

PROFESSOR WILLEM STORM VAN LEEUWEN AND THE ASTHMA PROBLEM¹

By

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One of my great regrets is that I never met Professor Storm van Leeuwen. When he came to America in 1919, he had already made significant contributions to the science of pharmacology, but at that time I was too immature to appreciate what an important person he was and how much more important he was to become. Aside from his scientific achievements, I understand that he was a delightful person "with a warm, outgoing friendliness." Professor McDowall¹ has written of his "wonderfully attractive personality which gave him so many friends: the geniality and lightheartedness which made him the joy of any party." What a pleasure, as well as a privilege, I missed. A photograph shows him in his boat with his eye on the water to windward and his rival far astern. It is no surprise that a man of his attainments took time out for relaxation and contemplation.

Storm van Leeuwen's start in medicine was delayed by malaria, contracted in the Dutch East Indies, but after only three years work he became, in 1911 at age 29, assistant to Professor Rudolf Magnus in Utrecht. When his teacher was recalled to Germany in 1914, Storm van Leeuwen took charge of the Pharmacological Institute in Utrecht. His researches there, on

¹ The first W. Storm van Leeuwen Lecture given at The Hague, May 14, 1958.

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the action of drugs: on poisons, as well as on analgesics and on vitamins, were productive, and his lectures were of high quality.

When the war ended, he wanted to enlarge his acquaintance and to learn what others were doing, and he came to America. He visited for brief periods with such man as Simon Flexner, Carl Landsteiner, and Jacques Loeb at the Rockefeller Institute in New York, with Yandell Henderson, Osborne, and Mendel in New Haven, and finally with I. C. Walker in Boston. Shortly after he returned to Holland, he was called to become Professor of Pharmacology at Leiden. His oration, given in March 1920, was on "The Influence of Colloidal Substances on the Action of Drugs on the Body," and this was the last paper on drugs as drugs.

Dr. I. Chandler Walker's work on human sensitization was in full swing in 1919, and the young Dutch Professor was impressed by it. He began to think about the asthma problem. In Holland, the application of Walker's methods was not so effective as in America. Pollens, animal danders, foods, and even bacteria could not provide a satisfactory explanation for the cause of trouble in many cases, and the discrepancy interested him. Before 1925, it was not appreciated that skin tests might be positive even though the corresponding substance failed to excite any clinical symptoms. We know now that diagnosis by skin test is always different from diagnosis by history and clinical experiment. The titles of Storm van Leeuwen's papers show the development of his thinking. As Walker began with bacterial vaccines, he began with tuberculin, and produced good results with it. (2) He found that skin tests with an extract of human dander gave reactions in asthmatics more than in normal persons, and he used the reaction as a diagnostic test for asthma in general. (3) He looked for toxic substances in the blood of his patients. (4) His extract, made by precipitating fresh blood in alcohol, was probably "H-Substance." He was intrigued by Ancona's observation (5) that grain infested with a parasite caused asthma in most of the individuals who were exposed to the dust of this rotten grain.

(6) He saw that this dust was irritating to normal animals, and he commented on the lack of any sharp distinction between irritating substances and the so-called allergens. He began to think of what he called "Miasmata" in the air of certain places, observing that when his patients went up into the mountains of Switzerland their asthma became much better.

(7) He looked for molds (fungi) as a source of miasmata.

(8) The little book which Storm van Leeuwen (9) published in 1925 is a remarkable document. Thirtythree years have passed since it appeared, and in that interval there is very little of real importance that has been added to our knowledge of the clinical aspects of asthma. The book is a clear, concise review of the early theories and observations about clinical allergy, and about its relation to experimental anaphylaxis.

The author was troubled about skin tests: that results with different methods were different and that there was no good way of standardizing the extracts. He insisted that his tests should give negative reactions in normal people, and then he made this important statement (Page 41): "*Intradermal skin reactions may serve to diagnose the allergic state, but not to make a specific diagnosis.*" (The italics are his). And two pages later he wrote: "... doubtless cases of allergy exist which give negative skin tests . . . with an extract of the allergen which causes the attacks." If more of those working with allergic individuals had read Dr. Storm van Leeuwen's little book when it first appeared, much duplication of effort would have been prevented, and the literature on allergy would have been less voluminous.

There is one interesting omission. Carl von Prausnitz had been a pupil of Dunbar, and Storm van Leeuwen knew about their work with pollantin in the treatment of hay fever. Whereas Prausnitz and Kustner (10) presented their studies of the passive transfer of the skin reaction in 1921, which was four years before, it is curious that the book does not mention this work, which for thirty-seven years has been the basis of so many investigations.

The important part of the book concerns the miasmata, and

his success in doing something about them. Storm van Leeuwen recognized that most of the causes of asthma came from dusts in the patient's home, and so in his clinic he constructed an allergen-free room. The air to this room was drawn from above the house through a long pipe which extended ten meters or more above the roof. This air was passed over a cooling unit which took out water and with the water, dust, and then in cold weather the air was warmed again by passing it over a warm water radiator. Meantime, the walls of the room were washed, and the bedding was washed and sterilized. When three out of four patients did very well in this room, small units were constructed in the patient's homes.

I did not realize until this winter that Storm van Leeuwen knew about kapok as a source of miasmata in poor quality mattresses and pillows. Back in 1925 he (11) described the combination of kapok and molds which Dr. Wagner and I (12) "discovered" eleven years later, in 1936. In all innocence, and with some pride, we presented our findings as an original finding. (I chide myself for not reading carefully even in a foreign language!) Since 1936, we have been able to clear the asthma in a considerable number of our patients simply by finding and removing the kapok in their homes. I suspect that many of Storm van Leeuwen's good results with his special room were due to nothing more than the simple elimination of kapok. I might add that since the war the importation of kapok from Java has been curtailed, and so that cause of extrinsic asthma is much less. Sponge rubber is vastly better.

It is clear that Professor Storm van Leeuwen knew all about allergy as the important exciting cause of asthma. He understood its treatment, first by elimination and then by specific desensitization. Whereas he could relieve about 75 per cent of his cases, there were still 25 per cent that he could not relieve so well. For these he tried non-specific therapy with tuberculin, peptone, and boiled milk and was often successful with these agents. He did not recognize the group which we call "Intrinsic," where the cause of trouble is something that the patient carries within himself and is in contrast to the Ex-

trinsic group, in which the cause is something that the patient meets on the outside. He knew about respiratory infections, but I am not sure that in 1925 he recognized their importance to the asthma problem as a whole. He says very little about psychogenic asthma. Perhaps in Holland the kinds of asthma are different from the kinds in Boston, but I doubt if that is true.

Intrinsic Asthma

Intrinsic asthma has always been of especial interest to me, and I would like to review some observations on it, and to present what I believe is new evidence that Asthma is a Constitutional Disease.

There are three kinds of studies that can be made in the clinic. The first is the clinical study of the patient. The difficulty in breathing is relieved by adrenalin and is controlled by adreno-cortico steroids. When it becomes severe, the patient becomes exhausted: his pulse is rapid, he sweats. He is said to have "allergic toxemia." Eosinophilia in blood and sputum may be found. Meantime, the asthma may be accompanied either before, during, or after the attack by vasomotor rhinitis, or eczema, or urticaria; and these other symptoms also yield to the same treatment with the same adrenal hormones, medullary and cortical. This multiplicity of symptoms is evidence of a disorder which is generalized.

The second method of study is by clinical classification. Attempts to classify patients with asthma on the basis of the exciting causes have been made repeatedly, (13) but the result is never satisfactory, and it has taken much too long to appreciate that in most of the cases the causes are mixed. In only some of them can one demonstrate that the attack depends upon one single, clear-cut factor.

Classification is difficult also because the picture changes as the patient grows older. The eczema in childhood that was due to a sensitiveness to egg was followed by hay fever due to pollen, and now in adult life the asthma is excited by infection, as well as by psychogenic disturbances. The fact that the symp-

toms can be produced by such a variety of exciting causes is further evidence of a poisoning. This important point will be amplified later.

The third method of investigation is by long-term follow-up studies. The concept of the disease as a whole is quite different from that gained by looking at a single attack. There are not many patients who have recovered completely and permanently from asthma.

A follow-up study of 272 private patients has been completed. (14) The number of cases is small because the list is restricted, first to those whose asthma was intrinsic: the exciting cause was something that the patient carried within himself; and, secondly, the study is limited to those patients who have been followed for at least fifteen years. Many interesting cases have been thrown out because they have not been known long enough. The follow-up has been by personal visits in a few cases, and by correspondence with the doctor at home, or with the patient and his family in more of them.

TABLE I
Intrinsic Asthma - Follow-up of 272 Patients.

No.		Women	Total Dead	Dead of asthma
Cleared	59 (21.7%)	45 (76%)	5	0
Improved	119 (43.7%)	84 (70%)	22	0
Unimproved	94 (34.5%)	52 (55%)	41	0
Total	272 (100%)	181 (66%)	68	7

Table I. shows the numbers of patients that are reported as "cleared," as improved, or as unimproved. Let us look first at the cleared group: at those patients who have described themselves as free of asthma. They include only 20 per cent of the whole group, but the study of their progress is of considerable interest and importance.

For interest, these cleared cases have been divided into those fifteen patients whose skin tests were positive, and the

larger group of forty-four patients in whom skin tests were entirely negative, even though made by the delicate intradermal method. The skin tests here are the last remains of the early allergic asthma and play no part in the later episode.

Chart 1 shows the fifteen patients in whose skin tests were positive. The progress of each patient is shown by a line that begins at the age of onset of asthma and proceeds in dashes to represent attacks, or a solid line to indicate continuous symptoms. The X is the age of the first visit, and the C is "cure" or clearance, followed by dots to denote the duration of this good condition until a new C indicates that "cure" is still maintained, or until a new upright mark indicates a new attack.

There are several observations: infections are the predominant cause of trouble. The asthma often began after an infection. In several cases wheezy colds occurred only two, three, or four times a year, so that "asthmatic bronchitis" becomes a more descriptive diagnosis. Vaccines have been given to almost all of the patients with intrinsic asthma, and in a few cases they have been very helpful.

It is of particular interest to find that in several patients there was a close time relation between the I. X. and C. — onset visit, and clearance. In these cases, the asthma, regardless of severity, was a relatively short disease, passing off in a year or two to leave the patient free again.

Only one (Case number 1. Chart 1) out of all the fifteen patients with positive skin tests had lesions in the paranasal sinuses. She was operated upon and that operation "cleared."

In a second group of 39 "cleared" intrinsic cases, all skin tests were negative. Chart 2 summarizes the progress of the first 15 patients in the same way. Here, too, is evidence of infection: the attacks have followed colds, and treatment with vaccines has relieved.

In some of the cases there were other factors.

The girl Athlete (Case 1. Chart 2) wheezed, sometimes quite badly, after strenuous tennis or squash racquets, so that at first there was anxiety about her heart or about some pathologic change in the lungs. When her head colds were

INTRINSIC ASTHMA - SKIN TESTS POSITIVE - "CURED"

	20	30	40	50	60	70
1. F.W. B	—	—	Two ops. on nose XS	— C	 C	
2. F.P. Mc.		(XC)	K.I. - Vaccines C			
3. F. V		—	Wheezing Colds —	(XC)	Vaccines with sterile abscess reaction C	
4. J.A. L		—	—	(XC)	 C	
5. S.E. M		—	Wheezing Colds —	Bad at Menopause —	Vaccines "Hygiene" C	
6. C.W. M			Mild attacks only —	 C		
7. H. C			(XC)	Better Diet. "Hygiene" C		
8. W. D			(XC)	"Relax" - Vacation C		
9. J.A. C			13 or 14 attacks a year —	XC	Peptic Ulcers - 9 C	84
10. J.E. D			(XC)	Vaccines C		
11. M. G			—	1 C	1X - C..... C	78
12. M. K			—	Vaccines 1X - C..... C	Retired C	
13. J. O'S			—	VMR - X - C..... C		81
14. H.W. S			—	VMR - X - C..... C		77
15. L.W. T			Wheezing Colds all his life —	—	Vaccines C	80

Chart I.

INTRINSIC ASTHMA - TESTS NEGATIVE - "CURE?"

	20	30	40	50	60	70	I.
1. D.H. W.	X	—	—	—	—	—	
	Girl Athlete	—	Married	—	—	—	
2. H.B. K.	—	—	Obesity	Wt. 238 to 162	—	—	
	—	—	X	—	—	—	
3. C. Mc.	—	—	—	—	—	—	
	—	—	—	—	—	—	
4. R. B.	—	—	—	—	—	—	
	—	—	—	—	—	—	
5. C.W. P.	—	—	—	—	—	—	
	—	—	—	—	—	—	
6. M. R.	—	—	—	—	—	—	
	—	—	—	—	—	—	
7. P.H. C.	—	—	—	—	—	—	
	—	—	—	—	—	—	
8. W. K.	—	—	—	—	—	—	
	—	—	—	—	—	—	
9. A.L. D.	—	—	—	—	—	—	
	—	—	—	—	—	—	
10. B. H.	—	—	—	—	—	—	
	—	—	—	—	—	—	
11. W. E. G.	—	—	—	—	—	—	
	—	—	—	—	—	—	
12. M. W.	—	—	—	—	—	—	
	—	—	—	—	—	—	
13. M. G.	—	—	—	—	—	—	
	—	—	—	—	—	—	
14. W.L. C.	—	—	—	—	—	—	
	—	—	—	—	—	—	
15. W. F.	—	—	—	—	—	—	
	—	—	—	—	—	—	

Chart 2.

bad, she had asthma of considerable severity. At age 38 she married, and within a few weeks the symptoms all cleared away.

Did this change depend upon the new environment – and was it allergy after all? Or was the improvement concerned with the security and satisfaction of a happy home? How does one tell which theory is correct? Do not the negative skin tests exclude allergy and support the clinical impression of an unstable emotional pattern?

In other cases, clearance of asthma has followed operations like bronchoscopy, hysterectomy, or the removal of gall stones. There were two patients (Cases 2. and 12. in Chart 2) who were enormously fat and whose asthma cleared when their weight was reduced by fifty odd pounds.

Asthma Improved

Of the total of 272 patients, only 59, or about one-fifth, have been cleared of asthma.

There is a larger group, consisting of 119 patients, whose asthma is "better": sometimes much better, but since attacks still recur, one cannot call them "cured." In 27 of these 119 cases, the skin tests were positive but, as in the "cleared" group, they were disregarded as having no clinical importance. For example:

A woman, age 47 (Mrs. J. S. S.), who worked in the woolen mill, showed skin tests positive to animals, feathers, orris, and cottonseed. When her pillows were changed and several abscessed teeth were extracted, there was no great improvement in the asthma which had plagued her since age 45. With vaccine treatment, she gained fifteen pounds and the asthma improved, so that she could go back to work. Five years later, at age 51, asthma recurred. Skin tests by another doctor showed again several positive reactions, but, as before, the elimination of certain foods from her diet, and injections of pollen extracts, did not help her. At age 63, however, she was much better, it not free.

The theory of allergy to dusts or foods could not be proved.

Table II. shows that the incidence of sinus trouble varies with the outcome. Forty-three of these improved patients, or 36 per cent, have had sinusitis, and this incidence is in marked contrast to that in the "cleared" group. The polyps have been removed once or several times in many of them, and with relief of symptoms which was temporary. Radical operations

TABLE II
Intrinsic Asthma End Results vs. Skin Tests and Nasal Sinusitis.

	Skin tests	Sinusitis (Total)	Polypi	Sinus Op.
<i>Cleared</i>				
Tests Positive	15	1	0	1
Tests Negative	44	6	3	1
	59	7 (11.8%)	3	2
<i>Improved</i>				
Tests Positive	27	10	5	2
Tests Negative	92	33	26	6
	119	43 (36.1%)	31	8
<i>Unimproved</i>				
Tests Positive	29	12	9	7
Tests Negative	65	25	18	8
	94	37 (39.3%)	27	15

on the sinuses have been performed in only 8, but in only two of these could one say that the asthma was changed fundamentally by the radical procedure. In most, the improvement after operation lasted for only a few months.

Twenty-two of those whose asthma was under good control: who were "improved," have died, but no patient in this group died of asthma itself. The typical picture of bronchi occluded by sticky plugs was not seen.

The 59 cleared cases, plus the 119 improved, make a total of 178 patients, or 67 per cent of the entire series, who have done well so far as asthma is concerned.

Asthma Unimproved

There were 94 cases, or 33 per cent, unimproved. When first seen, the clinical findings in them were much the same as in those with a better outcome. There was no sign to indicate the more serious prognosis.

INTRINSIC ASTHMA - UNRELIEVED - (SKIN TESTS NEGATIVE)

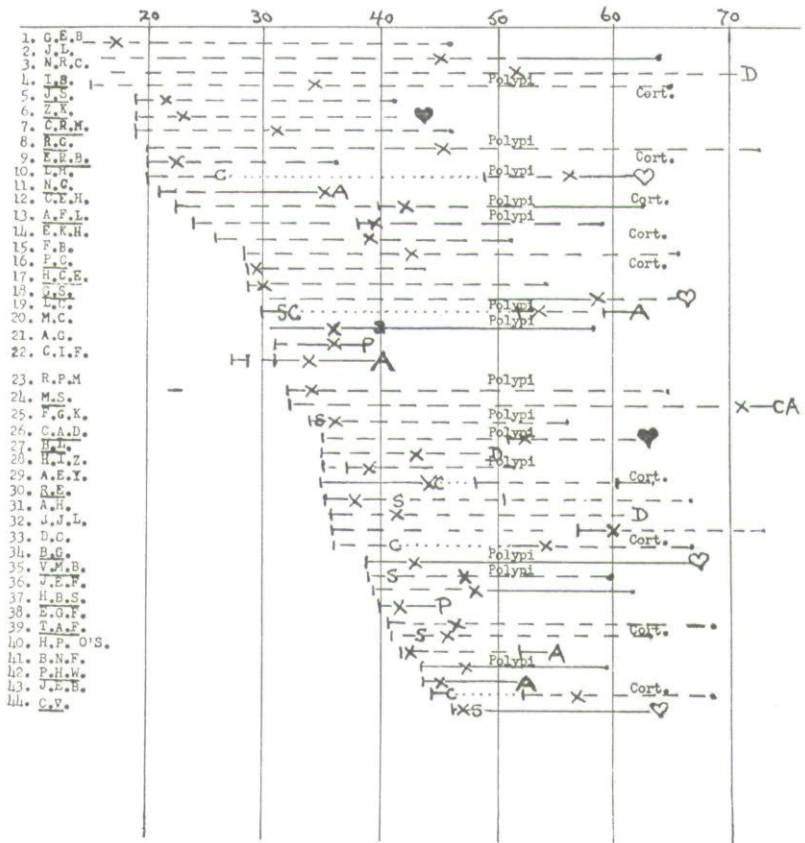


Chart 3.

Chart 3 shows 44 of the 65 "bad" cases whose skin tests were negative. The distribution of age at onset is quite the same in this bad group as in the cleared group. The sex factor is comparable. Nasal polypi and polypoid sinuitis were found in about a third of the cases. The charts show well that operations on the sinuses do little good to the longterm picture of asthma.

Fifty-four, or 57 per cent, of these bad patients have died.

Only 8 have died of asthma (and they are not all verified by autopsy). One of these is unusual.

A woman of 32 (C.I.F. Case 22. on Chart 3) developed asthma at age 27. It was not bad at first, but at age 32 the severity increased and the asthma persisted for eight years until her death at 40. Autopsy, made through the care of Dr. Kaplan of Salem, revealed not only the bronchial plugging of asthma, but the typical picture of diffuse periarteritis nodosa.

Other causes of death included six deaths from Cor Pulmonale – the open hearts on the chart – seven deaths from heart (coronary) disease, two from pneumonia, four from cancer – one a man with cancer of the lung – and there were fourteen cases in which the cause is unknown.

Other diseases in these patients are few. Hypertension was found in only four of the 94 patients, and in only one of these was there evidence of circulatory failure. Hyperthyroidism was present in two, and diabetes in one, but in none of these was the course of the asthma affected.

Emphysema

Whenever asthma becomes severe, the lungs are stretched: the X-ray shows bright lung fields with low, flat diaphragms. This secondary emphysema is acute, and it is reversible. Chronic "primary" emphysema, with changes in the lungs which are permanent and irreversible, is fortunately a rare disease. Incidental to this study of 272 patients with intrinsic asthma, there are six patients, five men and one woman, in whom the diagnosis of chronic emphysema places them in a separate and additional category, even though at first the signs and symptoms are quite comparable to asthma. The diagnosis depends upon the close relation of this asthma to exertion, and the fact that their nights are good. "Emphysema sleeps well: asthma has had nights," one can say.

In the six cases, the symptoms began at about age 50, but were not too bad until the sixties. These patients have lived until the middle seventies – a span of ten to twenty years after the beginning of symptoms. Three have died in a shorter time, presumably of right heart failure.

ASTRA - EXTRINSIC IN YOUTH - FREE INTERVAL - INTRINSIC LATER

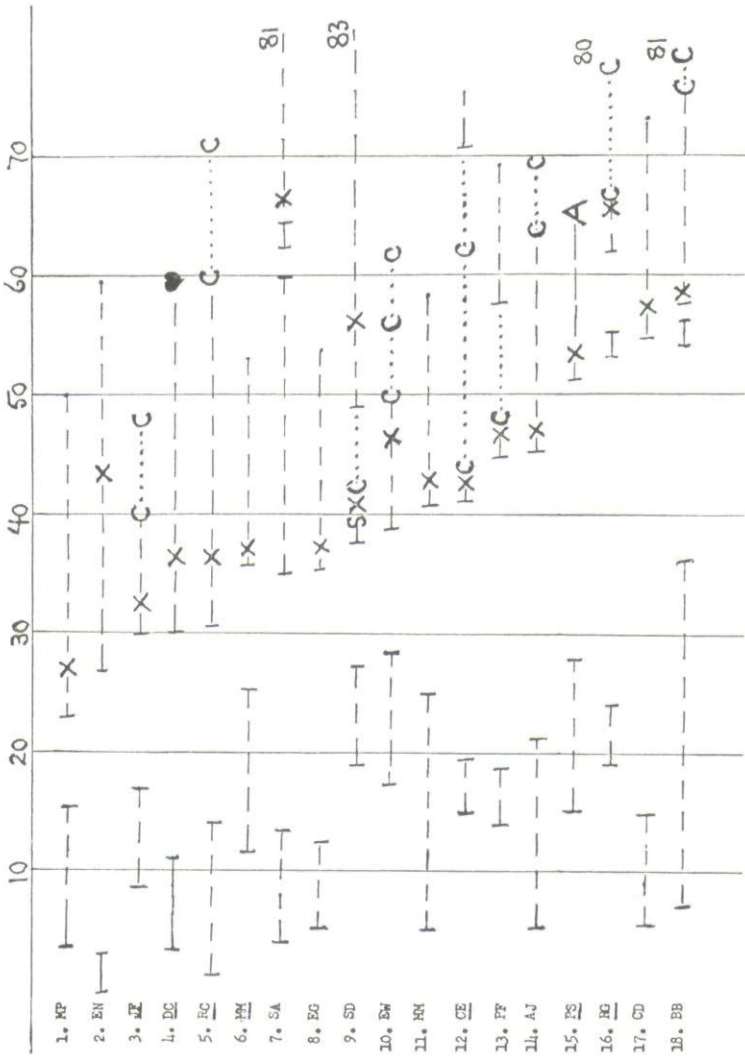


Chart 4.

TABLE III
The Ages Between Which Episodes Occur.

	Early asthma (extrinsic)	Interval	Years duration	Later asthma (intrinsic)
1. M.P.	4-14	14-23	(9)	23-50 Intrinsic
2. E.N.	3-7	7-28	(21)	28-60 Recurrent Bronchitis
3. J.F.	9-16	16-30	(14)	30-40 3 infections - still sensitive to cats
4. J.C.	5-12	12-30	(18)	30-60 Intrinsic - died Coronary
5. R.C.	5-15	15-31	(16)	31-60 Infections - 60 clear to age 70
6. M.M.	12-25	25-35	(10)	35-52 Infections. Obese
7. S.A.	5-12	12-35	(23)	35-80 Attacks at long intervals.
8. E.G.	7-12	12-35	(23)	35-52 Intrinsic
9. S.D.	19-28	28-38	(10)	38-43 Sinus Op. - 49-83 Intrinsic
10. E.H.	18-28	28-38	(10)	38-50 Obesity - Diet - 50 clear to age 62
11. M.M.	4-26	26-41	(15)	41-56 Depletion - Colds - Still sensitive to animals.
12. C.E.	17-20	20-41	(15)	41-43 Bronchitis - 43 clear to age 71 Emphysema
13. P.F.	13-18	18-44	(26)	44-47 Intrinsic - Divorced and clear to age 58
				58-69 Occ. attacks after colds
14. A.J.	5-21	21-45	(24)	45-63 "Trouble with Husband" - 63 clear to age 69
15. P.S.	15-27	21-51	(24)	51-65 Intrinsic. Dead of Asthma
16. R.G.	20-25	25-53	(28)	53-66 Infections - 66 clear to age 80.
17. C.D.	5-15	15-55	(40)	55-73 Bronchitis in winter
18. B.B.	8-37	37-54	(17)	54-81 Asthma with colds

Initials underlined are men.

A. Br. stands for "Asthmatic Bronchitis".

Cardiac asthma was a diagnosis made only twice: but the review of these two cases indicates that in them the asthma was quite independent of the heart disease.

Asthma in Youth – Recovered – Asthma Again Later

The charts show a very important finding. On Chart 3 is Case 10: a girl who developed asthma at age 20. Her asthma continued until age 26, when the family moved to a new home, and thereafter the girl was well until age 49. At that time asthma came again after a cold and sinusitis, and it increased in severity until she died at age 63 with a Cor Pulmonale. Case 19 was a young woman who at age 30 developed asthma and sinusitis which was due to the fumes of chemicals. When she changed to a new job, the asthma cleared, and she, too, was clear for twenty years. At age 52 she caught a bad cold, and asthma recurred and sinusitis also. This asthma continued, increasing in severity until it killed her at age 63.

There are plenty of cases in which asthma has recurred in attacks. In almost all, however, the exciting cause is always the same. Here, however, are two cases in which the same patient suffered attacks which were precipitated by causes of entirely different kinds.

Further study of still other records has revealed eighteen cases in which allergic asthma in young people was followed by a clear interval lasting from ten to thirty years, and this in turn by a later development of asthma of the intrinsic type – see Chart 4 and Table III.

This I believe to be an important observation, for it shows that asthma is the manifestation of a constitutional disease. The exciting cause is just that and nothing more. Whereas I have described "Two Kinds of Asthma" (15) in a paper which considered allergic asthma as quite different from "Bacterial Asthma" or "Psychogenic Asthma," this new evidence gives strong support to the idea that these diseases are all the same: that there is one constitutional background which is common to all cases, and that the many different exciting fac-

tors merely serve to pull the trigger in a gun which is loaded. The idea is not new. Dr. Henry Hyde Salter (16) wrote about it back in 1864, but he could not be sure of it.

This constitutional disease is characterized by eczema, hay fever, and asthma, and may show polypoid paranasal sinusitis as well as eosinophilia. Urticaria may be a symptom, and periarteritis nodosa develops in the severe cases. Irwin's (17) observations on the blood vessels of the guinea pig in anaphylactic shock point to the vascular component. All of these symptoms can be produced by histamine, and perhaps the basic disease concerns a disorder of histamine production or histamine liberation, or a change in the reaction of the body to histamine.

One should note, however, that the chain of events which results in the production of symptoms begins not with histamine, but with the antigenantibody reaction. It is very easy to "put the cart before the horse." When one considers the differences between allergic patients and normal individuals, the striking change is the capacity to develop sensitiveness, and perhaps also the low resistance to new infections. These changes must depend upon variations in the mechanism of immunity. In allergy the antibodies are predominantly attached to the tissue cells: in immunity they are predominantly free in the circulation. A variation in the mechanism by which antibodies are formed and released: a disorder of the mechanism which changes the excessive tissue reaction of allergy into the harmless response of immunity, would fit well with the clinical picture. When Dr. Jones (18) told me that horses with "Heaves" (asthma or emphysema) cannot produce diphtheria antitoxin in the normal expected quantity, his report fitted the concept —(assuming that "Heaves" is an allergic phenomenon!)

When one begins to think of what the immune disorder might be, such ideas as Gamma Globulin or defects of Complement, like Pillemer's Properdin System (19) come to mind, even if there is no evidence so far to support any of them. Furthermore, there are two slight obstacles to be overcome. One is the reversibility of the asthma: the fact of long intervals of freedom between attacks, which makes the concept of

a fundamental defect hard to justify. Enzymes, co-enzymes, and enzyme inhibitors are important – probably. The other is the fact that psychogenic disturbances, which have nothing to do with antibodies, can be an exciting cause. Perhaps, however, they can set up a conditioned reflex.

To be complete, one must mention disorders of adrenal function as a theory for the constitutional disease. Cortisone relieves asthma, as it relieves other chronic diseases, and there are cases that appear to be dependent on Cortisone. It is fortunate that most of them can be weaned away from the drug. Measurements of the steroid output in the urine do not show a diminution except during the stress of a severe attack. Addison's disease is not accompanied by asthma, except in a few cases. The theory of adrenal deficiency cannot be supported so far. We have much more to learn about the asthma problem.

SUMMARY

In this lecture, I have tried to summarize the important contributions which Professor Storm van Leeuwen made to clinical allergy. He knew all about the kind of asthma which depends upon the immediate reactions of allergy. He knew something about infections as complicating factors, but it is doubtful if he recognized that infections alone could act as the exciting cause of the attack. He says little about psychogenic asthma.

Whereas it is easy to regard the exciting cause of asthma as a satisfactory explanation for the whole disease, a new concept is required by the finding of several cases in which the patient developed asthma which at first was excited by extrinsic, allergic mechanisms. When he recovered, he enjoyed a clear interval lasting for several years. In later life asthma re-occurred, excited this time by intrinsic factors: by infections, by psychogenic disturbances, by general bodily disorders, or by combinations of these items. This sequence demonstrates that the exciting cause of asthma is that and nothing more. To find that in one patient attacks of asthma may be excited by two

different causes, gives strong support to the idea that Asthma is a manifestation of a Constitutional Disease. What this disease is, becomes the object of further study of the Asthma Problem.

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