Physiology. — *Models for the stimulation of the organ of smell.* By H. G. BUNGENBERG DE JONG and G. G. P. SAUBERT. (Communicated by Prof. J. VAN DER HOEVE).

(Communicated at the meeting of February 27, 1937).

However complex may be the whole series of succeeding events which ultimately lead to the sensation of smell, it is obvious that as a first link the molecules of the smelling substance penetrate from the gas-phase into a certain substrate of the cells of the organ of smell and in this substrate cause a fundamentally reversible change in condition.

It may further be considered likely that this change in condition is accompanied by a change in permeability. On the ground of generally physiological considerations it may then be expected that phosphatides will to a large extent take part in this substrate. Our own experience concerning the colloid chemistry of the phosphatides strongly supports this suggestion. Colloid systems, e.g. sols or coacervates of proteins, substances with the nature of carbohydrates, nucleinates, etc., are as a rule comparatively insensitive to the majority of the organic non-electrolytes. They do show changes in condition with a limited number, e.g. alcohol, acetone, etc., but only in relatively very high concentrations, while some are sensitive to phenols in considerably smaller concentrations.

On the other hand sols and coacervates of phosphatides are highly sensitive to the most divergent types of compounds in organic chemistry and this influence is often already perceptible in relatively very small concentrations [1]). This striking difference with the behaviour of the proteins, etc. is due to the fact that the phosphatides are not only hydrophil but also, owing to the presence of long hydrocarbon chains in the molecule, to a marked degree lipophil [2]).

As we have recently found, with regard to this sensitiveness to numerous organic non-electrolytes, colloid oleate systems are closely connected with the phosphatides [3]).

This is not surprising, since, though greatly differing in molecular structure, phosphatides and oleates have in common the long, partially unsaturated, hydrocarbon chains.

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[1]) H. G. BUNGENBERG DE JONG and R. F. WESTERKAMP, Biochem. Ztschr. **248**, 335 (1932).

[2]) H. G. BUNGENBERG DE JONG and J. BONNER, Protoplasma **24**, 198 (1935) and Summary in Proc. Royal Acad. Amsterdam **38**, 797 (1935).

[3]) A detailed publication will in due time be made in Protoplasma. Some of the obtained results as well as their interpretation have already been mentioned in the immediately preceding Communication.

With regard to what was suggested above concerning the first link in forming the stimulus of smell, it is interesting that coacervates both of phosphatides and oleates appear to be sensitive to the vapour of numerous organic non-electrolytes. The molecules which are transported by the gas-phase and have entered into the coacervate occasion changes in condition which are reversible and appear to be a decrease or increase of the average distance of the phosphatide and oleate molecules respectively in the coacervate.

Without entering into details, one of the morphological criteria for this decrease or increase may be mentioned here. We refer here to the vacuolization phenomena which on supply or eduction of the organic vapour may be perceived with the microscope on coacervate drops which are suspended in their equilibrial liquid.

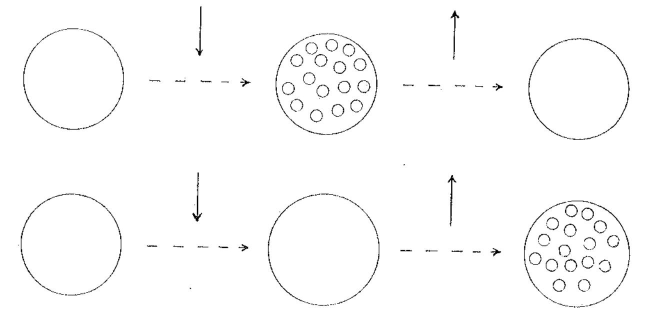

Fig. 1.

1st case (fig. 1A).

If on supply of the vapour (represented by ↓) vacuolization sets in, which after eduction of the vapour (represented by ↑) disappears again, it means that the organic non-electrolyte causes condensation of the coacervate: Under the influence of the introduced organic molecules, the phosphatide and oleate molecules respectively come to be situated at a smaller average distance from each other, while they separate a liquid, containing only a small amount of phosphatides or soap, in vacuolar form. Example for oleate coacervates: nitrobenzene.

2nd case (fig. 1B).

If vacuolization is observed, not on supply of the vapour, but after it has acted for some time and then is carried off, we may conclude to the reverse. Under the influence of the organic non-electrolyte the coacervate now slowly or quickly takes up liquid from the surroundings, which on eduction of the vapour separates again in the coacervate drop in vacuolar form. Example for oleate coacervates: paraldehyde.

In a certain sense and with some reserve these coacervates, which are sensitive to the vapours of organic substances, may be considered as models for the physiological substrate on which the smelling substance primarily acts. For not only are these coacervates sensitive to practically all sufficiently volatile substances and is the change in condition which was brought about reversible, but also the nature of this change in condition (decrease and increase respectively of the average distance between the essential highly molecular components: phosphatide and oleate molecules respectively) is such that in analogous systems containing far less water it would have to manifest itself as a change in permeability (for water, possibly anorganic ions).

It is further interesting that the action of an organic substance, according to its nature, may become manifest in one of two opposite qualities. This reminds us somehow of the principal classification, given by ZWAARDEMAKER [1]), of the odours into two groups: "odeurs nutritives" and "odeurs de décomposition".

Here is also offered a simple explanation of the remarkable fact that two smelling substances in exactly tuned concentrations in the air may lead to the disappearance of the sensation of smell.

However, our model offers still more points of contact with the physiology of smell. By the side of the above-mentioned two cases we know yet a third:

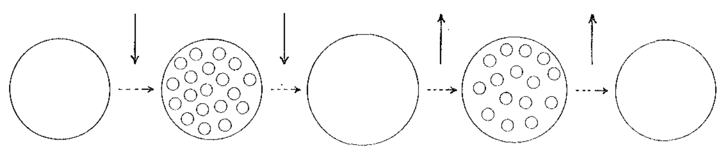

Fig. 2.

3rd case (fig. 2).

On supply of the vapour a temporary vacuolization sets in; similarly on eduction of the vapour (e.g. amylene hydrate in case of oleate coacervates). This means consequently that a small amount of the penetrated organic substance has a condensing action but a large quantity again enlarges the mutual distance of the oleate and phosphatide molecules respectively.

We are inclined to look for a connection here with the fact that certain smelling substances at a small concentration in the air give a pleasant sensation, at a higher concentration, however, an unpleasant one.

With a view to the physiology of smell the following results of a more elaborate research (partially obtained with other, also quantitative methods) are also worth mentioning.

1. In a homologous series each following term is already active at smaller concentrations than the preceding one.
2. The quality of the action may be reversed in some homologous series (e.g. alcohols, ketones, etc.).

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[1]) H. ZWAARDEMAKER, l'Odorat, Encyclopédie Scientifique publiée sous la direction du Dr. TOULOUSE, Gaston Doin, Paris 1925, p. 219.

For the normal alcohols in the case of oleate coacervates this reversal lies at the 4th term (for methyl, ethyl and n. propyl alcohol see fig. 1*B*, for n. butyl alcohol and higher homologues on the other hand see fig. 1*A*) [1]).

Ad 1. It may yet be remarked that even a highly molecular and practically non-volatile alcohol as cholesterol, brought into direct contact with an oleate coacervate, still causes condensation, not however, when the coacervated system is separated from the cholesterol crystals by the gas-phase.

In model experiments for the stimulus of the organ of smell consequently natural limits to the rule mentioned under 1) are formed by the decreasing vapour tension and insufficient solubility in the aqueous surroundings in which the coacervate drops are suspended. In the physiology of smell also an analogue is found, where the rule applies that substances with a boiling-point higher than about 300° do not give a sensation of smell.

Ad 2. The observed change in quality of the action on the coacervate somewhat reminds us of the change in quality of the odour in homologous series, although there the latter does not occur by leaps and bounds but gradually.

In order to reduce the range of the discussed model to its correct proportion, the poverty in possibilities of reaction, in connection with the great variety of odours, has to be taken into consideration. Attempts to interpret all the familiar data of the physiology of smell by the changes in condition of only one and the same substrate which is used in the model, must consequently fail in many respects. This is indeed the case, as may appear from *A*) and *B*) below.

A) The classification into „odeurs nutritives" and „odeurs de décomposition" does not coincide with each time one of the two possibilities of reaction (figs 1*A* and *B*) of the oleate coacervate. In either group substances are found enlarging the average distance between the oleate molecules in the coacervate as well as substances which bring about the reverse.

B) In the physiology of smell indeed transitions in quality of the odour are found in homologous series, but these seem to be limited to each of the mentioned principal groups, while transitions between „odours nutritives" and „odeurs de décomposition" do not seem to occur there. If in our model we should try to connect each of these principal groups with the two possibilities of reaction *A* and *B* of fig. 1, this model, as appears from 2.), in homologous series indeed exhibits transitions between these two principal groups.

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[1]) In the immediately preceding Communication this reversal of the action has already been briefly discussed and explained.

Summarizing, we may therefore say that our model indeed contains a fairly large number of elements which each give occasion to interesting analogies with the physiology of smell but that these elements are not mutually coordinated in the right way.

For an interpretation of the data of the physiology of smell on this basis it is inevitable that we do not confine ourselves to one single model for the substrate of smell but consider the cooperation of a whole series of these models with sensitivities which each time are again differently tuned.

Similarly in the physiology of smell for each of the 9 classes of odours at least specially tuned cells of the organ of sense had to be assumed, which, according to ZWAARDEMAKER, should even be spread sterically in 9 areas of the organ of smell.

With regard to a study of analogous models, where the sensitive substrate contains other essential kinds of molecules, we have only just started. They have already shown that here the classification of the volatile substances into two principal groups, according as their action causes the coacervate to contain more or less liquid, may turn out differently from that of the oleate coacervate.

By the side of this it is interesting that already another physical-chemical condition of the substrate, although the essential kind of molecules present in it is the same, can lead to this as well. We refer here to anisotropic oleate and phosphatide systems, which likewise are sensitive to a great number of organic vapours.

Benzene, for example, which has a strongly condensing effect on amorphous oleate coacervates (fig. 1*A*), occasions exactly the opposite in certain anisotropic oleate systems (Under liquid uptake from the surroundings the double refraction disappears). Just as in amorphous oleate coacervates, the change brought about in the condition of these anisotropic systems, on eduction of the vapour, is reversible: (the double refraction returns).

From all this it may appear that the models discussed here for the stimulation of the organ of smell are as yet in their initial stage and that only after a more elaborate research a more fertile comparison with the data of the physiology of smell will be possible.

Leiden, January 1937.

Neurology. — *Ueber eine direkte Verbindung von der Kleinhirnrinde nach dem Nucleus Deiters.* Von SVEN BERGGREN. (Aus dem Laboratorium der psychiatrisch-neurologischen Klinik, Utrecht.) (Communicated by Prof. C. WINKLER.)

(Communicated at the meeting of February 27, 1937).

Dem Nucleus Deiters, der als einer der wichtigsten Reflexzentren des Vestibularissystems angesehen wird, werden vor allem aus dem Nervus vestibularis und dessen sekundären Kernen und aus den medialen Kleinhirnkernen durch den Tractus uncinatus Fasern zugeführt.

Wenn man bei einem Normalpräparat von der Gegend ausgeht, wo das Corpus restiforme dorsalwärts umschlägt um in das Kleinhirn einzustrahlen, findet man die grossen Zellen des Nucleus Deiters an seiner Medialseite gelegen und darunter quergeschnittene Fasern. Diese Fasern bilden das sog. Corpus juxtarestiforme, das aus dem Nucleus triangularis N. VIII entsteht und mit dem Corpus restiforme nach dem Kleinhirn umschlägt um nach Durchbohrung des Anfanges des Bracchium conjunctivum als die sog. Fibrae perforantes in den medialen Kleinhirnkernen zu enden. Wenn man aber diese Einstrahlung der Fibrae perforantes in die Kleinhirnkerne näher betrachtet, scheint es, als ob einzelne der Fasern durch oder zwischen den Kernen nach der Kleinhirnrinde verfolgt werden könnten. Teilweise mag es sich bei diesem scheinbaren Durchbohren von Fasern nur um ein Begegnen von Fasern der Fibrae perforantes und Fasern aus der Kleinhirnrinde, die ebenfalls in den Kernen enden, handeln. Aus dem anatomischen Bild darf man aber vermuten, dass es unter den Fibrae perforantes auch ev. direkte Fasern zwischen der Kleinhirnrinde und den vestibulären Kerngebieten gäbe. Aus der Literatur ergibt sich auch, dass solche direkte Fasern, und zwar Neuriten der Purkinjeschen Zellen nach dem Nucleus Deiters, von LORENTE DE NÓ beschrieben worden sind. Als Ursprungsgebiet dieser Fasern, die mittels der Cajalschen Silberimprägnationsmethode gefunden wurden, wird der Flocculus, der Lobus medianus und der Lobus paramedianus angegeben. Aus den letzteren Gebieten sollten sie gekreuzt verlaufen.

Im Nachfolgenden mögen einige Marchipräparierte Kaninchengehirne beschrieben werden, welche eine Beschädigung der Rinde des Kleinhirns zeigten, und zur Beleuchtung dieser Fragen sehr geeignet waren. Die Serien sind aus dem Laboratorium von Prof. WINKLER und waren für andere Zwecke hergestellt, nämlich um die Marchidegeneration nach Mittelhirnläsionen zu studieren.

In drei von fünf Fällen ist die Läsion der Kleinhirnrinde eine ganz