ney is 40% of normal then the total filtrate must be reabsorbed to produce anuria. Alternative explanations, however, would be that the metabolic work for sodium reabsorption is greater in the anuric kidney or that oxygen is being utilized for other purposes. Thus the glomerular filtration rate might be reduced far more than renal blood flow in the anuric kidney.

The increase in renal flow seen during the recovery phase of the illness suggests that renal ischaemia may play some part in maintaining the oliguric stage of acute renal failure.

Summary. The renal blood flow was measured by a constant infusion of indocyanine green into a renal artery in 8 patients with acute oliguric renal failure. There was an average reduction of renal blood flow to 40% of normal. Renal oxygen consumption was similarly reduced. However, renal arteriovenous oxygen content difference was not significantly altered from control values. In the recovery phase renal blood flow and oxygen consumption increased to 70% of normal. The persistence of renal failure in the acute oliguric phase could not therefore be explained by total reduction in renal blood flow as had previously been postulated.

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Received November 16, 1962. P.S.E.B.M., 1963, v112.

Parabiotic Intoxication in F_1 Hybrid Mice After Immunological Depression of the Parent Strain.* (28215)

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Parabiotic union performed between F_1 hybrid mice and members of one of the parental strains frequently results in wasting of the F_1 partner ending in its death. This syndrome has been called parabiosis intoxication. While the affected F_1 partner develops a hunched and sickly appearance, loses weight and becomes severely anemic, the non-intoxicated parental strain partner becomes polycythemic. The similarity between the intoxicated parabiont and the animal suffering from homologous disease has been pointed out(1-4), and it has been suggested that some or perhaps all of the phenomena observed in parabiosis intoxication may depend upon an immunological reaction by the parental strain partner against the hybrid member of the parabiotic pair. Tokuda and MacGillivray(5) have recently suggested that immunologically competent cells of the parental strain partner might react against the tissue antigens of the hybrid, leading to constriction and occlusion of the capillaries carrying blood from the parental

* Aided by grants from U.S.P.H.S., Am. Cancer Soc., Minnesota Heart Assn., Am. Heart Assn., and the National Foundation.

strain partner to the hybrid, thus creating an unequal cross-circulation gradient between the partners leading to the anemia-polycythemia picture. On the other hand, Hall and Hall(6) felt that parabiotic intoxication did not have an immunological basis. Eichwald *et al.*(7) have recently expressed the view that the anemia-polycythemia occurs as a result of two separate mechanisms: one that depends upon a vascular pressure gradient which begins to operate immediately or shortly after vascular connections have been established, resulting in anemia in either partner, and another one appearing later which has an immunological basis and which initiates or maintains the anemic state in the F_1 hybrid partner.

The experiments to be reported here were performed to ascertain the role played by immunological mechanisms in parabiotic intoxication. In a first set of experiments isologous pairs of mice were joined in parabiosis to determine whether or not the anemia-polycythemia (AP) would develop in the absence of genetic disparity between parabiotic partners. Since it has been shown that neonatal thymectomy renders mice defective in their capacity to produce graft-*versus*-host reactions(8), to reject skin transplants from mice differing at the H-2 histocompatibility locus(9,10) and to produce circulating antibodies(10,11), in a second group of experiments parental strain mice thymectomized within 24 hours of birth were joined to their F_1 hybrids when they were 1½ to 2 months of age. In a third set of experiments the parental strain partners were lethally X-irradiated as adults 1-6 hours prior to the establishment of parabiosis, since it is known that X-irradiation causes depression of graft-*versus*-host reactions and inhibition or abolition of antibody responses(12,13). The experiments to be reported demonstrated that neonatal thymectomy of the parental strain partner had no effect upon the initiation and course of parabiotic intoxication. By contrast, lethal X-irradiation, while not eliminating the early AP, had a suppressive effect upon the later manifestations of this syndrome.

Materials and methods. Inbred mice of the A strain and F_1 hybrids resulting from the cross between A and $C_{57}Bl/1$ were employed in all experiments. Four experimental groups were prepared as follows: (1) normal A strain mice joined with (A × $C_{57}Bl/1$) F_1 hybrids, (2) (A × $C_{57}Bl/1$) F_1 hybrids with (A × $C_{57}Bl/1$) F_1 hybrids, (3) lethally X-irradiated A strain mice with (A × $C_{57}Bl/1$) F_1 hybrids, and (4) thymectomized A strain mice with (A × $C_{57}Bl/1$) F_1 hybrids. In all instances parabiotic partners were of the same sex, between 1½ and 2 months of age, and approximately of equal body weight. Parabiosis was of the celomic type, performed under Nembutal anesthesia. Mid-lateral incisions of skin, muscle and peritoneum were made, followed by union of the peritoneal cavities and muscle layers with 5-0 catgut and clipping of the skin with 11 mm wound clips. Parabiotic pairs were caged individually having free access to Purina Fox Chow and tap water. Thymectomies were performed at birth (0-24 hours after delivery) employing the technique routinely used in this laboratory(9). One group of A strain mice was given 700 r of total body X-irradiation. Conditions of irradiation were as follows: 220 KV, 15 ma (0.25 mm copper filter), target distance 60 cm, dose rate 47 r/minute. Hematocrit determinations were made on all parabionts at days 1, 5, 8, 12, and 16 after establishment of parabiosis. Blood was obtained by excising the tip of the tail under ether anesthesia and gently drawing blood into heparinized capillary tubes.

Results are presented in Table I and Fig. 1.

Parent-hybrid pairs. In all parent-hybrid parabiotic pairs the parental strain partner had become polycythemic and the hybrid anemic by the fifth day after union. In fact, in this group the mean hematocrit difference between the partners ranged between 18 and 23 on the 5th, 8th, and 12th days, dropping to 9 on the 16th day after union. Ten of the 11 pairs of this group died by the 21st day after parabiosis, one pair surviving to the 28th day. In all instances the hybrid partners appeared wasted and with the typical signs of intoxication from about the 8th day onward.

Isologous pairs. In 4 out of 10 isologous pairs AP was present 5 days after parabiosis as revealed by a hematocrit difference between the partners ranging from 16 to 26. The hematocrit values of the pair with the

TABLE I. Hematocrit Values of Parabiosed Mice.

Day	No. of pairs	Mean hematocrit		Mean hematocrit difference
	(1) Normal A—(A × C57Bl/1) F_1			
1	11	51 ± 1.9*	50 ± 3.0*	1 ± 3.3*
5	11	59 ± 5.0	41 ± 6.9	18 ± 10.0
8	9	59 ± 7.5	36 ± 7.2	23 ± 13.1
12	7	60 ± 8.1	38 ± 9.7	22 ± 15.9
16	5	49 ± 9.2	40 ± 9.9	9 ± 6.9
	(2) (A × C57Bl/1) F_1—(A × C57Bl/1) F_1			
1	4	48 ± 4.6	47 ± 1.7	1 ± 5.5
5	4	55 ± 3.0	34 ± 2.6	21 ± 3.5
8	4	53 ± 4.8	46 ± 1.8	7 ± 4.1
12	4	43 ± 8.3	42 ± 10.6	1 ± 3.8
16	4	44 ± 5.8	42 ± 4.6	2 ± 1.7
	(3) X-irrad. A—(A × C57Bl/1) F_1			
1	8	52 ± 2.2	53 ± 2.8	−1 ± 1.2
5	8	59 ± 4.4	28 ± 9.9	31 ± 14.3
8	4	52 ± 5.4	42 ± 1.5	10 ± 6.6
12	4	44 ± 3.3	43 ± 8.6	1 ± 6.5
16	4	43 ± 9.4	41 ± 10.9	2 ± 1.4
	(4) Thymect. A—(A × C57Bl/1) F_1			
1	10	48 ± 2.4	49 ± 3.5	−1 ± 2.0
5	10	58 ± 6.2	32 ± 7.0	26 ± 12.6
8	7	57 ± 6.0	38 ± 7.7	19 ± 11.3
12	6	57 ± 11.9	31 ± 10.6	26 ± 16.6
16	3	46 ± 22.0	23 ± 8.9	23 ± 22.4

* Standard deviation.

most extreme difference of the 5th day post parabiosis were 59 and 33. By the 12th day the hematocrit values of the members of these pairs had returned to normal, and all the animals survived permanently.

Irradiation. When the parental strain member of the pair was previously X-irradiated AP was present also at the 5th day, but in contrast to the parent-hybrid control group, AP had been completely eliminated by the 12th day. Thus, the later course of AP in the X-irradiated group was strikingly different from that seen in the control parent-hybrid group, and it closely resembled that seen in the isologous pairs which had shown AP at 5 days. Of 8 pairs alive at the 5th day after union, 4 survived to the 8th day. Both parabiotic partners in these 4 pairs were vigorous and healthy in appearance after the 8th day, and all survived beyond the 28th day.

Thymectomy. When parabiosis was performed between the thymectomized pure partner and its F_1 hybrid, AP on days 5 through 16 following parabiosis was not significantly different from that seen when a non-thymectomized partner was employed. Clinically the hybrid mice of the thymectomized group were suffering from intoxication, and all parabiotic pairs had died by the 21st day after union.

Discussion. The occurrence of AP 5 days after establishment of parabiosis in 4 out of 10 isologous pairs of (A × C_{57}Bl/1) F_1 hybrids indicates that immunological mechanisms are not necessarily required for early development of AP when parabiosis is performed between parents and F_1 hybrids. In this regard, Hall and Hall(6) reported parabiotic intoxication in littermate rats previously united in parabiosis if spinal cord transection was performed in one partner. This suggests that perhaps the early AP may be the result of a pressure gradient at the capillary level. Our findings that AP at 5 days was not at all depressed by neonatal thymectomy or lethal X-irradiation of the parental strain partner provide additional support for the concept formerly expressed by Hall and Hall(6) and Eichwald *et al.*(7) that the early development of AP is not basically immunological in nature. Lethal X-irradiation of the parental strain partner had a profound effect upon the later course of intoxication, as revealed by the fact that AP was eliminated by the 12th day, clinical wasting of the F_1 hybrid was not present, and survival of the pairs was prolonged. These effects can be best explained by assuming that X-irradiation eliminated a second phase of the parabiotic intoxication syndrome which depends upon an immunological reaction elicited by the parental strain partner against the hybrid. Thus, it is concluded, as Eichwald *et al.*(7) had previously proposed, that parabiotic intoxication observed in parent-hybrid parabiosis may pro-

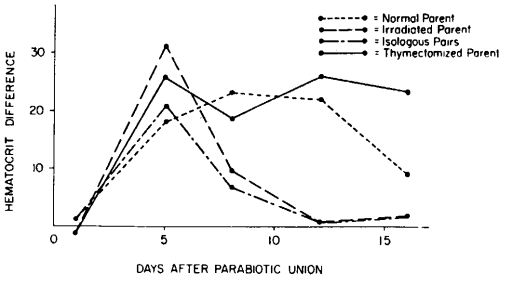

FIG. 1. Mean hematocrit differences between pairs of mice joined in parabiosis. The isologous pairs are (A × C_{57}Bl/1) F_1 hybrids. The other pairs are either normal, irradiated, or thymectomized A strain mice joined with (A × C_{57}Bl/1) F_1 hybrids.

ceed in two phases: an initial phase in which AP is present and whose mechanism may be the establishment of a pressure gradient from hybrid to the parent strain partner, and a second phase in which AP is initiated or maintained by an immunological reaction.

The failure of neonatal thymectomy of the parent strain partner to alter the course of intoxication might perhaps be explained on the basis that early thymectomy of this partner may not have completely abolished its immunological capacity to react against the tissue antigens of the F_1 hybrid, thus perhaps allowing the development of the immune phase of parabiosis intoxication. Indeed, it has been shown that adult lymphoid cells derived from mice thymectomized immediately after birth are extremely defective but not completely incapable of eliciting graft-*versus*-host reactions(14). Further, mice thymectomized at birth can produce antibodies when stimulated with certain antigens(15). Another possibility might be that the functional ability of the thymus of the intact F_1 hybrid may have restored the immunological capacity of the parental strain partner which had been thymectomized at birth. That this might be so is suggested by previous experiments showing restoration of immunological capacity in thymectomized mice by subcutaneous implants of homologous newborn thymus(14). We are currently investigating these possibilities.

Summary. (1) Four out of 10 isologous parabiotic pairs showed AP at 5 days but this was no longer present 12 days after union. (2) Neonatal thymectomy of the parental strain partner put in parabiosis with the corresponding F_1 hybrid did not significantly alter the course of parabiotic intoxication in the latter. (3) Lethal X-irradiation of the parental strain partner had no effect upon AP at 5 days, but AP was eliminated by the 12th day after union. In this instance clinical wasting was not present and survival of the pairs was considerably prolonged. (4) It is concluded that parabiotic intoxication observed in parent F_1 hybrid combinations proceeds in two phases: an early phase in which the anemia-polycythemia picture depends upon a vascular pressure gradient established from the F_1 hybrid to the parent, and a later phase in which the pressure gradient is sustained by an immunological reaction elicited by the parent strain partner against the hybrid.

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Received December 26, 1962. P.S.E.B.M., 1963, v112.