pathologic states are rare in the literature. Notable are the reports that a_2-macroglobulin levels are elevated in newly born humans through the first year(9) and in sufferers from rheumatoid arthritis and ankylosing spondylitis(10). There is also a report that a_2-macroglobulin levels are depressed in maternal plasmas toward the end of pregnancy(11). The most thorough study to date by Brown and associates(12) demonstrates major increases in human a_2-macroglobulin during nephrosis. Consequently, it has been suggested that a_2-macroglobulin and other large plasma proteins may aid in maintaining blood osmotic pressure in pathologies accompanied by depletion of smaller plasma proteins.

This report is the first to document the diminution of a vertebrate a-macroglobulin during a specific pathology. The progressive decreases of a-macroglobulin found during malaria in the duckling suggest that a-macroblubulin levels may be subject to influences, yet undescribed, which are not directly related to osmotic regulation. The possibility thus occurs that a-macroglobulins may be primary components of the defensive reaction of the vertebrate host to infection.

Summary. A plasma protein, identified as a high molecular weight a-globulin is shown to decrease strikingly during malarial infection in the duckling.

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1. Blumberg, B. S., Kuvin, S. F., Robinson, J. C., Teitelbaum, J. M., Contacos, P. G., J. Am. Med. Assn., 1963, v184, 1021.
2. Lunn, J. S., Chin, W., Contacos, P. G., Coatney, G. R., Am. J. Trop. Med. & Hyg., 1966, v15, 3.
3. Smithies, O., Adv. Prot. Chem., 1959, v14, 65.
4. Kunkel, H. G., Slater, R. J., Proc. Soc. Biol. and Med., 1952, v80, 42.
5. Edelman, G. M., Kunkel, H. G., Franklin, E. C., J. Exp. Med., 1958, v108, 105.
6. Smithies, O., Biochem. J., 1955, v61, 629.
7. Parker, W. C., Ph.D. Thesis, The Rockefeller Inst., 1963.
8. Sherman, I. W., Hall, R. W., J. Protozool., 1960, v7, 17.
9. Hitzig, W. H., Bull. Schweiz, Akad. Med. Wiss., 1961, v17, 228.
10. Mackiewicz, S., Fenrych, W., Ann. Rheum. Dis., 1961, v20, 265.
11. Schlagetter, K., Schwick, G., Z. Geburts. u. Gynacol. 1961, v157, 225.
12. Peterkofsky, A., Levine, L., Brown, R. K., J. Immunol., 1956, v76, 237.
13. Lowry, O. H., Rosebrough, N. J., Farr, A. L., Randall, R. J., J. Biol. Chem., 1951, v193, 265.

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Staphylococcal Infection in Normal and Splenectomized Monkeys.* (31544)

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Previous studies from this laboratory have demonstrated similar responses in normal and splenectomized monkeys following streptococcal(1) and pneumococcal(2) infections. Despite the great number of studies in experimental staphylococcal infections(3,4), little information on the reaction of monkeys to this organism is available. Verlinde and Makstenieckс(5) observed mild clinical reaction in monkeys following either intranasal or intratracheal inoculation with *Staphylococcus aureus;* slight bronchiolitis and limited foci of bronchopneumonia were observed. It is the purpose of this report to compare the results following aerosol and intravenous

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challenge of normal and splenectomized monkeys with staphylococci.

Materials and methods. Young pre-pubertal monkeys *(Macaca mulatta)* were splenectomized under pentothal-ether anesthesia. Controls were similarly treated, except that the spleen was manipulated but not removed.† The *Staphylococcus aureus* strain used was a phage type 80/81 and was a recent isolate from a patient at University Hospital. It was coagulase positive and hemolytic, but was not virulent for mice with or without mucin after intraperitoneal inoculation of 2.1×10^8 cocci. Growth from Bacto-Brain Heart Infusion blood agar plates incubated 20 hours after inoculation from 8-hour Trypticase Soy (BBL) broth cultures was washed off with 0.1% Bacto-gelatin in physiologic saline for use in the Henderson apparatus aerosol generator. Inocula to be given intravenously were prepared in physiologic saline. Aerosol challenge of monkeys was performed in a Model 3 Henderson apparatus(6). Intravenous challenge was made into the saphenous vein.

Base-line studies included physical examinations, hematologic, serologic and bacteriologic studies for 2 weeks prior to challenge. Monkeys were given a complete physical examination twice daily after challenge. Femoral vein blood was used for blood counts, cultures and C-reactive protein (CRP) tests daily or every other day, and weekly for serologic studies. Methods used for cultures and CRP tests have been described previously(1).

Antibody response was followed by agglutination tests employing killed(7) and living (8) suspensions and by a test for anti-alpha hemolysins. In the latter, serum was inactivated at 56°C for 30 minutes and then absorbed at 4°C with rabbit erythrocytes. Absorbed serum was diluted serially in 0.5 ml of Kolmer saline containing 0.1% Bacto-gelatin. After addition of 10 hemolytic units of alpha hemolysin (Wellcome Research Laboratories) contained in 0.5 ml of the same diluent and 1.0 ml of 1% rabbit erythrocytes, tests were incubated at 37°C for 1 hour, centrifuged for 3 minutes at 1500 RPM in an International Size 2 centrifuge, and read. The end-point was the greatest dilution of serum showing complete inhibition of hemolysis.

Results. Aerosol challenge. Exposure for 3 minutes of 2 monkeys each to an aerosol containing 1.7×10^7 and 1.4×10^8 organisms per liter, respectively, resulted in no obvious illness. There were no positive blood cultures, CRP or leukocytosis. Serologic changes were observed in only 1 monkey of the lower dose pair in which the anti-alpha hemolysin titer increased from base-line of 1:40 to a peak of 1:320 at 6 weeks. Nasopharyngeal culture was positive for 2 days in this animal, but none of the other monkeys showed positive cultures. Similarly, exposure of 4 monkeys splenectomized 8 months previously, and 2 controls, to an aerosol containing 1.0×10^7 organisms per liter resulted in no clinical or laboratory evidence of infection. Nasopharyngeal cultures were positive in 2 of 4 splenectomized monkeys for 2 and 3 days, respectively, and in both controls for 1 and 2 days, respectively. No leukocytosis, CRP or antibody changes were observed in any.

Intravenous challenge. Preliminary experiments in 2 normal monkeys (Nos. 28, 69) showed that after intravenous challenge with 2.2×10^{10} organisms, both became ill within 24 hours exhibiting fever, weakness, lethargy and anorexia. Monkey 28 became comatose on the 3rd day, and expired on the 4th day. No leukocytosis was observed, but left shift in neutrophiles did occur by the 2nd day. Blood cultures and CRP were positive within 24 hours, and until death at which time the staphylococcus was isolated from spleen, liver, kidney, lung, bone marrow, pericardial and spinal fluids. Monkey 69 recovered spontaneously, and was asymptomatic by the 14th day; blood cultures and CRP were positive for 10 and 14 days, respectively. Polymorphonuclear leukocytosis was observed from the 2nd through the 14th day. When sacrificed 65 days after challenge, no gross evidence of past infection was noted, and cultures were negative. Significant antibody change was observed only with the viable agglutination antigen with increase from base-line titer of 1:200 to a peak of 1:1600 by the 2nd week.

† Kindly performed by Dr. G. R. Johnson.

TABLE I. Effect of Intravenous Staphylococcal Challenge in Normal and Splenectomized Rhesus Monkeys.

	Exp 1—13 days P.S.* Dose: 6.1×10^9					Exp 2—24 days P.S. Dose: 5.4×10^{10}						Exp 3—45 days P.S. Dose: 9.0×10^{10}				Exp 4—90 days P.S. Dose: 1.6×10^9				
	Splen			Controls		Splen		Controls				Splen		Controls		Splen			Controls	
Monkey No.	47	57	60	19	80	14	19	94	66	5	6	11	45	3	74	75	2	42	65	76
Fever	+	+	—	—	—	—	+	+	+	+	—	—	+	—	—	+	+	+	+	+
Illness	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Death	+	—	+	+	+	+	+	+	—	—	+	+	+	+	+	—	—	—	—	—
Leukocytosis	+	+	+	—	—	+	+	+	+	—	+	+	+	—	—	+	+	+	+	+
CRP	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Blood culture	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Viable aggl. titer rise	D†	3‡	D	D	D	D	D	D	—	2	D	D	D	D	D	2	3	—	—	3
Killed aggl. titer rise	”	—	”	”	”	”	”	”	3	—	”	”	”	”	”	3	2	—	3	4
Anti-α hemolysin titer rise	”	—	”	”	”	”	”	”	—	—	”	”	”	”	”	2	2	—	3	—
Autopsy culture	+	—§	+	+	+	—	+	+	ND‖	ND	+	+	+	+	+	———		ND	———	

	Exp 5—90 days P.S. Dose: 1.6×10^{10}						Exp 6—255 days P.S. Dose: 2.07×10^8						Total 6 experiments	
	Splen			Controls			Splen				Controls		Splen	Controls
Monkey No.	25	53	96	51	52	72	34	35	36	37	38	39		
Fever	+	+	+	+	+	+	+	+	+	+	+	+	14/17¶	10/15
Illness	+	+	+	+	+	+	+	+	+	+	+	—	17/17	14/15
Death	—	—	—	+	—	+	—	—	—	—	—	—	6/17	8/15
Leukocytosis	+	+	+	ND	—	—	+	+	+	+	+	+	17/17	7/14
CRP	+	+	+	+	+	+	+	+	+	+	+	+	17/17	15/15
Blood culture	+	+	+	+	—	+	+	+	+	+	+	+	17/17	14/15
Viable aggl. titer rise	3	3	3	D	2	D	—	—	—	—	—	—	6/11	3/7
Killed aggl. titer rise	2	2	3	”	4	”	—	2	—	—	2	—	6/11	5/7
Anti-α hemolysin titer rise	2	3	3	”	—	”	—	—	—	—	—	—	5/11	1/7
Autopsy culture	——ND——			+	ND	+	——————ND——————						5/7	8/8

* P.S. = Post-splenectomy. † D = Negative at time of death. ‡ Tubes increase in titer. § Sacrificed on 64th day. ‖ N.D. =Not done.
¶ Numerator = No. positive; denominator = total No.

Six separate experiments (Table I) were performed to compare response of normal and splenectomized monkeys after intravenous challenge. In Experiment 1, 3 monkeys splenectomized 13 days previously and 2 controls were challenged with 6.1×10^9 organisms. Within 24 hours all 3 splenectomized animals exhibited weakness, anorexia and lethargy, and significant fever was recorded in 2 (Nos. 47, 57). Two monkeys (Nos. 47, 60) became progressively worse and died on the 5th day although they had become afebrile by the 3rd day. Both animals exhibited significant leukocytosis at 24 hours, only, and positive CRP and blood cultures from the 1st day until death. At autopsy, cultures were positive from heart blood, lung, bone marrow and pancreas in No. 47 and from heart blood, lung, liver, spleen, kidney and bone marrow in No. 60. The 3rd monkey (No. 57) exhibited similar symptoms for 3 days, but recovered spontaneously. On the 9th day an abscess was noted at the site of inoculation extending from knee to ankle. This began to drain spontaneously on the 12th day, and the staphylococcus was isolated from the pus. The lesion slowly resolved, and was healed by the 18th day. Blood cultures and CRP were positive for the first 18 and 12 days, respectively, and leukocytosis up to 44,000 per cu mm was observed for 22 days. The monkey was sacrificed on the 64th day at which time no gross pathology was observed, and cultures were negative. Both controls showed similar illness and laboratory findings (Table I) except for no appreciable leukocytosis, and died on the 3rd and 5th days, respectively. At necropsy the former yielded positive cultures from heart blood, spleen, pericardial and peritoneal fluid and brain; the latter had positive cultures from heart blood, liver, spleen, kidney, bone marrow and pericardial fluid. Serologic studies were negative in all 4 monkeys which died within 5 days, but the one splenectomized animal (No. 57) which survived showed increase in the viable agglutination titer from base-line of 1:200 to a peak of 1:1600 by the 2nd week; killed antigen agglutination and anti-alpha hemolysin tests showed no changes.

In Experiment 2 (Table I) 2 monkeys splenectomized 24 days previously and 4 controls were challenged with 5.4×10^{10} organisms. Both splenectomized monkeys developed weakness, anorexia and lethargy within 24 hours, became progressively weaker and dehydrated, comatose by the 5th day, and died on the 6th day. Fever was observed on the 1st day only in 1 of 2. Both exhibited leukocytosis, positive blood cultures and CRP from the 1st day until death. At autopsy, positive cultures were obtained from heart blood, lung and liver from No. 19, but cultures from No. 14 were negative. All 4 control monkeys showed similar symptoms within 24 hours. Two (Nos. 6 and 94) of 4 died on the 6th and 12th days, respectively; both animals exhibited daily positive blood cultures, CRP and leukocytosis after 24 hours until death. At autopsy the specific staphylococcus was recovered from liver, only, in No. 6 and from heart blood, liver, kidney, spleen and lung in No. 94. The 2 surviving monkeys became asymptomatic between the 4th and 6th days, although positive blood cultures were recovered up to 17 and 28 days in monkeys 5 and 66, respectively, and CRP was positive up to 7 and 17 days, respectively. Antibody changes were observed in these 2 animals only; the killed antigen agglutination titer increased in No. 66 from base-line of 1:80 to a peak of 1:640 in 2 weeks, while No. 5 showed a rise in the viable agglutination titer from a base-line of 1:800 to 1:3200 by the 2nd week.

In Experiment 3 (Table I) 2 monkeys splenectomized 45 days previously and 2 controls were challenged with 9.0×10^{10} organisms. All 4 showed weakness, lethargy and ataxia within 24 hours, coma between the 2nd and 4th days, and died on the 4th day. All exhibited positive blood cultures and CRP daily and positive cultures from most organs at autopsy. Leukocytosis was observed in both splenectomized monkeys but not in the 2 controls.

In Experiment 4 (Table I), 3 monkeys splenectomized 90 days previously and 2 controls were challenged with 1.6×10^9 organisms. Anorexia and weakness were observed in the 3 splenectomized animals for 3 days after challenge associated with fever in

2 for the 1st 7 days and in the 3rd animal on the 4th and 5th days; all recovered spontaneously. CRP was positive up to 14 days in 2 that exhibited positive blood cultures for 14 and 18 days, respectively, while the 3rd monkey had both CRP and positive cultures for 7 days. Both controls showed similar symptoms and recovered spontaneously; one had positive CRP and blood cultures for 14 and 10 days, respectively, while the other had positive tests for 10 and 7 days, respectively. Leukocytosis was observed for 24 days in splenectomized monkeys and for 7 and 14 days, respectively, in controls. Significant antibody titer changes were observed in all 3 tests in 2 of 3 splenectomized monkeys while 1 control showed significant rise in anti-alpha hemolysin and killed agglutination tests, and the other in both viable and killed agglutination tests.

In Experiment 5 (Table I), 3 monkeys splenectomized 3 months earlier and 3 controls were challenged with 1.6×10^{10} organisms. All 3 splenectomized monkeys became ill, but recovered spontaneously and exhibited positive CRP's for 14 days and positive blood cultures for 28 days in 2, and 14 days in the 3rd. Two of the 3 controls died on the 2nd and 10th days, respectively, after challenge and exhibited positive cultures both antemortem and postmortem. The 3rd control showed mild anorexia, lethargy and fever for 2 days, and recovered spontaneously. CRP was positive for 4 days, but blood cultures were negative. This monkey showed significant antibody rise in both agglutination tests while the 3 surviving splenectomized animals showed significantly increased titers in all 3 tests.

In Experiment 6 (Table I), 4 monkeys splenectomized 255 days previously and 2 controls were challenged with 2.07×10^8 organisms. None of the 6 died. Transient weakness and lethargy were observed for the first 3 days in all monkeys except control monkey No. 39 that was asymptomatic throughout except for fever. Anorexia lasting 5 to 9 days was noted in 3 of 4 splenectomized and 1 of 2 controls. Fever occurred in all for 4 to 5 days. Positive blood cultures were obtained for the first 3 days in all and in 3 of 4 splenectomized and 1 of 2 controls on the 4th day; only 1 (No. 37), a splenectomized monkey, still had a positive culture up to 9 days. CRP was positive in all at 24 hours; by the 8th day 2 of 4 splenectomized and 1 of 2 controls were positive and all were negative after the 14th day. When the monkeys were sacrificed 3 months later, no gross evidence of past infection was apparent and all cultures were negative. Antibody responses were observed in 1 of 4 splenectomized and 1 of 2 control monkeys by killed antigen agglutination tests only, in which both showed transient rise from base-line of 1:20 to 1:80 by the 2nd week.

TABLE II. Effect of Intravenous Staphylococcal Challenge in Monkeys Following Toxoid Administration.

	Toxoid group				Controls			
Monkey No.	11	20	83	92	29	55	91	99
Fever	+	+	+	+	+	+	+	+
Illness	+	+	+	+	+	+	+	+
Death	—	+	+	—	+	—	—	+
Leukocytosis	+	+	+	+	+	+	+	—
CRP	+	+	+	+	+	+	+	+
Blood culture	+	+	+	+	+	+	+	+
Viable aggl titer rise	3*	D†	2	2	D	4	3	—
Killed aggl titer rise	3	"	—	—	"	3	—	—
Anti-α hemolysin titer rise	—	"	—	—	"	2	—	—
Autopsy culture		+	+		+			—

* Tubes increase in titer.
† D = Negative at time of death.

Studies with toxoid. Four monkeys which had received 0.5 ml, subcutaneously, of staphylococcus toxoid (Lederle) at 3 weekly intervals were challenged intravenously 2 weeks after the last dose with 3.2×10^{10} organisms as were 4 controls not receiving toxoid (Table II). All monkeys in both groups became ill within 24 hours exhibiting weakness, lethargy, anorexia and fever. In those receiving toxoid 2 of 4 died on the 5th and 10th days, respectively, and 2 of 4 controls died on the 5th and 29th days, respectively. Blood cultures and CRP were positive in all from the 1st day until death. In the 2 survivors which had received toxoid, 1 had positive blood cultures and CRP for 7 days while the other had positive CRP and blood cultures for 10 and 24 days, respectively. In the 2 surviving con-

trols, blood cultures and CRP were both positive for 22 days in 1, and for 14 and 10 days, respectively, in the other.

No significant increase in antibody response in any of the 3 tests employed was observed following toxoid. After challenge only 1 monkey (No. 55), which was in the control group and survived, showed significant titer increase in all 3 tests. None of the others showed any alteration in anti-alpha hemolysin titer. In the viable agglutination test both survivors in the toxoid group (Nos. 11, 92) and control group (Nos. 55, 91) showed significant titer rises as did 1 (No. 83) surviving long enough to study serologically. With the killed agglutination antigen test, significant titer rise was seen in only 1 in each group (Nos. 11, 55).

Discussion. That all species of animals studied, including man, show a high degree of resistance to experimental challenge with potentially virulent staphylococci has been discussed recently(9). However, to our knowledge there have been no published data employing sub-human primates in experimental staphylococcal infection other than those described by Verlinde and Makstenieckes(5). Thus, the statement that "there is no ideal animal for staphylococcus experimental infections"(10) suggests that studies employing sub-human primates would be indicated. The present studies demonstrated that rhesus monkeys could be infected regularly following intravenous inoculation with a hemolytic staphylococcus with gradations of disease patterns varying from mild non-fatal to severe lethal infections. The clinical and laboratory observations paralleled those seen in man. Fatal infections in monkeys were not observed with a dose of 2×10^8 organisms which corresponds to Kapral's observation(11) that no deaths had been experienced in his studies with mice receiving less than 2×10^8 cocci, intraperitoneally; with the 18Z strain he employed, the LD50 for rabbits and mice was approximately 2 to 3×10^9 cocci. In the present studies, fatal infections followed doses exceeding 10^9 organisms. Aerosol challenge of monkeys resulted in no obvious clinical or laboratory evidence of infection. This observation also parallels those of Simon(12) who could produce no detectable disease in guinea pigs following exposure to a staphylococcal aerosol.

Various serologic tests have been described for studies of staphylococcal infections, but none has gained widespread usefulness. The inability regularly to demonstrate significant titer fluctuations following infection in humans has been described as a paradox of staphylococcal infection(9). The variability of serologic responses has also been observed in the present study. Similarly, although there have been numerous studies on assessment of efficacy of vaccines or toxoids in staphylococcal infection, as recently reviewed(4,13), immunization at present does not seem a promising approach. In these studies, toxoid immunization did not protect monkeys following intravenous infection just as intraperitoneal infection of mice was not altered(14).

There is still some disagreement as to whether splenectomized patients are more susceptible to infection (15,16). The hemolytic streptococcus, the pneumococcus and the staphylococcus have been among the agents most commonly involved in such infections. The present studies with staphylococci as well as those previously described from this laboratory with streptococcal(1) and pneumococcal (2) infections in monkeys showed no significant clinical or laboratory differences between splenectomized and non-splenectomized monkeys. This would suggest that if increased infections occur in splenectomized patients, it is the underlying disease process rather than the absence of the spleen that is responsible.

Comparison of infections in monkeys with streptococci(1), pneumococci(2) and staphylococci, as described in this study, revealed that all 3 agents caused no discernible disease following aerosol challenge. However, intravenous challenge with all 3 regularly was followed by illness, fever, leukocytosis, positive CRP, and positive blood cultures. Fatal infection was observed in 14 of 32 receiving staphylococci, and the mean survival time was 5.4 days, as compared to only 2.1 days in the 9 of 16 deaths following streptococcal challenge. On the other hand, none of 22 rhesus monkeys died following pneumococcal challenge although 4 of 5 cynomolgus monkeys died at 3, 4, 11 and 31 days, respectively, post-chal-

lenge. The dose in the latter group was 3.8 $\times$ 10^9 organisms as compared to doses also in excess of 10^9 streptococci or staphylococci required to cause fatal infections. In non-fatal infections, positive blood cultures were detected for 14 to 28, 10 to 56 and 10 to 28 days, respectively, after intravenous challenge with streptococci, pneumococci and staphylococci.

Summary. Aerosol challenge with staphylococci produced no demonstrable disease in rhesus monkeys. Intravenous challenge was followed by definite clinical and laboratory evidence of infection. Toxoid immunization did not alter the course of infection. No significant differences were noted between splenectomized and normal monkeys in all parameters measured.

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1. Saslaw, S., Carlisle, H. N., Proc. Soc. Exp. Biol. and Med., 1964, v117, 420.

2. ———, Antimicrobial Agents & Chemotherapy, 1964, 635.

3. Elek, S. D., Ann. N. Y. Acad. Sci., 1965, v128, 1.

4. ———, *Staphylococcus pyogenes* and Its Relation to Disease, Williams and Wilkins Co., Baltimore, 1959.

5. Verlinde, J. D., Makstenieeks, O., Arch. ges. Virusforsch., 1954, v5, 345.

6. Roessler, W. G., Kautter, D. A., J. Infect. Dis., 1962, v110, 17.

7. Baltch, A. L., Osborne, W., Canarile, L., Hasserdjian, A., Bunn, P. A., J. Immunol., 1962, v88, 361.

8. Boger, W. P., Frankel, J. W., Gavin, J. J., Proc. Soc. Exp. Biol. and Med., 1960, v104, 639.

9. Ekstedt, R. D., Ann. N. Y. Acad. Sci., 1965, v128, 301.

10. Frappier, A., Sonea, S., Panisset, M., Rev. Canad. Biol., 1955, v14, 152.

11. Kapral, F. A., Ann. N. Y. Acad. Sci., 1965, v128, 259.

12. Simon, H. J., ibid., 1965, v128, 351.

13. Rogers, D. E., Melly, M. A., ibid., 1965, v128, 274.

14. Koenig, M. G., Melly, M. A., Rogers, D. E., J. Exp. Med., 1962, v116, 601.

15. Smith, C. H., Erlandson, M. E., Stern, G. Hilgartner, M. W., New Eng. J. Med., 1962, v266, 737.

16. Thurman, W. G., Am. J. Dis. Child., 1963, v105, 138.

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Termination of Acquired Immunological Tolerance in Mice with Antigen Aggregates.* (31545)

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It has been previously shown that neonatal inoculation of human gamma globulin (HGG) renders mice tolerant to this antigen(1). This tolerant state lasts for about 14 weeks, but if inoculations of antigen are repeated, tolerance is prolonged(2) for as long as the tolerogen is maintained at suitable levels in the tolerant animal.

Acquired tolerance to soluble antigens resembles natural tolerance to self constituents, insofar as there exists in the host a suppression or a lack of antigenic stimulation capable of producing a specific immune response(3). In natural tolerance to self constituents the presence of autologous material in the body seems to exert a suppression of self rejection. In this respect the tolerogen behaves in the body as a self substance(3). On the other hand, in autoimmunity this mechanism of control or self protection is impaired even in the presence of the circulating autologous substances.

A state of acquired immunological tolerance to tumor antigens seems to be present in neoplasm(4). This is the case of tolerance to the

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