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SENSITIVITY IN THE GUINEA PIG.

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PASSIVE TRANSFER OF SKIN HOMOGRAFT SENSITIVITY
IN THE GUINEA PIG

by

Ronald Jon Siebeling

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1967
I hereby recommend that this dissertation prepared under my direction by Ronald Jon Siebeling entitled Passive Transfer of Skin Homograft Sensitivity in the Guinea Pig be accepted as fulfilling the dissertation requirement of the degree of Doctor of Philosophy.

Dissertation Director

Date

After inspection of the dissertation, the following members of the Final Examination Committee concur in its approval and recommend its acceptance:

Kenneth Kettmann 7/18/66

[Other signatories and dates]

*This approval and acceptance is contingent on the candidate's adequate performance and defense of this dissertation at the final oral examination. The inclusion of this sheet bound into the library copy of the dissertation is evidence of satisfactory performance at the final examination.
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ABSTRACT

Attempts to transfer passively skin homograft sensitivity from grafted guinea pigs to normal recipients at specific time intervals following transplantation were conducted.

Groups of out-bred guinea pigs received orthotopic skin homografts from a donor guinea pig of another strain. At specific time intervals of 7, 14, and 28 days the skin recipients were sacrificed. Regional lymph node cells, peritoneal exudative cells and serum were harvested, pooled and transferred passively to normal recipients. The cellular and serum recipients were challenged subsequently with skin homografts from the original skin donor.

Cells collected from the regional lymph nodes 7 days after sensitization transferred homograft sensitivity consistently. Peritoneal exudative cells competently transferred sensitivity to normal animals at 14 and 28 days. During this time period, the transfer capacity of the regional lymph nodes was reduced. Immune serum failed to sensitize normal guinea pigs.
INTRODUCTION

Successful exchange of tissue transplants between genetically diverse individuals of the same species (homografts) has not been accomplished to this date. In all instances reported transplanted tissues were eventually rejected by the recipient animals. On the other hand, if a skin graft was removed from the donor animal and placed elsewhere on the same animal it was accepted and survived (autografts). Homografts have been studied by embryologists, geneticists, physiologists, immunologists, and surgeons for many years. Loeb (1), from his observations on tissue rejection, first suggested that each individual possesses a unique tissue specificity.

Recognition has been given to Medawar and his colleagues, who first made a systematic attempt at elucidating the mechanism of tissue rejection. They were concerned with exchanging normal orthotopic skin grafts between genetically diverse animals of the same species (2,3). The results they obtained with rabbits gave impetus to other experimentation.

The observations of Medawar et al., suggested that tissue transplantation belonged within the scope of immunology. They noted that a skin graft when removed from a donor rabbit and placed on a recipient animal enjoyed a short period of harmony with the host for about 8 to 10 days. Then, for no apparent reason, the recipient animal reacted against the newly placed graft,
and the end result was death of the graft. This "first-set rejection" was usually completed by the 10th to 12th day. The observation which led Medawar to propose that graft rejection is immunological in nature was the "second-set rejection". This occurred when a second graft taken from the same tissue donor and placed on the original recipient was rejected in an accelerated and much more violent fashion, terminating in death of the graft by the 6th or 7th day. The "second-set response" suggested that the recipient had been stimulated in some manner by the first contact so that the animal demonstrated heightened sensitivity by ridding itself of the second graft in an accelerated manner. This was similar temporally to the anamnestic response as observed in classical humoral antibody responses (2,3).

Another feature of tissue graft rejection which suggests it is immunological in nature is the specificity of the reaction. Accelerated rejection of a tissue transplant will occur only if the recipient has been exposed previously to tissue from the same donor. A skin transplant from donor A to recipient C will not cause a sensitized state to skin from donor B, unless A and B are genetically identical. Thus individual tissue specificity exists as Loeb (1) suggested.

Sensitivity or immunity to skin grafts in animals remains at an active level for a year or longer (4). Homograft immunity can be induced by intact solid tissue grafts (2,3,4), by dissociated viable cell populations, and by cellular extracts (5). However, immunity of longest duration is obtained by exposure to solid tissue grafts.
Early investigations were concerned with the search for a humoral factor responsible for graft rejection. Participation of substances such as immunoglobulin in the destruction of tissue transplants has not been demonstrated. Stetson (6) maintained that serological methods now available are not sensitive enough to detect low titers of humoral antibody after stimulation by a single graft. Gorer (7) demonstrated, on the other hand, that in certain inbred mouse strains there was present a hemagglutinating antibody following tumor transplantation. Stetson and Jensen (8) reported detection of a cytotoxic antibody in the serum of tumor sensitized mice which specifically destroyed donor cells \textit{in vitro} but had no observable effect \textit{in vivo}. Evidence for specific antibody formation to tissue transplants has been reported for other animal species such as rats (9), rabbits (10,11,30), guinea pigs (12), chickens (10,13), and man (6). However, it has not been established that the humoral antibodies demonstrated in these studies are directly involved in the rejection phenomenon.

The widely shared skepticism that humoral antibodies are not significantly associated with tissue rejection is based on three lines of evidence. First, large doses of immune serum taken from graft recipients are unable to immunize passively a normal animal against a specific skin graft (4,14,15,16,24,25,27,28,29). Many attempts to transfer passively skin graft immunity in mice, rabbits and guinea pigs with serum have met with failure.

Only a few cases of successful serum transfer have been reported. However, in these instances, employment of an artificial mechanism, such as
local injection of immune serum directly into the graft site (17,18,19), or alteration of the graft permeability by direct application of histamine (20) has been involved. Steinmuller (9) observed transfer of homograft immunity in rats when he used immune serum, but transfer was restricted to a specific strain which served as serum recipients. The serum was effective only when collected on the 6th through 10th day after grafting.

The second objection to participation of serum antibody in graft rejection was raised by Algire, Weaver and Prehn (21). Tissue grafts were enclosed in millipore chambers which permitted the passage of humoral, but not cellular elements. The test grafts survived for extended periods, even when placed in previously sensitized recipients. This suggested that a humoral factor did not play an active role in graft destruction in these experiments.

A third argument was suggested by the work of Silverstein, Prendergast and Kraner (22). These investigators studied the immunological competence of the fetal lamb. They found that after the 77th day of gestation the fetus was fully competent to reject a skin homograft, in the same manner as an adult sheep. Beyond the 76th day of gestation, no immunoglobulins can be detected in the circulation of the fetus. This implied that graft rejection takes place without the presence of a humoral factor.

An alternative to a humoral antibody response in the form of a cell bound, or cytophilic antibody (23,26,42,43) has been proposed. Several investigators have reported the presence of leukocytic inflammatory cells at the...
site of grafted tissue (3,4,30,45). The presence of these cells were
observed by the 2nd or 3rd day and as time proceeded the cellular infiltration
increased and congregated at the graft-host interface. The greatest number of
cells were present at the height of graft rejection. The kind of cell which
invaded the graft depended upon the stage of rejection. Polymorphonuclear
cells were present in large numbers, particularly in the early days of graft
residence. As rejection progressed towards death the predominant cell
appeared to be mononuclear and identifiable as a small lymphocyte. The
histological picture changed with regard to the "second-set rejection" (45).

The significance of cellular infiltration into grafted tissue has been
investigated. Mitchison (14,24,25), demonstrated that immunity to specific
tumor transplants was readily transferred from tumor resistant mice to normal
mice by living "immunologically active" lymph node cells. At the same time,
serum failed to confer immunity. Billingham, Brent and Medawar (4) were able
to immunize passively normal mice against normal tissues with cells removed
from the regional lymph nodes of skin grafted mice. Najarian and
Feldman (27,28) transferred lymph node cells from skin sensitized guinea pigs
to normal animals and were able to immunize passively the recipient against
future skin grafts. Billingham, Silvers and Wilson (15,29) reported that
lymph node cells and blood leukocytes, and to a lesser extent, peritoneal
exudative cells from skin sensitized mice passively immunized a recipient to a
subsequent skin graft, or destroyed an already established graft on a tolerant
recipient.
As a result of these investigations, many workers believe that the destruction of tissue grafts is mediated by cells of the lymphoid type. Certain dermal hypersensitivities of the delayed type also appear to be directly mediated by sensitized leukocytic cells. Cells of this type have been observed in histological preparations of the skin reaction. A major criterion of delayed type hypersensitivity is that a sensitized subject will develop an erythematous, indurated, and sometimes necrotic skin reaction 24 to 72 hours after contact with the sensitizing substance.

Landsteiner and Chase (31) established a second major criterion for delayed type hypersensitivities when they successfully transferred contact chemical hypersensitivity from sensitive guinea pigs to normal animals with peritoneal exudative cells. Chase (32), Stavitsky (33), Kirchheimer, Weiser and Van Liew (42,43,44) reported similar results in the guinea pigs with tuberculin sensitivity. Jeter, Tremaine and Seebohm (34) demonstrated passive transfer of sensitivity to 2,4-dinitrochlorobenzene in the guinea pig with extracts of peritoneal exudative cells. Lawrence reported passive transfer of delayed hypersensitivity states with blood leukocytes to streptococcal antigens (35), diphtheria toxin (36), and tuberculin (37) in man. Porter (46) reported delayed tuberculin skin reactions in humans with agammaglobulinemia. In all cases, workers were unable to passively sensitize normal recipients with serum from sensitized subjects.

The histological picture of the skin reaction in a sensitive animal is very similar to that in homograft rejection. A predominance of mononuclear cells
is present at the reaction sites of both graft rejection and skin tests. Brent, Brown and Medawar (38,39) attempted to produce a delayed skin reaction in skin sensitized guinea pigs by intra-dermal injection of donor tissue extract. They observed a reaction which was both specific and possibly analogous to delayed type hypersensitivity. They found it very difficult to produce the same response in skin sensitized mice. Mannick (40) and Mannick and Egdahl (41) were able to reproduce the direct skin reaction in rabbits.

The histological picture of homograft rejection, the involvement of leukocytic cells in passive transfer experiments, and the failure to immunize normal animals against tissue transplants with serum and demonstration of a delayed skin reaction in sensitized animals, suggest that the homograft rejection phenomenon may be a delayed type hypersensitivity.

The purpose of this study was to investigate the nature of homograft rejection in guinea pigs. Leukocytic cell populations and serum were collected from sensitized guinea pigs at specific time periods and transferred passively to normal recipients. The recipients received test homografts from the donor whose skin had been used to sensitize the cell and serum donors. The establishment of a state of sensitivity to homografts by the leukocytes or serum in a normal recipient would be revealed by an accelerated rejection of the test graft on this recipient, which under normal conditions would reject this graft by the "first-set reaction". White graft rejection was used as an indication of a sensitized state in the cell and serum recipient. A "first-set rejection" of the test graft would indicate no heightened activity was present.
MATERIALS AND METHODS

Animals. Two strains of outbred, albino guinea pigs, designated as the Amana (A) strain and the Rockefeller (R) strains were employed throughout this investigation. Both male and female animals, weighing 500 to 800 grams, were used. Animals were housed individually in stainless steel cages and were fed Purina guinea pig chow and water, supplemented with ascorbic acid, ad libitum. In addition all animals received daily rations of cabbage.

Skin grafting procedure. The grafting technique employed was similar to that of Billingham and Medawar (48). Skin donor and recipient guinea pigs were anesthetized with sodium nembutal (30mg/Kg (49) injected intra-abdominally. Ether was used supplementally. The abdominal area of the skin donor and the left and right lateral chest walls of the skin recipients were clipped and shaved free of hair. The shaved skin surfaces were then scrubbed with soap and wiped dry with 70% alcohol. All skin grafts removed were full thickness. Strips 1 cm in width and from 6 to 10 cm in length were removed. The deficit was closed with metal wound clips. Excess fat and connective tissue were trimmed away from the under surface of the skin strips. Each strip was then cut into individual grafts approximately 1 cm square. The individual grafts were stored raw surface down on saline soaked filter paper or gauze. Abdominal skin was exclusively used in grafting because it was easily removed, thinner, and readily adaptable to a recipient bed.
Each of six to ten skin recipients received two sensitizing skin homografts from the test donor. The grafts were fitted orthotopically into recipient beds prepared laterally on each side upon the rib cage posterior to the scapular area. This particular location was chosen for several reasons: 1) readily accessible scapular lymph nodes drain this area; 2) the rib cage provided a stationary platform upon which to keep the graft immobile to prevent slippage and wrinkling; and 3) the graft in this position was inaccessible for biting and scratching. The beds which received the grafts were prepared by surgically removing a full thickness square of skin which approximated the size of the graft which replaced it. It was important that the panniculus dorsum remained intact when preparing the recipient bed. This structure carries capillaries and lymph vessels which were necessary to nourish and aid in the healing processes. Clotted blood and adipose tissue were removed from the bed before placement of the graft. The graft was held in position with a strip of 3-M Blenderm Surgical Tape, which was applied directly over the graft and surrounding area. No sutures were employed. The tape provided adequate pressure to prevent slippage and dehydration and also allowed visualization of the graft. Gauze pads were placed immediately over the taped transplant and the animal was wrapped with surgical tape to secure and protect the graft site.

Observation of the graft. The grafts were observed grossly for the first time on the 5th day following transplantation and every day thereafter until rejection was complete. The grafts were inspected for changes in color,
integrity of epidermis and dermal layers, and ability to produce bleeding upon scraping with a scalpel blade. Only gross examinations were made. The strip of tape covering the graft was replaced daily.

**Passive transfer methods.** At 7, 14, or 28 days following transplantation, passive transfer of cell populations and serum were performed. Procedures for harvesting cell populations and serum were those of Jeter et al., (34). Two days before collection of cells, each sensitized guinea pig received 25 ml sterile light mineral oil which evoked a cellular response in the peritoneal cavity. Forty-eight hours later, the animals were exsanguinated by heart puncture. Serum was collected, pooled, and 20 ml were injected intra-abdominally into a normal guinea pig.

The peritoneal cavity of each skin sensitized animal was opened aseptically and washed three times with Hank's Balanced Salt Solution (HBSS) (50) containing 0.2% gelatin and 2 mg heparin per liter. The peritoneal washings were collected and centrifuged at 500 X g for 20 minutes at room temperature. The cellular sediments were pooled, washed once and recentrifuged at 500 X g for 20 minutes. Packed cell volumes were determined, total cell counts and differential smears prepared and stained with either Wright or Giemsa stain. The pooled peritoneal cells were resuspended in 8 to 10 ml HBSS and injected into one or two recipient animals.

The scapular lymph nodes which drained the graft site were carefully dissected from the fat pad just below the scapula. Fat and connective tissue were trimmed away from each node. Two regional nodes were removed from
each sensitized guinea pig. The nodes were placed on a small mesh stainless steel screen which rested on a mortar. They were minced finely with a curved scissors and the cell populations were washed free with HBSS. A pestle was employed to express cells from the minced pulp. The cells suspended in the salt solution were centrifuged at 500 X g for 20 minutes. The cell sediment was pooled, washed once, and recentrifuged. Packed cell volume was recorded, total cell counts and differential smears prepared. The cell populations from the regional nodes were resuspended in 8 to 10 ml HBSS and injected into a normal recipient.

On a few occasions non-regional cervical and brachial lymph nodes were harvested and treated in the same manner as the scapular lymph nodes. A second recipient was used for these cells.

Passive transfer recipients. Cell and serum recipients were of the same sex and strain as the cell and serum donors, and weighed approximately 500 grams. Forty-eight hours after receiving the cells or serum, recipients were challenged on the left lateral chest wall with a test skin graft from the original test skin donor. In addition, each recipient received a control skin homograft from an indifferent skin donor to control specificity, and an autograft. The two control grafts were placed on the right lateral chest wall. The grafts were inspected on the 5th day following graft challenge.
EXPERIMENTAL RESULTS

Due to the limited number of reports published concerning the fate of first-set skin homografts in the guinea pig (52,53,49,28), initial experiments were performed to establish survival times and appearances of skin homografts exchanged between Rockefeller and Amana animals.

Grafts were observed daily after the 4th post-surgical day. On the 5th day they exhibited a pink to light red color corresponding to that of the surrounding host tissue. The graft by this time had healed into the bed. Pin-point bleeding could be demonstrated on the surface when it was scraped lightly with a scalpel blade. This suggested that a blood supply had been established. No macroscopic signs of rejection were evident on either the 5th or 6th day. During the 7th and 8th day inspection of the graft revealed a dramatic change in appearance. The epidermis had become firm and bleeding could no longer be produced. The color had deepened to a blotchy brick red or sometimes a bluish purple. The change in color was due to stasis of capillary blood flow and resulting hemorrhage as the rejection process was manifested. On the 9th to 10th day the graft epidermis had become necrotic and the entire graft could be pulled from the bed without effort. The color of the graft had transformed to a yellowish-brown, and white granulation tissue was seen below the sloughing graft. The "first-set response" was usually complete by the 9th to 10th day in both the Rockefeller and Amana recipients.
Following completion of the "first-set reaction", skin recipients were grafted a second time with tissue from the same donor. This was done in order to establish the survival time of a graft undergoing "second-set rejection". The accelerated response indicated a state of sensitivity existed as a result of previous exposure. The "second-set rejection" was manifested in two ways, either by the classical "second-set response" or the white graft rejection. A graft undergoing a "second-set rejection" exhibited initial acceptance through the 2nd or 3rd day, followed by an accelerated breakdown which was complete in 5 to 6 days. The white graft never exhibited the character of an accepted graft. It exhibited a chalky white color on the 1st day after placement and became soft and swollen by the 5th day. Bleeding was not produced upon scraping or cutting. The white graft was unique in that a blood supply was never established to the graft, as evidenced by the white color and failure to demonstrate bleeding.

Figure 1 presents the experimental plan followed throughout this investigation. The test skin donor was either a Rockefeller (R) or Amana (A) animal. Six to ten recipient guinea pigs were used, each received two orthotopic, close fitted, full thickness skin homografts. When the donor used was strain A, the recipients employed were strain R, and if the donor was R, then the recipients were A. Seven, fourteen, or twenty eight days after transplantation, the sensitization period, the skin recipients were sacrificed and cell and serum passive transfer studies were performed. The cell and serum recipients were animals of the same strain as the skin recipients. Forty eight
Skin Donor

Skin homografts

Skin Recipients
6 to 10 animals
7, 14, and 28 days
mineral oil (IP)
48 hours
sacrifice recipients
collect cells and serum

Peritoneal Exudative Cell Recipient

Serum Recipient

Lymph node Cell Recipient

Challenge Test Homograft

Fig. 1 EXPERIMENTAL PLAN
hours after passive administration of cells or serum, the recipients were
grafted with skin from the test skin donor. A skin homograft from an indifferent
donor, unrelated to the test donor, was used to control specificity and an
autograft control was placed on each recipient.

Passive transfer at 14 days. The first series of experiments
conducted were concerned with the transfer of leukocytic cells and serum
collected from the guinea pigs 14 days after skin grafting. A sensitization
period of 14 days was employed by previous investigators (31,32) in
chemical and tuberculin passive transfer experiments, and also 48 hours were
allowed to elapse before challenging with the sensitizing agent. The same
sensitization and latent periods were used in the transfer studies reported here.

In six attempts regional lymph node cells collected at 14 days gave two
white graft rejections, as presented in Table I. Differential smears revealed
90 to 95% of the cells present in the lymph nodes were small lymphocytes.
Three times the test graft was rejected by the "first-set response". It
appeared that more than $6.1 \times 10^8$ lymph node cells were needed to establish
a state of sensitivity. In the sixth experiment, the lymph node recipient died.
The indifferent homograft controls underwent "first-set rejection" in every case.
The autograft controls were accepted by the host and exhibited no signs of
rejection during the course of inspection.

Passive transfer of peritoneal cells yielded five white graft rejections
and one "second-set rejection" in six attempts, as shown in Table II. The
approximate number of cells conferring homograft sensitivity ranged
TABLE I
PASSIVE TRANSFER WITH REGIONAL LYMPH NODE CELLS
FROM SKIN SENSITIZED GUINEA PIGS TO NORMAL RECIPIENTS
AT 14 DAYS AFTER GRAFTING

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>No. of Cell Donors (R)*</th>
<th>Packed Vol. of cells ml.</th>
<th>Approx. No. Cells</th>
<th>Fate of Test Graft</th>
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<tr>
<td>15</td>
<td>10</td>
<td>0.50</td>
<td>$6.2 \times 10^8$</td>
<td>Recipient died</td>
</tr>
<tr>
<td>16</td>
<td>10</td>
<td>0.45</td>
<td>$5.8 \times 10^8$</td>
<td>Rejected at 8th day</td>
</tr>
<tr>
<td>17</td>
<td>10</td>
<td>0.70</td>
<td>$8.0 \times 10^8$</td>
<td>White Graft</td>
</tr>
<tr>
<td>18</td>
<td>10</td>
<td>0.90</td>
<td>$1.1 \times 10^9$</td>
<td>Rejected at 8th day</td>
</tr>
<tr>
<td>23</td>
<td>7</td>
<td>0.50</td>
<td>$6.1 \times 10^8$</td>
<td>Rejected at 8th day</td>
</tr>
<tr>
<td>24</td>
<td>6</td>
<td>0.80</td>
<td>$9.2 \times 10^8$</td>
<td>White Graft</td>
</tr>
</tbody>
</table>

(R)* Rockefeller strain
TABLE II
PASSIVE TRANSFER WITH PERITONEAL EXUDATIVE CELLS
FROM SKIN SENSITIZED GUINEA PIGS TO NORMAL RECIPIENTS
AT 14 DAYS AFTER GRAFTING

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>No. of Cell Donors (R)*</th>
<th>Packed Vol. of Cells ml.</th>
<th>Approx. No. Cells (X 10^9)</th>
<th>Fate of Test Graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>10</td>
<td>1.30</td>
<td>1.20</td>
<td>White Graft</td>
</tr>
<tr>
<td>16</td>
<td>10</td>
<td>1.30</td>
<td>1.25</td>
<td>Rejected at 6th day</td>
</tr>
<tr>
<td>17</td>
<td>10</td>
<td>1.75</td>
<td>1.65</td>
<td>White Graft</td>
</tr>
<tr>
<td>18</td>
<td>10</td>
<td>1.40</td>
<td>1.30</td>
<td>White Graft</td>
</tr>
<tr>
<td>23</td>
<td>7</td>
<td>1.50</td>
<td>1.45</td>
<td>White Graft</td>
</tr>
<tr>
<td>24</td>
<td>6</td>
<td>2.20</td>
<td>2.00</td>
<td>White Graft</td>
</tr>
</tbody>
</table>

(R)* Rockefeller strain
from $1.2 \times 10^9$ to $2.0 \times 10^9$ cells. Differential counts consistently showed 65 to 70% large mononuclear cells, 20 to 25% small lymphocytes and 5 to 10% neutrophiles present in this population. On three occasions the indifferent homograft control underwent white graft rejection along with the test graft. The autograft controls revealed no evidence of rejection at any time during the period of observation.

Six attempts were made to transfer homograft sensitivity with 20 ml of donor serum, collected at 14 days. The test grafts were rejected as "first-set reactions" in every instance. The indifferent homograft controls were rejected in the same manner as the test grafts. The autograft controls remained viable and intact for the duration of the experiment.

The results of the passive transfer studies at 14 days following transplantation are summarized in Table III. Rejections are recorded on the basis of test graft appearance 5 days after placement on the recipients. White graft rejection of the test graft was used as the criterion for passive transfer of homograft sensitivity. The peritoneal exudative cells from skin sensitized guinea pigs possess a great capacity to confer homograft sensitivity on normal recipients when employed at 14 days. These results correlate with the findings obtained by others (31,32) when transferring chemical and tuberculin sensitivity with peritoneal cells at 14 days. Cells from the regional lymph nodes exhibit an ability to transfer homograft sensitivity but not as consistently as peritoneal cells. Serum did not transfer sensitivity in six attempts, which also correlated with results of serum studies in chemical and tuberculin transfer studies.
### TABLE III

**SUMMARY OF PASSIVE TRANSFER EXPERIMENTS CONDUCTED 14 DAYS AFTER SENSITIZATION OF CELL AND SERUM DONORS WITH SKIN HOMOGRRAFTS**

<table>
<thead>
<tr>
<th>SOURCE OF CELLS</th>
<th>SERUM</th>
</tr>
</thead>
<tbody>
<tr>
<td>PERITONEAL EXUDATIVE CELLS</td>
<td>REGIONAL LYMPH NODE CELLS</td>
</tr>
<tr>
<td>5/6</td>
<td>2/5</td>
</tr>
</tbody>
</table>

**NO. OF REJECTIONS 5 DAYS AFTER GRAFT CHALLENGE**

* Placed 48 hr. after cellular and serum injection
The 14 day passive transfer studies brought about several questions. How soon after receiving a skin homograft does the leukocytic cell population become competent at transferring sensitivity? Once competence is attained how long do the cells retain this level of activity? Transfer of leukocytic cells and serum thus were done at 7 and 28 days following grafting to yield this information.

**Passive transfer at 7 days.** Table IV presents the results of regional lymph node cell passive transfer at 7 days after sensitization of the cell and serum donor guinea pigs. In five experiments the regional lymph node cells were able to confer white graft rejection sensitivity on normal recipients. The approximate number of regional lymph node cells which elicited the white graft response ranged from $6.0 \times 10^8$ to $8.5 \times 10^8$ cells. In one instance, experiment 26, the recipient failed to reject the test graft in an accelerated fashion. This particular recipient received only $5.0 \times 10^8$ cells, which was less than the cell numbers which gave transfer of homograft sensitivity.

There was no evidence of accelerated rejection with respect to the indifferent homograft control in the six experiments. The autograft controls exhibited no signs of rejection throughout the time of observation.

Peritoneal exudative cells produced three white graft rejections in six attempts. The approximate number of cells given to the recipients ranged from $6.5 \times 10^8$ to $1.2 \times 10^9$ cells. The ability to sensitize passively normal recipients with peritoneal cells cannot be correlated to cell numbers with the data available. The indifferent control homografts were rejected as a
TABLE IV
PASSIVE TRANSFER WITH REGIONAL LYMPH NODE CELLS
FROM SKIN SENSITIZED GUINEA PIGS TO NORMAL RECIPIENTS
AT 7 DAYS AFTER GRAFTING

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>No. of Cell Donors</th>
<th>Packed Vol. of Cells ml.</th>
<th>Approx. No. Cells ($X 10^8$)</th>
<th>Fate of Test Graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>10(R)*</td>
<td>0.50</td>
<td>6.0</td>
<td>White Graft</td>
</tr>
<tr>
<td>21</td>
<td>10(A)**</td>
<td>0.60</td>
<td>6.5</td>
<td>White Graft</td>
</tr>
<tr>
<td>22</td>
<td>10(A)</td>
<td>0.75</td>
<td>8.0</td>
<td>White Graft</td>
</tr>
<tr>
<td>26</td>
<td>9(R)</td>
<td>0.40</td>
<td>5.0</td>
<td>Rejected at 9th day</td>
</tr>
<tr>
<td>29</td>
<td>10(R)</td>
<td>0.80</td>
<td>8.5</td>
<td>White Graft</td>
</tr>
<tr>
<td>35</td>
<td>9(R)</td>
<td>0.65</td>
<td>7.6</td>
<td>White Graft</td>
</tr>
</tbody>
</table>

(R)* Rockefeller strain
(A)** Amana strain
"first-set response" with the exception of experiments 21 and 26. In these two cases the indifferent grafts were rejected as white grafts. The test grafts in both of these experiments were white graft rejections. The control autografts on the six peritoneal cell recipients showed no signs of rejection, as shown in Table V.

Passive transfer of 20 ml of serum, from sensitized guinea pigs to normal recipients, failed in six attempts to sensitize passively the recipients to reject the test graft in an accelerated manner. In indifferent homograft controls were rejected by the "first-set reaction", and the autograft controls remained viable and intact throughout the observation period.

Table VI summarizes the six experiments attempting passive transfer of homograft sensitivity with cells and serum after 7 days skin sensitization of the cell and serum donor guinea pigs. Cells from the regional lymph nodes were consistently competent at sensitizing passively a normal recipient to a state of rejecting a test homograft by white graft reaction. Cells from the peritoneal cavity conferred homograft sensitivity about half of the time. Serum did not transfer skin sensitivity at 7 days.

Passive transfer at 28 days. Four attempts were made to sensitize passively a normal guinea pig recipient with cells from the regional lymph nodes of animals 28 days following skin grafting. In four attempts, the test homograft was rejected in a normal "first-set reaction", as shown in Table VII, which indicated there was no demonstrable activity present. The range in cell numbers employed in these four experiments was $5.5 \times 10^8$ to $7.0 \times 10^8$. 

TABLE V
PASSIVE TRANSFER WITH PERITONEAL EXUDATIVE CELLS
FROM SKIN SENSITIZED GUINEA PIGS TO NORMAL RECIPIENTS
AT 7 DAYS AFTER GRAFTING

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>No. of Cell Donors</th>
<th>Packed Vol. of Cells ml.</th>
<th>Approx. No. Cells</th>
<th>Fate of Test Graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>10(R)*</td>
<td>1.10</td>
<td>1.2 x 10^9</td>
<td>Rejected at 8th day</td>
</tr>
<tr>
<td>21</td>
<td>10(A)**</td>
<td>0.65</td>
<td>7.0 x 10^8</td>
<td>White Graft</td>
</tr>
<tr>
<td>22</td>
<td>10(A)</td>
<td>0.65</td>
<td>6.5 x 10^8</td>
<td>White Graft</td>
</tr>
<tr>
<td>26</td>
<td>9(R)</td>
<td>1.55</td>
<td>1.5 x 10^9</td>
<td>White Graft</td>
</tr>
<tr>
<td>29</td>
<td>10(R)</td>
<td>0.80</td>
<td>7.5 x 10^8</td>
<td>Rejected at 7th day</td>
</tr>
<tr>
<td>35</td>
<td>9(R)</td>
<td>1.00</td>
<td>1.1 x 10^9</td>
<td>Rejected at 8th day</td>
</tr>
</tbody>
</table>

(R)* Rockefeller strain
(A)** Amana strain
### TABLE VI

SUMMARY OF PASSIVE TRANSFER EXPERIMENTS CONDUCTED 7 DAYS AFTER SENSITIZATION OF CELL AND SERUM DONORS WITH SKIN HOMOGRAFTS

<table>
<thead>
<tr>
<th>SOURCE OF CELLS</th>
<th>SERUM</th>
</tr>
</thead>
<tbody>
<tr>
<td>PERITONEAL EXUDATIVE CELLS</td>
<td>REGIONAL LYMPH NODE CELLS</td>
</tr>
<tr>
<td><strong>NO. OF REJECTIONS</strong></td>
<td><strong>3/6</strong></td>
</tr>
<tr>
<td>5 DAYS AFTER GRAFT CHALLENGE*</td>
<td></td>
</tr>
</tbody>
</table>

* Placed 48 hr. after cellular and serum injection
TABLE VII
PASSIVE TRANSFER WITH REGIONAL AND NON-REGIONAL LYMPH NODE CELLS FROM SKIN SENSITIZED GUINEA PIGS TO NORMAL RECIPIENTS AT 28 DAYS AFTER GRAFTING

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>No. of Cell Donors</th>
<th>Cell Source</th>
<th>Packed Vol. of Cells ml.</th>
<th>Approx. No. Cells (X 10^8)</th>
<th>Fate of Test Graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>10(R)*</td>
<td>RLN</td>
<td>0.55</td>
<td>6.0</td>
<td>Rejection at 9th day</td>
</tr>
<tr>
<td>30</td>
<td>10(R)</td>
<td>RLN</td>
<td>0.50</td>
<td>5.5</td>
<td>Rejection at 9th day</td>
</tr>
<tr>
<td>31</td>
<td>8(A)**</td>
<td>Pooled RLN&amp;NRLN</td>
<td>0.60</td>
<td>7.1</td>
<td>White Graft</td>
</tr>
<tr>
<td>32</td>
<td>9(A)</td>
<td>RLN</td>
<td>0.60</td>
<td>7.0</td>
<td>Rejection at 9th day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NRLN</td>
<td>0.40</td>
<td>4.5</td>
<td>Rejection at 9th day</td>
</tr>
<tr>
<td>34</td>
<td>8(R)</td>
<td>RLN</td>
<td>0.50</td>
<td>5.8</td>
<td>Rejection at 8th day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NRLN</td>
<td>0.35</td>
<td>4.0</td>
<td>Rejection at 9th day</td>
</tr>
</tbody>
</table>

(R)* Rockefeller strain
(A)** Amana strain
RLN - Regional lymph nodes
NRLN - Non-regional lymph nodes
regional lymph node cells. On two occasions, $4.0 \times 10^8$ and $4.5 \times 10^8$, non-regional lymph node cells were harvested and injected into recipients, and no evidence of accelerated test graft rejection was observed. When regional and non-regional lymph nodes were pooled to give $7.1 \times 10^8$ cells (experiment 31) the test graft was rejected as a white graft. In the seven experiments, the indifferent homograft control was rejected as a "first-set rejection". The autograft controls were not rejected in any of the recipient animals.

Passive transfer of homograft sensitivity with peritoneal cells was attempted eight times in five separate experiments. Table VIII presents the results of studies 28 days after sensitization. On three occasions the peritoneal cells were divided into two pools to determine the lowest number of cells which would competently sensitize a normal recipient. White graft rejection was observed in the test graft seven times in eight attempts. In experiments 32 and 34, $6.5 \times 10^8$ cells were given to peritoneal cell recipients. In experiment 32 homograft sensitivity was not transferred, while in experiment 34 the test graft was observed as a white graft rejection. Three of the indifferent homograft controls were also rejected as white grafts and four others were rejected as "second-set grafts". The autograft controls exhibited no signs of rejection throughout the period of observation.

Passive transfer of homograft sensitivity was attempted with serum collected from guinea pigs 28 days following skin sensitization. The test
### TABLE VIII

**PASSIVE TRANSFER WITH PERITONEAL EXUDATIVE CELLS**

**FROM SKIN SENSITIZED GUINEA PIGS TO NORMAL RECIPIENTS**

**AT 28 DAYS AFTER GRAFTING**

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>No. of Cell Donors</th>
<th>Cell Source</th>
<th>Packed Vol. of Cells ml.</th>
<th>Approx. No. Cells</th>
<th>Fate of Test Graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>10(R)*</td>
<td>PE‡</td>
<td>2.5</td>
<td>$2.35 \times 10^9$</td>
<td>White Graft</td>
</tr>
<tr>
<td>30</td>
<td>10(R)</td>
<td>PE(A)</td>
<td>1.0</td>
<td>$9.00 \times 10^8$</td>
<td>White Graft</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(B)</td>
<td>3.0</td>
<td>$2.80 \times 10^9$</td>
<td>White Graft</td>
</tr>
<tr>
<td>31</td>
<td>8(A)**</td>
<td>PE</td>
<td>2.5</td>
<td>$2.30 \times 10^9$</td>
<td>White Graft</td>
</tr>
<tr>
<td>32</td>
<td>9(A)</td>
<td>PE(A)</td>
<td>0.7</td>
<td>$6.50 \times 10^8$</td>
<td>Rejected at 9th day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(B)</td>
<td>3.3</td>
<td>$3.10 \times 10^9$</td>
<td>White Graft</td>
</tr>
<tr>
<td>34</td>
<td>8(R)</td>
<td>PE(A)</td>
<td>0.7</td>
<td>$6.50 \times 10^8$</td>
<td>White Graft</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(B)</td>
<td>1.7</td>
<td>$1.65 \times 10^9$</td>
<td>White Graft</td>
</tr>
</tbody>
</table>

(R)* Rockefeller strain

(A)** Amana strain

PE‡ - Peritoneal Exudative Cells
homografts exhibited no signs of accelerated rejection, which indicated no transfer of homograft sensitivity with serum.

The results of passive transfer studies at 28 days are presented in Table IX. The rejection activity of the regional node decreased since day 7 until day 28 when there was no detectable activity. In one instance the regional and non-regional lymph node cells were pooled and they conferred homograft immunity to a recipient. The peritoneal cells maintained the high level of activity at 28 days which was first seen on day 14. Serum remained inactive at 28 days.
TABLE IX

SUMMARY OF PASSIVE TRANSFER EXPERIMENTS
CONDUCTED 28 DAYS AFTER SENSITIZATION OF
CELL AND SERUM DONORS WITH SKIN HOMOGRAFTS

<table>
<thead>
<tr>
<th>SOURCE OF CELLS</th>
<th>SERUM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PE**</td>
</tr>
</tbody>
</table>

| NO. OF REJECTIONS 5 DAYS AFTER GRAFT CHALLENGE* | 7/8 | 0/4 | 0/2 | 1/1 | 0/5 |

* Placed 48 hr. after cellular and serum injection

** Peritoneal exudative cells

⁺ Regional lymph nodes

++ Non-Regional lymph nodes
DISCUSSION

Skin homograft sensitivity can be transferred to normal guinea pigs by leukocytic cell populations collected from guinea pigs sensitized to skin. The guinea pig was chosen as the experimental animal because it best exhibits delayed type hypersensitivity.

Peritoneal exudative cells competently transferred an accelerated graft rejection response to normal recipients at 14 and 28 days, as evidenced by the white graft rejection phenomenon. Landsteiner and Chase (31) established cellular transfer of sensitivity as a major criterion of delayed type hypersensitivities. Peritoneal cell transfer of chemical, tuberculin and bacterial hypersensitivities has been investigated and in all cases these cells consistently transfer a state of sensitivity (32,33,34,35,36,37).

Serum collected from skin sensitized animals and transferred at 7, 14, and 28 days failed to confer skin sensitivity. Transfer of chemical, tuberculin, and bacterial hypersensitivities with serum cannot be effected in these systems, as reported by a number of investigators (32,33,34,35,36,37).

Regional lymph node cells transferred sensitivity when harvested at 7 and 14 days. Billingham, Brent, and Medawar (4) transferred skin sensitivity with regional node cells up to 30 days after sensitization in mice. Mitchison (24) reported that regional node cells would confer tumor immunity only when collected and transferred during the active rejection of the
sensitizing tumor. Najarian and Feldman (28) observed accelerated rejection of test grafts in guinea pigs which had received regional node cells collected from skin sensitized animals at the time of "first-set rejection".

There appeared to be a gradual distribution of competence initiated in the regional lymph nodes in the early stages of sensitization, which progressed to a whole body response, as represented by the peritoneal exudative cells. Activity gradually shifted from the 7th through 14th days with the regional lymph nodes demonstrating competence up to this time and peritoneal cells gaining activity at this time.

Competence to reject skin homografts appears to reside in the lymphocytic cells which are present in the regional lymph nodes. The mode of induction or stimulation has not been elucidated (56). The node cells exhibit their competence as early as the 7th day, as shown in passive transfer experiments reported here. As the activity diminishes in the regional lymph nodes at 14 days this reduction in competence should be accounted for. The reduced activity may be the result of departure of competent lymphoid cells from the regional nodes which then populate distant lymph nodes, the spleen, and the general blood circulation after the 7th day (60). As the peritoneal cell population gains competence to transfer homograft sensitivity, it is possible that the activity lies with the lymphocytic cells present in this population. Alternatively, the monocytic cells may possess activity, a possibility that must be considered. At 7 days, when activity was at a high level in the regional nodes, approximately $6.0 \times 10^8$ cells were required to sensitize
passively a normal recipient. At 14 days a greater number of regional node cells were needed to effect transfer. Also at 14 days the peritoneal cell population consistently transferred skin sensitivity if $1.2 \times 10^9$ cells were employed. Twenty to twenty-five per-cent of this population consisted of small lymphocytes, or approximately $2.4 \times 10^8$ to $3.0 \times 10^8$ lymphocytic cells were present. At 28 days transfer of skin sensitivity could be transferred with $9.0 \times 10^8$ peritoneal cells of which $1.8 \times 10^8$ to $2.25 \times 10^8$ cells were lymphocytes. In both cases the number of lymphocytes present in competent peritoneal cell populations was well below the $6.0 \times 10^8$ cell lymphocytes needed to effect transfer at 7 days when the regional lymph nodes were active. At 14 days $8.0 \times 10^8$ to $9.2 \times 10^8$ lymph node cells transferred sensitivity on two occasions. At 28 days $5.5 \times 10^8$ to $7.0 \times 10^8$ lymph node cells would not transfer sensitivity.

With respect to numbers it does not appear that the lymphocyte population within the peritoneal cell exudate was great enough to sensitize a recipient. Coe, Feldman and Lee (59), employing lymphocytic cell populations collected from the thoracic duct of rats sensitized to soluble proteins, reported that it was not cell numbers that limited transfer of activity, but the cell types in the population. If the monocytic cells present in the peritoneal cell population possess competence to transfer skin sensitivity how do they gain this activity? At this time there is no satisfactory technique whereby the monocyte population can be separated from the peritoneal exudate and studied as a homogeneous population. There may be a direct stimulation of
the monocytic cell, as cells of this type may be found in the lymph nodes, but because of their low numbers the sensitization period may be more prolonged. The monocytic cells may be carrying a cytophilic antibody produced by other competent cells which were stimulated by tissue antigen. There may be a transformation of competent lymphocytes into committed monocytes whose activity is that of destruction of foreign tissue (57). It appears that the monocytic cells do possess the activity to sensitize a recipient to specific tissue grafts.

The accelerated rejection state transferred by sensitized cells was the white graft rejection phenomenon. Rappaport and Converse (59) reported the occurrence of the white graft rejection in second-set skin homografts in human beings when grafted within 7 days after the "first-set rejection". Lehrfield, Taylor and Converse (61) observed a similar response in second-set skin grafts on the rat. The white graft rejection was investigated by Henry et al. (54) from both a microscopic and histological standpoint and they suggested the white graft was a more accelerated response than the classical "second-set response". These investigators proposed the mediation of a humoral factor and suggested a similarity existed between the Arthus phenomenon and the white graft rejection, primarily on the basis of histological findings. Young, Hopkins and Esparza (55) reported passive transfer of white graft sensitivity from skin grafted rabbits to normal animals with immune serum. Perez-Tamayo and Kretschemer (45) claimed the state of white graft rejection is of short duration existing shortly after the "first-set rejection" which is mediated by a
circulating factor which interferes with the establishment of capillaries to the graft. As the titer of the serum factor decreases, in 7 to 10 days, the animal responds to a second graft by the classical cellular "second-set response". The transfer studies reported here do not endorse this hypothesis. Serum collected from skin sensitized guinea pigs at 7, 14, and 28 days, within the required time after "first-set rejection", failed to transfer homograft sensitivity of any kind. Large quantities of serum were transferred to recipients and if a factor was present it could not be demonstrated in this manner. However, regional lymph node cells collected and transferred at 7 and 14 days and peritoneal cells collected and transferred at 14 and 28 days were very competent at transferring white graft sensitivity to normal guinea pigs. Histological examination of the rejected tissues was not made and comparisons were not done.

The indifferent homograft control on several occasions also was rejected as a white graft. It is conceivable that the indifferent skin donor shared common tissue antigens with the test skin donor and as a result were rejected in an accelerated fashion. Alternatively, the transferred state of skin sensitivity may be somewhat non-specific, in that subtle differences between the tissue antigenic structure of the test skin graft and the indifferent tissue were not recognized.
SUMMARY

The hypothesis that homograft rejection is mediated by an immunological response of delayed-type hypersensitivity was investigated. Skin homograft sensitivity was transferred with lymphoid cells and peritoneal exudative cells in the guinea pig. Regional lymph node cells collected 7 days after graft placement consistently transferred sensitivity. Peritoneal exudative cells competently transferred homograft sensitivity to normal guinea pigs at 14 and 28 days. During this time period, the transfer capacity of the regional lymph node cells was reduced. Immune serum failed to sensitize normal recipients. These findings correlate with results of cellular passive transfer studies for chemical and tuberculin hypersensitivities in the guinea pig.
LITERATURE CITED


