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UPTAKE OF AGGREGATED IMMUNOGLOBULIN BY THE MOUSE KIDNEY. II. EFFECT OF HYDROCORTISONE

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Summary.—The uptake of radiolabelled (^{125}I) aggregated human IgG (AggIgG) by the renal cortex, liver, spleen and lung was evaluated quantitatively in mice treated with hydrocortisone (HC) (25 mg) 72 h previously. AggIgG was administered in a dose of 1·5 or 3·5 mg/g body wt i.v.; tissue and blood were obtained at 1, 4 and 24 h. Renal cortical and mesangial uptake of AggIgG was significantly increased in HC animals. A rise in blood level was also observed in association with decreased splenic uptake, normal or slightly increased hepatic uptake and unchanged lung uptake. A significant increase in the kidney:lung and kidney:spleen ratios of AggIgG was induced by hydrocortisone, suggesting a relatively greater rate of loss from the spleen and liver than the renal cortex. The increased mesangial uptake may be a consequence of higher blood levels of AggIgG, as well as a direct effect of HC on the mesangium.

A VARIETY OF MACROMOLECULES are sequestered in the mesangium after administration to animals (Michael, Fish and Good, 1967; Farquhar and Palade, 1962; Latta and Maunsbach, 1962; Menefee *et al.*, 1964; Mauer *et al.*, 1972, 1974; Elema, Hoyer and Vernier, 1976; Michael *et al.*, 1979). The relationship of this function to that of the reticuloendothelial system (RES) remains poorly defined. After the injection of aggregated human IgG (AggIgG) into mice pre-treated with endotoxin, lowered circulating levels of AggIgG were associated with increased uptake by liver and spleen but not by kidney cortex; an increase in mesangial uptake was observed by immunofluorescence microscopy only at 1 h but not at later times (Shvil, Michael and Mauer, 1980). The present study was designed to explore this relationship further by examining the effect of hydrocortisone on tissue and mesangial uptake by AggIgG in mice.

MATERIALS AND METHODS

Forty-nine Swiss Webster randomly bred male mice weighing 20–23 g (Bio-Labs., St Paul, MN) were injected s.c. with 25 mg hydrocortisone acetate (HC; Merck, Sharp and Dohme, West Point, PA). Forty-eight control mice (C) were injected with 0·5 ml of 0·15M NaCl. Seventy-two hours after the administration of the HC or saline, the C and HC mice were injected i.v. with aggregated human IgG ^{125}I (AggIgG); either with a "low" dose—1·5 mg/10 g body wt [HC (1·5) or C (1·5)], or with a "high" dose—3·5 mg/10 g body wt [HC (3·5) or C (3·5)]. The preparation of the AggIgG is described in detail in the companion paper (Shvil, Michael and Mauer, 1980).

Control and HC injected mice were killed under ether anaesthesia in groups of 6–10 animals at 1, 4 and 24 h after administration of AggIgG. Blood samples were obtained and the mice perfused with 0·15M NaCl; the liver, kidneys, spleen and lungs were removed and prepared for ^{125}I counting and immunofluorescence microscopy as described in the preceding paper (Shvil *et al.*, 1980). The wet weights of the unperfused liver, spleen, lungs and kidneys were determined 1, 4 and 24 h after the administration of either dose of AggIgG.

Because the preparation of AggIgG contained 7S IgG, the relative proportions of 7S IgG and >7SA ggIgG were determined in separate experiments by linear sucrose (10–50%) gradient centrifugation (Shvil *et al.*, 1980). Sera of control and HC mice were analysed after the administration of low and high doses of AggIgG.

TABLE I.—*The concentration of AggIgG in blood and tissues of control and hydrocortisone mice at 1, 4 and 24 h after administration of 2 different doses of AggIgG*

	Time after AggIgG (h)	AggIgG (1·5 mg/10 g body wt)					AggIgG (3·5 mg/10 g body wt)				
		Control		Hydrocortisone			Control		Hydrocortisone		
		N	Mean ± s.d.	N	Mean ± s.d.	P‡	N	Mean ± s.d.*	N	Mean ± s.d.	P‡
Blood											
> 7S AggIgG μg/ml	1	6	157·8 ± 39·4	8	742·4 ± 456·4	< 0·01	5	451 ± 65·5 (807 ± 122)†	7	1483·6 ± 281 (1854 ± 357)†	< 0·000004
	4	8	6·8 ± 1·5	7	14·4 ± 5·8	< 0·005	8	35·4 ± 13·7	8	696·3 ± 261·3	< 0·00001
	24	10	1·5 ± 0·17	9	3·27 ± 0·69	< 0·0001	9	5·02 ± 0·46	9	5·38 ± 0·61	N.S.
7S IgG μg/ml	1	6	151·6 ± 37·8	8	325 ± 200	< 0·05	5	*	7	371 ± 70	
	4	8	104·6 ± 22·3	7	203 ± 81	< 0·01	8	352 ± 136	8	314·4 ± 118	N.S.
	24	10	72·8 ± 7·7	9	82·4 ± 17·3	N.S.	9	155 ± 14·2	9	165 ± 18·7	N.S.
Liver											
μg AggIgG/mg	1	6	2·34 ± 0·241	7	2·94 ± 0·499	< 0·05	6	2·64 ± 0·668	7	2·77 ± 1·20	N.S.
	4	8	1·10 ± 0·626	8	1·62 ± 0·412	< 0·05	7	3·35 ± 0·999	8	3·17 ± 0·443	N.S.
	24	8	0·0295 ± 0·00603	9	0·0654 ± 0·0417	< 0·025	8	0·0988 ± 0·0507	7	0·179 ± 0·0506	< 0·01
Kidney											
μg AggIgG/mg	1	6	0·221 ± 0·0349	8	0·513 ± 0·206	< 0·005	7	0·463 ± 0·0800	7	0·783 ± 0·272	< 0·025
	4	7	0·145 ± 0·0840	8	0·247 ± 0·0810	< 0·05	8	0·425 ± 0·233	8	0·638 ± 0·146	< 0·05
	24	9	0·0390 ± 0·0270	9	0·0520 ± 0·0245	N.S.	9	0·0565 ± 0·0193	9	0·129 ± 0·050	< 0·001
Spleen											
μg AggIgG/mg	1	6	1·61 ± 0·370	8	4·48 ± 2·66	< 0·025	7	2·46 ± 0·655	7	6·56 ± 5·31	< 0·005
	4	8	0·490 ± 0·309	8	0·753 ± 0·354	N.S.	8	1·48 ± 0·538	8	2·35 ± 1·21	N.S.
	24	10	0·0700 ± 0·0110	9	0·0390 ± 0·160	< 0·0001	9	0·172 ± 0·0630	9	1·60 ± 0·0370	N.S.
μg AggIgG/spleen	1	6	30·4 ± 4·27	8	22·0 ± 8·32	0·05	7	56·8 ± 10·1	7	39·3 ± 18·0	0·025
	4	8	11·1 ± 4·39	8	5·60 ± 3·33	0·01	8	32·7 ± 13·1	8	18·6 ± 9·92	0·025
	24	10	1·72 ± 0·417	9	0·296 ± 0·153	0·0001	9	3·33 ± 1·22	9	1·46 ± 0·598	0·005
Lung											
μg AggIgG/mg	1	7	0·431 ± 0·092	8	0·729 ± 0·517	N.S.	7	0·966 ± 0·356	7	1·25 ± 0·569	N.S.
	4	8	0·208 ± 0·093	8	0·207 ± 0·05	N.S.	8	0·606 ± 0·071	8	0·619 ± 0·181	N.S.
	24	10	0·0041 ± 0·009	9	0·0059 ± 0·0111	N.S.	9	0·047 ± 0·039	9	0·093 ± 0·041	N.S.

* The concentration of > 7S AggIgG in blood in the 1h control animals of this group was derived by subtraction of the 4h value for 7S IgG from the TCA-precipitable protein since partition of > 7S AggIgG and 7S IgG at 1 h was not successful.

† Total TCA-precipitable protein.

‡ *P* value for significant differences between control and hydrocortisone groups.

RESULTS

The blood levels of AggIgG in HC (1·5) and HC (3·5) mice were significantly higher than values obtained from C (1·5) and C (3·5) mice 1 and 4 h after administration of AggIgG (Table I). At 1 h, the level in HC (1·5) was higher than that observed in C (3·5), even though more than twice the amount of AggIgG had been administered to the latter group. This effect was amplified at 4 h when the blood level in the HC (3·5) group was 20–100 times higher than those observed in the other 3 groups at this time. By 24 h, the concentration in the blood had decreased to 0·3–1·0% of the 1 h level in all 4 groups. In contrast, the levels of 7S IgG at 24 h had decreased to 25–50% of the 1 h level. Although the concentration of 7S IgG at 1 and 4 h was higher in HC (1·5) than C (1·5), a similar difference was not observed between HC (3·5) and C (3·5).

A slight though significant increase in concentration of AggIgG/mg dry weight of liver was observed at 1, 4 and 24 h in HC (1·5) when compared with C (1·5); similar differences were observed only at 24 h in HC (3·5). HC induced an increase in the weight (mean ± s.d.) of the unperfused liver (HC = 1·35 ± 0·26 g; C = 1·06 ± 0·15 g; $P < 0·00001$). However, when AggIgG was

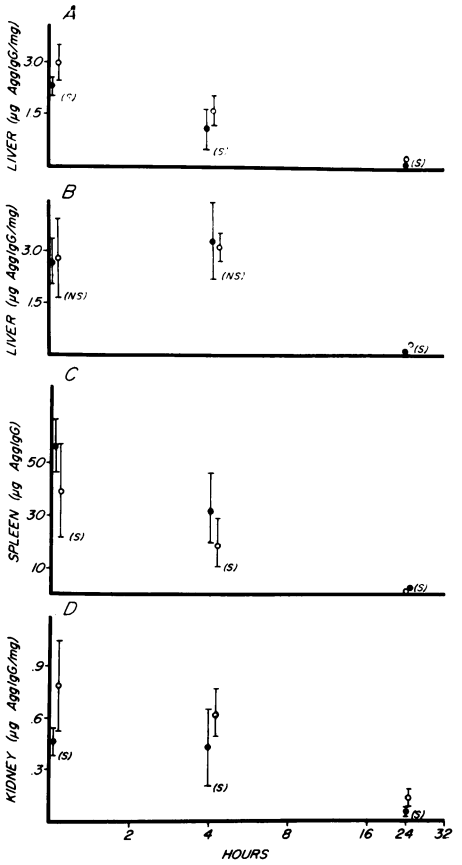

FIG. 1.—Plots of AggIgG concentration (mean ± s.d.) *vs* time for liver after administration of AggIgG in a dose of 1·5 mg/10 g (A) or 3·5 mg/10 g (B); for spleen (C) and renal cortex (D) after administration of AggIgG in a dose of 3·5 mg/10 g. The differences between hydrocortisone (○) and control (●) mice are indicated as significant (S) ($P < 0·05$) or non-significant (NS).

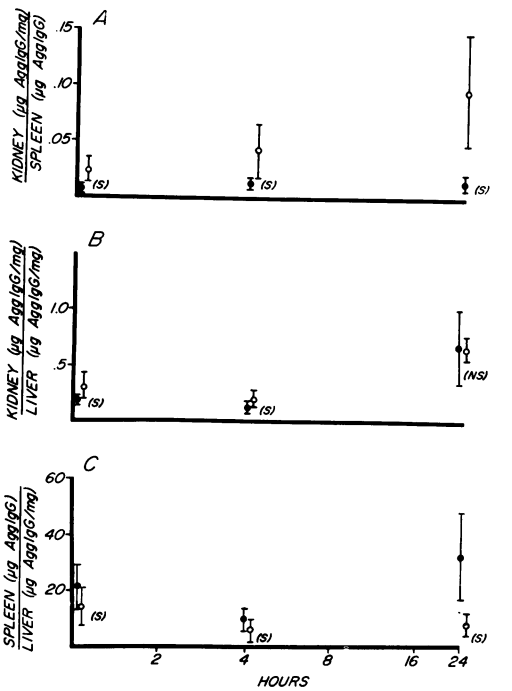

FIG. 2.—Plots of organ ratios of AggIgG concentrations (μg/mg for kidney and liver and μg/organ for spleen) against time in control (3·5) and hydrocortisone (3·5) mice (A) kidney:spleen; (B) kidney:liver; (C) spleen:liver. The differences between hydrocortisone and control mice are indicated as significant (S) ($P < 0·05$) is non-significant (NS).

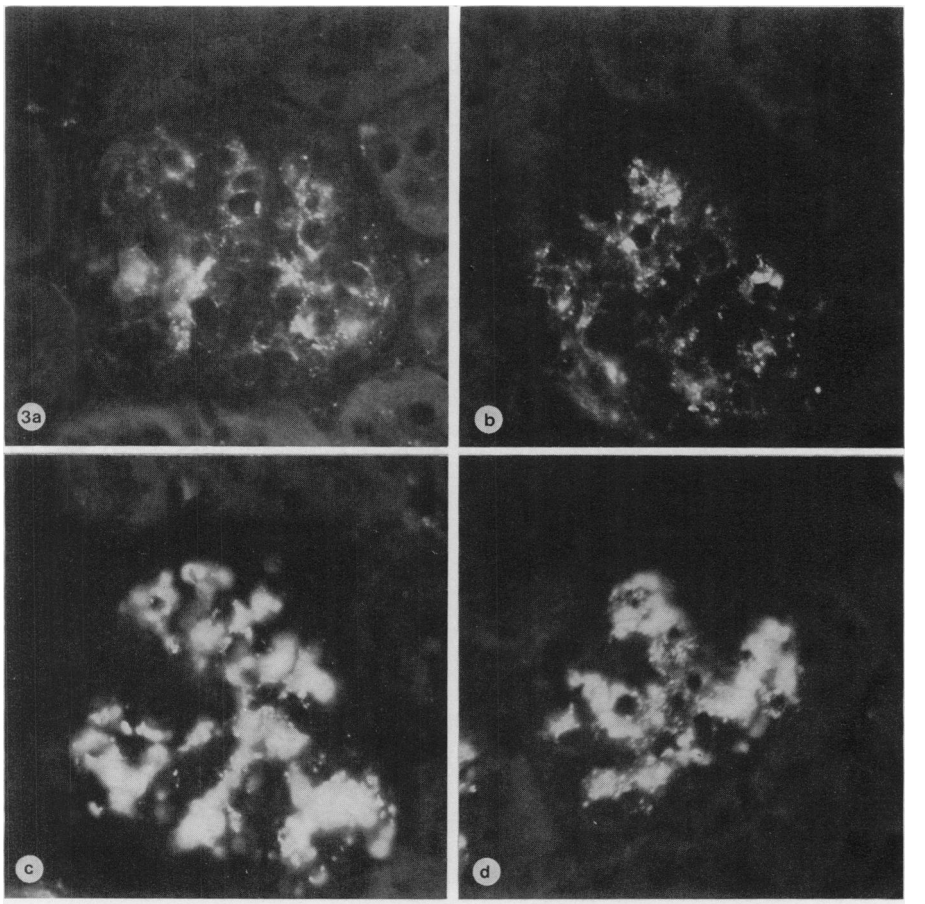

FIG. 3a–d.

FIG. 3.—Immunofluorescence microscopy of mouse kidneys demonstrating the presence of AggIgG primarily within the mesangium. (a). Control (C) mice given 1·5 mg of AggIgG per 10 g body wt and killed 1 h later [C (1·5)—1 h]; (b). C (1·5) at 4 h; (c). HC (1·5)—1 h; (d). HC (1·5) 4 h; (e). C (3·5)—1 h; (f). HC (3·5)—4 h; (g). C (3·5)—4 h; (h). HC (3·5)—4 h. (Stained with FITC-conjugated rabbit anti-human IgG; ×533.)

expressed as total liver concentration (μg/AggIgG/ whole liver), the findings were similar to those obtained on a unit weight basis. Hydrocortisone induced a very significant decrease in splenic wet weight (mean $\pm$ s.d.): (HC = 32 $\pm$ 14 mg; C = 82 $\pm$ 23; $P < 0{\cdot}0001$) and dry weight (HC = 7·2 $\pm$ 2·5; C 22·7 $\pm$ 5·9; $P < 0{\cdot}00001$). Because of these changes, the data in Table 1 are presented both as μg AggIgG/mg spleen and μg AggIgG/whole spleen. There was a significant decrease in the amount of AggIgG/whole spleen at 1, 4 and 24 h in HC (1·5) and HC (3·5), when compared with respective controls. In contradistinction, the concentration of AggIgG per mg of dried spleen is increased in HC, significantly so at 1 h, a finding which probably reflects the striking decrease in splenic weight in the HC mice. No significant differences in AggIgG concentration were observed in lung of HC mice as compared to control mice at any time interval. Contrary to the findings in spleen and lung, a significant increase in the concentration of AggIgG in the kidney cortex was observed at 1 and 4 h in HC (1·5) and HC (3·5), and in addition at 24 h

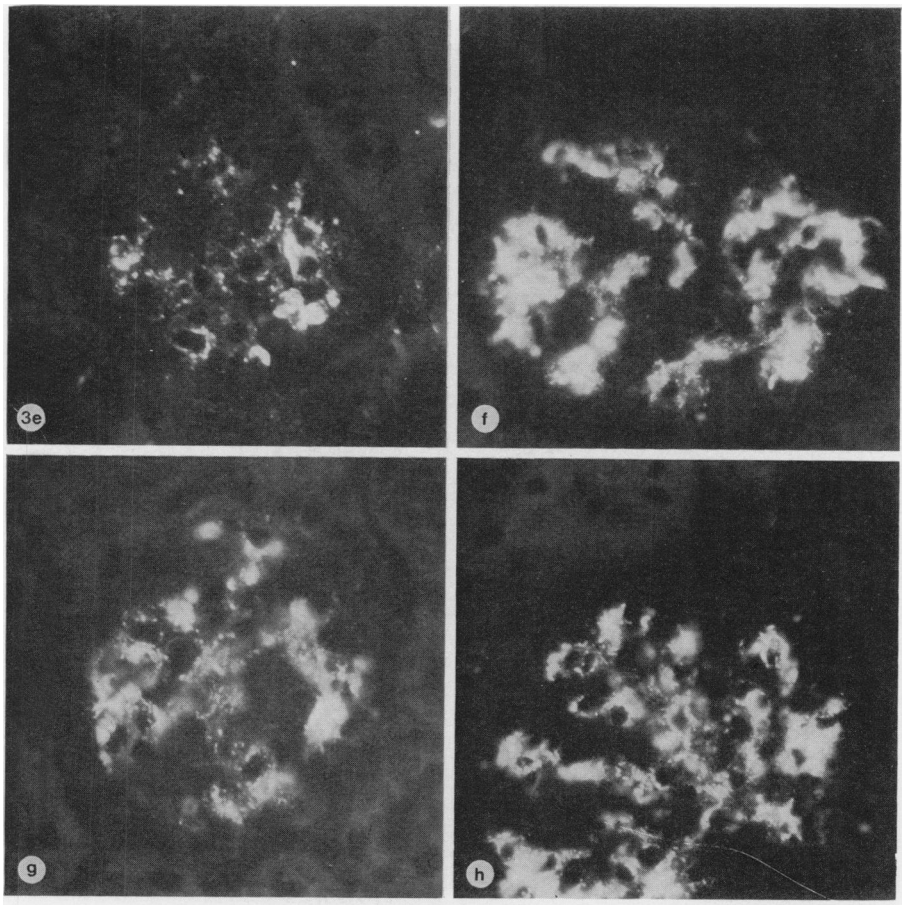

FIG. 3e–h.

TABLE II.—*Immunofluorescence for mesangial deposition of human AggIgG at* 1, 4 *and* 24 *h after administration of* 2 *different doses to control and hydrocortisone mice*

	Mesangial immunofluorescence for human IgG (arbitrary score)									
	AggIgG (1·5 mg/10 g body wt)					AggIgG (3·5 mg/10 g body wt				
	Control		Hydrocortisone†			Control		Hydrocortisone		
Time (h)	N*	Mean ± s.d.	N	Mean ± s.d.	*P*	N	Mean ± s.d.	N	Mean ± s.d.	*P*
1	6	0·35 ± 0·27	7	2·13 ± 1·28	< 0·0075	6	0·538 ± 0·321	6	3·21 ± 0·44	$< 10^{-7}$
4	5	0·36 ± 0·39	7	1·73 ± 0·54	< 0·0005	8	1·42 ± 0·62	7	2·62 ± 0·68	< 0·005
24	6	0·15 ± 0·12	9	0·48 ± 0·33	< 0·05	6	0·073 ± 0·069	9	0·886 ± 0·487	< 0·0025

* N—number of mice.
† Hydrocortisone was administered 72 h before AggIgG.

in HC (3·5). A comparison of time-concentration plots for liver, spleen and kidney illustrate the differences described above (Fig. 1).

The effects of HC on the ratios of the AggIgG concentrations in kidney : spleen, kidney : liver and spleen : liver were evaluated at all 3 times (Fig. 2). The trend of the results of these ratios was similar in the HC (1·5) and HC (3·5) compared to C

groups and therefore only data from the HC (3·5) and C (3·5) mice are presented. The kidney: spleen ratios remained constant in C mice at 1, 4 and 24 h. In contrast, HC produced a progressive increase in this ratio between 1 and 24 h, which probably reflects a relatively greater rate of loss of AggIgG from the spleen. HC induced a significant increase in the ratios of AggIgG concentrations in kidney: liver at 1 and 4 h when compared with C. This ratio increased in HC and C animals between 4 and 24 h, indicating a relatively greater rate of loss of AggIgG from the liver compared to the kidney in both groups. The spleen: liver ratios were significantly decreased in HC compared to C mice at all times. These ratios decreased in both HC and C mice between 1 and 4 h. However, between 4 and 24 h the spleen: liver ratio increased markedly in C mice, but did not change in the HC mice because of a relatively diminished rate of AggIgG loss from the liver of HC mice.

Immunofluorescence microscopy showed increased mesangial localization of AggIgG in the HC groups compared with their respective controls at all times (Fig. 3, Table II). HC (3·5) and C (3·5) had higher mesangial scores than the respective values in groups HC (1·5) and C (1·5) at 1 and 4 h.

The correlation coefficient (r), relating AggIgG concentrations in renal cortex to quantitative mesangial immunofluorescence for control mice (1·5 and 3·5), is 0·54 at 1 h ($P < 0·05$) and 0·64 at 4 h ($P < 0·02$); for HC mice (1·5 and 3·5) it is 0·85 at 1 h ($P < 0·0002$) and 0·67 at 4 h ($P < 0·01$). Correlations performed for data from the 24h period are not statistically significant.

DISCUSSION

The relationship of reticuloendothelial system (RES) function to the uptake and processing of circulating macromolecules by the mesangium is unclear. Earlier work from our laboratory indicates a parallelism in the kinetics of mesangial and RES handling of AggIgG (Mauer *et al.*, 1972, 1974), although mesangial uptake of AggIgG in one of these studies (Mauer *et al.*, 1974) appeared to depend, in part, upon overloading of the RES.

The administration of hydrocortisone (HC) resulted in elevated AggIgG blood levels at 1 and 4 h in the high-dose HC group and at all times in the low dose group. Earlier experiments on blood kinetics of soluble immune complexes in mice treated with HC (Haakenstad, Case and Mannik, 1975) were interpreted as indicating that HC impaired the initial rapid disappearance of complexes from the circulation caused by increased vascular permeability. Since AggIgG has been shown to have many of the biological properties of antigen–antibody complexes (Ishizaka *et al.*, 1967), it might be argued that the higher blood levels in the HC mice are a consequence of hydrocortisone inhibiting the increased vascular permeability induced by AggIgG. Although this thesis would be supported by the increased levels of 7S IgG at 1 and 4 h in the HC (1·5) mice, no such increase in 7S IgG was seen in the HC (3·5) animals. For example, at 4 h the concentration of AggIgG in the blood of HC (3·5) was 20-fold that of C, whereas the concentration of 7S IgG was not different. Thus, the effect of HC on AggIgG blood levels cannot be fully explained by the action of HC on decreasing vascular permeability. In the studies of Haakenstad, Case and Mannik (1975), splenic uptake of immune complexes was not different when HC and control mice were compared, whereas in our studies decreased AggIgG uptake was demonstrated in the spleens of HC mice. These differences may be methodological and could be related to our measurement of protein-bound ^{125}I in tissues rather than total radioactivity. However, the decreased macromolecular uptake by the whole spleen in HC animals may reflect effects on other RES tissues and, hence, contribute to the elevated AggIgG blood levels. In addition, sequestration of antigen–antibody complexes and AggIgG in vessels and non-RES sites

may be altered by corticosteroid treatment, a circumstance not evaluated in the present or prior investigations (Haakenstad *et al.*, 1975). HC may influence RES organs in different ways. For example, in HC mice comparison of organ concentrations shows significant deviations: liver uptake was unchanged or increased, whole spleen uptake was diminished and lung uptake was unchanged. In addition, the influence of HC on spleen compared with liver demonstrates a decreased AggIgG ratio (spleen: liver), reflecting a lower rate of loss from the liver in the 24h period after administration of AggIgG.

Is the heightened mesangial uptake of AggIgG a consequence of an increase in the blood level of AggIgG, or the direct action of HC upon mesangial traffic of macromolecules or renal haemodynamics? Previous studies from our laboratory have demonstrated increased AggIgG or colloidal carbon uptake by the mesangium in the proteinuric kidneys of rats with unilateral amino-nucleoside nephrosis or anti-GBM nephritis where blood levels of AggIgG delivered to both kidneys were identical (Hoyer, Mauer and Michael, 1975). The reason for the increased uptake in both of these experimental models has not been defined. That the amount of AggIgG administered, or the circulating blood level, is of importance has been shown in previous experiments (Michael *et al.*, 1967); (Mauer *et al.*, 1972, 1974), demonstrating a direct relationship between the dose of AggIgG administered, the blood levels achieved and the quantity of AggIgG localizing in the mesangium. Thus, in the present study it is not possible to separate the effects of increased blood level of the macromolecule from a direct effect of HC on glomerular haemodynamics or mesangial traffic.

Haakenstad and Mannik (1976) compared the disappearance kinetics of soluble immune complexes prepared with reduced and alkylated antibodies (AgAb-red and -alk) with those of intact antibodies (AgAb) in mice. These AgAb-red and -alk complexes fixed guinea-pig complement inefficiently and had decreased *in vitro* macrophage adherences compared with AgAb (Mannik *et al.*, 1971; Arend and Mannik, 1972). In rabbits, the blood disappearance kinetics of AgAb-red and -alk and AgAb were not dependent upon an intact complement system (Arend and Mannik, 1971), a finding confirmed by kinetic studies using AggIgG in rats (Mauer *et al.*, 1974). In mice, AgAb-red and -alk persisted longer in the circulation and were associated with decreased hepatic and increased mesangial uptake when compared with intact AgAb (Haakenstad, Striker and Mannik, 1976). Although these authors concluded that the increased mesangial uptake of AgAb-red and -alk could be explained by increased blood levels, increased splenic localization was observed which was thought to be due to nonspecific trapping or deposition. However, one cannot exclude the possibility that the increased splenic and mesangial levels in these studies reflect, at least in part, specific uptake of AgAb-red and -alk by the spleen and mesangium.

In our present studies the higher kidney: liver ratios of HC (3·5) mice at 1 and 4 h reflect increased kidney levels at these times. The rising kidney: spleen ratios in HC mice, in contrast to unchanging ratios in C mice, result from more rapid disappearance of AggIgG from the spleen and a slower disappearance rate from the kidney of HC mice. These ratios further emphasize the differential effects of HC on uptake and removal rates of macromolecules by different organs.

Although the elevated levels of AggIgG in kidney tissue of HC mice correlate with the marked increase in mesangial AggIgG in these animals, it is unlikely that the tissue levels simply reflect increased mesangial trapping. None the less, since at 4 and 24 h staining for human IgG in kidneys of HC and C mice was confined exclusively to the mesangium, it is likely that the elevated tissue levels reflect in part the increased quantities of AggIgG seen in the mesangium.

Despite the complexities of the results

from these experiments, certain conclusions can be reached. It is clear that the reticuloendothelial system cannot be considered uniform in its component responses to hydrocortisone and endotoxin. Anti-inflammatory steroids have been shown to inhibit a number of specific macrophage functions: Prostaglandin synthesis (Hong and Levine, 1976); plasminogen activator induction and synthesis (Hamilton, Vassalli and Reich, 1976; Vassalli, Hamilton and Reich, 1976); migration of activated cells (Thompson and van Furth, 1970); LPS or PPD activation of colony-stimulating factor, latex phagocytosis, and antibody-dependent lysis (Ralph *et al.*, 1978). However, other functions in macrophage cell lines are not inhibited, including antibody-dependent phagocytosis and lysis of sheep erythrocytes and tumour targets; and latex bead phagocytosis (Ralph *et al.*, 1978). Experimental manipulations which influence the RES have been suggested to have an inverse effect upon mesangial uptake of macromolecules (Ford, 1975). In the present studies, the increase in mesangial sequestration induced by HC may be a consequence of higher circulating levels of AggIgG and/or an effect on glomerular haemodynamics and mesangial traffic. In studies of immune-complex trapping by the kidney, the blood level would appear to be a more important determinant than delivery rate, hydrostatic pressure, or ultrafiltration rate (Hebert, Allhuser and Koetke, 1978). However, at this time it is not possible to determine whether the experimental manipulations described in this paper influence mesangial function directly or indirectly.

REFERENCES

AREND, W. P. & MANNIK, M. (1971) Studies on Antigen–Antibody Complexes. II. Quantification of Tissue Uptake of Soluble Complexes in Normal and Complement-Depleted Rabbits. *J. Immunol.*, **107**, 63.

AREND, W. P. & MANNIK, M. (1972) *In vitro* Adherence of Soluble Immune Complexes to Macrophages. *J. exp. Med.*, **136**, 514.

ELEMA, J. D., HOYER, J. R. & VERNIER, R. L. (1976) The Glomerular Mesangium. Uptake of Intravenously Injected Colloidal Carbon. *Kidney Int.*, **9**, 395.

FARQUHAR, M. G. & PALADE, G. E. (1962) Functional Evidence for the Existence of a Third Cell Type in the Renal Glomerulus. *J. Cell Biol.*, **13**, 55.

FORD, P. M. (1975) The Effect of Manipulation of the Reticuloendothelial System Activity on Glomerular Deposition of Aggregated Protein and Immune Complexes in Two Different Strains of Mice. *Br. J. exp. Path.*, **56**, 523.

HAAKENSTAD, A. I., CASE, J. B. & MANNIK, M. (1975) Effect of Cortisone on the Disappearance Kinetics and Tissue Localization of Soluble Immune Complexes. *J. Immunol.*, **114**, 1153.

HAAKENSTAD, A. I. & MANNIK, M. (1976) The Disappearance Kinetics of Soluble Immune Complexes Prepared with Reduced and Alkylated Antibodies and with Intact Antibodies in Mice. *Lab. Invest.*, **35**, 283.

HAAKENSTAD, A. I., STRIKER, G. E. & MANNIK, M. (1976) The Glomerular Deposition of Soluble Immune Complexes Prepared with Reduced and Alkylated Antibodies and with Intact Antibodies in Mice. *Lab. Invest.*, **35**, 293.

HAMILTON, J., VASSALLI, J.-D. & REICH, E. (1976) Macrophage Plasminogen Activator Induction by Asbestos is Blocked by Anti-inflammatory Steroids. *J. exp. Med.*, **144**, 1689.

HEBERT, L. A., ALLHUSER, C. & KOETKE, S. (1978) Some Hemodynamic Determinants of Immune Complex Trapping by the Kidney. *Kidney Int.*, **14**, 452.

HONG, S. L. & LEVINE, L. (1976) Inhibition of Arachidonic Acid Release from Cells as the Biochemical Action of Anti-inflammatory Corticosteroids. *Proc. Natl Acad. Sci.*, **73**, 1730.

HOYER, J. R., MAUER, S. M. & MICHAEL, A. F. (1975) Unilateral Renal Disease in the Rat. I. Clinical, Morphologic and Glomerular Mesangial Functional Features of the Experimental Model Produced by Renal Perfusion with Aminonucleoside. *J. clin. Lab. Med.*, **85**, 756.

ISHIZAKA, T., ISHIZAKA, K., SALMON, S. & FUDENBERG, H. (1967) Biological Activities of Aggregated Gamma Globulin. VIII. Aggregated Immunoglobulins of Different Classes. *J. Immunol.*, **99**, 82.

LATTA, H. & MAUNSBACH, A. B. (1962) Relations of the Centrolobular Regions of the Glomerulus to the Juxtaglomerular Apparatus. *J. Ultrastruct. Res.*, **6**, 562.

MANNIK, M., AREND, W. P., HALL, A. P. & GILLILAND, B. C. (1971) Studies on Antigen–Antibody Complexes. I. Elimination of Soluble Complexes from Rabbit Circulation. *J. exp. Med.*, **133**, 713.

MAUER, S. M., FISH, A. J., BLAU, E. B. & MICHAEL, A. F. (1972) The Glomerular Mesangium. I. Kinetic Studies of Macromolecular Uptake in Normal and Nephrotic Rats. *J. clin. Invest.*, **51**, 1092.

MAUER, S. M., FISH, A. J., DAY, N. & MICHAEL, A. F. (1974) The Glomerular Mesangium. II. Studies of Macromolecular Uptake in Nephrotoxic Nephritis in Rats. *J. clin. Invest.*, **53**, 431.

MENEFEE, M. G., MUELLER, C. B., BELL, A. L. & MEYERS, J. K. (1964) Transport of Globulin by the Renal Glomerulus. *J. exp. Med.*, **120**, 1129.

MICHAEL, A. F., FISH, A. J. & GOOD, R. A. (1967) Glomerular Localization and Transport of Aggregated Proteins in Mice. *Lab. Invest.*, **17**, 14.

MICHAEL, A. F., NEVINS, T. E., RAIJ, L. & SCHEINMAN, J. I. (1979) Macromolecular Transport in the

Glomerulus: Studies of the Mesangium and Epithelium *in vivo* and *in vitro*. In *Contemporary Issues in Nephrology*. Eds. B. M. Brenner and J. H. Stein. New York: Churchill Livingstone. pp. 167–213.

RALPH, P., ITO, M., BROXMEYER, H. E. & NAKOINZ, I. (1978) Corticosteroids Block Newly Induced but not Constitutive Functions of Macrophage Cell Lines: Myeloid Colony-stimulating Activity Production, Latex Phagocytosis and Antibody-dependent Lysis of RBC and Tumor Targets. *J. Immunol.*, **121**, 300.

SHVIL, Y., MICHAEL, A. F. & MAUER, S. M. (1980) Uptake of Aggregated Immunoglobulin by the Mouse Kidney. I. Effects of Endotoxin. *Br. J. exp. Path.*, **61**, 22.

THOMPSON, J. & VAN FURTH, R. (1970) *Mononuclear Phagocytes*. Ed. R. Van Furth. Oxford: Blackwell Scientific Publications Ltd.

VASSALLI, J.-D., HAMILTON, J. & REICH, E. (1976) Macrophage Plasminogen Activator: Modulation of Enzyme Production by Anti-inflammatory Steroids, Mitotic Inhibitors and Cyclic Nucleotides. *Cell*, **8**, 271.