PATHOPHYSIOLOGY AND PHARMACOLOGY OF COUGH

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At a scientific convention in 1951 the author lectured on an experimental contribution to the pathophysiology of cough. The cough in question was caused by irritating the tracheal mucosa of anesthetized animals in which the glottis was bypassed; breathing took place by means of a tracheal canula. The increase in expiratory pressure in the pleural space was used as a measure of the strength of the cough. During seizures the pressures reached heights of about +40 cm H_2O but otherwise remained below that of the external atmosphere.

In the discussion following this lecture an expert in respiration doubted that the animals had coughed at all. The strongly positive peaks of expiratory pleural pressure were not acknowledged as an equivalent of cough. The fact that the glottis was excluded and that the animals were anesthetized probably contributed to these negative attitudes.

This is typical of the present-day situation in the field of cough. Every layman knows about cough. For him it is of great importance. Science however has somewhat neglected the act of coughing. Little experimental work has been done and there is much disagreement when the subject is brought up for discussion.

In consideration of all this it becomes advisable to discuss first what is known concerning the phenomenology, genesis and possible modifications of coughing—within the framework, however, of our present knowledge of respiratory regulation. We thus can obtain from this an idea of the pathophysiology of cough. In Section II below we shall differentiate the pharmacodynamic possibilities already known and refer to newer ones.

I. PATHOPHYSIOLOGY OF COUGH

A. Phenomena Involved in a Single Cough

In the act of coughing, part of the expiratory air is pushed out with increased speed. This is probably the most typical event and is always present. Only an increase in the velocity of expiratory air causes, with or without additional narrowing of the respiratory tract, the sound which is typical of cough.

It serves no purpose to try to define cough on the basis of quantitative measurements of expiratory air velocities. We do not have enough knowledge concerning the resistance present. Even simple expiration can be taken as "cough" when the glottis is narrowed and a relatively small portion of air is thrust out with moderate speed. In contrast, because of only slight resistance in the respiratory tract, a large amount of air may be pushed out with great speed to cause, perhaps, only a "cough-like" sound.

In principle an increase in the velocity of expiratory air can be achieved in two ways—by the elastic power of the lungs and thorax, by the active participation of the expiratory musculature, or by both acting together.

The first possibility requires a comment. In many species, as in humans, expiration normally takes place only passively. According to the degree of relaxation of the inspiratory

musculature, the thorax is thus put in its resting state through elastic power. In calm respiration the contracted state of the inspiratory musculature is not suddenly and completely relaxed at the beginning of expiration. On the contrary, relaxation returns only gradually. Therefore this slows down the elastic power which should bring the thorax to its expiratory position. Expiration takes place only slowly and the velocity of air expired is relatively small. In certain cases of activated respiration such as, *e.g.*, that produced by hypercapnia, reduction of the inspiratory activity may take place abruptly and thus the velocity of expiratory air is increased.

We do not know if this first mechanism participates in the act of coughing. But we are sure that the second, active participation of the expiratory musculature, is important. This can be seen especially in species which normally do not expire actively as, for example, cats. During coughing, active muscular components can be demonstrated in the expiratory processes of this species. This leads to expiratory air velocities which are much greater than those seen in variously activated types of respiration, as for example by CO_2, even when the total of the expiratory air volume is the same (18). Therefore we should designate activated expiration as a typical characteristic of cough.

The active participation of the expiratory musculature must be due to a corresponding central activity located in the medulla oblongata (30). Detailed analyses point to certain structures in the dorso-lateral part at the level of the olivary bodies (2). There are reasons to assume that vagal mechanisms also participate in expiratory activation. For example, it has been shown that substances such as morphine, codeine, pethidine (meperidine, Demerol), and methadone have mutual components acting via the vagus. They increase prolongation of expiration which occurs when the trachea is closed at the end of an inspiration [for further details see (3)]. However, it is just these substances which are considered as prototypes of centrally acting antitussives. Whether or not this is true has to remain unanswered for the present. In any case the question of intracentral relationships between vagal mechanisms on the one hand, and mechanisms for active expiration during coughing on the other, needs further experimental investigation.

According to the foregoing an essential part of the act of coughing would be that *part of the expiratory air be thrust out at high speed by mechanisms in which active expiratory forces take part.*

To the circumstances of a single cough also belong certain characteristics of the inspiration immediately preceding the expiratory effort. In general this is deeper than normal. Occasionally a striking parallel can be found between the depth of this inspiration and the strength of the following expiratory effort (31). The question is whether or not there is a causal relationship. One reason in favor of it would be that an expanded thorax offers, mechanically, better dispositions for a strong expiratory effort. This is probably the case but certainly is not the only causal relationship. Evidence for this comes from the following experiments in cats (4): Cough was produced by irritation of the tracheal mucosa by insufflating powdered soap. When inspiration during a cough seizure took place in the pleural space, instead of in the lungs, by the opening of a previously prepared system of pleural cannulas bypassing the normal respiratory pathways,

then active expiration (as indicated by the intrapleural pressure) did not occur. And this was true even though the thorax was expanded to its normal inspiratory position. A reflex due to air streaming into the pleural space may be excluded as the cause of this cough suppression (4). Another explanation perhaps could be that occlusion of the respiratory pathway eliminated movement of air on the tracheo-bronchial mucous membrane and therefore impeded spreading of the irritant into further areas. This also could be excluded as a cause (53). *Per exclusionem* we finally find an explanation in the volume of pulmonary expansion, for should the lungs not be expanded beyond their normal expiratory position, an expiratory thrust would not be possible. Further investigation has shown that the dynamic expiration typical of cough becomes possible again only to that degree to which pulmonary expansion is allowed. Expiratory effort reaches its normal strength at a pulmonary volume which is only a little smaller than that seen in uninhibited inspiration (37).

The cat experiments led to the idea of a possible causal relationship, besides the already mentioned mechanical factor, between the degree of initial inspiration and the strength of the expiratory thrust. The connecting link would be the *Hering-Breuer* reflex, *i.e.*, the fact that as lung expansion increases the activity of the inspiratory center is more and more inhibited. Inhibition of inspiratory activity however in no way implies *ipso facto* activation of expiration. But it is not absurd to assume that thereby favorable conditions arise for the origin of cough. The causal relationship thus should be sought among the following: increased pulmonary volume; increased activity of the stretch receptors; increased inhibition of the central inspiratory activity with a correspondingly increased readiness for expiration; and a more facile bringing together of all expiratory tendencies with, therefore, a more pronounced expiratory thrust under otherwise equal conditions.

We should therefore like to propose that *the inspiration immediately preceding the expiratory thrust* is an integral part of the act of coughing. It is *an important connecting link between the stimulus and the resulting response*: the deeper the inspiration the stronger the expiratory thrust, under otherwise equal conditions.

Up to now we have considered exclusively the single cough. Thereby, also, we took into consideration the possible relationships only between the expiratory thrust and the preceding inspiration. In the cough seizure, however, other relationships are possible, such as those between the expiratory thrust and the inspiration following it. Thus, for example, it is conceivable that, in the sense of Head's after-reaction (22) a strong expiration (and a cough act is such) may also lead to a stronger succeeding inspiration. Thus there arises a vicious circle. Together with some other reasons this explains why coughing seldom occurs as one individual thrust but is usually a series of expulsions, *i.e.*, a fit of coughing.

A special behavior of the glottis also belongs in the description of cough. The glottis is closed for a short time and then suddenly opened very early in the process of expiration.

Closing of the glottis causes reinforcement of the expiratory thrust in various ways. We can assume that various mechanisms participate in the expiratory action of cough. We can be sure of one: the activity of the respiratory muscula-

ture. Most probably these various mechanisms are not completely synchronized. Moreover, to achieve their maximum effect they require a certain amount of time. Closing of the glottis assures this. Thus in a certain sense occlusion of the glottis stores and therefore coordinates their energies. Besides this it can be assumed that by glottic occlusion expiratory efforts are reinforced reflexly. At any rate this is well known in normal expiration. Sudden occurrence of respiratory resistance leads by proprioceptive pathways[1] to an increased expiratory effort (13). This corresponds with what could be expected on the basis of general biological experience. Why should this not also hold true for an especially strong expiration such as that characteristic of cough?

On sudden opening of the glottis, the expiratory impulses, reflexly reinforced and coordinated by the delay, will lead to an especially high initial speed of expulsion of air.

When we think of the behavior of the glottis within the bounds of our general knowledge of respiratory regulation the fact that the glottis closes is not so unusual as one might imagine. Closing of the glottis causes a maximum narrowing of the respiratory tract in that region. Narrowing in the respiratory pathway during cough, however, also occurs in other places. For example, it is likely that active bronchospasm also exists. We can conclude this from experiments on cats with opened thoraces, in which irritation of the mucosa, which normally leads to cough, causes constriction of the bronchi (55). In addition the respiratory pathways are compressed passively during cough. This is due to the fact that on the one hand extension of the pressure over the lung parenchyma occurs rapidly, and on the other the resistance of the respiratory tract to the expiratory air is relatively large. Therefore, there exist pressure differences between the lung parenchyma and the respiratory tract (41). In this manner cross sections of the respiratory pathways might become narrowed down to 25% or less (43, 51). Under pathological conditions complete occlusions may occur (23). Further, we should remember that the glottis contracts even during normal expiration (48). Therefore in the behavior of the glottis in cough it is above all its sudden opening which seems distinctive.

In most cases of cough the behavior of the glottis is as described. But this is not necessarily so. Cough is also possible without the glottis. For example, anesthetized cats breathing through a tracheotomy tube react to tracheo-bronchial irritation of the mucous membrane with a fit of coughing which, externally judged, does not seem to differ from an attack in cats with an intact glottis. Therefore closing and opening of the glottis should be considered as only a facultative, though useful, auxiliary mechanism to coughing.

We have mentioned the following characteristics of cough: increased expiratory air velocities; active participation of the expiratory musculature; presence of an initial inspiration; closing and opening of the glottis. However these are surely not its only characteristics, and further research should reveal others. Some investigators have described—especially dramatically in (40)—active bronchial peristalsis. However the proof offered up to now for the presence of such bronchial peristalsis has not been convincing (see also (43)).

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[1] Interpretation of the experiments described in (13) has been disputed recently (39).

B. Genesis of Cough

Cough is considered to result from a reflex. Thus the question concerning its genesis is equivalent to that concerning its reflexogenic zones and their adequate stimuli.

Reflexogenic zones generally are found in the mucous membrane of the respiratory tract. This conclusion is based on the knowledge that cough exists concurrently with disease of the respiratory tract and that artificial irritation of the normal mucous membrane of the respiratory tract causes cough. Controlled irritation in experiments has led to detailed localization of reflexogenic zones. Thus the most susceptible area for the production of cough is found in the region of the trachea and the large bronchial tubes, with a maximum in the region of the bifurcation. Sensitivity is reduced a short distance peripheral to this (30, 33, 51, and others). Cough may also be precipitated from the region of the laryngeal mucous membrane, especially on the posterior laryngeal wall (48 and others). Scarcely any reflexogenic zones can be found in the pharynx. In most cases the pertinent afferent fibers usually run into the vagal branches (see 8, 10, 36, and others) but occasionally also into the sympathetic nerve trunks [see (8)].

The receptive elements may, at least in experiments, be stimulated in various ways. Mechanical, chemical, thermal, electrical and other types of irritation all cause cough (26, 30, 33, 38). Therefore we should like to propose that there are no "specific cough receptors" on the mucous membrane of the respiratory tract, but that sufficient stimulation or irritation by any factor leads to cough. This hypothesis is analogous to Goldscheider's theory of pain, and is supported by the experience that a tracheo-bronchial "irritative" cough almost always is combined with sensations such as tickling, burning, pain, *etc.*

For the special situations present in an attack of coughing it would be interesting to know the adaptation of the various receptive elements. The first experiments along this line have shown that cough-precipitating chemoreceptors in the trachea and bronchi adapt themselves only relatively slowly to the irritant (53, 54, 55). In contrast, cough-precipitating mechanoreceptors in the region of the bifurcation adapt themselves relatively quickly (54, 55).

Since cough on the one hand preferentially originates at the mucous membranes of the trachea and the large bronchial tubes and, on the other hand, leads to increased expiratory velocities, it may be considered in its whole character as a protective reflex. In the region of the trachea and the large bronchial tubes the total cross section of the respiratory tract is especially small and thus in these parts the velocity of the air expired will be especially high. Therefore irritating foreign substances may be removed mechanically, *i.e.*, "coughed out". In this respect the expiratory thrust can be very effective. This was impressively demonstrated by experiments in which lead bullets were placed into the bronchi; each time they were thrown up into the mouth cavity by a single slight cough (51). The larger the total cross section of the respiratory tract the less effective will be the cough. The total cross section increases greatly towards the periphery, *i.e.*, alveoli, of the lungs. It is, however, difficult to say from exactly which level of bronchial ramifications outwards cough becomes ineffective. It may be as-

sumed that by extensive bronchoconstriction the limit of effectiveness can be shifted towards the periphery.

While irritating of the mucous membrane of the respiratory tract is probably the most common cause of cough, it is certainly not the only one. Pressure on the trachea (29) as well as pulling the trachea (12) under suitable conditions may lead to cough. Irritative conditions of the pleura may be accompanied by cough as, *e.g.*, in dry pleurisy. Tactile stimulation in the external auditory canal, pressure on the liver and spleen, compression of the carotid sinus, *etc.* all may lead to cough (44 and others). Certain circulatory conditions also may cause cough as, for example, congestion of the lungs in left cardiac insufficiency (7). In addition, we encounter cough for which we can neither localize nor even assume a reflexogenic zone. For such cases a central genesis must be considered. We know nothing about the significance of all these special types of cough. Possibly they have none. In this case they could be considered as failures in respiratory regulation. They may come about or be made possible because repeated coughing after some time causes the establishment of readily elicited reflex pathways. Once these are paved other impulses also may use the same pathways to produce cough, provided that the cough mechanisms and precipitating impulses somehow meet. This possibility seems present to a great extent especially in cough. We already have found close relationships to various types of afferents even in simple tracheo-bronchial irritative cough.

C. Possibilities of Modifying Cough

Cough has been described in Section I A. Exceptionally, however, some of the events mentioned, such as occlusion of the glottis and deepening of the initial inspiration, may be missing. We do not know why.

Coughing may occur as a single cough, as a group of a few coughs or as an extended seizure. The reason for a seizure in many cases can be explained by the fact that the peripheral stimulus is active for corresponding length of time. But in some cases it seems that it is dependent upon characteristics in the central organization (for example, in whooping cough).

The pathways in the medulla oblongata responsible for cough seem to have various connections with central substrates in higher regions. So-called "nervous" cough probably takes place via these connections. There must also be connections to conscious areas because, as is generally known, cough may be suppressed voluntarily. When irritation is too severe the moment of the expiratory thrust may at least be postponed for a few seconds. This is of practical importance (for example, the disturbance to attention while driving an automobile or disturbance to the surroundings during a concert may be postponed to a more convenient moment). We have no details concerning the mechanisms of these modifying connections but it is important to point out that they exist. They may serve as points of attack for antitussives.

In connection with the various possibilities of modifying cough we should point out two factors: the summation of irritation and the paving of the reflex course. They cannot explain the modification of cough but they may contribute to its understanding.

As to summation—If we try to cause cough by electrical stimulation of the laryngeal nerve, the pleura, *etc.*, it is seen that in general a single stimulus is not sufficient, even when it is maximal. Thus a summation of stimuli seems to be required centrally. Summation however requires a minimal period of time. Even when only a short period, it increases the chances that other mechanisms may meanwhile influence the cough.

As to paved reflex pathways—it is known that cough can also occur voluntarily. The component events of such a cough may be the same as those of the normal cough reflex. This is not self-evident considering the fact that cough is a rather complicated autonomous reflex. However it becomes more easily understandable if we assume that the cough is directed over paved reflex pathways. When any part of its reflex path is stimulated, the reflex as a whole proceeds over the remainder of its usual pathways in its usual form.

We may summarize our fragmental knowledge on the pathophysiology of cough as follows.

We speak of cough when air is expelled forcibly and with sound. Active expiratory effort participates in this phenomenon. Furthermore, it must be mentioned that cough in most cases occurs as a reflex and thus the reflex arc consists of an afferent part, a central mechanism and an efferent part. Of the afferent part we know that it has receptor zones in the respiratory tract. The afferent impulses run with branches of the vagus and the sympathetic trunks. Of the efferent part we can identify the striated expiratory musculature involved and the pertinent motor nerves. Parts of the bronchial musculature and its pertinent efferent vagal fibers are probably included also.

Very little is known about the manner in which the active afferent fibers influence the central discharge. Nevertheless we believe we know some mechanisms of this process. For one, the well-known pulmonary stretch reflex seems to play a role in that it prepares the way to expiratory activity by means of the preceding inspiration. Also, the expiratory thrust seems to be reinforced reflexly by means of an active increase in expiratory resistance.

The cough reflex taken as a whole demonstrates the phenomenon of "paved pathways", *i.e.*, it travels along treaded paths. Thus it can be initiated by mechanisms other than respiratory stimuli. In addition its central components are subjected to many influences, inhibitory as well as facilitatory.

A "cough center" is assumed to exist by many investigators who ascribe to it the function of central disposition of the afferent impulses (many of which are still unknown) responsible for cough. It is possible that such a "cough center" does exist. On the other hand it should not be forgotten that all the central mechanisms which we know as being active in cough are not "cough specific" when examined individually. Expiration can also be activated physiologically as, for example, in hyperventilation during and after severe physical strain. The lung stretch reflex is an important modulator of normal respiratory activity. Even closing of the glottis is not peculiar to cough alone since it is also part of other respiratory reflexes, such as the respiratory arrest which can be induced by irritation of the nasal mucosa. The same holds true for active bronchial constriction. The peculiarity of cough lies only in the special coordination of all these components. Many other reflexes also demand such special coordination (for example, hiccup and sneezing). However in many of these there is no insistence upon the existence of a specific center. Therefore at present it is only a matter of opinion as to whether or not to accept the idea of a "cough center". If it is accepted, the danger may arise that we will not appreciate our actual ignorance concerning central cough mechanisms. Besides this the intriguing attempt to consider cough as a part of normal respiratory regulation and to classify it accordingly would be suppressed.

II. POSSIBILITIES OF SUPPRESSING COUGH

We shall not consider here the many medicaments recommended as antitussives, since we do not intend to discuss the pharmacology of antitussives but the pharmacology of cough. Therefore we shall base our discussion on pathophysiological functions, since they all may be used as points of attack by pharmacological agents. Whether such medicaments really suppress cough depends considerably on the importance of the function in question to the cough to be treated. We shall try to illustrate the theoretical possibilities existing by means of practical examples. In doing this, however, we sometimes shall have to satisfy ourselves with rather vague suppositions because what we have found true for the pathophysiology of cough holds true to an even greater extent for the pharmacology of cough remedies: in many cases we know nearly nothing about their mechanism of action. This is not surprising since verification of a change (by medicaments) in the occurrence is predicated by knowledge (pathophysiology) of the occurrence itself.

Before treating the possibilities of pharmacological action against cough, we should consider the oft-asked question, "Is it advisable at all to suppress cough?" The answer in each concrete case will be given when the apparent advantages of the cough are compared with its possible harmfulness.

Cough may be considered of advantage when, for example, it is caused by the presence of an irritant on the mucous membrane in the respiratory tract which can be removed by coughing. This clear-cut case is seldom met in practice. Numerous, however, are the cases where cough occurs as a manifestation of inflammation of the respiratory tract. Here the irritating agent is unknown. It might be present in the inflammatory secretion itself. In this case it would be difficult to judge if its temporary removal by cough is of advantage because the production of secretion, and therefore of irritant, might be increased as a result. Or, inspired air itself may be the irritating agent since it is not of body temperature and is usually too dry. This could be the case if we assume that the receptors are rendered hypersensitive by the inflammation. Here cough may be considered as useless. "Productive" cough is commonly considered to be of advantage. Therefore the tendency is to be afraid to suppress such a cough. We doubt, however, that this is rational because we can assume that expectoration removes only a small part of the secretion produced. The greater part is probably absorbed by the inflamed mucous membrane. On the other hand we can assume that a few strong coughs may produce the same volume of expectoration as a continuous troublesome cough. It would therefore seem logical to suppress each productive cough provided it is severe or troublesome enough. If at the same time it were obstructive, we should instruct the patient to cough voluntarily from time to time.

A cough can be harmful, in the broadest sense of the word, because it interferes with general good health. Interruption of sleep is especially troublesome. Cough may also lead to undesired effects on the circulatory and respiratory systems. These are generally due to the high increase in intrathoracic pressure, which may reach values of up to 300 mm Hg (47). In the circulatory system,

increase in intrathoracic pressure leads to reduction of the blood supply to the right heart, which leads in turn to a reduction in the cardiac output. The blood supply to the brain may be thereby reduced (47) and temporary loss of consciousness may occur (28). The spinal pressure may be increased (20) especially if the venous pressure in the systemic circulation is increased. Normally, however, this does not take place because the venous valves prevent the positive intrathoracic pressure from affecting the systemic veins (34). But conditions are different if at the same time circulatory insufficiency is present. Then the veins may be overstretched and their valves may act insufficiently (34). After a coughing attack the pressure in the right ventricle may be increased for a minute or so by approximately 10 cm water (46). In the *respiratory system* a large increase in intrathoracic pressure may lead to intrapulmonary rupture of the tissues and to emphysema. The final explanation may lie in an uneven distribution of the pressure during expiration. As rare side-effects mediastinal emphysema and air embolism may be mentioned. Very rare is invagination of the tracheal membrane with complete occlusion (23).

Therefore the question "Is it advisable to suppress cough?" may be answered as follows: Slight cough is useless as well as harmless and no remedies are required. Severe cough may be harmful and therefore should be suppressed. Expectoration, if required, may be achieved by a few voluntary coughs at any time.

1. Possibilities of action on the afferent pathways. In most cases cough results from a reflex. Therefore reflexogenic zones exist. It thus should be possible to abort cough by anesthetizing the reflexogenic zones. The ideal procedure would accordingly appear to be local anesthesia but this requires first that the reflexogenic zone must be known, and secondly must be accessible mechanically. These conditions are met when the cough reflex starts from the region of the larynx. There irritation may be eliminated by painting with an anesthetic. The result is a selective prevention of cough. However, only few cases offer such favorable sites. In most cases the reflexogenic zones can neither be localized nor approached with sufficient accuracy. In tracheo-bronchial irritant cough, for example, inhalation of anesthetic aerosols is only moderately selective in its effects. Anesthesia of the pharynx plus perhaps the mouth and nose have to be accepted as side-effects.

The question then arises as to whether or not selective anesthesia could be achieved in ways other than mechanical—*i.e.*, by pharmacodynamic means. This would be possible with an anesthetic having a special affinity for the receptors responsible for cough. At present we know of no such anesthetic. There is also little hope that one will be developed, since the receptors are so heterogeneous (see above).

Under certain circumstances blocking the afferent pathways is a possibility. For this purpose the afferent nerves must be recognized and must be approachable mechanically. However, even if these conditions are met the procedure is of use only in exceptional cases. One possible indication, for example, is cough difficult to abort which is caused by a one-sided bronchial tumor. In this case anesthesia of the vagus stem may be effective.

Drugs classified as ganglionic blocking agents also may act as antitussives. Hexamethonium, for example, is said to abort cough artificially induced by lobeline while codeine is

said to have practically no effect here (24). We do not know which site is responsible for the effect. Perhaps the points of attack are not at all on the afferent side of the reflex. The ganglionic blocking agents are mentioned only as a possibility to be taken into consideration after the usual better known and more harmless cough remedies have failed.

2. Possibilities of action, on the efferent pathways. The efferent pathways conduct impulses of various types. Some of these are known to us—those which activate the striated expiratory musculature, the muscles of the glottis and the bronchial muscles. By the pharmacodynamic elimination of any one of these systems, it should be possible to diminish cough because the part concerned will fail to participate. The most pronounced diminution could probably be achieved by blocking the expiratory musculature. This is possible pharmacodynamically by neuromuscular blocking agents. The procedure is of no therapeutic value, however, because side-effects are obviously too severe, *i.e.*, general paralysis. A muscle relaxant with a selective effect on the expiratory musculature alone would be more promising, but such a preparation is not yet available. Neither is it likely that its elaboration would be worthwhile because it probably would still have undesirable side-effects. There are quite a few "expiratory muscles"—the serrati postici, sacrospinalis, muscles of the abdomen, *etc.*,—which serve other purposes also and not only cough.

3. Possibilities of action on the coordinating mechanisms in the medulla oblongata. These possibilities seem more promising. In this area all factors leading to cough are united. A preparation acting with sufficient selectivity should be able to abort any sort of cough, whether it arises from tracheal irritation, the external auditory canal, voluntary exertion, or other cause.

The prospects are interesting but difficult to achieve at present. We already have mentioned that what we know of the coordinating mechanisms is little more than the fact that they exist. Therefore for the time being we cannot say for sure that any particular preparation acts here. It is assumed that codeine does so even though there is no definite proof that this is the case. The assumption is based on several observations. Experience has shown that codeine has a suppression effect on most kinds of cough. This probably can be said only of drugs which act on mechanisms common to all kinds. That this action of codeine might be central is assumed because of its many other central points of action. Codeine causes depression of respiration, analgesia, and other depressing as well as stimulating effects. The fact that codeine nevertheless can be quite a selective antitussive makes it very probable that its primary point of action is on special central substrates important for cough. Cough, provided it is not too severe (see below), may be suppressed with codeine without the production of other central respiratory effects. In this respect codeine differs from most compounds which depress central nervous functions. For the time being, therefore, it represents the prototype of an antitussive with a central point of attack. This, however, should not lead us to consider codeine as the ideal drug for cough. The antitussives of this type still require much improvement. The selectivity of codeine often is insufficient in severe cough where higher dosages are required. Then side-effects such as nausea, constipation and somnolence occur frequently.

A mechanism similar to that of codeine is assumed, by analogy, for dihydrocodeinone; pholcodine (the 2-morpholinoethyl ether of morphine) and other morphine derivatives; for dextromethorphane (Romilar®; (+)-3-methoxy-N-methyl-morphinane) and other similar drugs.

4. Possibilities of action on the auxiliary mechanisms of initial inspiration. We have pointed out above the influence of the initial inspiration: by means of reflexes it provides a special background for expiration. The reflex starts in the stretch receptors of the lung. Cough is more severe when these are strongly excited. Therefore, through anesthesia of the stretch receptors it should be possible to reduce cough by the extent to which this reflex contributes to it.

How can stretch receptors be anesthetized in practice? Mechanical application of an anesthetic obviously is not possible since the stretch receptors are neither well localized nor mechanically approachable. They are found partly in the pleura or its vicinity (32, 52) and partly in other regions (55). On the other hand a selective pharmacodynamic approach may be possible here. The stretch receptors seem to be relatively homogenous elements (in contrast to the receptors from which cough starts) and therefore it should be possible to find a selective anesthetic which anesthetizes them only. Benzononatine (Tessalon®; nona-ethylene-glycol-mono-methyl-ether-(p-n-butylamino)-benzoate) seems to be such a substance (3a). Selective stretch receptor anesthesia is achieved with it.

For coughs which, like the bronchogenous irritative cough of the cat (see page 46), do not occur without initial inspiration, benzononatine would be expected to be the preparation of choice. Further clinical experience with this preparation will teach us which forms of cough belong to this type. However, according to clinical reports now available, benzononatine seems to have a good antitussive effect in many types of cough, especially those accompanying pleural or bronchial affections (23a). It seems to be well tolerated, since no side-effects have been reported in any of the clinical reports published up to now.

5. Possibilities of action on the auxiliary mechanisms of expiratory resistance. In this case substances which prevent occlusion of the glottis or bronchospasm should be considered. Substances having the first mentioned effect are not yet known. But we do have substances which relax bronchospasm. They seem to be of value for certain types of cough. Caramiphen (Taoryl®; bis-[1-(carbo-β-diethylaminoethoxy)-1-phenyl-cyclopentane]-ethane disulfonate), Carbetapentane (diethyl-amino-ethoxyethyl-1-phenyl-1-cyclopentane-carboxylate) and other substances which relax bronchospasm are said to be effective in some sorts of cough. One is tempted to assume that in such cases bronchospasm plays a special role in the cough in question ("spastic cough"). However, since the substances concerned also have central actions it is difficult to say to what extent the bronchial action participates in the therapeutic effect. Besides this we still would have to find out to what degree the substances which relax bronchospasm diminish expiratory resistance reflexes. There are other possibilities of explanation which could come into question. Let us assume that in a spastic cough bronchospasms were present, as pathologic side-effects, in the inspiratory phase also. In this case their relaxation would lead to a decrease in the velocity of inspiratory air. This however could lead to a decrease in intensity of the local cough stimulus.

From a theoretical point of view substances which relax bronchospasm might

be expected to have a cough-reducing effect in some cases. Practical experience seems to confirm this. We believe that it would be both useful and promising to investigate systematically compounds of this kind, such as adrenaline, in aerosol form.

6. Possibilities of action on higher centers. There are some types of cough which apparently originate in higher cerebral centers. In such cases sedatives, for example, may exhibit antitussive effects.

III. THE EVALUATION OF ANTITUSSIVES

1. In animal experiments. Cough in animals usually is caused artificially. This may be done in various ways. Our knowledge of the pathophysiology of cough opens up various possibilities. Some of them already are used practically. These are the cough methods of experimental pharmacology. They cannot all have the same interpretation. Despite this, or for just this reason, all these methods can be put to good use, provided they are judged within the bounds of our pathophysiological knowledge. The importance of these bounds may be demonstrated by describing four different methods. In the first method cough is produced by electrical stimulation of the dorso-lateral part of the medulla oblongata (2) of decerebrate cats. It is clear that with this method substances acting on the afferent part or above the decerebrating lesion cannot be recognized. The method is suitable, however, for substances having an effect on the efferent part. Probably substances acting on the coordinating central mechanisms also may be recognized. Our experience up to now tends to support this (6). Whether or not this method is suited to the auxiliary mechanisms of initial inspiration and expiratory resistance cannot be predicted because we do not yet know exactly on which central functions the electrical stimulation becomes effective. The situation is completely different in a second method whereby cough is produced by electrical stimulation of the vagus nerve (45) in unanesthetized dogs. The method allows use of the same animals for repeated experiments. It probably does not allow recognition of substances acting on the afferent part. However, the method seems to be suited *a priori* for all the other pharmacodynamic possibilities mentioned above (types II 2, 3, 5, 6 and possibly 4). In fact it may be preferable for substances having their points of attack on higher central substrates because experience has shown that, especially in dogs, psychic factors gain more and more influence after repeated tests. In a third method cough is caused by blowing soap powder into the trachea. Anesthetized cats in which the larynx is bypassed (4) are used as experimental animals. Substances acting on higher substrates are probably not recognized with this method because of the anesthesia. Neither can substances acting on the glottic mechanism be recognized of course. However, all other pharmacodynamic possibilities (types II 1, 2, 3, 4) may be examined by this method. It seems to be especially suited (4) to one of these, the auxiliary mechanism of initial inspiration (type II 4). In the fourth method cough is caused by slight external pulling of the trachea of unanesthetized cats. The animals must have artificially induced pleurisy (12). All the above mentioned pharmacodynamic possibilities may be examined with this method. But this does

not *eo ipso* mean that this method is more suitable than the other three. In order to develop antitussives having differentiated points of attack the less universal methods or suitable combinations of these are more appropriate.

Besides the four methods described various other equivalent means of producing cough may be mentioned. Some used during the past few years have been mechanical irritation of the tracheal mucous membrane of unanesthetized dogs (27); having the unanesthetized guinea pig breathe in irritative gases (11) or, the unanesthetized dog, irritating aerosols (56); chemical stimulation of the tracheal mucous membrane of anesthetized cats (35) and unanesthetized dogs (42); electrical stimulation of the N. laryngicus cranialis of anesthetized cats (9) and unanesthetized dogs (27); electrical stimulation of the tracheal submucosa of unanesthetized dogs (50); and electrical stimulation of the pleurae of anesthetized dogs (17).

In judging the value of an antitussive, however, we must take into consideration not only the type of cough on which it acts but also the manner in which its effect is measured. Usually it is the intensity of the individual expiratory thrust which is measured as the velocity of air expired or the side-pressure caused. If cough is considered as a defense reflex then this actually measures in a certain sense the degree of success of the cough. In this case the method is justified. However it should not be forgotten that actually the air speed at the site of measurement, usually the trachea, is not so important as that in those places where the cough reflex arises. Furthermore the intensity of the expiratory thrust may also be measured through the pleural pressures because the positive pressure peaks of the pleurae are due to the activity of the expiratory muscles. This, however, is a characteristic (see page 46) of all coughs. Above all it is the activity of the expiratory musculature which is responsible for the increase in expiratory air speed. In fact it has been shown in cats that the maxima of expiratory air speed or of pleural pressure are equally well suited in characterizing the strength of a single cough [see (18)].

The intensity of the expiratory thrust is not the only criterion possible however. There are others which might be useful. The amount by which the number of coughs can be reduced over a certain period of time (14, 19, 57, *etc.*) and the depth of the first inspiration after a cough (35) have been used as measurements. But the same thing holds true for all these methods as for the types of cough (see page 52)—they are useful only to the extent to which the component measured is of importance to the pathophysiology of cough.

2. In clinical practice. In clinical practice the judgement of antitussives is usually made in cases where cough is a symptom of some other condition. Here is just where the response of a cough to an antitussive is relevant. In principle all types of cough lend themselves to such judgement. It is important, however, that they be characterized as well as possible within the bounds of our pathophysiological knowledge. Thus, for example, the special cough of a nervous person, the "spastic" cough of pertussis, the deep cough of productive bronchitis and the irritative cough of pleuritis sicca are certainly different from one another in many respects. Therefore, it cannot be expected that one and the same antitussive may have the same favorable effect in all these cases, especially when

antitussives with differential points of action are employed—and these are the preparations which would be most desirable.

Clinical testing of an antitussive agent is not simple. The many possibilities of modification (see page 48) and their overshadowing by strong subjective feelings accompanying cough make critical analysis difficult. For these reasons some investigators have resorted to the experimental production of cough in humans. To produce cough they have used inhalations of irritant gases (25 and others) or aerosols (1), and intravenous injections of lobeline (21, 24 and others) or paraldehyde (16). Clinical investigation of artificially induced cough in humans surely is of value because it can help in the characterization of antitussive substances. However, it cannot be decisive in evaluating the clinical usefulness of such agents.

It has already been emphasized that, with respect to experiments on animals, the type of cough as well as the methods used for its evaluation are important. The same holds true for clinical evaluation. Here, judgement is generally made on the basis of many criteria which sometimes are not too well characterized. In seeking a more objective evaluation various factors have been taken into consideration, such as the number of times coughing takes place over a certain time span (15 and others); taking into consideration a combination of the frequency and bothersomeness of a cough (5 and others); leaving characterization entirely up to the patient (49). All these methods of evaluation may lead to findings which in some way or another are of practical importance, provided, of course, that they are evaluated within the bounds of our pathophysiological knowledge. Above all it is important for the investigator to be aware of what the individually measured criteria could mean when interpreted. For example, as regards the possibility of an intrapulmonary rupture of tissue it might be especially important to know the peak value of intrapleural (or intraesophageal) pressure during the individual cough. As regards a brusque diminution in the minute volume of the heart, the length of a single fit of coughing might attain some special importance. In determining how troublesome a cough is, the frequency with which the individual cough seizures take place might be of importance. The probability of painful sensations in the chest might become greater as the speed of velocity of expired air increases and so on. At present these are only assumptions. It remains for the clinical investigator to pass judgement on them.

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