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VENTILATORY STUDIES OF THE LUNGS IN ASTHMA

The nitrogen elimination efficiency of the lungs during oxygen breathing in patients with asthma bronchiale. A method for objective registering of even mild asthmatic breathing examined in provocation tests.

By

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In analyses of asthmatic patients, it is important to establish, through exposure or provocation tests, if the patient gets asthma from the allergen to which he is supposed to be hypersensitive. In asthma, inhalation seems to be the most common way of exposition. If the patient is hypersensitive to the antigen inhaled, asthmatic symptoms of differing degrees of severity very often result. An objective registering of the asthma thus produced facilitates the judgment of the exposure or provocation test, provided that the method also registers the changes occurring in mild asthma. Even if it might be desirable to have normal auscultatory findings from the lungs before the provocation test, this is in practice not always obtainable. Some difficulties may therefore arise in judging the effect of an inhalation with the guidance of the clinical findings only. In such cases especially, an objective registering of some of the changes in the lung function occurring in asthma is of value for judging the provocation test.

As early as 1921, Meakins showed that the oxygen saturation falls during asthmatic attacks. This seems, however, to be the case only in severe asthma. As has been shown by Coll-

dahl in both animal experiments (1941-43) and in asthmatic patients (1947), the respiratory minute volume increases in mild asthma but decreases in severe asthma. The same is the case with the oxygen intake. In mild asthma the oxygen intake increases so that it meets the requirements of the body and therefore no oxygen debt appears. In severe asthma the oxygen intake is diminished and, in spite of considerable breathing work, it may not come up to the basal value, thus causing an oxygen debt in the organism so that the oxygen consumption in the first part of the post-asthmatic period is considerably increased.

In his provocation tests Arner has used the fall in the oxygen saturation of the haemoglobin as a method for objective estimation of the asthma attack. He has used an oxymeter to measure the variations in the oxyhaemoglobin level. Our experience shows, however, that no fall in the oxygen saturation of the blood occurs in mild asthmatic changes, which is in accordance with the above mentioned investigations by Colldahl.

In order to find an easy way of objective registering of minor asthmatic changes also, we have studied the washing out of N_2 from the lungs during oxygen breathing with a view to finding out if any change in this occurs even when the asthmatic symptoms are mild. Using fractional alveolar air analysis, earlier investigations by Roelsen, among others, have shown that there is an uneven ventilation in the different parts of the lungs in asthmatic and emphysematic patients. This is especially the case with asthmatic patients during attacks. Owing to the rather difficult and time-consuming gas analyses and the complicated sampling techniques this method was never extensively employed in clinical work.

In 1941, Cournand published a simple method by which severe changes in the pulmonary ventilation could be detected. In this test the patient, after 7 minutes' oxygen breathing, had to make a maximal expiration and the last part of the air breathed out was collected and analysed for nitrogen. If the nitrogen content had fallen to values below 2.5 %, the pul-

monary ventilation of the individual was regarded as satisfactory, while values above 2.5 % were regarded as pathological. The method is simple but gives no information as to the form of the elimination curve between 0 and 7 minutes. According to investigations by Courmand, the test is negative in mild asthmatic attacks.

In 1946, Boothby and Helmholtz found that, if a subject breathes in a closed spirometer system, which was filled with O_2 before the test began, and if the volume of nitrogen eliminated during the test and accumulated in the spirometer is determined and plotted in a double logarithmic coordinate system against time, there will be a break in the curve when the nitrogen present in the lungs at the beginning of the test is washed out. The rest of the curve represents nitrogen from the tissues of the body. In 1947, Boothby, Lundin, and Helmholtz studied both healthy persons and patients with respiratory changes. They found that in this way it was possible to obtain valuable information as to the pulmonary function. They were able to estimate the washing-out time, i.e. the time from the beginning of the test to the appearance of the above mentioned point of change in the elimination curve, which indicates the time needed for the nitrogen present in the lungs at the beginning of the test to be washed out. By measuring the vital capacity at the end of the experiment they also were able to determine the different volumes of the lungs, such as functional residual, complemental, reserve air, and total capacity.

Such a test, which required the determination of at least 10-12 points on the nitrogen elimination curve by gas analyses, which had to be done in a Haldane apparatus, could, however, only be of a theoretical interest. When the US Navy in 1947 placed a nitrogen analyser at the disposal of Boothby and his co-workers, lung function tests could be accomplished on a larger scale on both normal and pathological material. It then appeared that the test could be considered comparatively simple and easy to carry out. (Boothby, Lundin, Helmholtz, 1948.)

It takes, however, a certain time to calculate the volumes at the different time moments and a closed spirometer system of the type used may be too expensive for most clinics. Boothby and Lundin therefore tried to simplify the test by determining only the washing-out time. This was done in different ways, i.e. by sampling the alveolar air according to Otis and Rahn and by analysing it in the nitrogen analyser. Finally they arrived at the method described below as the most simple and this was used in the present work in several provocation tests on asthmatic patients.

Several American authors, among them Fowler, have during the last few years developed similar methods, where a nitrogen analyser has been used.

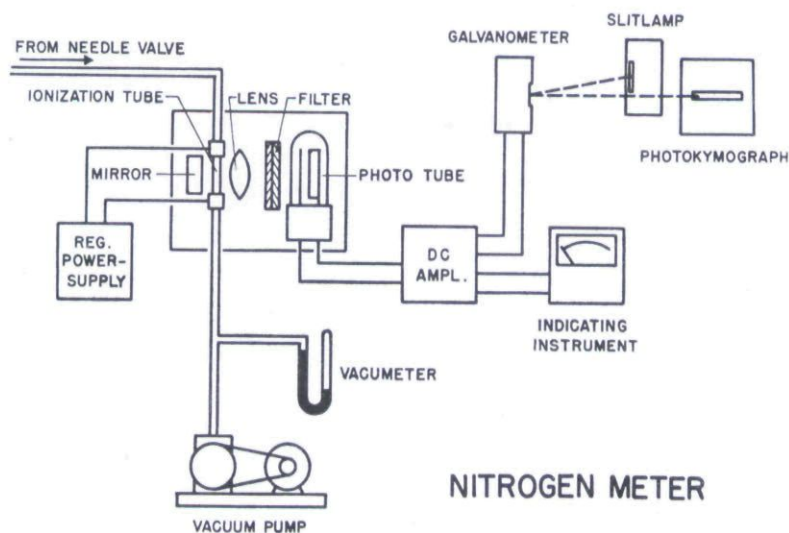
METHOD

As a measure of the ventilatory efficiency of the lungs we have used the fall in alveolar nitrogen percentage during oxygen breathing. This fall is measured by a modified Lilly-Anderson nitrogen meter (fig. 1) and continuously recorded. We have found it convenient to follow the diminution in alveolar nitrogen down to 2 %, and have used the time this takes as an index of the ventilatory efficiency. The value 2 % is used, as this is a percentage when it is still easy to measure percentage changes. Nitrogen percentage changes are difficult to measure when the value falls to 1 % because of the asymptotic fall in nitrogen percentage.

It has been possible to obtain measurements in this low nitrogen percentage range by using a nitrogen meter with two sensitivity ranges, the high sensitive range being 10 times as sensitive as the other. During the oxygen breathing we have also followed the changes in oxyhaemoglobin percentage with a Millikan oxymeter.

At the beginning the patient, attached to the apparatus by a mouthpiece, breathes room air through a three way valve and a Lovén valve. The nitrogen content of the expired air is continuously analysed. The last part of the expiration is

what we call alveolar air. By turning the three way valve we connect the patient to an oxygen cylinder from which oxygen, 99.7 %, is breathed by the help of a reducing valve and a demand regulator. Immediately before the start of the oxygen



NITROGEN METER

Fig. 1.
Nitrogen meter, schematical drawing.

breathing, the camera which records the nitrogen percentage is started. In the beginning the nitrogen meter is working on the low sensitivity range, and at a suitable moment the instrument is shifted over to the higher sensitivity. The fall in nitrogen percentage is followed on a galvanometer in parallel with the recording oscillograph. When the galvanometer is down to the value which represents 2 % nitrogen, the patient is changed on to air breathing.

In cases with prolonged nitrogen elimination and irregular breathing we take as the washing-out time the time where on three breaths in succession the nitrogen percentage of the alveolar air has been 2 % or less.

In some cases we have followed the change in oxyhaemo-

globin saturation with a Millikan oxymeter. The oxymeter is self-compensating and is adjusted at the start to about 95 %. The increase during oxygen breathing and fall during the ensuing air breathing is followed.

In the experiment the subjects are well rested, but are not in a standard or steady state. This is because our experience shows the negligible influence of a minor degree of activity on the washing-out time from the lungs.

The inhalations have usually been carried out by the help of a Barach-spray driven by compressed air. The patient has inhaled 1 ml of the solution every time. About 10 minutes are needed for this.

The antigens used for testing and inhalation have been produced by the Apoteksvarucentralen Vitrum, Stockholm. For patients with dust hypersensitivity an extract made of dust from the patient's home has been used for inhalation. These extracts have been produced at the Allergy Laboratory, Medical Clinic, Lund.

RESULTS

1) *Normal values:*

In normal patients the washing-out time varies, i.e. with the functional residual volume and the metabolic rate. The washing-out time is usually about 2.5-3.0 minutes, but it may vary between 1.5 and 4 minutes. In the same individual under normal conditions it is, however, more or less constant.

In this work, we have mainly compared the patient's washing-out time during symptom free periods with washing-out times at different degrees of asthmatically aggravated breathing. In a later work we intend to investigate more closely the relation between washing-out time on the one hand and functional residual air and ventilatory volume on the other. Further, we intend to determine the exact, normal values for different ages and sexes.

2) *Provoked asthma:*a) *Patients having quite normal pulmonary status before the provocation test:*

In these cases the washing-out time is initially quite normal, i.e. about 2-3 minutes. By inhaling allergen extracts of increasing concentrations a stage is reached at which an obviously prolonged washing-out time is obtained, and at the same time the patient feels the first asthmatic symptoms in the form of a slight oppression in the chest and the first ronchi occur. As an example a provocation test with horse epithelium from patient No. 1 is quoted (table 1).

TABLE 1

Subject	Date	Inhalation	Washing-out time min.
B. A.	20/9 1950	—	2.0
		Coca's sol.	2.0
		Horse epithel. extr. 10^{-12}	2.3
		" " " 10^{-11}	2.3
		" " " 10^{-10}	2.3
		" " " 10^{-6}	2.0
		" " " 10^{-5}	2.5
		" " " 10^{-4}	7.1

The patient was quite free from ronchi during inhalations of antigen extracts of concentrations up to 10^{-5} . During the last minutes of the inhalation of 10^{-4} , the patient felt oppressed in the chest and coughed once now and again. After having finished the inhalation a faint wheezing was heard at the end of the expiration. By auscultation some distinct ronchi also were heard. These slight symptoms remained for about $\frac{3}{4}$ hour. After this inhalation the washing-out time increased to 7.1 minutes.

Patient No. 1 was hypersensitive also to cat and dog epithelium. In both the provocation tests with cat and dog

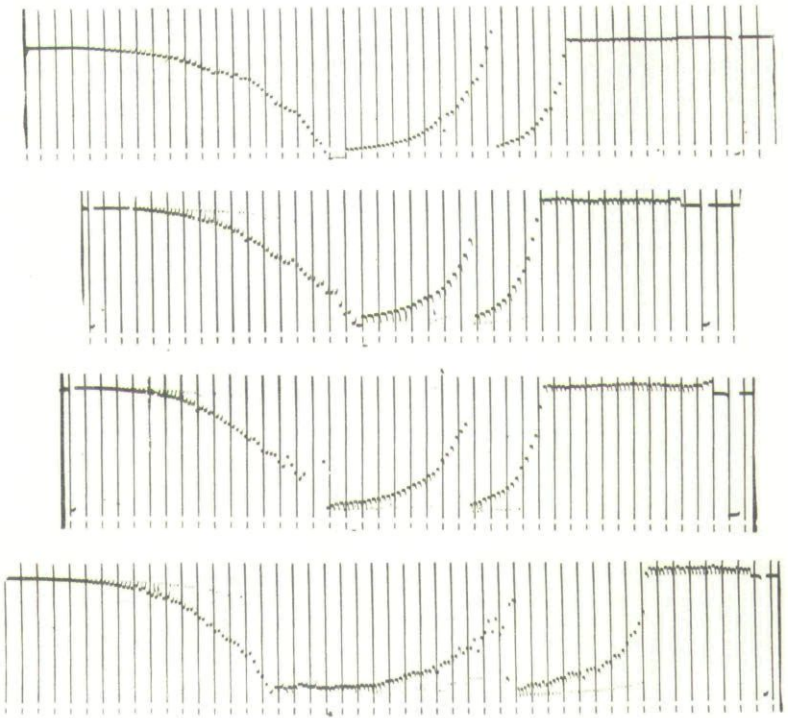


Fig. 2.

Washing-out curves from patient B. A. in provocation tests with cat epithelium.
10 seconds between time marks. To be read from right to left.

Curve 1 (upper curve): Breathing after inhalation of Coca's solution.

Curve 2: Breathing after inhalation of cat epithel. extr. 10^{-2}

Curve 3: " " " " " " 10^{-5}

Curve 4: " " " " " " 10^{-4}

epithelium an obvious prolongation of the washing-out time was obtained, and at the same time the patient exhibited slight symptoms. The patient reported an indefinite feeling of oppression in her chest. By auscultation some ronchi were heard. After 20 minutes the changes had completely disappeared.

In these provocation tests with dog and cat epithelium, where the subjective and clinical changes were the smallest

imaginable, an increase of the washing-out time to about double was obtained. Fig. 2 shows the nitrogen elimination curves from the provocation test with cat epithelium. In these provocation tests with only slight asthmatic changes no fall in the oxygen saturation of the haemoglobin appeared as measured with the Millikan oxymeter.

b) *Patients having slight asthmatic breathing before the provocation test:*

If the patient has a slight asthmatic breathing before the test, the washing-out time is prolonged. This prolonged wash-

TABLE 2

Subject	Date	Inhalation	Washing-out time min.
R. S.	7/12 1950	—	8.5
		Coca's sol.	9.9
		Mucor extract 10^{-3}	7.5
		" " 10^{-2}	10.1
		" " 10^{-1}	20
		—	21.9

ing-out time is, however, as a rule fairly constant on repeated washing-out tests, if these tests are repeated after each other on the same day, provided, of course, that the asthmatic symptoms are unchanged. It is therefore usually possible to carry out provocation tests on such patients. Since, in these cases even before the test begins, a rough breathing sound is heard on the lungs and sometimes some ronchi too, the objective registering of the washing-out time is of particular value for judging the changes appearing after the inhalation of different antigen extracts.

Table 2 shows an inhalation test on a patient who was hypersensitive to different sorts of mould. Before the beginning of the inhalations he had no subjective symptoms

except a rough breathing sound, especially at the end of the expiration. No change either subjective or objective appeared after the inhalation of Coca's solution and mucor extract to a concentration of 10^{-3} . After the inhalation of 10^{-2} no certain subjective change occurred, but on auscultation a somewhat less pure breathing sound than earlier seemed to be heard. The washing-out time did not show any obvious change. After inhalation of mucor extract 10^{-1} the patient felt a severe oppression in his chest and had an aggravated breathing work. Ronchi were heard on auscultation. The washing-out time was doubled, and was still unchanged in a second test, which was started 35 minutes after the first one was finished.

In this provocation test three inhalations (Coca's solution, mucor extract 10^{-3} and 10^{-2}) had thus been carried out without any significant change of the washing-out time. After the inhalation of mucor extract 10^{-1} obvious changes appeared in the clinical and subjective symptoms and in the washing-out time. It is not very likely that these changes were dependent upon a non-specific irritation by the solution medium (Coca's solution); in that case the changes would have appeared earlier. Fig. 3 shows the washing-out time curves after inhalations of mucor extract 10^{-3} and 10^{-1} respectively.

From the curves it is evident that the fall in nitrogen content at the beginning of the washing-out time period is unchanged, even when the washing-out time is considerably prolonged. This is likely to depend on the fact that, during this period nitrogen in the air-passages and well ventilated alveolar parts is removed just as quickly. Later on, in the case of prolonged washing-out time, the badly ventilated parts of the lungs cause a diminished fall in the nitrogen content of the air breathed out. This appears as a levelling out of the curve. We intend to interpret the different types of curves more closely in a coming work.

The washing-out time has been studied in provocation tests on about 30 patients. The conformity of the results is good.

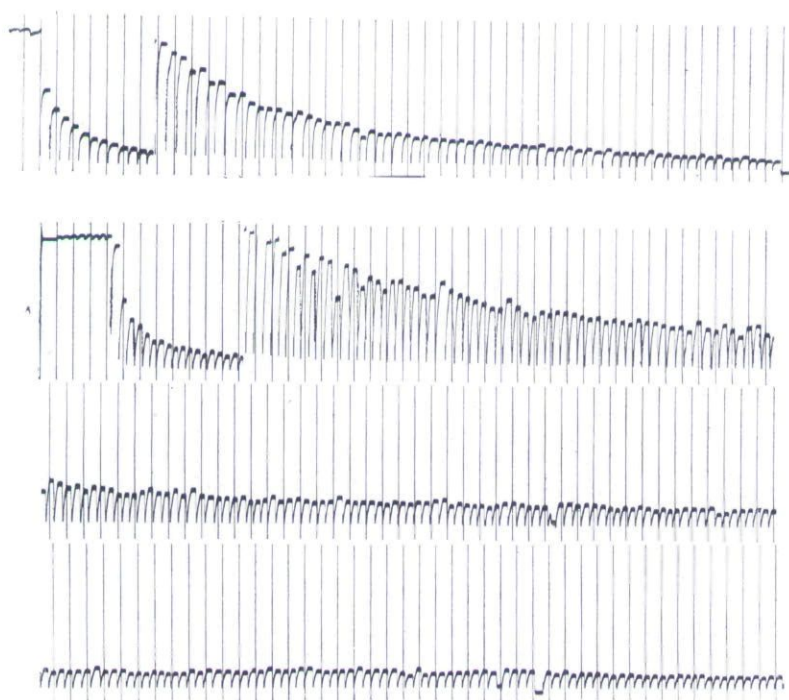


Fig. 3.

Washing-out curves from patient R. S. after inhalation of mucor extract.

To be read from left to right.

Curve 1 (upper curve): After inhalation of mucor extract 10^{-3} . Curves 2, 3, and 4 are one curve cut into three pieces representing the washing-out curve after inhalation of mucor extract 10^{-1} .

DISCUSSION

From Roelsen's investigations it is evident that the poorly ventilated lung parts in asthmatic and emphysematic patients seem to be emptied during the last part of the expiration. We wondered whether it was more desirable to register the nitrogen percentage in the last phase of the normal expiration or in the mixed total amount of every expiration. In these tests we have made a compromise.

By placing the needle valve of the nitrogen analyser on

the expiration side of a Lovén valve there is a certain mixing of the expired air. To wash out the air content of the valve with oxygen, about 150 ml oxygen is required with a running velocity of 2 liters per minute, before a stable minimum value is registered on the nitrogen analyser. The registered nitrogen concentration in the alveolar air thus represents, on normal breathing volume, mixed alveolar air from the last half or third of the alveolar air fraction. We regard this as a convenient compromise between an analysis of the last part of the alveolar air, which can be carried out by sampling through a needle valve close up to the mouth, and an analysis of mixed air from the whole expiration obtainable by, for instance, placing the needle valve distally to a mixer of a suitable size. In the first case even very small underventilated lung parts might be discovered, in the latter case rather great underventilated parts might escape discovery. Registering only the final nitrogen percentage in the last fraction of the alveolar air gives, however, no good idea of the size of the pulmonary parts with too slow a washing-out time.

From our method we get information if a rather large part of the lung can be considered underventilated. In this work we have only described changes in the washing-out time in provoked asthmatic cases. The method is, however, also very suitable for studying the course of the disease or to follow the result of treatment.

SUMMARY

A quick method is described where the ventilatory changes in even the mildest forms of provoked asthma can be objectively registered with a minimum of active co-operation by the patient. As a criterion of the ventilatory changes, that time has been used which is required for the patient to wash out the nitrogen from the lungs on resting breathing after the transition from air to oxygen breathing. The nitrogen washing out is followed by continuously registering the nitrogen content of the alveolar air by the help of a so-called nitrogen

analyser. As well as for provocation tests the method has been used by the authors for studying the course of the disease in asthmatic subjects.

Patient No. 1.

B. A., born 1936, schoolgirl. Treated at the Medical Clinic 4/9-7/10 1950 and 15/6-23/6 1951. Diagnosis: Asthma bronchiale.

No asthma or other certain allergic diseases known in her family.

Since 6 years' age the patient has periodically had asthma varying from one day to one week. The attacks are provoked from contact with dogs, horses, and cats. The patient has also developed symptoms from dust. She has tried riding but had to give it up, as she got asthma as soon as she came into contact with horses. Patting a dog or a cat is enough for the asthma to appear. Her symptoms have increased during the last few years.

On arrival the patient had some ronchi. She was quite unaffected. Blood pressure 125/80. Sedimentation rate 14/40. Haemoglobin 90 %. R.B.C. 4.8 mill. W.B.C. 6500.

Differential count 5/9 1950: N 55, E 11, B—, L 25, M 9.

Sputum culture 8/9 1950: Moderate growth of β -streptococci.

Pulmonary X-ray 6/9 1950: Slight emphysema. Otherwise nothing pathological within hili and pulmonary fields.

X-ray of the nasal sinusoids 6/9 1950: Normal air passage.

Intracutaneous tests (animal epithelium excluded):

concentrated dust: ++

dust, wheat: +

Intracutaneous titrations 19-26/9 1950 (before the hyposensitization):

Horse epithelium 10^{-10} : +

Dog „ 10^{-4} : +

Cat „ 10^{-4} : +

Cow „ 10^{-3} : +

Provocation tests:

20/ 9 1950 horse epithelium up to 10^{-4} : positive

27/ 9 1950 dog „ „ 10^{-6} : positive

3/10 1950 cat „ „ 10^{-4} : positive

Before the provocation tests the vital capacity was 3.5 lit.

The patient was hyposensitized with horse, dog, and cat epithelium extract. At the last examination in August 1951, the patient was considerably improved. Hyposensitization with dust extract postponed for the present.

Patient No. 2.

R. S., born 1919, mechanic. Treated at the Medical Clinic 15/11-21/12 1950. Diagnosis: Asthma bronchiale.

One 4 years old child had asthmatic symptoms at the age of 2 years.

At 9 years' age the patient had pneumonia. 10-13 years old milder recurrent bronchitis. At the age of 25 bronchitis again.

In connection with a severe bronchitis at 25 years of age the patient got asthma. Later periodically asthmatic symptoms. Sometimes also sinusitis. Severe symptoms with often recurrent asthma 2 months before his admission at the Medical Clinic.

The patient does not know any special cause of his asthma.

Earlier not examined for allergy.

On his arrival the patient had asthmatic breathing with a lot of ronchi. Blood pressure 130/85, sedimentation rate 7/22, haemoglobin 98 %, R.B.C. 5.2 mill.

Differential count:

16/11	N 49.5	E 11	B 0.5	L 35	M 4	W.B.C. 7600
11/12	43.0	31	—	25	1	14700
15/12	41.0	33	—	24	2	14600

Quantitative counting of eosinophiles 11/12:

at 10,00 5570 per mm³

at 12,45 5650 per mm³

at 15,00 5250 per mm³

Sputum culture: Predominant growth of α -streptococci.

Pulmonary X-ray 25/11 1950: The middle lobe is occupied by a parenchymal infiltration which looks like an unspecific process. The lobe limits are marked as a sign of a pleural reaction. It is possible that the process is dependent on an infiltration with eosinophilia.

X-ray of the sinusoids of the nose: The frontal cavities are small. The other sinusoids are rather large. In the right maxillary cavity there is a 5 mm thick mucous membrane swelling.

X-ray 13/6 1951: The parenchymal process within the middle lobe has almost disappeared. No new changes in the lungs.

Fungus culture from the patient's home 20/2 1951 (plates were exposed in the patient's home): Growth of penicillium and hormodendrum.

Intracutaneous tests:

mucor, thimothy: ++

botrytis, hormodendrum, penicillium, horse epithelium: +

Intracutaneous titrations:

Mucor	10^{-5} : +
Horse epithelium	10^{-4} : +
Thimothy	10^{-4} : +
Hormodendrum	10^{-4} : +
Botrytis	10^{-3} : +
Penicillium	10^{-3} : +

Provocation tests:

27/11 1950	horse epithelium	up to 10^{-2} :	negative
28/11	thimothy	" "	10^{-1} : negative
29/11	mucor	" "	10^{-2} : positive
1/12	penicillium	" "	10^{-1} : positive
4/12	botrytis	" "	10^{-1} : negative
7/12	mucor	" "	10^{-1} : positive

Before the provocation tests the vital capacity was 4.0-4.2 lit.

The patient was hyposensitized to mixed extract of mould 11-15/12 1950. When leaving the clinic the patient was almost symptom free and at the last examination in August 1951 he was still almost symptom free.

REFERENCES

1. *Arner, B.*: Nord. Med., 1949: 42: 1257.
2. *Arner, B., Wiholm, S., and Öhnell, L.*: Acta allergol., 1950: 3: 156.
3. *Boothby, W. M., Lundin, G., and Helmholtz, A. F. Jr.*: Gaseous nitrogen elimination test to determine pulmonary efficiency. Proc. Soc. Exper. Biol. and Med., 1948: 67: 558.
4. *Colldahl, H.*: Kungl. Fysiograf. Sällskapets i Lund Förhandlingar, 1941: 11: 19 and 1942: 12: 19.
5. — Gaswechsel und Gewebsatmung beim experimentellen Asthma des Meerschweinchens. Acta Physiol. Scand., 1943: 6: Suppl. XVIII.
6. — Acta Med. Scand., 1947: 128: 551.
7. *Cournand, A., et al.*: Studies on intrapulmonary mixture of gases. IV. Significance of pulmonary emptying rate and simplified open circuit measurements of residual air. J. Clin. Investigation, 1941: 20: 681.
8. *Fowler, W. S.*: Lung function studies: II. Respiratory dead space. Am. J. Physiol., 1948: 154: 405.
9. *Meakins, J.*: J. Path. and Bact., 1921: 24: 79.
10. *Roelsen, E.*: Diss. Copenhagen 1937 (Arnold Busch Forlag).

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