the vesicles. It is produced by nonneuronal cells like the endothelial cells of blood vesicles. From the site of production it diffuses in to the neuronal and non neuronal cells where it, exerts its action.

**The Ginger-Jake Syndrome:** During prohibition of a popular ginger extract with triorthocresyl phosphate led to an epidemic of partial paralysis that came to be known as the Ginger-jake syndrome. The case serves as a dramatic example of neurotoxic potential of organophosphorous substances. Extract from the Jamaica ginger had been used in the United States since the 1860s as a medicinal tonic. A typical preparation contained 70 to 80 percent alcohol by weight and reportedly aided in digestion prevented respiratory infections, and promoted menstrual flow. Nicknamed "Jaked" the tonic became especially popular in the early 1900s in areas where local legislation outlawed the sale of alcoholic beverages. During prohibition the legal sale of ginger extract was limited to a "fluid extract" which contained 5 grams of ginger per cubic centimeter of alcohol (usually ethanol). Since the high concentration of ginger yielded a solution too irritating to drink, the requirement was supposed to confine its use to medicinal purposes. Department of Agricultural agents would occasionally check for the appropriate ginger content by boiling off the alcohol and weighing the solid residue. However bootleggers soon saw the possibility of dissolving small amounts of ginger into alcohol and substituting adulterants, such as molasses or castor oil, for the remaining required solid content. The result was a potable alcohol source that could be sold at bargain prices. In 1930, perhaps in response to an increase in the price of castor oil, one bootlegger tried Lyndol, a heat resistant oily material used in lacquers and varnishes as an adulterant. When consumed, the triorthocresyl phosphate in Lyndol caused axonal degeneration in neurons of the central and peripheral nervous system. Depending on the severity of the case, symptoms ranged from temporary numbness and tingling in the extremities to permanent partial paralysis. Estimates vary widely, but between 20,000 and 100,000 people were permanently affected before all the poisonous shipments were seized.\(^{40,41}\)
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