

IMMUNOLOGICAL STUDIES OF POLLINOSIS

II. PASSIVE SENSITIZATION OF MAN THROUGH TRANSFUSION¹

MARY HEWITT LOVELESS

*From the New York Hospital and Department of Medicine, Cornell University
Medical College, New York, N. Y.*

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There are numerous reports in the literature of reactions occurring in hypersensitive recipients after their transfusion with normal blood containing allergens. The development of similar reactions in normal recipients following their transfusion with reaginic blood has been recorded in a few instances. In 1919 Ramirez (1) first suggested this possibility when he described the occurrence of asthma in a man who had received a transfusion two weeks previously. The initial attack developed shortly after the recipient had entered a horse-drawn vehicle, and a second paroxysm came on the next morning while the patient was walking in a park. Both the recipient and the donor were subsequently found to possess cutaneous reactivity to horse dander, a situation which suggested strongly that the donor's susceptibility had been transferred to the recipient. Although a previous transfusion of 800 ml of blood from the same donor had not caused asthma in another recipient, no assurance was given that this recipient had been exposed to horse dander.

In 1926 Mills and Schiff (2) transfused a hemophiliac subject with 500 ml of blood from a donor who was sensitive to horse serum. A cutaneous site in the recipient tested some hours previous to transfusion had revealed no sensitivity to horse serum. Within a half hour following transfusion, however, this area became the seat of wheal formation. A case report pub-

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lished by Holder and Diefenbach (3) and another by Tedstrom (4) suggest that post-transfusion urticarias may be referable to a hypersensitive donor.

E. F. Grove (5), attempting to transfer sensitivity from man to monkey by means of intravenous injections of reagin-bearing serum, concluded that sensitization of the skin was questionable in the lower monkey and negative in the chimpanzee. Nevertheless, one of the lower monkeys developed signs suggestive of asthma on being given 5 ml of ragweed-pollen extract intravenously the day after receiving human serum containing reagins for ragweed-pollen.

The first planned transfusion-experiments upon man were carried out by Garver (6) in 1939. Each of three recipients was transfused with 500 ml of blood obtained from donors whose multiple sensitivities were demonstrated by the presence of positive cutaneous reactions and of humoral reagins. Cutaneous reactivity to such antigens as spinach, string beans, dust, horse dander, timothy and ragweed pollens was detected in the recipients as early as 14 hours after transfusion, reached its maximum by the fourth or fifth day, and had largely disappeared by the fourteenth day. The search for hypersensitivity in the recipients was limited to qualitative cutaneous tests.

In the present investigation, controlled tests were performed on the skin, conjunctiva, nasal membrane, and serum of each of 3 subjects transfused with reagin-bearing blood. These patients, hospitalized because of lymphosarcoma, Banti's disease, and Still's disease, respectively, were transfused during September of 1938 with from 400 to 1000 ml of blood taken from patients ill with uncomplicated and untreated ragweed-hayfever. The time of onset, duration, and intensity of the acquired cutaneous and mucosal sensitivities were determined. Constitutional effects of the sensitization were also noted.

TECHNIC

Five patients, ill with ragweed-pollinosis, served as blood-donors for the experiment. Their symptoms had been continuous over a period ranging from 17 to 37 days prior to the time they acted

as donors. Sodium citrate was added to the blood as an anti-coagulant in an amount sufficient to give a final concentration of 0.35 per cent. The blood was administered within a few hours after it had been drawn, with the exception of one specimen which was stored at 5°C for 1 day and another specimen which was refrigerated for 2 days. Each specimen was titrated for reagins and for thermostable antibodies (7) to ragweed-pollen.

In contrast to the donors, the recipients, with the possible exception of one, gave no evidence of hypersensitivity when studied by cutaneous, conjunctival, nasal, and serological tests. Throughout the transfusion-experiments, tests were restricted in number because it was assumed that any appreciable amount of antigen introduced in this manner would influence the course of the sensitization.

Intracutaneous testing was done with a series of injections of .02 ml of ragweed-pollen extract in concentrations varying between 5 and 10,000 protein-nitrogen units² per ml. The threshold of cutaneous sensitivity was expressed in terms of the weakest extract that served to elicit a visible specific reaction in the skin within 20 minutes.

The presence of conjunctival sensitivity was determined by instilling one drop of pollen-extract from a 26-gauge needle into the conjunctival sac of the left eye, the right eye of the subject being reserved for comparison. Starting with the most dilute solution and using increasingly stronger extract at 20-minute intervals, it was possible to ascertain the weakest concentration that produced the first detectable ophthalmic reaction. The degree of conjunctival sensitivity was then expressed in terms of the protein-nitrogen (P.N.) content of the solution which elicited this minimal reaction.

As a test for the presence of mucosal sensitivity, dry ragweed-pollen was insufflated into one nostril. The intensity of response was judged by the amount of coryza, edema and pallor of the membrane, sneezing, and sense of obstruction that developed. Nasal smears were made in a number of instances before and

²1 protein-nitrogen unit = .00001 mg of phosphotungstic-acid-precipitable nitrogen.

after the production of specific nasal reactions. No excess of eosinophils was noted in them, and the data on these studies have been largely omitted from this report.

The blood serum of each recipient was titrated for reagins to ragweed-pollen before and after transfusion. The titer is expressed in P.N. units and is based upon the amount of antigen required to neutralize the skin-sensitizing power of 1 ml of the unheated serum, in accordance with a technic of passive transfer previously described (7).

It should be remembered in examining the data that the figures apply to the recipient's state of sensitivity at the particular intervals arbitrarily chosen for the tests, and that somewhat different figures might have been obtained had more frequent tests been practicable.

EXPERIMENTAL

PLI, a male of 44 years, weighing 59 kilograms, was ill with Banti's disease. Ragweed-extract containing 10,000 P.N. units per ml failed to elicit any response when .02 ml was introduced intracutaneously previous to transfusion. When one minim of 10,000-unit extract was dropped into the conjunctival sac, neither conjunctival reddening nor itching resulted. No reagins for ragweed-pollen could be demonstrated when the patient's serum was examined by the Prausnitz-Küstner technic.

As indicated in table 1, this man received (on September 9, 1938) 150 ml of blood obtained from EI, a patient who had been indisposed with moderately severe hayfever since August 21. EI's blood was administered two days after it had been drawn. It contained no demonstrable thermostable antibody for ragweed-pollen. The 100 units of ragweed-extract required to neutralize the skin-sensitizing capacity of 1 ml of the EI serum were therefore referable to reagin.

A sample of serum, obtained from the recipient 30 minutes after his transfusion, showed a definite capacity to sensitize normal skin passively to ragweed-pollen. In order to neutralize this capacity, ragweed-extract in the proportion of 8 units to 1 ml of serum had to be used. One hour following transfusion,

TABLE 1
The relation between the reagin-content of transfused blood and the sensitivity transferred to the recipient

BLOOD USED FOR TRANSFUSION				PASSIVE SENSITIVITY ACQUIRED BY RECIPIENT'S TISSUES FOLLOWING TRANSFUSION WITH REAGIN-BEARING BLOOD									
Transfusion num-ber	Donor	Amount	Reagin-content*	Recipi-ent	Tissue tested	Sensitivity established		Sensitivity maximal		Sensitivity receding		Sensi-tivity absent	
						Time after transfusion	Degree†	Time after transfusion	Degree†	Time after transfusion	Degree†		
1	EI	150	100	PLI	Skin Eye Nose Serum	2 hrs. 1 day Not tested 30 min.	units 10,000 1000 8	days 2 1	units 5 1000	days 5, 8 2	units 10, 100 5000	5 1	
2	SB	500	200	PLI	Skin Eye Nose Serum	4½ hrs. 4½ hrs. Immed.	10 1000 10	3, 7, 24 7, 10 3	7½ 100 Dry pollen	10, 17, 31 7	15, 10, 10 Dry pollen	45 17 10 10 45	
3	PO	500	25	WHI	Skin Eye Nose Serum	1 day 2 days Not tested	10,000 10,000 Serum lost	2 2	1000 10,000	3	5000	6 3 9	
4	AG	500	300	WHI	Skin Eye Nose Serum	2½ hrs. 2½ hrs. 1 day Immed.	1000 10,000 Dry pollen 35	1 1, 4, 8 4	5 1000 Dry pollen	4, 8, 11, 29, 48 8, 11	10, 10, 25, 1000, 1000 Dry pollen	11 29 3	
5	PE	400	100	GAD	Skin Eye Nose Serum	1½ hrs. 5 days 28½ hrs. Immed.	10,000 10,000 Dry pollen 25	5 5 9	8 10,000 Dry pollen	9, 30, 50, 84 Not studied	10, 100, 1000 10,000	154 9 30	

* Expressed in terms of the number of P.N. units of antigen required to neutralize 1 ml of unheated serum.

† In the case of the skin and conjunctiva, the degree of sensitivity is expressed in terms of the most dilute extract which sufficed to elicit a specific response. The figures represent the P.N. units of antigen contained in each ml of this extract. The nasal mucosa was tested by the insufflation of dry pollen. The reagin-content of the blood was judged by the P.N. units of extract required to neutralize the skin-sensitizing capacity of 1 ml of serum.

10,000-unit extract introduced into the conjunctival sac caused no reaction. However, a cutaneous site, which had given a negative response to 10,000-unit antigen one hour after transfusion, developed a huge wheal and marked pruritus within two hours after transfusion.

By the following day, the recipient's blood had lost all its ragweed-combining power, as indicated in plate A. Twenty-four hours after transfusion a slight reaction followed the intracutaneous introduction of 100-unit extract, whereas 10-unit solution elicited no response. The conjunctival test now resulted positively with 1000-unit extract, weaker solutions giving no reaction and stronger ones causing more marked responses.

Extract containing 5000 units per ml caused a slight conjunctival reddening and itching, and 5-unit extract sufficed to elicit a cutaneous response when tests were done on the second day after transfusion.

By the fifth day, no ophthalmic response was obtained even when 10,000-unit solution was used for testing. At this time 10-unit extract was required for the minimal response of the skin. By the eighth day, the cutaneous requirement had risen to 100-unit extract and the eye failed to react to the strongest test-solution.

On the 9th day (September 17, 1938), following a serological study which revealed no reagins for ragweed pollen in his blood, PLI was given a second transfusion consisting of 500 ml of blood freshly obtained from a second donor, SB. The donor was unequivocally hypersensitive to ragweed-pollen as indicated by cutaneous, conjunctival, and clinical tests, having been ill with slight pollen-hayfever and with severe pollen-asthma since August 11. His serum required 200 units per ml for its neutralization (see table 1) and contained only a trace of thermostable antibody for ragweed-pollen.

Serum of the recipient prepared immediately following transfusion required 10 units per ml for its neutralization. When the subject was seen 4½ hours after his transfusion, sites that had been intracutaneously tested with 100-unit and 1000-unit extracts on the previous night were found to have developed marked

urticarial reactions. Additional tests were then done and 10-unit extract was found sufficient to cause a specific reaction, whereas 1000-unit extract promptly produced a wheal of 1 cm diameter, showing that cutaneous sensitivity had been established (table 1). The threshold of response in the conjunctiva was located at 1000,

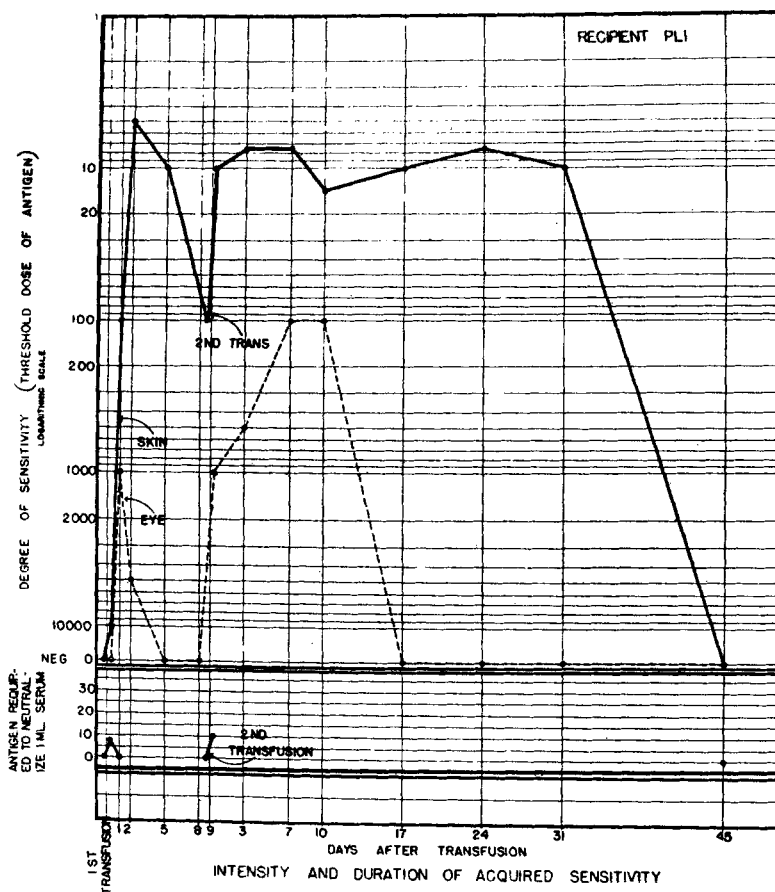


PLATE A

and the use of 10,000-unit solution led to marked redness and itching. Dry pollen blown against the nasal mucosa failed to elicit a positive response. The cutaneous sites developed sufficient pruritus to disturb the patient's sleep.

The subsequent course of the acquired sensitivity may be seen

in plate A and table 1. The greatest cutaneous sensitivity was attained by the 3d day, when $7\frac{1}{2}$ -unit extract sufficed to elicit the threshold response. Sensitivity was maintained at approximately this level until after the 31st post-transfusion day. By the 45th day it was no longer detectable even with the use of 10,000-unit solution. The conjunctival sensitivity was maximal on the 7th and 10th days, 100-units solution serving to cause erythema and slight itching. By the seventeenth day, 10,000-unit extract failed to cause any irritation. Dry pollen applied to the nasal mucosa failed to elicit any signs or symptoms until 3 days after the second transfusion, at which time marked nasal obstruction and sneezing resulted promptly after the pollen entered the nostril. Twenty minutes after this test, the patient had generalized pruritus which lasted for $1\frac{1}{2}$ hours. On the 7th day after transfusion, insufflated dry pollen caused nasal obstruction and an unfulfilled inclination to sneeze, whereas by the 10th day no nasal signs or symptoms followed the test.

WHI was a male aged 39 years, weighing 54 kilograms, and complaining of marked weakness and pallor. He had coughed slightly each morning for several years, expectorating a small amount of mucopurulent material. Upon being admitted to the hospital during August of 1938, sibilant and sonorous râles, which disappeared after he coughed, were heard in the lungs of this patient, and a diagnosis of chronic, low-grade bronchitis and sinusitis was made. He denied ever having experienced paroxysms of dyspnea but recalled having had a rather wheezy cough upon one occasion eight years previously. Nothing else suggestive of hypersensitivity could be discovered in his past or familial history or by physical examinations. On September 7 he received 500 ml of blood freshly obtained from PO, a ragweed-sensitive subject who had been ill with severe hayfever for 18 days and who had received no therapeutic injections of ragweed-pollen extract at any time. The amount of extract required to neutralize the skin-sensitizing capacity of this donor's serum was 25 units per ml of serum, as indicated in table 1, transfusion #3, and the amount of thermostable antibody for ragweed-pollen was found to be insignificant.

The effects of 500 ml of this blood upon the recipient were similar to those described above for the first transfusion-experiment. Unfortunately, a blood-specimen secured from the recipient promptly after his transfusion was accidentally discarded. Tests performed before and immediately after transfusion failed to reveal any sensitivity to ragweed-pollen in the patient's conjunctiva, skin, or serum. However, within a few hours, wheals spontaneously developed in the cutaneous sites formerly tested, and these areas remained indurated until the next day. One day after transfusion, intracutaneous tests induced no immediate reactions but wheal-formation developed within a few hours in the sites tested with 10,000-unit extract. Less concentrated extracts also gave rise to delayed reactions, but these were difficult to evaluate and were disregarded. The first cutaneous reactivity has been considered as occurring 24 hours after transfusion in response to 10,000-unit extract. The cutaneous sensitivity reached its peak on the second post-transfusion day when 1000-unit solution provoked the threshold-response. By the third day, the cutaneous sensitivity had fallen to the point where 5,000-unit solution was required for a minimal reaction. By the sixth day all sensitivity had disappeared. The conjunctival sensitivity showed the same trend but at a lower level, making its first appearance on the second post-transfusion day, when 10,000-unit extract elicited the threshold-response, and disappearing altogether by the third day. On the seventh day, all tests resulted in negative reactions. Dry pollen now applied for the first time to the nasal mucosa caused no objective or subjective change in the nose.

On the ninth day (September 16), no sensitivity being detectable in either the tissues or the serum, a second 500 ml transfusion with reagin-bearing blood from another donor was administered. The donor, AG, had been afflicted with severe hay-fever and slight asthma since August 15. Ragweed-pollen extract in a ratio of 300 units to 1 ml of serum was required to neutralize the skin-sensitizing capacity possessed by the blood of this donor (table 1). Immediately after the transfusion, the recipient's blood required 35 units per ml of serum for its neutralization.

Within $2\frac{3}{4}$ hours, a cutaneous site that had reacted negatively to 10,000-unit antigen just before the transfusion spontaneously developed a wheal 5 cm in diameter. The threshold of sensitivity in the skin lay at 1000 units of antigen. By $5\frac{3}{4}$ hours after the transfusion the area of the previous cutaneous tests was occupied by a wheal 8 cm in diameter, and the recipient had developed a constitutional response which will be described below.

The course of the patient's acquired sensitivity may be seen on plate B. One day after the second transfusion with reaginic blood the degree of hypersensitivity in the recipient's skin had reached a maximum, 5-unit extract being adequate to elicit a threshold-reaction. On the 4th and 8th post-transfusion days, 10-unit extract provoked the threshold-response, whereas on the 11th day 25-unit extract was required. By the 29th day, it was necessary to introduce 1000-unit solution for a comparable result, and this degree of sensitivity obtained when the patient was last tested on his 48th post-transfusion day. Comparable tests with timothy-pollen on the 11th day resulted negatively.

The conjunctival sensitivity showed a similar trend at a lower level. It was detected $2\frac{3}{4}$ hours after transfusion with 10,000-unit test-solution and was maximal on the 1st, 4th, and 8th days when 1000-unit solution sufficed to elicit a reaction. By the 11th post-transfusion day all reactivity had disappeared (table 1).

Nasal sensitivity to ragweed-pollen did not make its appearance until the day following the second reaginic transfusion. At this time the insufflation of dry pollen led within 10 minutes to sneezing, local pruritus, and nasal obstruction. In contrast to the other half of the nose, the membrane of the tested side showed pallor, edema, and excessive mucus. By the 4th day, the acquired sensitivity had reached its maximum. Nasal obstruction, profuse watery discharge, and marked sneezing developed within five minutes after ragweed-pollen had been blown against the mucosa. Shortly thereafter the patient complained of itching in the region of his eustachian tubes. Nasal smears studied before and after this test revealed occasional eosinophils in those specimens taken after the insufflation. On the 8th day, the responsiveness of the mucosa had diminished, and by the 11th day only a slight coryza and edema were elicited by the insufflation of pollen.

No sensitivity could be demonstrated on the 29th day when the next tests were performed.

On the 3rd day following transfusion, the recipient's serum was tested for the presence of reagins to ragweed-pollen, but no skin-sensitizing capacity could be shown.

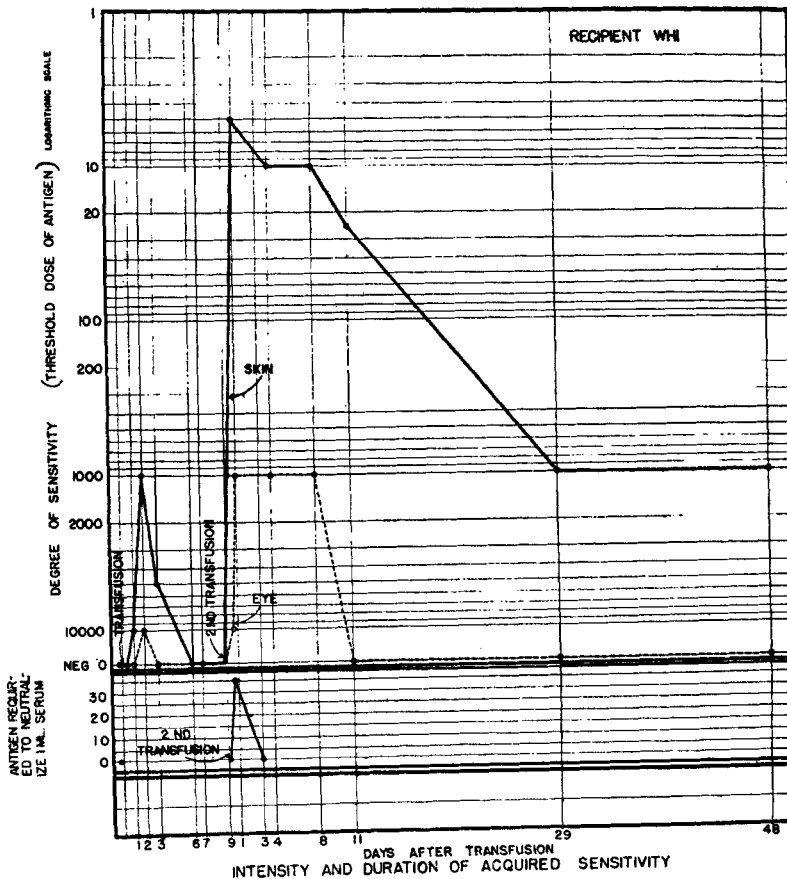


PLATE B

There were interesting general reactions in this recipient during the post-transfusion period. In order that the reader may evaluate certain factors other than transfusion which may have influenced the patient's clinical course, table 4 has been compiled to show the various levels of rectal temperature and of leukocyte-concentration in the peripheral blood before and after the trans-

fusion. (It is probable that the cytological findings are of little significance from the immunologist's viewpoint, since the patient was the victim of lymphosarcoma which could have caused all the cytological abnormalities listed in the table.)

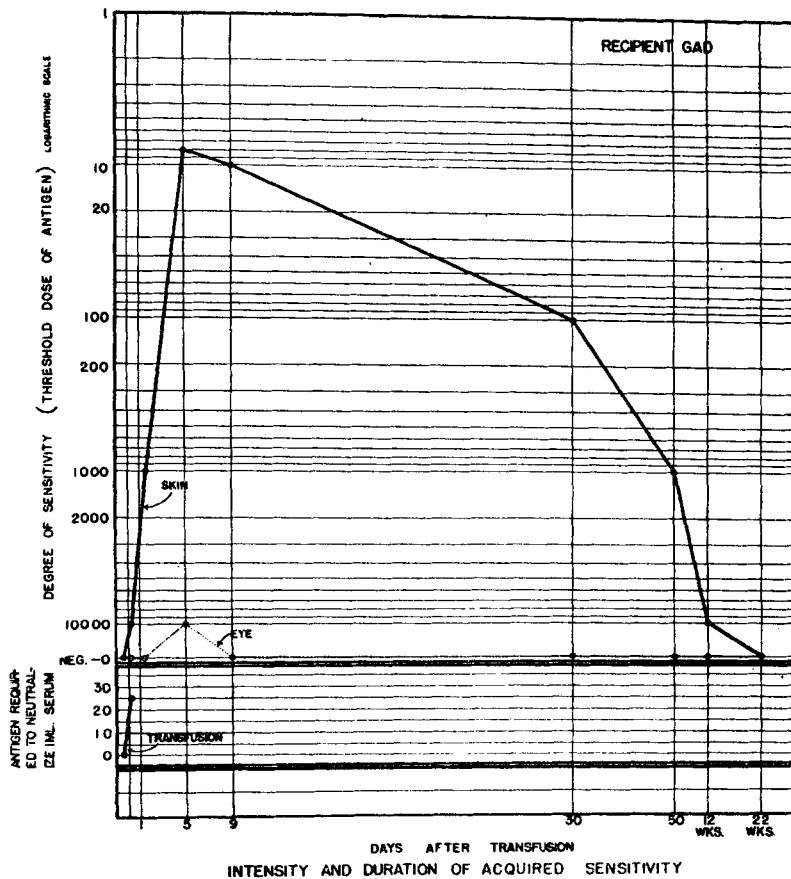
Among the general reactions was a large area of edema which appeared over the recipient's sacrum approximately 6 hours after his second transfusion with reaginic blood during the late afternoon of September 16. He had been tested for acquired hypersensitivity $2\frac{3}{4}$ hours after this transfusion. Several hours after the edema developed, the subject complained of a "sense of tightness and shifting discomfort" in his chest, which he had never before experienced. His sleep was disturbed by this dyspnea and also by pruritus in the region of his toes, arms, thighs, malleoli, sacrum and at the sites of earlier cutaneous tests. Edema developed in one eyelid. The cutaneous symptoms subsided gradually during the next day but dyspnea, coughing, and pulmonary rhonchi persisted. The patient volunteered the statement that this cough differed from his usual colds and that he had had no previous "chest" cough for 6 years. By the 5th day after the 2d transfusion with reaginic blood, the sputum showed streaks of pus whereas it had previously been clear and viscid; the rectal temperature rose to 39°C , the pulse-rate was 98 and the respiratory rate was 22. The cough, small rises in temperature, and slight dyspnea continued for over 2 weeks. By the 20th day after the 2d transfusion, symptomatic treatment and 5 transfusions with normal blood had induced sufficient recovery to allow the patient to undergo an exploratory laparotomy. Inoperable lymphosarcoma of the retroperitoneal lymph nodes was found. Marked dyspnea, associated with coughing and increased respiratory and pulse rates, followed the operation. These symptoms were attributed to an exacerbation of the patient's bronchitis, although atelectasis was also considered as a possible explanation. No signs of consolidation were found on physical or roentgenological examination at any time during the next three weeks, although numerous rhonchi and occasional moist râles at the pulmonary bases were frequently heard. Dyspnea of sufficient severity to necessitate the occasional use of oxygen, rises in respiratory rate

and in temperature continued for several weeks. It is of interest that on October 10, during one of a number of transfusions with normal blood, the recipient had to be given adrenalin for the relief of asthma. On November 20, approximately 11 weeks after his second transfusion with reaginic blood, the patient died. *Postmortem* examination confirmed the diagnosis of lymphosarcoma of the retroperitoneal and mesenteric nodes. There were no significant findings in the thorax except some fibrous pleural adhesions on the right side and a slight enlargement of the tracheobronchial lymphnodes.

GAD, a male, aged 15 years, was believed to be suffering with Still's disease. Neither his familial nor his personal history was positive for atopy. The results of tests done upon his eye, skin, and serum did not reveal any sensitivity to pollens or other antigens. In view of his secondary anemia, he was given 400 ml of blood that had been obtained two days earlier from PE, an untreated victim of uncomplicated ragweed-hayfever. One ml of the serum of PE required 100 units of extract for its neutralization, the bulk of this being bound by reagin and only a trace being inactivated by thermostable antibody (see table 1). Immediately after transfusion, the recipient's serum was tested and found to have acquired a capacity to neutralize 25 units of ragweed-pollen extract per ml. Unfortunately, subsequent studies of this patient's blood were not possible. An hour and a quarter after the transfusion, the boy showed a slight cutaneous response to 10,000-unit extract, as indicated in table 1 and plate C. This strength of solution failed, however, to cause any ophthalmic reaction. Twenty-eight and a half hours following the transfusion there was a slight but definite cutaneous reaction to 1000-unit extract. At this time dry pollen blown against the nasal mucosa led to slight "stuffiness" and coryza, although the conjunctival reaction to 10,000-unit extract was negative.

After four more days the recipient gave a slight response to 8-unit extract by intracutaneous test and a slight conjunctival reaction after 10,000-unit solution had been instilled. Nasal stuffiness followed the introduction of dry pollen. By the 9th post-transfusion day, his conjunctiva did not respond to the

strongest extract; the 10-unit extract elicited a small reaction in the skin and dry pollen introduced into the nose caused a slight edema and coryza. On the 30th day conjunctival and nasal tests resulted negatively and 100-unit extract was then required to elicit a cutaneous threshold reaction. The conjunctiva and



nasal mucosa were thereafter unresponsive. By the 50th day, 1000-unit extract was required to produce a reaction in the skin, and by the 12th week 10,000-unit antigen was necessary. By 22 weeks, even the skin failed to give any response to the strongest antigen. No detectable clinical signs of allergy developed in this patient at any time as a result of his transfusion.

None of the five transfusions described above was followed by chill, temperature-change, or any other so-called transfusion-reaction.

DISCUSSION

By grouping the immunological data gathered in this investigation, it is possible to make a few inferences on the subject of passive sensitization by means of transfusion. Table 1 specifies the reagin-content of the various transfused bloods. It lists, also, the corresponding reagin-titer found in the recipient shortly after transfusion. As would be expected, the reagin-content of

TABLE 2

Relative speed with which reagins in transfused blood reached various tissues of three nonsensitive recipients following five transfusions (as determined by specific reactions of tissue to antigen)

TISSUE TESTED	INTERVAL BETWEEN TRANSFUSION AND FIRST SPECIFIC RESPONSE TO TESTS WITH ANTIGEN				
	Recipient PLI		Recipient WHI		Recipient GAD
	Transfusion # 1	Transfusion # 2	Transfusion # 3	Transfusion # 4	Transfusion # 5
	hours	hours	hours	hours	hours
Serum.....	$\frac{1}{2}$	Immediate	Not tested	Immediate	Immediate
Skin.....	2*	$4\frac{1}{2}$ *	24	$2\frac{3}{4}$ *	$1\frac{1}{4}$ *
Conjunctiva....	24	$4\frac{1}{2}$ *	48	$2\frac{3}{4}$ *	120
Nasal mucosa...	Not tested	72	Not tested	24*	$28\frac{1}{2}$

* First post-transfusion test performed.

the recipient's serum shortly after transfusion was less than that of the corresponding donor's serum. In most instances, the skin-sensitizing power of the recipient's serum was roughly proportional to the dilution of the blood of the donor by that of the recipient. The degree of hypersensitivity acquired by the several tissues and the time following transfusion at which this sensitization was first detected are noted in table 1. Apparently the circulating reagins are quite rapidly removed from the blood stream, for cutaneous hypersensitivity was detectable as early as $1\frac{1}{4}$ hours after transfusion (table 2). Conjunctival and nasal responses were obtained as early as $2\frac{3}{4}$ and 24 hours respectively, after transfusion. Sensitization of the recipient's skin reached a max-

imum in from 1 to 5 days and remained at this level as long as 24 days, as table 1 indicates. The eye attained its maximal reactivity within from 1 to 5 days, whereas the peak of nasal response was found from 3 to 9 days following transfusion.

Sensitiveness then diminished until no response was elicited by the strongest testing-strengths of antigen. In the case of the skin, considerable variation was found in the duration of the acquired sensitivity. The least effective transfusion was #3 (listed in table 3) which induced a cutaneous reactivity to ragweed of more than 3 days' but less than 6 days' duration. At

TABLE 3

Relative speed with which reagins from transfused blood disappeared from various tissues of recipient

TISSUE TESTED	TIME AFTER TRANSFUSION WHEN LAST POSITIVE REACTION AND FIRST NEGATIVE REACTION WERE OBTAINED									
	Recipient PLI				Recipient WHI				Recipient GAD	
	Transfusion # 1		Transfusion # 2		Transfusion # 3		Transfusion # 4		Transfusion # 5	
	Last positive reaction	First negative reaction	Last positive reaction	First negative reaction	Last positive reaction	First negative reaction	Last positive reaction	First negative reaction	Last positive reaction	First negative reaction
Serum.....	½ hour	24 hours	5 min.	45	days (Specimen lost)	9	5 min.	3	5 min.	NT
Skin.....	8 days		31 days	45	3	6	48 days		12 weeks	22 weeks
Eye.....	2 days	5 days	10 days	17	2	3	8 days	11	5 days	9 days
Nose.....	NT	NT	7 days	10	NT	NT	11 days	29	9 days	30 days

NT, not tested.

the other extreme was transfusion #5 which was followed by a positive cutaneous reactivity to ragweed-pollen for 12 weeks. When the next test was carried out during the 22d week, the reaction had become negative. The most enduring sensitization of the conjunctiva occurred after transfusion #2 which was followed by positive reactions to the antigen over a period of at least 10 days. The most prolonged nasal sensitivity resulted from transfusion #4 which conferred a reactivity lasting 11 days. This acquired hypersensitivity was found to have disappeared by the 29th day when the recipient was next tested.

Although the number of transfusion-experiments reported herewith is small, the data suggest that reagins acquired through transfusion are removed from the circulation in less than 24 hours, and make their appearance first in the skin and later in the conjunctival and nasal membranes. The acquired hypersensitivity lasts longer in the skin than in the other tissues. This tenacity of the skin for reagin may explain the existence of cutaneous hypersensitivity in some subjects who give no nasal, conjunctival, serological, or clinical reactions to the antigen.

The constitutional symptoms noted in two of the recipients resembled closely a type of generalized reaction commonly seen in hypersensitive individuals who have received an overdose of antigen. Following his 2d transfusion, one recipient (PLI) experienced generalized pruritus which came on within 20 minutes after antigen had been applied to his skin, eye, and nose, with marked local responses. Two and three-quarter hours after his second transfusion, another recipient (WHI) was found to have developed spontaneously a huge wheal at the site of a previous cutaneous test. Tests performed on the skin, eye, and nose of the recipient at this time led within 3 hours to generalized pruritus, edematous swellings in the skin and asthmatic breathing. Some special hereditary susceptibility of his bronchial mucosa might be held by some (8) to explain the development of "asthma" in this subject whereas none occurred in the other two recipients of reagin-bearing blood. It was beyond the scope of this work to attempt to determine whether the asthmatic breathing—which resulted presumably from an antigen-reagin reaction in an already irritated (infected) bronchial mucosa—was analogous to true bronchial asthma.

From a practical point of view, the transfusion-experiments emphasize the importance of avoiding the use of atopic subjects as blood-donors. From an immunological point of view, the experiments strengthen the theory that in man sensitization of the skin, conjunctiva, nasal mucosa, and possibly other tissues to pollen is intimately related to a blood-borne factor, reagin. The latter should be distinguished from the thermostable antibody with which it is commonly found associated in the blood of *treated*

TABLE 4

Showing fluctuations in body-temperature and peripheral-leukocyte count of subject, WHI

DATE (1938)	MAXIMAL RECTAL TEMPERATURE	LEUKO- CYTES PER ML OF BLOOD	EOSINO- PHILS	CLINICAL STATUS AND THERAPY
	°C.		per cent	
8/18 to 9/3, incl.	37.6	4,800	9	Slight, chronic bronchitis
		6,600	9	Slight, chronic bronchitis
		7,200	14	Slight, chronic bronchitis
9/4, 9/5	38.0			
9/7	37.6			500 ml PO reaginic blood; tests*
9/8 to 9/10, incl.	37.6			Tests*
9/11	38.2	6,500	8	
9/12	37.8			
9/13	38.0			
9/14	38.4			
9/15	38.0			Tests*
9/16	38.2			500 ml AG reaginic blood; tests* constitutional reaction; asthma
9/17	38.4			Tests.* Cough, sibilant râles
9/18, 9/19	38.0			Tests.* Cough, sibilant râles
9/20	38.2			Tests.* Cough. Transfusion
9/21	39.0			Cough, sibilant râles, purulent sputum
9/22 to 9/26, incl.	37.6	7,800	3	Cough, sibilant râles, purulent sputum
9/27	37.6			Tests*
9/28 to 10/2, incl.	37.6			Transfused with normal blood
10/3 to 10/5	37.4	10,600	1	Daily transfusion with normal blood. Few sibilant râles
10/6	38.6			Laparotomy. Transfused with normal blood. Rapid pulse, cough, dyspnea, rhonchi
10/7	38.0			Dyspnea, rhonchi and cough
10/8	38.4			Dyspnea, rhonchi, cough, rhinitis
10/9	38.8			
10/10	38.8	20,000		Slight asthma during transfusion
10/11	39.0			Rhonchi. Dyspnea
10/12	38.0	78,000	0	Rhonchi, Oxygen tent. Trans- fusion
10/13	38.4			Rhonchi, Oxygen tent
10/14	38.8			Rhonchi, Oxygen tent
10/15	38.8	73,500	0	Tests.* Rhonchi, no moist râles
10/16, 10/17	38.8			Cough, moist râles both bases

* Cutaneous and conjunctival tests with ragweed-pollen extract.

TABLE 4—*Concluded*

DATE (1938)	MAXIMAL RECTAL TEMPERA- TURE	LEUKO- CYTES PER ML OF BLOOD	EOSINO- PHILS	CLINICAL STATUS AND THERAPY
	°C.		<i>per cent</i>	
10/18	38.8	38,100	2	
10/19	38.2			
10/20	38.8			X-ray therapy
10/21	38.2			Transfusion with normal blood
10/22	39.8			X-ray therapy; transfusion with normal blood
10/23	38.2			
10/24	38.8	21,500	0	X-ray therapy
10/25	38.6			X-ray therapy. Transfusion
10/26	38.6			X-ray therapy
10/27	38.2	12,600	0.5	X-ray therapy
10/28	38.6			X-ray therapy. Lungs improved
10/29 to 11/1, incl.	37.6			X-ray therapy
11/2	37.6			X-ray therapy
11/3	38.0	7,100	0	X-ray therapy. Tests*
11/8	38.4	10,300	1	X-ray therapy
11/20				Expired

pollen-sensitive patients. The thermostable antibody to pollen (referred to as an "inhibiting" or "blocking" factor (9) before its capacity to neutralize its pollen-antigen in the manner characteristic of an antibody had been demonstrated (7)) competes with reagin for the homologous antigen and may be related to immunity whereas reagin confers hypersensitiveness.

CONCLUSIONS

1. Blood-donors, proven hypersensitive to ragweed-pollen by means of cutaneous, conjunctival, serological, and clinical tests, transferred their hypersensitivity to recipients previously not allergic to pollen.

2. The sensitizing factor present in the transfused blood was removed from the circulation of the recipients, and was taken up by the skin, conjunctiva, and nasal mucosa. The recipient's skin was the first tissue to manifest acquired hypersensitivity and the last to relinquish it.

3. Two of three recipients experienced reactions to antigen

which resembled generalized responses seen commonly in hypersensitive patients who have received an overdose of antigen. One of the recipients had "asthma" after his second transfusion with reagin-bearing blood.

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