**Wellcome Film Project**

# The Molecular Basis of Narcosis

## The Scientific Basis of Medicine

**Presented by Dr John Nunn and Dr Michael Halsey.**
**Introduced by Dr Ian Gilliland.**

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**<Opening titles>**

**<Dr Gilliland to camera>**

Dr Nunn is Head of the Division of Anaesthesia at the Clinical Research Centre at Northwick Park Hospital. He was previously Professor of Anaesthesia at the University of Leeds and has been Leverhulme Research Fellow and Hunterian Professor at the Royal College of Surgeons of England. He is the author of many well-known papers on the physiology of respiration and on anaesthesia, and has made many fundamental contributions to the basic science of the subject, such as this discourse, the molecular basis of narcosis.

Dr Halsey, also from Northwick Park, will join Dr Nunn. Dr Nunn.

**<Dr Nunn to camera>**

This is the first of a pair of lectures in which we shall be dealing with the inhalational anaesthetic agents. First lecture, we'll deal with theories of the molecular basis for action, and the second with known effects of these agents at the cellular, subcellular and molecular level.

The inhalational anaesthetic agents are part of a very large group of substances which share the property of inducing reversible loss of consciousness when they are inhaled. Now they have two important properties in common. Firstly, they have no common features of chemical structure. Secondly, the partial pressure at which they induce narcosis is inversely proportional to their lipid solubility. Now, if we take the first slide, we shall see a selection from this very large group of substances.

**<Nunn narrates over slide displaying list of inhalational anaesthetic agents>**

The first on the slide is hydrogen; now, this has a narcotic potency which means that it becomes narcotic at pressures as high as 138 atmospheres, a very high pressure, which has, of course, never been attained by man. The second substance, however, on the list, nitrogen, is narcotic at a pressure of 33 atmospheres and this, of course, is of significance and of practical importance in deep sea diving. Now, nitrous oxide is narcotic at 1 atmosphere and this is the basis for its use in clinical anaesthetic practice. Xenon is important because it is one of the inert gases and you will see that it is slightly more potent than nitrous oxide. Then we come to cyclopropane, which is a liquid boiling at -33 degrees Celsius and therefore can be given as a vapour and it can be administered at a 6 or 7 times the anaesthetic concentration which you can see is 9.2% of 1 atmosphere.

The last three agents on this list, diethyl ether, halothane and methoxyflurane, are three popular liquid anaesthetic agents currently used in anaesthetic practice. They're all volatile and their vapours exert a saturation vapour pressure which is 10 to 20 times the partial pressure required for the production of narcosis. Note that methoxyflurane is narcotic at a concentration of $0.16^{th}$ of an atmosphere and this is the most powerful agent in the armamentarium of the anaesthetist at the present time.

**<Nunn to camera>**

Now, throughout this lecture we shall refer to the dose of an anaesthetic not as for other pharmaceutical substances but in this particular case in terms of partial pressure expressed in atmospheres. Now, this is a particularly convenient measure for the anaesthetics because in equilibrium, with a constant gaseous environment of an inert gas, the partial pressure of that agent in each compartment of the body comes to be equal to that in the inspired gas. Under these conditions, the partition coefficients of the agents, in the various compartments of the body, become irrelevant and our consideration of the problem is thereby simplified a great deal.

Equilibration of an entire patient with an inspired gas mixture takes a very long time, but the partial pressure of an anaesthetic in the alveolar gas of the patient reaches equilibrium with arterial blood, and indeed with brain, in a reasonably short time. And therefore the partial pressure of an agent, in the alveolar gas, is a convenient measure of the effective level of an anaesthetic in a patient.

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I draw your attention especially to the lowest alveolar concentration of an anaesthetic which suppresses the reflex response to a surgeon's incision. Now, this has been measured recently in great many instances and is known as the minimal alveolar concentration for anaesthesia, abbreviated to M A C or more familiarly to MAC, a concept which has been developed by Dr Eger of San Francisco and we shall be referring throughout these lectures to MAC values, which, indeed, you saw as the effective concentrations in figure 1.

Now, chemically, the inhalation anaesthetic agents are relatively inert. Xenon certainly and possibly some other agents are totally inert within the body and are exhaled unchanged. Recent studies, with isotopes, have shown that for most of the other inhalation anaesthetic agents there is, in fact, and in some cases rather

unexpectedly, extensive biotransformation of these substances, particularly in smooth endoplasmic reticulum of the liver.

**<Nunn refers to diagram on display board and narrates over it, using indicator stick>**

Our diagram, which I have here, shows breakdown products for a common inhalation anaesthetic, halothane. Now, the metabolic chains are fairly complex and lengthy, but there are two endpoints of importance: one is trifluoroacetyl-ethanolamide, here, and down a separate chain to trifluoro-acetic acid. Fortunately, both of these products are relatively nontoxic.

**<Nunn briefly to camera and then narrates over slide with superimposed cascading list>**

Now, what is the significance of biotransformation of anaesthetic agents? If we turn to the next slide, at the top of the list, we see mechanism of anaesthesia. Does biotransformation in any way appear to be relevant to the mechanism of anaesthesia? The short answer is probably not, and in the case of xenon, of course, there can be no doubt that biotransformation cannot play any role whatsoever in narcosis due to xenon. And the inference is that this is also true of other agents.

Next on the list is the uptake and distribution of anaesthetics. Is it possible that biotransformation appreciably retards the build up of anaesthetic concentrations in the body? And, again, the answer is almost certainly no with the possible exception of the agent trichloroethylene, which undergoes particularly extensive biotransformation. And in most cases, biotransformation is irrelevant to the problem about intake and distribution.

Finally, on this slide we consider toxic effects, toxic side effects: nephrotoxicity, well, here is a case where products of biotransformation may be relevant and I'm referring here to the fluoride ion which is released in very large quantities during anaesthesia with methoxyflurane. Hepatotoxicity – well, nothing's ever been proved for certain in

this direction, but biotransformation products are concentrated in the liver and they are always suspect and are the subject of a good deal of research at the present time. Chronic toxicity – this refers to contamination of operating theatre atmospheres in which staff are exposed to low concentrations of anaesthetics for long periods of time, and it is, of course, conceivable that metabolic products of the anaesthetics do accumulate in anaesthetic staff. This again is a field in which a good deal of research is continuing at the present time.

**<Nunn to camera>**

Well, now before we go any further perhaps we ought to attempt a definition of anaesthesia, and by anaesthesia I mean a reversible production of a state of unconsciousness associated with suppression of reflex activity. Now, the production of unconsciousness is, by and large, an all or none affair. But the suppression of reflex activity is graded and the anaesthetist can distinguish very clearly between light anaesthesia and deep anaesthesia. Light anaesthesia, the patient is unconscious but a good deal of reflex activity persists; deep anaesthesia, there is progressive loss of reflexes such as, for example, the laryngeal and carinal reflexes which disappear rather late, and reflexes related to the maintenance of blood pressure and, of course, also control of breathing, which may ultimately be lost in very deep anaesthesia.

**00:09:45:05**

Now, turning to the site of action of anaesthetics in the production of narcosis, I suppose it's reasonable to assume that they act in the brain, but it's very difficult to go much further than that. Regrettably, we just do not know which part of the brain is primarily involved in anaesthesia; whether it is the cortex or the reticular activating system, we simply do not know, but most workers in the field suspect that it is not an overall depression of the entire brain but that it will turn out that there is some part of the brain which is peculiarly sensitive to the effects of anaesthetics.

Now, as far as the neurone is concerned, we can consider synaptic transmission and axonal conduction. And the classical experiments of Larrabee and Pasternak in 1952 established that synaptic transmission was far more sensitive to anaesthetics than was axonal conduction. And since that time, it has been accepted by all that the synapse is almost certainly the site of action of the anaesthetic. However, we don't know which synapses are involved, we don't know where they are, we don't know what type of synapse is particularly involved nor what is the chemical transmitter of this particular type of synapse. And there is always the haunting possibility that anaesthesia is not due to block of synaptic transmission at all but, on the contrary, to facilitation of inhibitory synapses. And it is well known that anaesthetics on many biological systems will exhibit excitatory phenomena as well as depression. Now you can see from all of this that our knowledge of the site of action, the neuronal and central nervous system level, is indeed far from complete.

Now let us turn to the molecular site of action and the starting point here properly is the relationship between lipid solubility and potency.

**<Nunn refers to graph on display board and narrates over it, using indicator stick>**

Now we turn to another diagram on the right. Here on this axis <*indicates x-axis*>, we have the oil/gas solubility coefficient at 37 degrees Celsius in olive oil, which has solubility parameter of 8.6. On this axis <*indicates y-axis*>, we have the narcotic pressure expressed in atmospheres, again MAC values for these six anaesthetics which you can see: nitrous oxide, going right down to methoxyflurane as the most potent agent. The line is drawn with slope of unity and you can see that the correlation is extremely good.

**<Nunn to camera>**

Correlation was noted as long ago as 1899 by Meyer, stressed again by Overton in 1901, and since that time, data have been successfully refined right up to recent times, particularly Peyton in Oxford and Eger in San Francisco, and it is on their data

that the diagram which you have just seen has been based. I think everybody in the field is in agreement that correlation between lipid solubility and potency is very good indeed and is too good to be ignored in the formulation of any theory of narcotic action. But it is not quite so clear what this correlation means. Now, this requires a consideration of intermolecular forces and it is proper that a clinical anaesthetist should hand over this stage to a physical chemist. Now I'm passing you to Michael Halsey, who is the physical chemist of the Division of Anaesthesia of the Clinical Research Centre. Michael.

**<Dr Halsey to camera>**

Thank you. One of the primary criteria which we have already mentioned for anaesthesia is it is a completely reversible state. This suggests that the forces between the anaesthetic molecules and the site of action, wherever it may be, are of a very weak nature, and thus, the forces between anaesthetic molecules and their site of action are the intermolecular forces type rather than of a chemical bond.

**<Halsey narrates over slide with cascading list showing types of energy in various molecular bonds>**

The next slide illustrates the type of energies which are involved. First of all, in chemical bonds, whether they be covalent or electrostatic, the energies involved are of the order of 50 to 800 kilojoules per mole. On the other hand, when one is dealing with intermolecular forces, the energies involved are in order of magnitude smaller, namely between 5 and 60 kilojoules per mole. In this energy range occur a number of different interactions and these I've listed particularly three of them which are of concern to us in this talk. First of all, then, the van der Waals interactions which are responsible for the imperfections in gases – in gas molecules interacting with each other. Secondly, there are the hydrogen bonds which are, of course, well known in any biological system. And finally, there are the hydrophobic interactions which are responsible for maintaining much of the tertiary structure of proteins and, although these be of a nature of entropy rather than enthalpy, all the energies involved in these three groups appear to be about the same.

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**<Halsey to camera>**

Now, one scientist who has had a great influence on this whole area of chemical bonding is Linus Pauling. And in 1961, he and S L Miller independently proposed a theory of molecular basis of anaesthesia. They attributed anaesthesia to the formation in the brain of minute micro hydrate crystals between anaesthetic molecules and water molecules which occur predominantly in the brain; the brain, in fact, consists of approximately 78% water. And this can be illustrated by some models that were made by Dr D C White and his colleagues at Aberdeen and have been kindly loaned for the programme.

**<Halsey walks over to 3-dimensional models of molecules and demonstrates these while narrating>**

First of all, this indicates three different types of hydrate structure. In each one, the water molecule is at each apex, and linking the water molecules is a whole series of hydrogen bonding, and this, in fact, forms a cage-like structure. Now, if one takes a xenon molecule, which in this case will be accurately represented by this small plastic ball, and puts it inside the molecule, one can see that it's trapped in there and, in fact, the forces holding the whole system together are the hydrogen bonds between the water molecule and the van der Waals interactions between the xenon atom in the centre and the water molecules surrounding it. Pauling and Miller also postulated that there would be further stabilisation forces between the hydrates formed in this way and the protein side chains which occur in the brain.

Now, what is the evidence for all these interactions? And here again, one also has a correlation.

**<Halsey walks towards moveable graphs on display board and narrates over these>**

In this case, the correlation is between anaesthetic potency, again measured in MAC as we've already defined it, on the vertical axis, against some measure of the stability of the hydrate, in this case the hydrate dissociation pressure at nought degrees centigrade. And for the five agents that have been listed here, the points relating these two effects lie here: the nitrous oxide here, the xenon here, the cyclopropane and then chloroform. And there is a reasonable correlation between the hydrate dissociation pressure and the anaesthetic potency, suggesting that the two effects may indeed be related in the production of anaesthesia.

This can be compared with the correlation with lipid solubility. This is using the same format as the one on the left-hand side, but it, in fact, has exactly the same coordinates as were used in the early slide. Again, a MAC is on the vertical axis, but in this case the oil/gas partition coefficient is on the horizontal. Now, for the five agents listed, one can see that there is also a correlation with lipid solubility. And so in 1961, the evidence for two possible sites of action was equally good, but since that time there has been much investigation into new agents and the testing of the correlations. One of the most interesting is sulphur hexafluoride. In the case of its lipid solubility correlation, the point lies here, whereas in the case of the hydrate theory, the point lies way off the line of best fit for the earlier points. Furthermore, the similar situation has been studied for the other agents particularly used in anaesthesia: here is fluroxene and ether, which have lipid solubility potencies that lie on the line, but their hydrate dissociation pressure is, in fact, only a minimum value because they do not form hydrates on their own, and so the hydrate dissociation pressures either lie here or, in fact, further off the line in that direction. Similarly, for halothane and for methoxyflurane, the lipid correlation continues to be very good, whereas the hydrate correlation is not so good. Thus if one compares the two correlations together, one sees, on the one hand, that there is a relatively poor correlation between anaesthetic potency and hydrate stability; on the other hand, for the lipid correlation, one sees that the points all lie on a straight line relating the anaesthetic potency to the oil/gas partition coefficient.

**<Halsey to camera and then refers to illustration of Davson-Danielli membrane on display board, using indicator stick>**

Now, this really cannot be an accident and it is therefore important to realise what possible hydrophobic sites there are in the body. Well, the first and most obvious is illustrated in this diagram of the membrane. This is the traditional diagram of the Davson-Danielli membrane in which there is two outer protein sheets with an inner sandwich of a bimolecular lipid layer. The correlation data that we've already pointed out suggests that anaesthetics cannot interact in the extracellular fluid or in the axoplasm or indeed in the very outer parts of the protein sheath. On the other hand, the solubility parameter that has been determined for hydrophobic interaction is consistent with the anaesthetics interacting in a bimolecular lipid layer, somewhere in the region of the [missing word – tape jumps].

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**<Halsey briefly to camera then walks over to 3-dimensional model of protein molecule and demonstrates this while narrating>**

Now, what are the other possible hydrophobic sites in the body? One of these is the interaction of hydrophobic sites in protein. We have over here a protein molecule, which has been,[unknown word], which has been based on the coordinates provided by Perutz and his workers of the haemoglobin. This, in fact, illustrates two parts of the haemoglobin molecule, on one part is the alpha chain, which is in this region, whereas on the other part of the other side is the beta chain in this region. The haem, which is, of course, responsible for the interaction with oxygen, sits in an area of the protein over here and it fits into there. On the other hand, it is also known that haemoglobin can interact with anaesthetics, and in a different part of the molecule, over here, Schoenburn showed that xenon could interact. And if one looks closely at this area, one notes that it is, in fact, a very dark area in this particular model and this indicates that it is a very hydrophobic area, in contrast with the surrounding hydrophilic area.

Similar studies have also been done on myoglobin by Kendrew and Watson, and other different types of anaesthetic interaction have been demonstrated in proteins. And the important thing is that anaesthetics may interact with proteins and produce a conformational change in the protein structure and, in some cases at least, also produce an overall functional change in the proteins.

**<Halsey returns to seat, narrates to camera>**

Now let us return to some of the other evidence that there is for hydrophobic interactions and, in particular, I'd like to deal with two aspects: one is the interaction of anaesthetic potency with temperature and the other is the interaction of anaesthetic potency with pressure.

The first, namely the interaction with temperature has been carefully studied both in animals and in man. And it's known, for example, that as the temperature decreases, the anaesthetic potency increases, but it's also known that the hydrophobic solubility alters. And when one realises that the basic theory of the hydrophobic interactions is that all agents produce anaesthesia at a constant concentration, at a particular hydrophobic site, one can immediately understand the anaesthetic interaction with temperature, namely that regardless of the temperature, the product of the anaesthetic MAC, if one likes, the oil/gas solubility remains constant. Furthermore, one knows that temperature on its own can be an anaesthetic and this has led to some very interesting speculations concerning the possible conformational changes that may occur with lower temperatures.

The other aspect that we should deal with is that of pressure. Now, pressure and anaesthesia have been particularly studied in this country at the pharmacology department in Oxford. For this reason, we went down last week to the pharmacology department in Oxford to talk to some of the workers there.

**<Halsey narrates over film clip showing scientists at work in Professor Peyton's laboratory in Oxford>**

Here we are in Professor Peyton's hyperbaric physiology laboratory in the university Department of Pharmacology. I asked Dr Brian Smith, a lecturer in physical chemistry and one of the leading workers in this field, to explain some of the basic concepts.

**<Smith to camera and then refers to diagrams illustrating effects of anaesthesia on tadpoles>**

One important feature of anaesthetic action was discovered by Johnson and Flagler, two American scientists, in 1950. They studied the effects of pressure on tadpoles that had been given anaesthetics. In this diagram, we see some tadpoles swimming freely in a beaker of water. If an anaesthetic is added, the tadpoles fall to the bottom. In the same way, if pressure, say, 100 atmospheres of pressure, is applied the tadpoles will again, though for different reasons, fall to the bottom of the vessel. However, and this is the interesting observation of Johnson and Flagler, that if pressure and anaesthetic are applied together then the tadpoles swim freely.

In this laboratory we found that this phenomenon, pressure reversal, as it has become known, occurs for other species: newts and mice. In the case of mice and indeed all mammals, the pressure has to be applied using an inert gas rather than through the water as with the tadpoles. Pressure reversal can give some clue as to how anaesthetics may act. If we regard pressure as primarily squashing or compressing the site of action, then the fact that pressure will reverse anaesthesia suggests that the important effect of an anaesthetic is to expand the site of action. And this is one of the few clues we have as to how anaesthetics might work.

**<End of film clip>**

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**<Halsey briefly to camera, then refers to and narrates over diagram illustrating expansion effect of anaesthesia on membrane>**

Interaction between anaesthesia and pressure is also illustrated in this diagram over here. Here in a very simple diagrammatic form, we have a possible hydrophobic site, namely a membrane. It's known from work of Seaman and his colleagues that when anaesthetics dissolve in a membrane, there is approximately 0.4% expansion of that membrane. However, when we add pressure to the system, one squashes the system down until one reaches the same size as the initial state, and thus the animal wakes up. If, however, one uses pressure alone without any anaesthetic, one squashes the membrane to a still smaller volume and this, probably, is associated with a phenomenon of pressure narcosis. However, if one takes the awake animal, with both anaesthesia and pressure, and adds still more anaesthetic, it's possible to expand the membrane yet again and produce anaesthesia, both with pressure and in exactly the similar way as has been without pressure.

**<Halsey to camera>**

But now, enough of pressure and back to John.

**<Nunn to camera>**

Thank you, Mike. Well, now we're going to move on to the subject of side effects of anaesthetics. There is overwhelming evidence that anaesthetics act at many different sites. Some are not relevant to narcosis and some, or possibly all of them, are, however, responsible for side effects of anaesthetics. Now, these side effects are very important and they have greatly contributed to our understanding of the molecular basis of action of anaesthetics because they provide model systems which are very much easier to understand and to investigate than narcotic actions on neurones and so forth.

Now, side effects are equally important from the clinical standpoint because they are a major factor in deciding which are good anaesthetics and which are bad anaesthetics. We can distinguish between narcosis and side effects in this way: that narcosis is a predictable phenomenon and given a new anaesthetic, we know that the partial pressure required for narcosis can be predicted with great accuracy from

its lipid solubility. We also observe that any two anaesthetic agents induce narcosis in a manner which is very similar in the two cases. Now, this is not true for side effects. Side effects are not predictable from one anaesthetic to another; for example, cyclopropane and diethyl ether both cause over action of the sympathetic nervous system, other agents, such as halothane and methoxyflurane, do not. And this difference does not correlate with any obvious chemical grouping within the anaesthetic agents concerned or in the physical property. Furthermore, side effects, when they do occur, do not always occur at a partial pressure which is directly proportional to the partial pressure required for narcosis. Side effects, therefore, vary not only quantitatively but also qualitatively.

**<Nunn refers to diagrams on display board and narrates over them>**

Now, this diagram shows what we mean. Here are three anaesthetic agents, A, B and C. This rectangle indicates narcosis and all three agents very properly produce narcosis. Now, here are two side actions. Agent B is something of a blunderbuss and produces narcosis and both side actions. Agent C is rather better and produces narcosis and only side action. If we regard these side actions as undesirable, then A emerges as the best anaesthetic agent, and B as the worst.

Now let's look at a specific side effect and see what this difference means. This side effect here is depression of respiratory sensitivity to inhaled carbon dioxide and that is shown on this axis <*indicates y-axis*>. Respiratory response to CO2, and that is the normal and that is zero response.

On this axis <*indicates x-axis*> I've shown cyclopropane and halothane concentrations expressed as iso-narcotic units. They are, in fact, the MAC values; that is 1 MAC for halothane and that is twice the MAC and 3 times the MAC there. And you can see that at, for instance, 1 MAC or indeed 2 MAC, halothane produces greater respiratory depression than does cyclopropane.

**<Nunn to camera>**

So, from the standpoint of respiratory depression, halothane is a less desirable anaesthetic than cyclopropane, however, I hasten to add there are other considerations and other side effects in which the order of preference may be reversed so that halothane probably emerges, on balance, to be preferable to cyclopropane when all the side actions are taken into consideration.

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Now, this target selectivity is not at all easy to explain on the basis of the action of an anaesthetic by solution in a bulk lipid phase, such as a lipid membrane. Under these circumstances, one would expect that all anaesthetics would act in a rather similar manner, having regard to their different lipid solubilities. And for the side effects, we shall show in the next programme that this is clearly not the case. It's rather easier to visualise target selectivity in the case of hydrophobic bonding sites which Michael has been talking about.

**<Nunn refers to 3-dimensional models of hydrophobic receptor sites while narrating>**

Now, this is a rather simplistic model of a hydrophobic receptor site, and we're going to offer to this hydrophobic receptor site, anaesthetics which will be distinguished according to size. Here is the smallest one and we find that this one bonds in the site without producing a conformational change. Now, a larger anaesthetic molecule, here, bonds into this site and does result in a conformational change and it might be expected that this would result in a change of properties. Now going to a still larger anaesthetic, we find that this anaesthetic won't enter the site at all, and there are many examples where a large anaesthetic molecule is inactive in a situation in which a smaller one is active.

So recapitulating for this particular receptor site, it was the middle-sized anaesthetic which produced the conformational change in this instance. But now let's change the receptor and look at a different receptor – this might be in a different organ or different organelle of the cell, but, nevertheless, one which is affected by

anaesthetics. Now taking our medium-sized anaesthetic molecule, which produced the conformational change in the other receptor site, we now find that this one will bond into this particular receptor without producing any conformational change and therefore would be unlikely to produce any change in properties. But if we take the larger anaesthetic molecule, which in the previous example would not enter the receptor site at all, we now find that it will enter and results in a conformational change; so that this anaesthetic will produce a conformational change and a change of properties in this receptor site, and this anaesthetic will produce a conformational change in this receptor site and perhaps induce a change of properties there.

Now, this type of approach can explain an infinite range of differences in actions of anaesthetics and specificity in the action on various targets. Now this, in fact, is an essential ingredient to any theory of how anaesthetics act because it is a fact of life to the clinical anaesthetist that no two anaesthetic agents are alike in their side effects.

Now, before we leave these models, perhaps we might just look at them and see whether they can be used to illustrate the phenomenon of pressure reversal. This is a rather special spring-loaded hydrophobic receptor site and you can see that if it receives the largest anaesthetic molecule, there is a conformational change. Now, my hand here, the grip of my hand, is going to represent hydrostatic pressure, and the hydrostatic pressure, you can see, will restore the receptor site to its original volume. Now, that is, I suppose, rather a simplistic illustration of pressure reversal and in particular it is rather hard to see, at the present stage of our understanding, how one part of a protein molecule that can be expanded by the insertion of an anaesthetic into a binding site, and by application of pressure overall to the whole molecule, how this can be possibly be restored to its original shape, but such are the observations as they stand at the present time.

Well, now in closing, I'm going to return you to Michael Halsey, who is going to summarise the present position of our understanding of the molecular basis for action of inhalational anaesthetic agents and is also going to outline the growing points of research in this field. Michael Halsey.

**<Halsey to camera>**

Thank you. It's the ultimate aim for anybody researching into mechanisms of anaesthesia to determine how these chemically inert substances can produce a reversible depression of the central nervous system. It appears that anaesthetics affect synaptic transmission rather than axonal conduction, but the nature of the synaptic block has not yet been fully explained. However, in spite of this, when anaesthetics act to cause anaesthesia, it seems beyond any reasonable doubt that they are acting at a site which has hydrophobic properties. This suggests action in two particular hydrophobic areas. The first of these are the lipids of the membrane; this idea is particularly associated with the names of Meyer and Overton. The second of these is that anaesthetics interact with hydrophobic areas in macromolecules in, for example, proteins. And this idea was probably first postulated by Orstrichen[?].

Now, the current research into anaesthetic mechanisms is concentrated in several areas. First, there are the experiments, on whole animals and in man, on anaesthetic potency and its interaction with factors such as temperature and pressure. Then there are the neurophysiological effects which are attempting to identify the critical areas of the brain as far as anaesthesia is concerned. There are also the neuropharmacological experiments which are attempting to elucidate the mechanism of synaptic transmission and of how anaesthetics, in some way, block this process. There are also effects of anaesthetics on various model systems, whether these be specific proteins or perhaps lipids in biomolecular membranes. Finally, there are studies on whole biological systems at the subcellular, cellular and organ level, and it's this last group of interactions which we're going to discuss in our next presentation.

**<End credits>**