AN EPIDEMIOLOGICAL CONTRIBUTION TO THE KNOWLEDGE OF THE RESPIRATORY DISEASES.

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(With 7 Graphs.)

CONTENTS.

I. Introduction.

In the following pages the results will be described of an inquiry into the respiratory diseases in Holland between September 1925 and June 1926.

Among the causes of such diseases as coryza, bronchitis, pneumonia—tuberculosis will be excluded—we clearly distinguish two important ones. In the first place we recognise their infectious character, even if the specific causal organisms cannot be identified. In the second place we recognise the influence of the cold season. Opinions differ a good deal as to the relative importance of these factors: microbe and temperature. For one person the microbe is the main thing, the cooling influence of the season of secondary importance; for another the converse may be true.

Needless to say it is important to examine the problems more closely. A glance at the monthly curve of mortality in our regions shows that the yearly recurring winter-peak represents an important hygienic factor.

For many people the idea of *infection*—in the sense of morbid change as a result of invasion by and growth of micro-organisms—is inseparably connected with the idea of *contagion*. And yet a distinction should be made here. The time is past, when exclusively the obligatory parasitic

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organisms, transferred from one victim to another, could be considered the sole cause of disease. There is a growing interest in usually harmless bacteria and viruses that live as *commensals* generally with healthy hosts on the surface of the skin and the mucous membranes, and only cause disease under special circumstances.

I had an earlier opportunity of calling attention to what I called "the borderland between commensalism and parasitism[1]." Bacteriological experiences in the tropics[2] first roused my interest in the commensals inclined to parasitism, among which are to be counted besides *Staphylococcus*, *Streptococcus*, *Pneumococcus*, *B. coli*, *B. paratyphosus* B., *B. proteus*, *B. pseudotuberculosis rodentium*, *Pasteurella*, *Meningococcus* and *B. diphtheriae*. Studying these from a bacteriological point of view we come to the question of adaptation. I pointed out the misapprehension of placing all the symptoms of variability in bacteria within the frame of genetics and with several collaborators I have examined bacteriological variability as an individual function[3].

Then a clear light was thrown on the fact that with commensal organisms—in contrast with strict parasites—the function of variability in the sense of power of adaptability is highly developed[4].

We know now how the study of the invisible viruses also brings out facts belonging to the borderland between commensalism and parasitism. The virus of herpes—which obtains a hold with diseases as pneumonia and meningococcose—is one of the most striking examples. Encephalitis postvaccinalis too is thus most simply explained. And in the comparative pathology of infective diseases commensal protozoa are known to play a part.

The theory of contagion by means of commensal microbes has even more clearly than that of contagion by means of strict parasites a non-bacteriological side. Its definition implies that the physiological defences of the host must be overthrown before his commensal will be able to adapt itself as a parasite. It is true though, that with every infection one has to take favouring circumstances into consideration. But the further one goes in the direction of commensal infections, the more preponderating does the factor of circumstances appear. And finally, arrived at the domain of commensals, one has to acknowledge that there, *from an aetiological point of view, the favouring circumstance is of primary importance.*

The circumstances that weaken the physiological defences against the intrusion of the commensals are of all kinds. I have pointed this out before,

[1] (1917) Het grensgebied van commensalisme en parasitisme. *Ned. Tijdschr. v. Geneesk.* **1**, 994.

[2] (1909) Jaarverslag van het Pathologisch Laboratorium te Medan over 1908. *Geneesk. Tijdschr. v. Ned. Indië*, 1909; (1910) Over het voorkomen en de beteekenis van den Paratyphus B. bacil, *Ned. Tijdschr. voor Geneesk.* **2**, 1456; (1910) De lijkopeningen in het hospitaal der Deli-Maatschappij te Medan, *Ibid.* **2**, 2150 enz.

[3] (1922) Aenderungen bei Bakterien, aufgefasst als adaptive und regressive Aenderungen während der individuellen Existenz. *Centralbl. f. Bakteriol.* 1. Abt., Orig. **88**, 257.

[4] (1919) Variabilität und Parasitismus. *Centralbl. f. Bakteriol.* 1. Abt., Orig. **83**, 401; (1919) *Ned. Tijdschr. v. Geneesk.* **2**, 784 enz.

when in the aetiology of commensal contagion I put decrease of resistance on the part of the host before "change of virulence" and "massed attack" of the commensals. I mentioned by name "the not-infrequent break through of intestinal commensals into the 'milieu intérieur' with consequent disease of the abdominal organs, the commensals obtaining a hold when the normal cohesion and the normal nutrition of the tissues is impaired (infection of wounds, puerperal fever), secondary infections, *the significance of catching cold* and a poor state of nutrition *in the genesis of spontaneous infections*[1]." With this quotation—in which I italicise a few words—I think that the line of thought which led me to epidemiological research upon respiratory diseases has been sufficiently elucidated. We have to acknowledge that parasitical microbiology has failed aetiologically in this field. So let us accept another working hypothesis and try to test the notions of "colds" and "catching cold" by ascertaining in how far *disturbance of the regulation of the heat of the body* may be considered the primary cause of commensal infection.

1. *Experimental data.*

It is easy to understand that several pathologists have tried to ascertain experimentally the significance of refrigeration for the effecting of infection. Everyone remembers Pasteur's experiment, how he succeeded in breaking the natural resistance of a fowl against *B. anthracis* by artificial lowering of its temperature. Neither this classical experiment nor the numerous experiments made on animals by others throw much light upon the aetiology of respiratory diseases of man.

Experiments on human beings are of more importance. It is certainly worth noting when one reads of persons who, under the conditions of certain physiological experiments at a low temperature, regularly caught a cold. But we have also to give attention to Chodounsky with his protocols, which, according to him, prove that cooling down is of no significance as a cause of illness. Chodounsky was able to take very hot or very cold baths and then expose himself to an icy draught without getting ill. But he was spared no criticism. Notwithstanding his advanced years—he made these experiments at the age of 57 and 63—Chodounsky was strong and hardened by a daily application of cold water. Indeed we know from his protocols that his thermoregulating system functioned excellently. As a matter of fact these cold stimuli, with which he did not succeed in catching cold, did not lower his temperature but, as in the classical experiments, made it rise.

The result of Chodounsky's experiments makes us reflect that besides individual practice individual tendency and temporal disposition also take away the value from experiments made by one person.

So it would be more correct to experiment with a great number of test-persons; but an insurmountable objection would be the danger of pneumonia.

[1] (1917) *Ned. Tijdschr. v. Geneesk.* **1**, 995.

2. *Epidemiological data.*

The desired data relating to a large number of persons can also be obtained in another way.

Schade[1] made a good choice by studying the official *monthly* statistics of the German army in time of peace and showed that respiratory diseases rise and fall at the same time as diseases directly dependent on the influence of cold (affections of the skin in consequence of freezing). Even statistics obtained during the war under special circumstances show this parallelism. Greenwood[2], Young[3] and others have studied the influence of weather conditions on the mortality of respiratory diseases and have found temperature to be the meteorological factor most closely correlated with the rate of mortality.

A direct epidemiological research into the minor respiratory diseases has been conducted by the Public Health Service of the United States. This service had the co-operation of 11,000 students as individual informants and of 775 families, the heads of which reported on 2500 persons. This research, started in October 1923, was continued with the group of students for 18 months and with the families for 2 years. Two reports of the results have been made already by Townsend and Sydenstricker[4].

The principal result of this research is the synchronous occurrence of these diseases in the various parts of North America. The P.H. Service received its reports from San Francisco as well as from Washington, New Orleans and Chicago, and notwithstanding this the lines, picturing the course of the local epidemics, show broadly the character of synchronism. A sharp increase to about 30 cases of illness per 100 informants in October is followed everywhere by a gradual decrease to about 14 per cent. by the end of December. At the beginning of January a very acute rise to about 25 per cent. is then seen everywhere, followed by a gradual decline towards spring.

One and the same conclusion may be drawn from the comparison between the cases of the students and those of the families, which, for the year 1924, have been completely worked out in the second report. Between the two groups of informants there is no definite relation; only that they have both been composed of persons from all sorts of places in North America. Yet the lines of the student-colds and of the family-colds show remarkably parallel courses.

Both the results of the German and of the American research thus lend a strong support to the idea that a disturbance of the thermo-regulation may count as a primary cause of disease.

It would be difficult to find an easier explanation for the parallelism of "disease through cold" with "colds" (Schade) and the synchronism of "colds"-epidemics in widely distant places (Townsend and Sydenstricker).

[1] *Handb. d. norm. u. path. Physiol.* (Bethe C.S.), **17**, 426.
[2] Greenwood, M., *Min. of Health Reports*, No. 4.
[3] Young, M. (1924), *J. Hygiene*, **23**, 151.
[4] (24. x. 1924 + 14. i. 1927) *Public Health Reports.*

II. AN INQUIRY IN HOLLAND.

The reading of the first report of the Americans was for me an inducement to organise a Dutch research. Because of the considerations mentioned in the introduction to this paper, I had intended to obtain morbidity statistics of the pneumonias through the co-operation of physicians, but circumstances made me give up the plan. Struck by the results of the American research I have returned to the idea. Not only did I want to test this result because of its important tendency, but I also hoped for the possibility of thus bringing to light in a roundabout way further particulars as to the epidemiology of "influenza" and "pneumonia." I also expected to be able to penetrate deeper into the question of "the contagiousness of colds"—already rendered less probable through Schade's parallelism and the American synchronism. For the sake of accuracy I made a not unimportant change in the American technics on two points. In the first place I obtained as informants not students but almost exclusively heads of families (doctors, dental surgeons, masters, chemists, officials and other intellectuals); secondly I did not send the questionnaires twice a month, but once a week. I shall revert to the significance of these alterations.

1. *Organisation of the Dutch Inquiry.*

The research lasted 37 weeks, from September 20th, 1925 (first week from September 20th–26th) till June 5th, 1926 (37th week from May 30th–June 5th). The number of participators at the beginning amounted to about 7500; this number decreased a little in the course of the research, through removal, loss of interest or other circumstances. The data worked up relate to 6933 persons, viz. 6598 persons divided over 1523 families and 335 persons divided into a few groups. The head of the family had promised his willingness to co-operate by signing a slip, on which he gave the family name, address, initials, sex and age of the members of his family. These data were hectographed on 35 (later on increased to 37) lists of questions, 35 envelopes too were hectographed with the family name and address. The lists and envelopes meant for one family were numbered 1–35 and then all were sorted according to the weeks. So by September 25th we had in readiness 35 parcels, each of about 1600 envelopes (with the lists of questions and reply envelopes enclosed) of which parcels one was sent every week. They were always dispatched on Friday afternoon, so that the collaborators always had the list of questions for the past week in their possession on Saturday. In my opinion this administrative regularity has been highly favourable to the regular filling-up and returning of the lists.

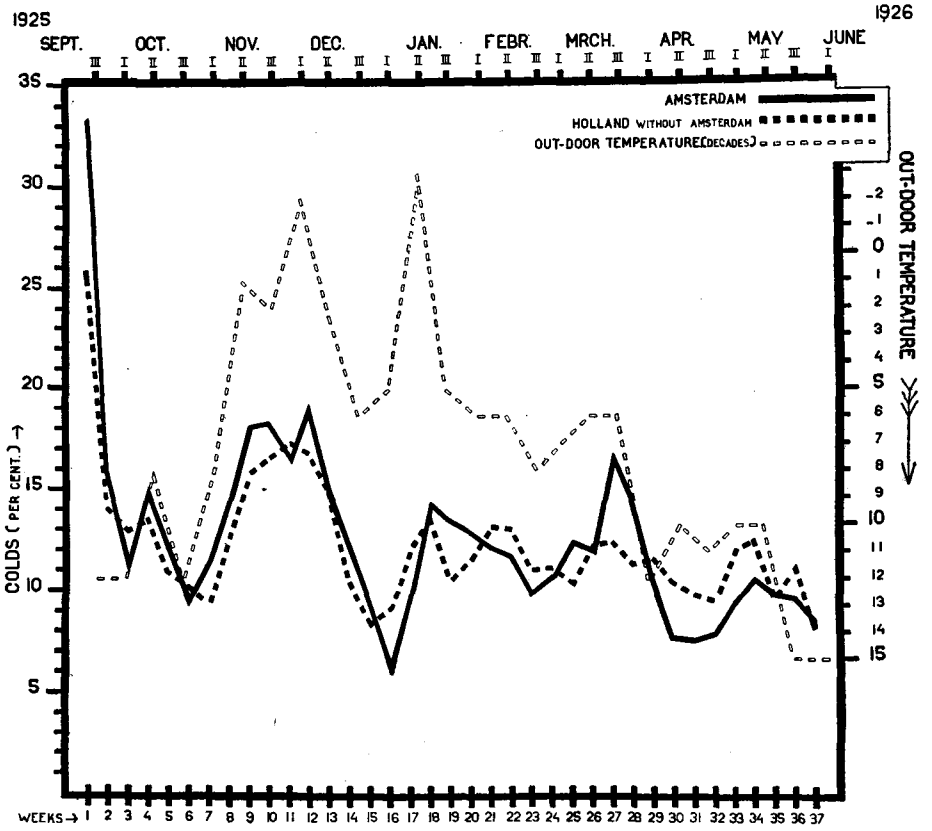
The weekly list of questions was composed very simply. For each member of the family a blank space was left to be filled in with *no* (no new cold) or *yes* (caught cold). In case of cold there was also stated: nose cold, sore throat (angina), hoarseness (laryngitis), cold with cough (bronchitis) or slight influenza. This diagnostical distinction was drawn up in consultation with Prof. Ruitinga. No inquiry was made about serious diseases.

The answers received were divided into seven geographical groups as follows:

I. Amsterdam (1159 informants).
II. Northern Noord-Holland (581).
III. Rotterdam, The Hague, Delft, Leiden, Dordrecht, etc. (1667).
IV. Utrecht and Het Gooi (826).
V. Zeeland (745).
VI. Limburg and Noord-Brabant (864).
VII. Groningen, Friesland, Drenthe, Overijsel and Gelderland (1091).

2. *General course of the reported colds.* (See Graph III.)

The reports upon the first week (September 20th–26th) immediately gave a high percentage, 27 per cent.; as was to be expected, there being a striking number of people with a cold when the first lists of questions were dispatched. 1900 of our 7000 collaborators reported a cold. The following weeks the figures dropped very quickly; the 7th week gave only 9 per cent. Then a very quick



Graph I. The percentages of colds of Amsterdam (1159 informants) and the remaining Netherlands (5774 informants) for 37 weeks, compared with the average temperatures of the air in the Netherlands in the decades of the same period.

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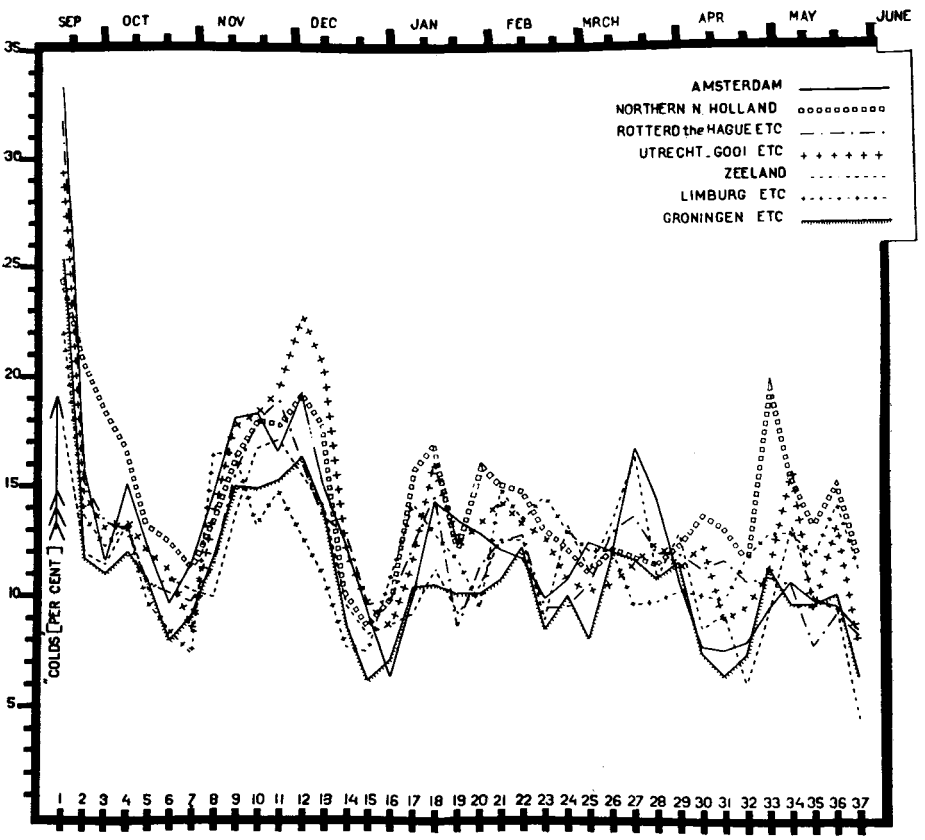
rise follows during the 8th and the 9th week, which continues during the 10th, 11th and 12th week. During the 15th and 16th week very low figures were reached again. Then again a rapid rise follows; the third peak is less high again than the second and the first; then the line oscillates with peaks in the 21st–22nd week and in the 27th week. In April there is a tendency to drop, which is interrupted in May. The inquiry ends with the new drop in June. In order to examine the synchronism I compared in the first place the group of Amsterdam with "the rest of the Netherlands."



Graph II. The percentages of colds of seven geographic groups. Amsterdam (1159 informants), Northern Noord-Holland (581), Rotterdam, the Hague, Delft, Leiden, Dordrecht, etc. (1667), Utrecht and Gooi (826), Zeeland (745), Limburg and Noord-Brabant (864), Groningen and the other provinces (1091).

In Graph I the result is to be found, which is eloquent. We have to do here with weekly-lines, relatively short periods; and yet the parallelism of the lines is fairly distinct. In other words, the informants from Amsterdam and from the other parts of the Netherlands reported approximately the same percentage of colds at the same time.

One can go further and construct a line, as has been done in Graph II, for

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each of the seven geographic groups. Even then it appears that the character of the general line is to be found in all the group-lines.

All the seven group-lines begin the first week with a high percentage; all the group-lines drop quickly in the following weeks. Together they rise in the 8th and 9th week, remain high in the 10th, 11th and 12th week (in which latter week Amsterdam, Northern Noord-Holland, Utrecht and Groningen show an extra peak) to reach the lowest points in the 15th and 16th week together again. The 3rd peak is formed by six out of the seven lines in the 18th week and remains for all of them beneath the summit of the 2nd peak, just as for all of them the 2nd peak lays beneath the summit of the first. Then a period follows of not very big divergences, throughout which the common resemblance persists. The geographical percentages remain in each other's neighbourhood, just as the falls and rises, notwithstanding the smallness of the separate samples. *So the synchronous character of the Dutch epidemics of colds, especially during the first half of the period, when the oscillations were greatest, is very sharply outlined.*

3. *Changes in the temperature of the air during the research.*

The joint oscillations of the "colds"-lines raises the question, whether similar oscillations are to be found in the weather conditions of the same period.

As our objective is the cooling power of the outdoor air we have not only to think of the temperature but also of the motion of the air and its state of moisture. With an eye to the habits of our informants, however, we have to take special account of the temperature indoors. Now, with the airy Dutch way of building, it is true that the latter is not independent of the motion of the outdoor air, but as a part of the cooling factor indoors we can hardly consider that motion. So when examining the weather conditions during the period of the inquiry I provisionally restricted myself to the temperature of the air. The clear results that were at once put into my hand when I drew a diagram of the easily attainable decade-temperatures is one of the causes of this provisional restriction.

In Graph I one finds represented the temperature of the air at the same time with the two "colds"-lines of Amsterdam and the remaining Netherlands. The line has been obtained from the average temperatures of the Netherlands for periods of 10 days[1]. The temperatures above zero have been carried below the zero-line and the reverse. When the temperature falls the line rises.

Thus the peaks the line shows are peaks of cold. (N.B.) The parallelism of "colds"-lines and temperature-line—after September—is evident. First we are struck by the small peak of "colds" in the 4th week, which coincides with the small peak of cold of the 2nd October decade (October II). Then we see the strong cooling in November II and III and December I, the two tops of November II and December I have been levelled in the general "colds"-line. In

[1] *K. Ned. Meteorolog. Instituut, Maandoverzicht van de weersgesteldheid in Nederland.*

Graphs I and II they are clearly present for Amsterdam, Northern Noord-Holland, Utrecht and Groningen. The drop of the "colds"-lines in the 15th and 16th week corresponds to a valley of warmth (December III and January I); the "colds"-peak of the 18th week to the peak of cold of January II; above the next irregular "colds"-lines with a tendency towards dropping we again find a temperature-line with corresponding irregularities. More especially I draw attention to the peak of cold of March II and III and the "colds"-peak of the 27th week. The cold month of May too (May I and II), which induced us to prolong the inquiry by two weeks, is very clearly represented in the "colds"-lines.

Separate consideration is due to the fact that the high September 20th–26th peak with which all the seven "colds"-lines open does not answer to a peak of cold of the decade-line. On closer inspection the first September decade appears to have had an average temperature of 12° C.; September II rose to 14° C., September III descended to 12° C. So a *warm* second decade is apparently followed by severe "colds."

The solution is, as I suspect, in the *cold nights*, that characterised the week of September 11th–16th and which cannot be detected in the average of decade II because of the high day temperatures.

Then arose the great number of colds, of which we noted many in the first week of our inquiry. Many who took part in the research remember this.

In Table I is given the maxima and minima of those September days (De Bilt)[1]. One sees how the temperature mounted to 18 and 19° C. in the daytime and cooled down to 2·3° C. at night.

Table I.

Date	Max.	Min.	Date	Max.	Min.	Date	Max.	Min.
1	19·0	14·8	11	12·1	**2·4**	21	19·1	11·8
2	17·7	11·6	12	17·6	**7·5**	22	16·9	7·5
3	17·8	12·6	13	18·0	**5·8**	23	16·9	9·9
4	15·9	8·1	14	18·2	**2·3**	24	16·1	6·8
5	11·8	7·1	15	18·4	**2·7**	25	16·7	5·7
6	13·3	8·4	16	18·0	**5·7**	26	15·6	6·9
7	15·9	9·5	17	19·4	**10·5**	27	14·4	8·8
8	16·6	10·9	18	16·6	**9·8**	28	15·8	7·3
9	15·0	10·7	19	17·8	**9·0**	29	16·4	2·8
10	14·3	9·3	20	18·1	**10·9**	30	16·9	6·6

Maximum and minimum temperatures (Centigrade) of September 1925 (De Bilt). A group in the second decade has been printed in heavy type; it represents the series of cold nights mentioned in the text. The land averages of the three decades are respectively 12, 14 and 12° C.

Summarising the data of the previous pages we are able to state that *there appears to be a connection in time between the colds-epidemics in our country and that their joint occurrence runs hand in hand with falls in the temperature of the air.*

[1] *K. Ned. Meteorol. Instituut, Yearbook* 1925, p. 62.

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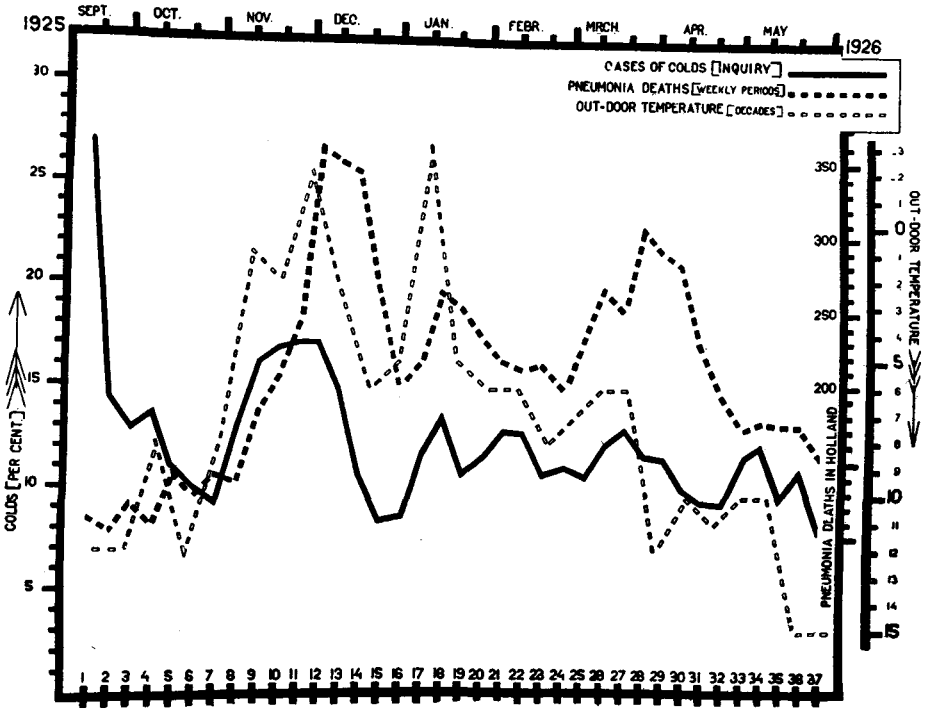
4. *Mortality from pneumonia in the Netherlands during the period of the colds inquiry.*

As I remarked before there is reason to try to include also the mortality from respiratory diseases in our inquiry. For in the Netherlands there is seldom or never any question of contagion in cases of typical genuine pneumonia; and also the cases of illness that, on ending fatally, appear in the statistics of the causes of death as acute and chronic bronchitis present themselves as spontaneous infections furthered by the cold season.



Graph III. The percentages of "colds" of the 6933 informants for 37 weeks, compared with the joint mortality from bronchitis, pneumonia, etc. (causes of death 20, 21, 22 and 23 of the international list) during the same weeks in the Netherlands and with the temperature of the air.

The reports—published every month by the Central Office for Statistics—were not sufficiently detailed. For a comparison I wanted the *weekly* numbers for the 37 weeks of the inquiry. Officials of the above-mentioned office—with the kind permission of Prof. Methorst—worked up these figures for me. In this way I obtained data of the mortality from acute bronchitis, chronic bronchitis, lobar pneumonia and other respiratory diseases (with the exception of tuberculosis). What I call mortality from pneumonia or the pneumonia-line in the following pages and graphs relates to the *joint* mortality from these four causes of death in absolute numbers.

If we compare in Graph III the course of the Dutch pneumonia-line with

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that of the Dutch "colds"-line for the 37 weeks from September 20th, 1925 to June 4th, 1926 we are struck by the fact that:

1. The pneumonia-line in September does *not* begin with a peak.
2. The pneumonia-line in November, December and January closely follows the "colds"-line.
3. There exists a parallelism between the lines also for February, March, April and May.
4. The March–April peak of the pneumonia-line is much more striking than the corresponding elevation of the "colds"-line.
5. We notice that the pneumonia-line rises and falls a little later than the "colds"-line. This does not tell against a correlation, as the latter is a measure of incidence, the former one of mortality.
6. The remark under 5 also applies to the relation in time between the pneumonia-line and the temperature-line (also depicted in Graph III); the similarity between the oscillations of both is plain.

On closer inspection of some of the points mentioned it appears that the absence of a September maximum from the pneumonia graph offers a very characteristic difference from the "colds"-line.

I am inclined to take this as evidence of the aetiological independence of the common cold compared with the other so-called refrigeration diseases (bronchitis acuta, chronica and pneumonia).

More difficult is the explanation of the high March–April peak of the pneumonia-line. There are cold-peaks and "colds"-peaks about that time, but the pneumonia peak far exceeds them.

In order to obtain a closer insight I extended my data in two ways.

5. *Mortality from old age in the Netherlands during the period of the inquiry into colds.*

In the first place I inquired into the fact—again with data extracted for me in the Central Office for Statistics—how the mortality from *old age* in the Netherlands had varied during the period in question. As a matter of fact a good many old people die in winter.

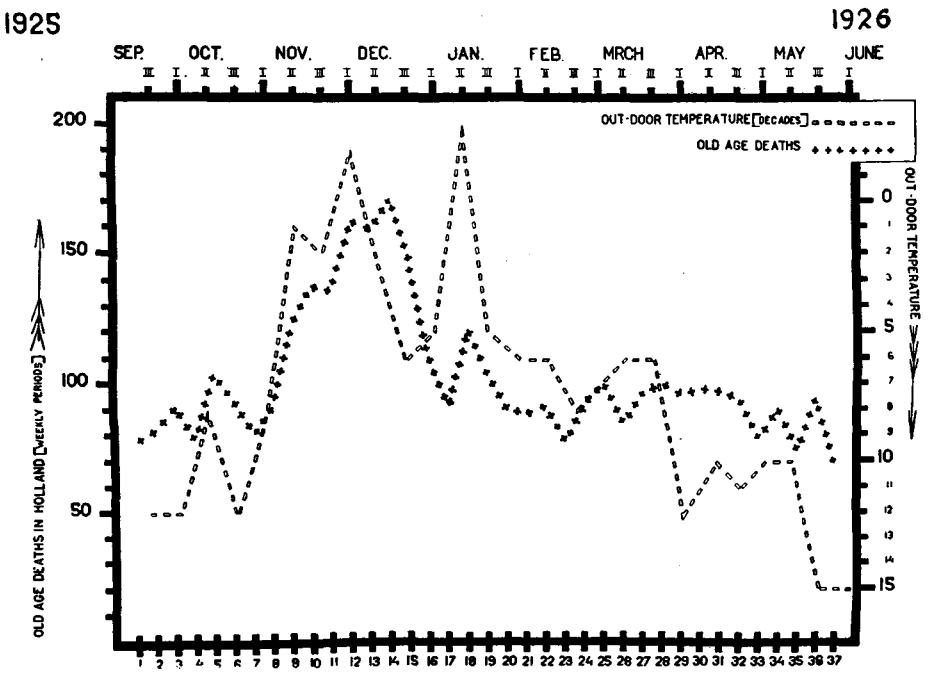
In a separate graph (IV) the parallelism of temperature and old-age mortality is depicted. *The old-age line has no March–April peak like the pneumonia-line* (Graph V).

The second thing to be done now was to find out whether the March–April mortality from pneumonia was to be put down to a specific cause.

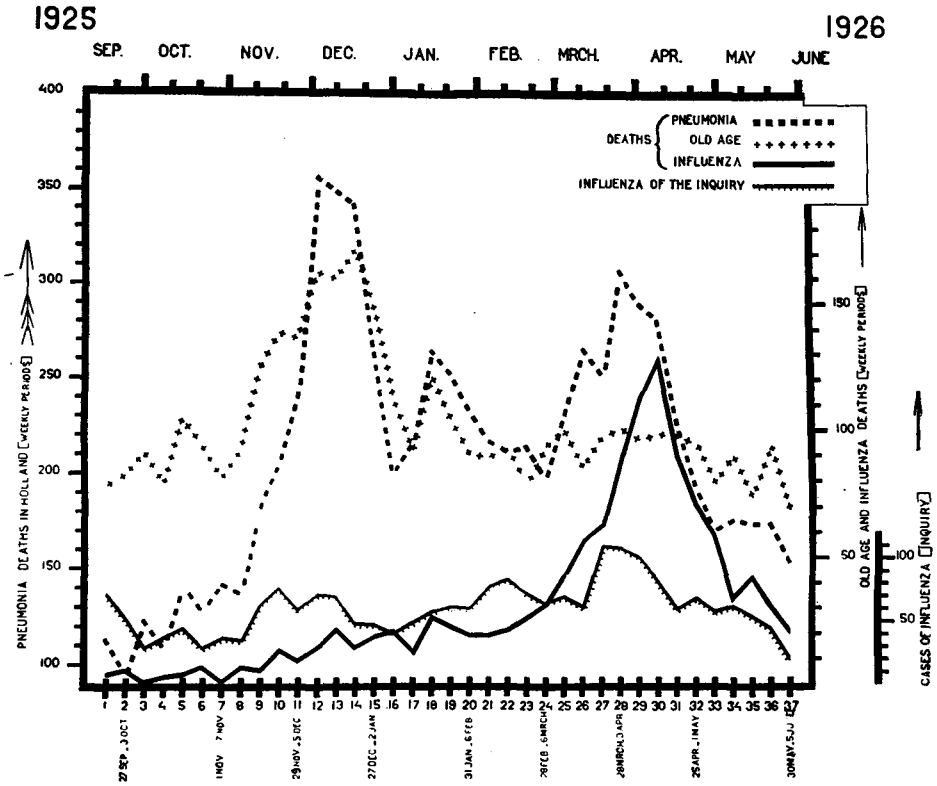
It stands to reason that our first thought is of influenza.

6. *Mortality from influenza in the Netherlands during the period of the colds inquiry.*

With regard to influenza I had available two kinds of data: the cases mentioned as "slight influenza" in our inquiry and the deaths reported as



Graph IV. Mortality from "old age" for 37 weeks in the Netherlands, compared to the temperature of the air.



Graph V. Mortality from old-age bronchitis, pneumonia, etc. and from influenza in the Netherlands, for 37 weeks of the "colds" inquiry compared with the cases of influenza of the inquiry.

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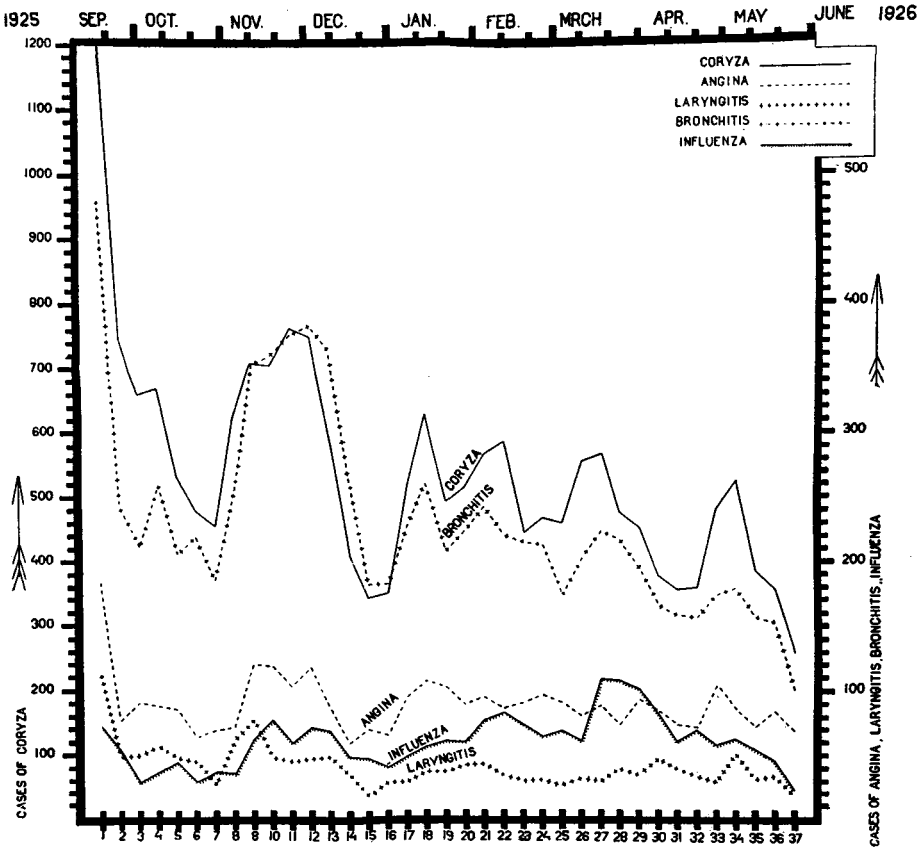
being the result of influenza in the Netherlands. The latter data were again worked up for me by officials of the Central Office for Statistics.

As I had occasion to mention I begged the collaborators in the inquiry to report the nature of their "cold" and to distinguish between coryza, angina, laryngitis, bronchitis and "influenza." We have grouped the figures thus obtained according to the weeks and now get the result that has been shown in Graph VI.



Graph VI. The joint figures of the various forms of "colds," obtained by the colds inquiry for 37 weeks. Compared with the lines of the other forms the line for coryza is on a half-scale.

Coryza preponderates and has been put on a half-scale in the graph compared to the other forms. We see that bronchitis runs absolutely parallel to coryza and that angina and laryngitis too show the same character in their course notwithstanding the smallness of the figures.

Thus this whole group of indispositions is most easily understood in its connection with the cooling-factor.

The influenza of the inquiry behaves differently (Graph VI). At first this follows the colds, *then it takes its own course.*

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While the four other forms have a tendency to drop towards spring, influenza increases gradually and has its *highest peak* in the 27th, 28th and 29th week; only then its decline begins. Though we need not attach much importance to the diagnosis in the first period, *there can be little doubt as to the reality of its own course in the second period.* This doubt is entirely eliminated when we now consider the mortality from influenza in the Netherlands. It is to be found in Graph V together with the old-age line, the pneumonia-line and the influenza-line of the inquiry.

In the first place we remark that the tendency of the inquiry-influenza[1] to gradually increase during the second period of the research appears still more clearly in the mortality from influenza. This is not to be wondered at, as we suspected already that the inquiry-influenza of the first period in the main was nothing but ordinary "cold." A second indication of its identity is that the peak of the *mortality* from influenza lies later than the peak of the cases of *disease* indicated.

I suggest that the following analysis of the mortality from pneumonia is reasonable. During the first period of the research there have been two important causes of pneumonia. In the first period the mortality from pneumonia was principally dependent on disturbed thermo-regulation.

The pneumonia mortality in the second period has not been on the whole directly dependent on a strong refrigeration. It originated during a period of cooling, when colds were to be noticed, but no increased "old-age mortality." The pneumonia mortality of the second period however coincided in its increase and in its culminating point of increase with "influenza mortality." Both mortalities concurred with the influenza cases of our inquiry.

The epidemiological research thus enables us for the third time to make a better aetiological classification. First we distinguished the pneumonia from "colds" then the influenza from "colds" and at last we distinguished between refrigeration pneumonia and influenza pneumonia.

On account of the above-mentioned facts influenza has been given a separate place from that of diseases resultant on catching cold or commensal infections as cold, pneumonia and "old-age mortality." But this does not mean that cooling has not a share in the aetiology of influenza and more specially in the aetiology of "influenza mortality."

As appears from general experience we have to do here with a disease in which "contagion" has a hand; and, at least for our country, an influence of the season is generally unmistakable. With regard to the influenza of our inquiry there is no difference. The line of the inquiry indicates an increase in early spring, which is to be attributed to contagion. Yet disease and mortality concurred with the rather cold decades of March, which, though not cold enough to raise old-age mortality distinctively, were yet marked clearly enough by the coryza-line as a period of catching cold, though part of that coryza will have been founded on influenza. So our data too speak in favour

[1] Meaning cases of influenza reported to us by our informants during the period of the inquiry.

of the idea, that influenza is not a commensal infection that occurs through catching cold, but a parasitic infection, which in a period of catching cold easily gets entangled with pneumonia.

Closing remarks.

The results of the Dutch inquiry summarised in this section may be most clearly explained by accepting the theory that an important part of the respiratory diseases is based on infection by commensal microbes, which occurs after the physiologic defences have been weakened by a disturbance of thermo-regulation.

The question whether in this case contagion is indeed excluded will be treated on the strength of a further compilation of the data at my disposal in section III.

III. THE CONTAGIOUSNESS OF COLDS.

In the previous section, in which the results of the Dutch research have been described, the theory that an important part of the respiratory diseases is based on commensal infection is found workable.

But this does not yet settle the question of contagion. It is shown by more than one experience that commensal infection may acquire a parasitic character. We know circumstances under which microbes, usually commensal, increase their forces of attack to such a degree, that they are able also to vanquish the normal powers of defence. So in that case we see healthy persons falling victims to a contagion that had its origin in a commensal infection.

The classical example of this is the observation of Heuser, who fed mice with the whites of eggs; with these animals a commensal organism resembling paratyphoid B gained the mastery in such a way that they died from paratyphoid B infection. Then the sick animals themselves became a source of infection; for now the infection passed from them to healthy, normally fed, animals.

Thus commensal infection (*individual indigestion*) *led to parasitical infection* (*epidemic*).

Human epidemiology too knows examples of contagion by commensals. We cite in the first place *Meningococcus*, *Pneumococcus*, *Staphylococcus*, *Streptococcus* and *B. diphtheriae*. We also think of the viruses of poliomyelitis, encephalitis and influenza that, without maintaining themselves permanently as commensals, yet show a tendency towards commensalism.

In two ways the power of attack of the commensal micro-organism increases. It may find an opportunity of multiplying largely and conquer in a massed attack whatever offered resistance to the usual number. It may also increase in virulence—which means in *parasitic adaptation*. If in barracks people are massed together, of which a single one is carrier of commensal meningococci, it can be imagined how, by a gradual circulating of the nasal-mucus-flora among the members of this small community, at last a more sensitive individual is found with whom the meningococci multiply more

abundantly than they normally do; and how from this individual a greater number of already better adapted microbes spread till at last their number and virulence have been raised in such a way that the epidemic of meningitis breaks out. Observations of infections (pneumococcal and streptococcal) in obstetric and surgical clinics before Semmelweisz and Lister point in the same direction.

Now our question is: Do we observe this with "colds" too?

Granted that a number of people fall ill through commensal infection, does this exclude now all possibility of contagion? Everyone knows how much in daily life the contagiousness of "colds" is taken into consideration. Many medical men and laymen have a fixed opinion about that. On the occasion of the inquiry I invited the collaborators to answer a few questions, among others: "Have you formed an opinion about the contagiousness of colds?"

Of the 2132 persons that returned the questionnaire, 164 left the question unanswered, 698 had no opinion; of the others 902 accepted "colds" as contagious (without any reservation); 172 acknowledged besides contagiousness other factors (cooling, disposition); 137 did not believe in contagion as a rule and 59 did not accept any contagiousness at all. So about half the collaborators consider a "cold" a contagious disease.

Data of the inquiry concerning contagiousness.

The geographical data of the colds given in Section II (Graphs I and II) certainly form a strong argument against the supposition that a cold generally passes from one person to another. The "colds"-lines going up and down in the various parts of the country at the same time and their relation to the oscillations of the temperature of the air are hard to understand otherwise than as an indication of commensal infection.

Special stress may be put here on the corresponding relations between the number of cases of disease and the number of informants. This conformity in percentages, too, strongly tells against the supposition, that the contagion should have spread gradually among people from foci. I want to illustrate this further with a series of other figures, the striking regularity of which shows the equal distribution of colds all over the country in another way.

Table II records the numbers of collaborators of the geographical groups, while mention is made of the whole number of the cases of "cold" they reported during the period of 37 weeks.

Table II.

	Informants	Cases of disease	Cases per informant
Amsterdam	1159	5013	4·3
Northern Noord-Holland	581	2426	4·2
Zuid-Holland	1667	7216	4·3
Utrecht, Gooi	826	3938	4·8
Zeeland	745	2898	3·9
Limburg, Brabant	864	3819	4·4
The other Provinces	1091	4343	4·0
	6933	29653	4·28

We see that for the whole country the average number of cases of cold per informant has amounted to 4·3 *and that the various groups among them diverge relatively little.*

I have tried to test the contagiousness or non-contagiousness of colds in yet another way.

Let us imagine the informants divided into two groups, A and B; and either group subdivided, with this difference, however, that B is divided into smaller groups than A. Let us take it now that by some outside cause the same number of cases of disease (in proportion to the number of persons) is scattered over both groups; and let us assume too that from those scattered cases will spring new cases as a result of contagion; then it is clear that with a moderate scattering more subdivisions of group B will remain free than of group A, and that in this way the individuals of group B run less chance of getting infected.

My material allowed me to trace the influence of such a comparative "isolation." For we can group the informants into members of large families (group A) and of small families (group B) and consider the families as the above-indicated subdivisions.

If I distinguish families of 5-and-more-persons from families of 4-and-fewer-persons I count:

Group A. 670 large families with 3835 persons (5·7 per family).
Group B. 853 small families with 2763 persons (3·2 per family).

Now let us imagine what will happen when in group A and in group B "colds" occur proportionate to the number of informants. *Then more small families remain untouched than large ones.*

The number of members of small families that do not get into touch with cases of "colds" is comparatively larger than that of large families. So *the risk of contagion*—always supposing this to exist—*is smaller for the members of small families.*

If as a rule the commensal infection in families were to spread as parasitic infection, we may expect fewer cases of colds among the group of informants from the small families than in that of the large families. The calculation of the figures given does not render this result.

Table III.

	Number of families	Number of persons	Average number of persons per family	Cases of colds	Average per person
Large families	670	3835	5·7	16,510	4·3
Small families	853	2763	3·2	11,729	4·2
	1523	6598		28,239	4·28

One sees how small the difference is; the members of the large families suffered from colds 4·3 times during the period of research; those of the small families 4·2 times.

This difference is, moreover, explained by the fact that children under 15

suffer a little more from colds than adults; so because of their structure the large families are slightly more susceptible.

It follows from the above that during an inquiry held among more than 1500 families with 6600 persons between September 1925 and June 1926 nothing has been proved of the contagiousness of colds.

IV. The Temperature of the Air and of the Body.

If we accept the conclusion that the occurrence of the respiratory diseases is in a large measure dependent on the influence of meteorological factors that make the body susceptible to commensal infection, this does not explain the mechanism by which this increased susceptibility is produced. Is it the cold air current that drives the blood from the mucous membranes and thus opens the way for the commensal microbes; or does the temperature of the body drop in consequence of the cooling power with the result that, because of changed distribution and decreased function, the protective action of humours and cells diminishes too?

The first view is certainly the less satisfactory one. Daily experience teaches already that on the whole[1] the inhalation of cold air does not cause a cold. One might be sooner inclined to think of a general cooling down of the body, *of a disturbance in the thermo-regulation.*

If on the strength of this supposition we look again at the data as to the temperature of the air[2] in the period of the inquiry, we are struck by the fact that both the difference between maximum and minimum within 24 hours and the dropping of the average temperatures for a certain period go hand in hand with colds.

With regard to September I have already pointed out the series of cold nights preceding the outbreak of colds, which we were able to register. The oscillations of the colds (old-age mortality and pneumonia) in the following months are clearly connected with the average temperature of the air, as the graphs of the first sections have shown already. For further elucidation I put in a table the complete list of the day averages of the observations at De Bilt[3], by the side of which the weekly figures of the inquiry have been put. It is to be seen quite plainly again how the warm days of October 21st to November 3rd are attended by a fall of the "colds" percentages and how the cold that sets in in the second week of November and continues till the middle of December is accompanied by a rise of those percentages.

The question we have to put now is: *Can we measure the lowering of the body temperature that we may suppose to exist on the strength of the epidemiological results?*

The faculties that enable the body to regulate its temperature have been studied extensively during the development of the classic physiology. And

[1] Individual susceptibility for dry (East) wind or cold mist is not denied.

[2] In the first sections I explained why, at present, I restrict myself to this datum.

[3] From the Yearbook for 1925. The observations for 1926 have not yet been published.

Table IV.

October			November			December		
Date	Temperature	"Colds" %	Date	Temperature	"Colds" %	Date	Temperature	"Colds" %
4	12·9		1	6·7		29 N.	−3·6	
5	10·3		2	7·9		30 N.	−0·8	
6	13·1		3	11·5		1	−2·4	
7	10·5	13·0	4	10·6	9·4	2	−1·4	17·2
8	8·4		5	9·4		3	−4·2	
9	7·0		6	7·0		4	−6·9	
10	6·7		7	5·1		5	−10·6	
11	8·6		8	6·2		6	−8·4	
12	8·0		9	4·9		7	−6·9	
13	7·0		10	3·4		8	−0·3	
14	4·7	13·8	11	1·8	13·1	9	2·2	17·2
15	5·5		12	−0·8		10	3·3	
16	6·3		13	−1·3		11	3·2	
17	6·9		14	−0·8		12	2·7	
18	11·4		15	−0·5		13	0·4	
19	6·2		16	−0·2		14	−1·0	
20	5·6		17	0·3		15	−3·5	
21	16·1	11·1	18	0·2	16·2	16	−4·0	14·9
22	15·1		19	−0·9		17	2·8	
23	12·8		20	0·1		18	5·3	
24	10·4		21	3·5		19	1·8	
25	8·7		22	3·3		20	3·7	
26	9·1		23	2·3		21	5·8	
27	11·6		24	2·9		22	6·6	
28	10·8	10·1	25	2·5	16·9	23	3·0	10·7
29	9·3		26	1·5		24	2·2	
30	10·8		27	0·5		25	−0·2	
31	12·7		28	0·3		26	2·5	
						27	7·7	
						28	7·2	
						29	10·9	
						30	11·6	8·5
						31	8·8	
						1 J.	5 (?)	
						2 J.	5·5 (?)	

Average day temperature (De Bilt) during October, November, December, 1925, compared to the percentages of "colds" of the corresponding weeks.

he modern school of Leonard Hill built a new science of ventilation by fundanental research work on the cooling power of the air and the heat-loss of the ody.

But the data on "human poikilothermia," *i.e.* the slight variations which, n normal circumstances, the body temperature shows under influence of his cooling power are rather few.

Sticker[1] mentions Davy's observations, who, attending a sermon in a hurch with a temperature of 0° C., found his mouth-temperature to be 34°. 3. H. Vos[2], too, found a remarkable difference of the mouth-temperature of is patients at Hellendoorn on cold days and on warm days. Women proved o be more thermo-labile than men; some people further are distinguished for heir thermo-stability.

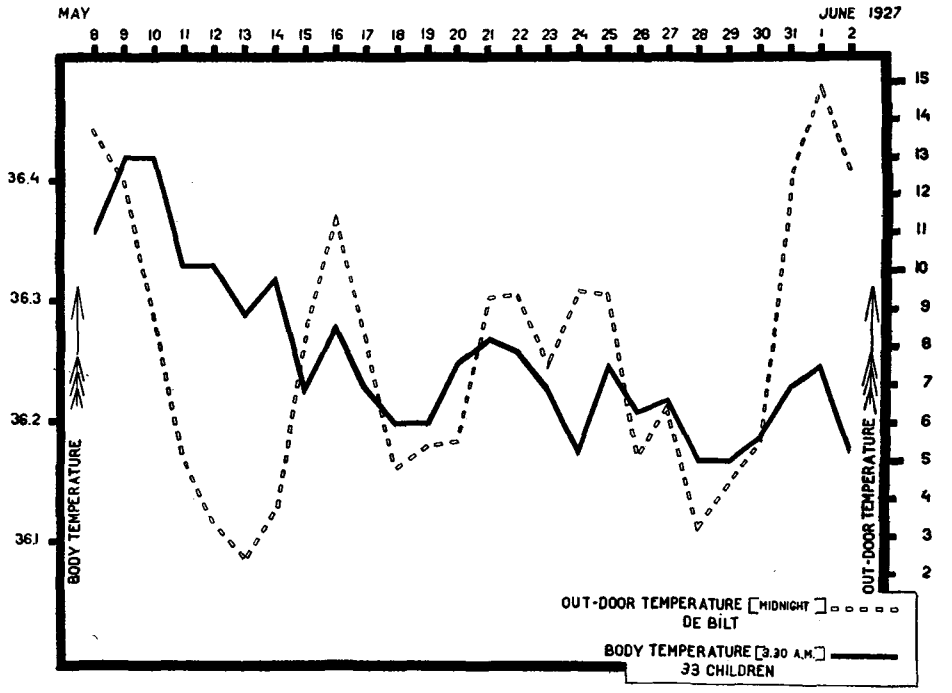
An important contribution to this physiological question is also found in the eport of the New York commission on ventilation[3]. This commission ascerained that the average rectal temperature of a group of healthy persons taken

[1] (1916) *Erkältungs Krankheiten und Kälteschäden*, Berlin: Springer.

[2] (1908) *Ned. Tijdschr. v. Geneesk.* **2**, 1691.

[3] (1922) *Ventilation, Report of the New York State Commission on Ventilation.*

in the laboratory at 8 o'clock in the morning depends to a certain degree on the temperature of the previous night. This dependence, however, was only very clear in June, July and August, diminished in September, October and increased again towards spring, apparently in connection with the greater precautions against cooling down that are taken at night in winter. Poikilothermia seemed to me of such great importance for the question we are studying that I wanted to see the observations of Vos and the American commission confirmed. Therefore I applied to Dr G. J. Huet, chief physician of the sanatorium for children "Hoog-Blaricum," whose interest in the subject



Graph VII. The average body-temperature of 33 patients free from fever in the sanatorium for children "Hoog-Blaricum," in the forenoon at 3.30, compared with the air-temperature at midnight (De Bilt).

of normal temperature is known from his publications[1]. With great readiness he fell in with my wishes and chose some 30 children—free from fever, pupils of the sanatorium school—whose temperature he caused to be taken rectally with the utmost care from May 8th–June 1st at 3.30 a.m. and 4.30 p.m.

Both averages of temperature in their oscillations show conformity with the temperature of the open air. In Graph VII we see the children's average temperature during the latter part of the night compared with the temperature of midnight (De Bilt).

The fact, now well established by these various inquiries, that the temperature in normal conditions is not completely determined by the body itself,

[1] (1927) *Ned. Tijdschrift v. Geneesk.* **1**, 2064.

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but, in spite of the thermo-regulating system, is affected by the cooling power of the air, certainly deserves full attention with the pathogeny of the diseases caused by catching cold.

Now it may be all the more easily imagined how at times of very variable temperature or sudden falls of temperature of the air, the chance increases that the decrease of the body temperature may exceed the physiological limit and the body be rendered susceptible to commensal infection.

For *the prophylaxis of the respiratory diseases*, knowledge of this weak spot in the system of the thermo-regulating organs seems to me important. It is here that the outside influences find their point of attack; here the defences will have to be massed.

As I intend to return to this subject later, I only want to outline in a few words how this defence is to be imagined on the strength of the inquiry.

Everything preventing the lowering of the temperature of the body, or furthering the rising of a lowered temperature to its normal level, may be considered a prophylactic against infection of the respiratory organs by commensal viruses.

If we group these prophylactics, we at once distinguish them as *passive and active ones.*

The passive means preserve the heat of the body or supply heat to the body. They include clothing, covering, artificial heating and the consumption of hot foods and drinks; vigilance against what might be called *refrigeratio insensibilis* by sedentary work and confinement to bed and moving to another country in winter may also be included in this group.

The *active* means are bodily exercise, massage and the application of cold and other stimuli to raise the production of the heat of the body.

I do not think there can be any doubt but that a further examination of the value of these passive and active means will be beneficial to the fight against winter illness and winter mortality.

V. SUMMARY.

The results of an inquiry into colds and slight influenza—held by me with the obliging collaboration of 7000 informants in the Netherlands from September 1925 till June 1926—do not contradict the hypothesis propounded in the introduction, that various respiratory diseases depend upon a disturbance in the thermo-regulation, in consequence of which the body becomes receptive to commensal infection.

In the first place a proportionally equal number of colds was reported at the same time from the various parts of the country during the period of observation, while the increase and the decrease of these colds ran parallel to the falling and rising of the temperature of the air. Further, when calculating the figures from large and from small families, it was proved that the members of small families have no lesser chance of infection than the members of large families.

This joint result tells against the contagiousness of colds in the period of observation.

The outbreak in September stood alone; the preceding period had not been marked by a low average temperature but by a series of cold nights. During the following month the occurrence of colds was accompanied by the mortality from old age and by the joint mortality from bronchitis and pneumonia.

An increased mortality from pneumonia in March–April, linked up with a moderate lowering of the temperature of the air, was not accompanied by "old-age mortality" and only moderately by "colds"; it went together however with an increased mortality from influenza. The influenza cases of the inquiry too had increased by that period of time. So the influenza showed itself as a parasitic infection, which takes its own epidemic course. Still the possibility remains of the virus, at times of reigning influenza, having also widely spread among the healthy. At any rate the idea that catching cold reduces resistance to influenza or pneumonia is supported by the data.

The opinion obtained from the results of the inquiry, that most colds and pneumonia, as well as many cases in which old age has been given as the cause of death, are founded on a disturbance of the thermo-regulation, has drawn attention to physiological oscillations of the temperature of the body in relation to that of the temperature of the air. As the thermo-regulating system is not able to fix the temperature of the body completely, even under normal conditions, but allows a certain poikilothermia, it is clear that by a considerable drop in the temperature of the air these oscillations of the temperature of the body become so large that they may cause a disturbance.

The prophylaxis of the diseases from catching cold will have to be directed towards the application of "passive" prophylactics (for preserving and supplying heat by imminent cooling), as well as of "active" prophylactics (raising the production of heat by the body).

Finally I wish to state that on this domain too the development of the ideas shows as a spiral. There is no great difference between the idea of Ruhemann[1] who, thirty years ago, spoke of "schlummernde und lange in dem Organismus thatenlos verweilende Mikroorganismen" that are stirred to growth and virulence by influenza and catching cold and our opinion upon commensal infection.

For years however interest in obligatory parasitism has hampered the outlook on the borderland of commensalism and parasitism and has diverted attention from the various factors that cause commensal infection.

[1] *Ist Erkältung eine Krankheitsursache und in wiefern?* G. Thieme, Leipzig.

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