Experimental Study of Radiobiological Mechanisms

By

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"放射線生物学的作用機構に関する実験的研究"

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著者等は放射線照射の生物学的作用機構の解明を企て，放射線照射によつて細胞が変性死滅すれば，その分解産物に対して自家抗体を生じ純二次的生物学的に一次的作用を増幅する事を免疫反応によつて実証し，私共はこれを自家抗体説と名付けて公表した．本実験は以上の説が正しいならば細胞の変性を起させる方法の如何に拘らず（放射線に限らず）自家抗体が発生すべきであるとして家兎の片腎を使つて実験を試み之を実証した．従つて放射線照射を受た細胞は一次的作用とこの純二次的生物学的作用の共同作用によつて影響される事を確認した．

I. Introduction

The effective and proper clinical application of radiation primarily depends on a thorough knowledge of the changes that occur when the living body is exposed to radiation. This is the fundamental mechanisms of so-called the radiobiological action which forms the fundation of radiotherapy, the prevention of radiation disasters and the study of radiation injuries. Unfortunately, the mechanisms of such actions have not been adequately cleared. This is an imporatnt matter and in a sense a very hazardous situation. Nevertheless, in spite of the inadequate understanding of the mechanisms of these biological actions, certain standards have been established for the prevention of disasters and radiation is being widely used in the clinic in diagnosis and therapy. Toconfess, however, it disturbs me that such applications are not rational regardless of the ultimate good result obtained.

Even with respect to the permissible dose, which has been established for the prevention of disasters, there are uncertainties in the criteria used in making this determination. In radiotherapy of cancer, which had been presumed to be ineffective in the past because of the insufficient focal dose, it is now possible to apply a dose 10 times greater without difficulty and the degree of homogeneity of the rays is far beyond comparison with what it had been in the past.

However, have the results been improved by 10 times? Of course, wonderful results are achieved depending on the site of the lesion, but there frequently are occasions in which detrimental effects outweigh the beneficial effects. Although they tend to be overshadowed by super-voltage techniques, it is not infrequent that normo-voltage or low-voltage (body cavity tube) produce even better results.

The basic mechanisms of radiobiological actions had been explained to us by the point heat theory of Dessauer and the necrohormone hypothesis of Caspari. In either the point heat theory or the hit theory, the first change to occur following exposure of the living body is the destruction of the irradiated cell due to the so called direct primary effect. Next, this primary effect is further intensified by the secondary biological effect of the destructed products of the cells, termed necrohormone by Caspari. This theory has been honored until the present since it skillfully explains the chain of complicated biological reactions that occur even though the exposure to radiation energy is for a very short period of only 5 or 10 minutes. This theory, however, is still not completely satisfying. The radiation energy routinely used is very small being of the magnitude of less than 10/100 calories which is even less than the energy involved in raising the hand. Although this small energy is delivered to the body for such a short period, what causes it to be amplified into such a powerful biological force?

The great contrast between the final results, such as death or mutation, and the original changes due to radiation at the level of the atom is amazing. Inevitably, various hypotheses have been developed on the mechanisms of the radiobiological actions in an attempt to establish a link between these conditions. Inasmuch as we are engaged in work involving radiation, we believe that we must have some hypothesis which is at least reasonable and fits the actual situation with respect to the mechanisms of radiobiological actions.

Although there is no disagreement that the primary effect in the physical aspect appear as changes at the level of the atom, the explanation that the secondary biological effect are dependent simply upon the amount of necrohormone, in other words, that necrohormone produce both specific and non-specific actions according to the Arnt-Schultz law is not satisfying.

Therefore, we have made a hypothesis concerning this biological amplification, in which, it was suggested that the destructed products act as an autoantigen and that the autoantibodies produced result in autoimmunity, which causes such an amplification of effects. This hypothesis was confirmed in our study on radiotherapy of cancer and reported in a previous paper[1]. In the present report, we have attempted to confirm this further with respect to irradiated subjects in general and have performed various experiments using rabbit in order to establish a theory on the mechanisms of radiobiological actions.

In this paper, the kidneys were selected for study since they are located separately on each side of the body. An experiment was done to see what effects damage to one kidney would have upon the other kidney. Furthermore, the changes in serum proteins, which participate in the transportation of antigens and antibodies, were followed daily by paper electrophoresis in the same rabbit.

There is at yet no definite guide to the clinical evaluation of the degree of radiation damage. When radiation is to be delivered to the living body, it is important to know how much autoimmunity is produced by certain amounts of tissue destruction. Under the assumption that perhaps some information may be obtained from changes in the serum protein fraction, a study was done previously on both the changes in the pattern and the quantitative changes as reported in the paper on the serum protein of A-bomb survivors.[2] A similar study was done in the present report and some additional findings have been

obtained. The past methods of radiation exposure have been reviewed in the light of these experimental results in the hope that we may contribute to future treatment and the prevention of disasters.

II. Review of Literature

Ueno[3] has made the following important suggestions on the mechanisms of the biological actions. In other words, there presumably are 3 factors involved in the radiobiological actions. That is, the ionizing radiation, the matter which compose the living body and the condition of the matter. Moreover, the radiobiological actions have at least 2 characteristics. One is the latent period and the other is the so-called biological amplification.

No hypothesis incorporating the above factors and these 2 characteristics has been developed yet which completely explains all the biological effects thus far found. In a review of literature, the theory of Yamamoto, Tarusov, etc. concerning the toxic effects of higher unsaturated fatty acids has attracted much interest, but it is doubtful whether these acids are primary products. Some scholars claim that this theory is useful since they feel that toxins are certainly produced following irradiation, but we wonder whether toxins are actually produced. If the effects were to follow the Arnt-Schultz law such as in Caspari's necrohormone hypothesis, it would not be possible to solve this problem simply by the production of toxins.

Recently, the concept of enzyme disturbance of Kaplan has been further expanded to the enzyme liberation theory of Bacq and Alexander, the intercellular barrier theory of Passinskey and the mean cell model theory of Kuzin in which attention is directed primarily at the specificity of the enzyme state within the cell. They claim that the biological amplification can be explained on the basis of these hypotheses. The characteristic point of these hypotheses is the barrier as described according to a concept of a membrane. In addition to this, Ueno has suggested the possibility of some trigger mechanism for the occurrence of the biological action, such as an interruption of one of the metabolic systems or an interruption of the system which controls nucleic acids. He feels that studies from such a standpoint would contribute to the progress of biology. This is truly a fascinating opinion.

As mentioned in the introduction, we hertofore had viewed our experiences according to Caspari's necrohormone theory. Although the conditions under which the primary radiation is delivered certainly play an important role, our long experience has shown the secondary biological reactions of the whole body to be no less imporatnt. As previously mentioned, the original radiation energy of such short duration is transformed to secondary biological effect and amplified to a great energy. Although there are fluctuations over time, there is a gradual decrease in intensity as confirmed by biological and morphological studies of irradiated subjects.[4]

In 1959, we began the studies on preoperative irradiation of cancer. Our work, which had been based upon the cancer immunity theory, was expanded to the problem of radiation exposure and the immune reaction. We finally arrived at the autoimmunity theory as presented in a previous report.

In 1957, Prof. Taruwasa had presented an assigned report to the Japan Radiology Society entitled "Serological Study on Actions of Radiation upon the Living Body" which was an accumulation of many years of work. This was based upon a concept entirely the same as ours. In his study, the following questions were raised. When the organs in the body are exposed to X-ray, do the degenerated tissues become antigenic and produce autoantibodies? Moreover,do the liberated antigenic material, when present in excessive amounts, act as an antigenic toxin which suppresses the functions of the organ tissues

whereas, when present in small amounts, serve to activate the function of organ tissues? Further, do the autoantibodies produced in response to this antigen result in anantigen-antibody reaction, which could one cause for the radiation intoxication phenomena? Still further, do these auto-antibodies,on the one hand, cause the tissues to become allergic so as to produce such secondary symptoms as radiation pneumonia, etc., and, on the other hand, act as a cytotoxin which suppersses the function of the respective organs?

Various experiments had been performed to clarify these points and it was reported that some progress had been made toward the solution. In his conclusion, it was stated that irradiated tissue components become antigenic and autoantibodies are produced within the body. His presentation ended with the comment that he hoped to do further fundamental theoretical studies based upon which studies relating to the actual situation in irradiation of man will be done.

If the original changes at the atomic level due to radiation result in degeneration of the cell, these changes are in the realm of the molecule and it is not difficult to imagine the development of a dynamic force in the form of a change at the biological level. A main writer of this paper, Makidono, had discovered in 1951 that the decompsed product of cells, which had degenerated due to exposure to radiation, can cause so-called allergic symptoms. This occurred at the time that X-ray ulceration developed 10 years after radiation dermatitis of the fingers and plasm had been suffered in about 1940. Each time aggravation of the ulcers or infection occured, articular rheumatism and such nervous symptoms as uneasiness developed. This has repeatedly occured each year until the present. The possibility of autoantibody production was suspected and since that time tubulation and observation of clinical cases were begun. For example, interesting findings were noted in cases treated for athlete's foot and tuberculosis of the lymph nodes as well as in treatment for asthma and urticaria. Various unexplainable cases have been reported in literature[6], but actually it appears that the unusual situations that are difficult to understand seen during radiation therapy may be readily explained on the basis of an allergic reaction due to antibodies.

At this point, a few comments shall be made on the general concept of autoantibodies. When the tissues of the living body are in normal condition, antibodies against one's own tissue are not produced. When there are degenerative changes of the tissue, however, the production of antibodies has been found to occur. These are autoantibodies and this represents the development of autoimmunity.

This concept was further confirmed in our previous report on the effect of preoperative irradiation and subcutaneous cancer tissue implantation on the antibody levels[7] and study of cancer immunity and its clinical application[8] in which autoantibodies were demonstrated by sensitized cell agglutination reaction in cancer-bearing subjects showing self-destruction of cancer.

Therefore, in the present study, as described in the plan of experiment, pre-treatment of rabbit was done,such as injections of a homogenate prepared from the excised left kidney, damage to the left kidney by X-ray and by cauterization,to see what changes would occur in the normal kidney on the opposite side. Further, the liver and spleen which are associated with immunity were examined for possible effects and at the same time the serum proteins which participate in the transit of such changes sere investigated. The results in general seem to indicate that the purely secondary biological in the radiological mechanisms may be best explained on the basis of the development of autoimmunity, which serves as the driving force that gives dynamic strength to the resopnse in the living body.

III. Material and Method

1) Experimental animals: Normal adult rabbits weighting about 2 kg.

2) Experimental pre-treatment

a) Experimental pre-treatment

Group A: Homogenate, which had been prepared from 3 gr of the extrirpated left kidney by supersonic wave treatment in 10 cc of physiological saline solution and frozen for storage, was given subcutaneouly in doses of 0.5 cc for 7 consecutive days to produce immunity.

Group B: This is the irradiated group in which the kidney, which had been pulled out of the body from the dorsal side under aseptic conditions, was exposed to a single dose of 1800 r by body cavity tube with the surrounding ares shielded with 2 mm lead plates. Immediately after irradiation, the kidney returned to within the body and sutured.

Group C: This is the burn group in which the surface and aprenchyma of the kidney, which, as in group B, had been pulled out of the body from the dorsal side under aseptic conditions, was cauterized by red-hot needles over an area involving about 1/3 of the entire kidney and then returned to within the body.

Table 1. Plan of Experiment

Group A: The group given injections of homogenate of lest kidney

No.	Date of blood specimen prior to pre-treatment		Date of extirpation of left kidney	Date of injection of homogenate of left kidney							Date of blood specimen after injection and date of sacrifice				Pre-treatment
													Sacrifice		
10	29 May	8 June	14 June	24/VI									Extirpation of liver, and spleen		Death due to shock after 3 cc of subcutaneous injection
11	〃	〃	〃	〃	25	26	27	28	29	1/VII	9/VII	16	VII/16	〃	0.5 cc subcutaneous injection
12	〃	〃	〃	〃	〃	〃	〃	〃	〃	〃	〃	〃	〃	〃	0.5 cc subcutaneous injection
13	30 May	10 June	〃	〃											0.5 cc subcutaneous injectton. Died on 10 June
14	〃	〃	〃	〃	25	26	27	28	29	1/VII	9/VII	16	24	31	0.5 cc subcutaneous injection. Sacrificed on 31 July

Extirpation of kidney, liver spleen and kidney done immediately after sacrifice

Group B: X-ray irradiation to left kidney

No.	Date of blood specimen prior to pre-treatment		X-ray irradiation	Date of blood specimen and date of sacrifice after X-ray irradiation to left kidney													
				1		2		3		4		5		6		7	
15	30May	10June	15June	25/VI		1/VII	Sacrificed										
16	31May	11June	〃	〃		〃	〃										
17	〃	〃	〃	〃		〃	〃	9/VII		17/VII	Sacrificed						
18	〃	12June	〃	〃		〃		〃		〃	〃						
19	1Jun	11June	〃	〃		〃		〃		〃		24/VII		31/VII		7/VIII	
20	〃	〃	〃	〃		〃		〃		〃		〃		〃		〃	

Extirpation of liver, spleen and kidney done immediately after sacrifice

Group C: Burns of left kidney

No.	Date of blood specimen prior to pre-treatment		Date of cauterization of left kidney	Date of blood specimen and date of sacrifice after cauterization of left kidney											
				1		2		3		4		5		6	7
21	1June	11June	17June	26/VI	Died 29/VI	2/VII	Sacrificed								
22	3June	12June	〃	〃											
23	4June	〃	〃	〃		2/VII	〃								
24	3June	13June	〃	〃		〃		10/VII		18/VII	Sacrificed				
25	4June	12June	〃	〃		〃									
26	〃	〃	〃	〃		〃						24/VII		31/VII	31/VII

Extirpation of liver, spleen and kidney done immediately after sacrifice

Table 2. Histological Findings for Group A

Case No.: 11
Date of sacrifice: 16/VII
Remarks: Two weeks after 7 injections of 1.5 cc kidney homogenate
Histological findings:

Liver Central veins are distended and sinusoids contain a small number of pseudoacidophile cells and albuminoids. Liver cells show mild generalized cloudy swelling.

Spleen Lymph follicles are atrophic. The peripheral areas show mild reticulum cell proliferation.

Kidney Glomeruli show atrophic area and vacuolar degeneration of capillary endothelial cells is seen.

Case No.: 12
Date of sacrifice: 16/VII
Remakrs: Same as preceeding case
Histological findings:

Liver Central veins are distended and sinusoids contain a large number of pseudoacidophile cells and alubminoid material. Liver cells show mild cloudy swelling.

Spleen Lymph follicle are atrophic. The peripheral areas show mild reticulum celld proliferation.

Kidney Vacuolar degeneration of endothelial cells of glomerular capillaries is marked. Comparatively severe vacuolar degeneration of epithelia of principal portion of renal tubules is seen, but there are no hyaline casts. On the other hand, abluminodi material is seen in Bowman's capsule and a pattern of serous glomerulitis is seen. There is mild congestio of the stroma of the straight renal tubule.

Case No.: 14
Date of sacrifice: 16/VII
Remarks: Two eeks after 7 injections of 0.5 cc kidaney homogenate
Histological findings:

Liver Central veins are distended and pseudoacidophile cells in the sinusoids are mended. However, liver cells do not shtow marked degeneration.

Spleen Lymph follicles are atrophic and mild reticulum cell proliferation is seen in pulp cords.

Kidney Although there are atrophic areas of the glomeruli, there is swelling so that the Bowman's space is almost occluded. Comparatively marked vacuolar degeneration of epithelia of principal portion of renal tubules is seen.

Table 3. Histological Findings for Group B

Case No.: 15
Date of sacrifice: 1/VII
Remarks: Two weeks after completion of course of X-ray
Histological findings:

Liver: Central veins are mildly distended and a small number of pseudoacidophile cels are seen in the sinusoids, but the liver cells are unremarkable.

Spleen: Atrophy of lymph follicles is comparatively marked and reticulum cell proliferation is seen in pulp cords.

Kidney: Right side: Glomeruli show atrophic areas, but the lesions are mild in comparison with the left. Left side: Glomeruli are generally swollen with areas of infiltration by erythrocytes. A small number of erythrocytes are contained in the principal portion of the renal tubules.

Case No.: 16
Date of sacrifice: 1/VII
Remarks: Same as preceeding case
Histological findings:

Liver: Mainly, the central zone of the hepatic lobules is necrotic where pseudoacidophilic reaction is seen. Mild vacuolar degeneration of liver cells of the intermediate zone is noted.

Spleen: Lymph follicles are atrophic and reticulum cell proliferation is seen in the pulp cord with pseudoacidophile cells.

Kidney: Right side: Glomeruli show atrophic areas and degeneration of epithelia of tubules is seen.
Left side: Glomeruli show areas of atrophy and nests of comparatively marked lymphocyte infiltration are seen in the peripheral regions. Bile pigment cases are noted sporadically in the renal tubules.

Case No.: 17
Date of sarcrifice: 17/VII
Remarks: Four weeks after completion of course of X-ray
Histological findings:

Liver: Central veins are mildly distended and sinusoids contain a small number of pseudoacidophile cells. Mild cloudy swelling of liver cells is seen.

Spleen: Atrophy of lymph follicles is marked and proliferation of reticulum cells is seen.

Kidney: Right side: Glomeruli show areas of atrophy and marked degeneration of epithelia of tubules is seen.
Left side: Changes of glomeruli are mild but vacuolar degeneration or desquamation of epithelia of tubules is comparatively marked.

Case No.: 18
Date of sacrifice: 17/VII
Remarks: Same as preceeding case
Histological findings:

Liver: Central veins are distended and a small number of pseudoacidophile cells and lymphocytes are contained in the sinusoids. Liver cells are not remarkable.

Spleen: Atrophy of lymph follicles is marked and proliferation of reticulum cells is marked in the pulp cord.

Kidney: Right side: Glomeruli show atrophic areas and mild degeneration of epithelia of renal tubules is seen.
Left side: Glomeruli show areas of atrophy and mild lymphocyte infiltration is seen in the peripheral regions. Mild vacuolar degeneration of epithelia of renal tubules is seen.

Table 4. Histological Findings for Group C

Case No.: 21
Date of sacrifice: 2/VII
Remarks: Two weeks after cauterization of 1/3 of exposed left kidney
Histological findings:

Liver: Central veins are distended and mild vacuolar degeneration or atrophy of liver cells is seen.

Spleen: Mild atrophy of lymph follicles is seen with proliferation of reticulum cells in pulp cords.

Kidney: Right side: Some areas of glomeruli show swelling with narrowing of Bowman's space in which a small amount of albuminoid fluid is contained.
Left side: Some areas of glomeruli show swelling of vascular endothelial cells. Nests of lymphocyte infiltration are seen sporaeidally in stoma of principal portion of renal tubules. Mild vacuolar degeneration of epithelia of tubules is seen.

Case No:. 22
Date of sadrifice: 29/VII
Remarks: Died 10 days after cauterization of 1/3 of exposed left kidney
Histological findings:

Liver: Infiltration by a small number of pseudoacidophile cells is sseen in the sinusoids, but the liver cells are unremarkable.

Spleen: Lymph follicles are atrophic and marked changes are seen in the pulp cord. That is edema and hemorrhage surrounded by infiltration by eosinophils are seen.

Kidney: Right side: Mild vacuolar degeneration of endothelial cells of glomeruli and infiltration of erythrocytes into the Bowman's space are seen. Moderate granular degeneration of epithelia of principal portion of renal tubules is seen.
Left side: Extensive necrosis is seen surrounded by marked infiltration by pseudoacidophile cells and lymphocytes where hemorrage is seen. Degeneration and desquamation of epithelia of tubules in surrounding area is makred.

Case No.: 23
Date of sacrifice: 2/VII
Remarks: Two weeks after cauterization of 1/3 of exposed left kidney
Histological findings:

Liver: Sinusoids are distended and contain erythrocytes. Hepatic cords are mildly atrophic.

Spleen: Lymph follicles are atrophic with mild hemorrhage and pseudoacidophile cell infiltration of pulp cord.

Kidney: Right side: Glomeruli are generally edematous with narrowing of Bowman's space. Infiltration by a small number of erythrocytes and albuminoid material is seen. The renal tubules contain a small number of erythrocytes and albuminoid material with granular degeneration of the epithelia.
Left side: Extensive necrotic foci are seen. Marked degeneration with desquamation of epithelia is seen in renal tubules of the peripheral regions.

Case No.: 24
Date of sacrifice: 18/VII
Remarks: Four weeks after cauterization of 1/3 of exposed left kidney
Histological findings:

Liver: Marked pseudoacidophile cell infiltration is seen in sinusoids. There is mild cloudy swelling of liver cells.

Spleen: Lymph follicles are mildly atrophic with reticulum cell proliferation in the peripheral regions.

Kidney: Right side: In some areas of the peripheral region of the glomeruli are seen infiltrative foci mainly by lymphocytes. There is mild cloudy swelling of epithelia of renal tubules.
Left side: Extensive necrotic foci are noted surrounded by marked lymphocyte infiltration.

Case No.: 25
Date of sacrifice: 18/VII
Remarks: Same as preceeding case
Histological findings:

Liver: Central veins are markedly distended and mild vacuolar degeneration of liver cells is seen.
Spleen: Follicles are atrophic and reticulum cell proliferation is seen in the pulp cord.
Kidney: Right side: Mild vacuolar degeneration of endothelial cells of glomeruli and mainly granular degeneration of epithelia of tubules are seen.
Left side: Extensive necrotic foci are seen with degeneration of epithelia of tubules of peripheral region.

b) Experimental method

(1) Rabbits were sacrificed at daily intervals and the normal right kidney was immediately extirpated and fixed in formalin for histological inspection. Staining was by hematoxylin-eosin.

(2) Examination of serum protein was done by paper electrophoresis.

The necessary surgical procedures in the pre-treatment for these experiments were carried out with the cooperation of Dr. Tatsugoro Takeuchi while the histological findings were obtained under the guidance of Dr. Monzen, chief of the Department of Laboratories, Hiroshima Prefectural Hospital. Examination of the serum protein was done with the guidance and cooperation of Dr. Matsutani, assistant chief of the Department of Laboratories, Hiroshima Prefectural Hospital.

The plan of experiment is summarized in table 1.

IV. Results of Experiments

The experiments were done in 6 parts, the results of which are as follows.

1) The results of the histological examination for group A are shown in table 2. It is evident that, at the time of our examination, not only were considerably severe pathological changes noted in the right kidney but some effects were also seen in the liver and spleen.

2) The results of the histological examinations for group B are shown in table 3. This table shown that there were extensive necrotic foci in the irradiated left kidney with severe disturbances due to radiation but in addition the non-irradiated right kidney likewise definitely showed similar pathological changes. Moreover, the liver and spleen also showed considerable effects although there were considerably variations in the degree of the changes among the cases.

3) The histological findings obtained for group C are shown in table 4. Since degenerative changes of the cells had been produced by cauterization of one portion of the left kidney, variations according to the degree of cauterization and the site examined are inevitable. It is interesting, however, that the histology of the right kidney in all cases showed the same degree of disturbances. The table indicates the considerable effects produced in the liver and spleen.

Some of the histological findings are illustrated in figure 1 to 4 for group A, figures 5 to 7 for group B and figures 8 to 11 for group C.

4) The migration of the serum portein fraction of group A was examined daily and the results are shown in table 5.

First, with respect to the migration pattern, all cases showed a normal N-pattern prior to extirpation of the left kidney One week following nephrectomy, beta or gamma patterns appeared indicative of changes in the migration of protein. One week following the course of injections of the homogenate prepared from the left kidney, the pattern was found to vary among the different cases and even two weeks

Histological Findings of Group A

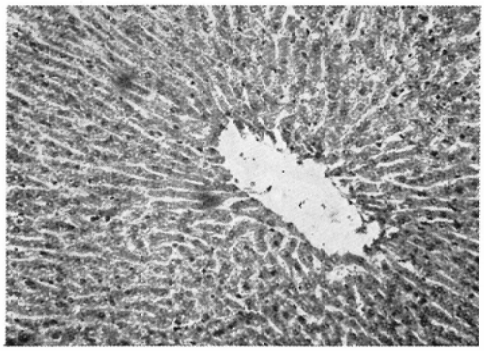

Figure 1. Case No. 11: Liver Central vein is distended.

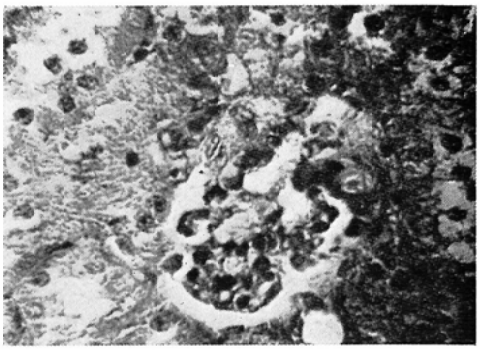

Figure 2. Case No. 11: Right Kidney Glomerulus is atrophic.

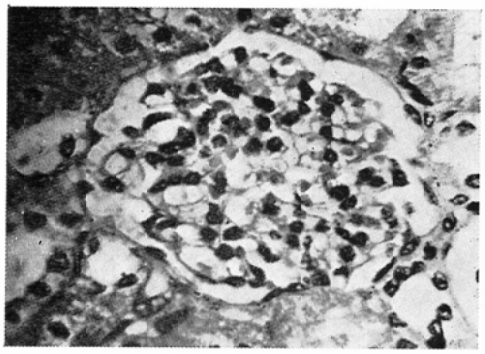

Figure 3. Case No. 11: Right Kidney Vacuclar degeneration of capillary of glomerular wall and degeneration of renal tubules.

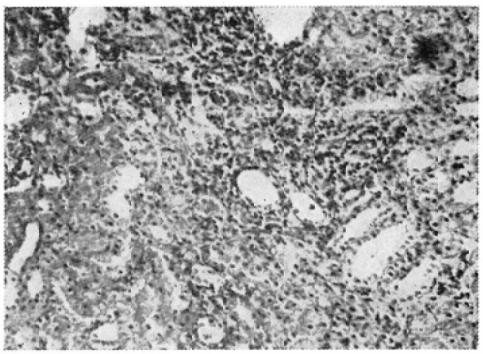

Figure 4. Case No. 12: Spleen Lymph follicles are atrophic and proliferation of reticulum cells is seen in medullary cord.

Histological Findings of Group B

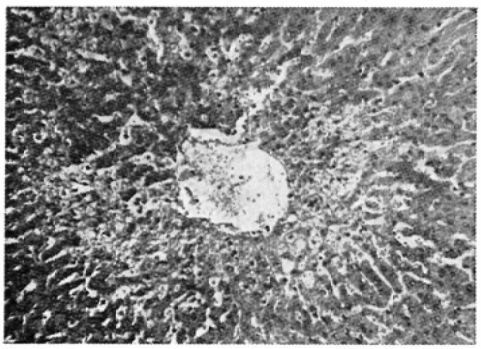

Figure 5. Case No. 16: Liver Central zone of hepatic lobule is necrotic.

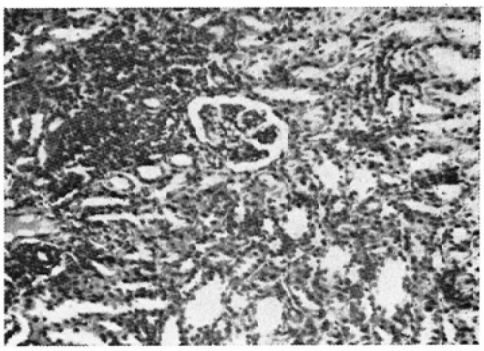

Figure 6. Case No. 16: Right Kidney In some areas glomeruli are atrophic. Degeneration is found in spithelia of renal tubules.

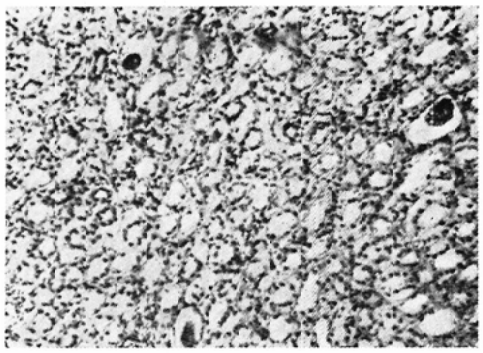

Figure 7. Case No. 16: Left Kidney Glomeruli are atrophic in some areas. Nests of lymphocytic infiltration can be found in periphery. Bile pigment casts are seen in renal tubules.

Histological Findings in Group C

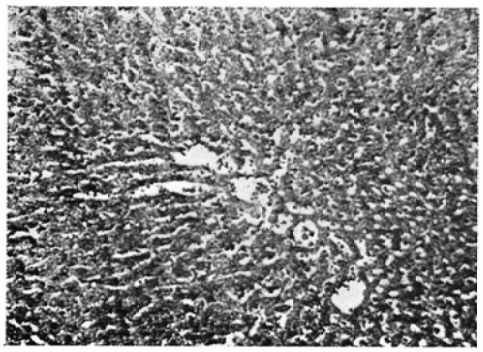

Figure 8. Case No.23: Liver Sinusoids are distended. Hepatic cords are slightly atrophic.

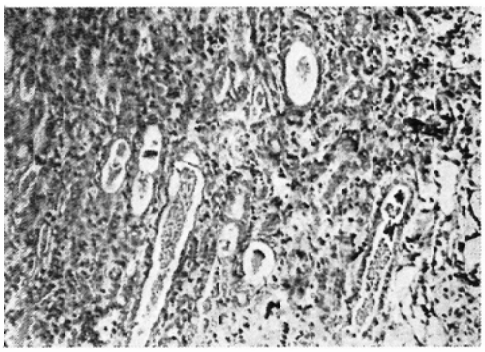

Figure 9. Case No. 21: Right Kidney Hyaline casts are contained in straight renal tubules.

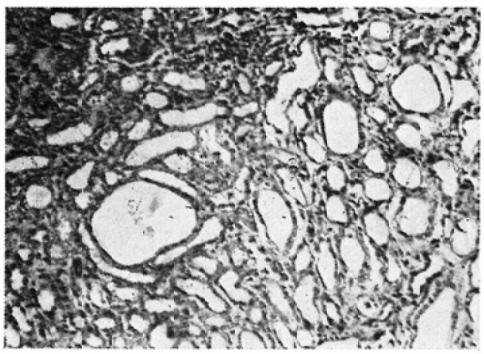

Figure 10. Case No. 21: Right Kidney Lymphocyte infiltration of stroma of principal renal tubules and flattening of epithelia of renal tubules are found.

Figure 11. Case No. 24: Spleen Follicles are slightly atrophic. Proliferation of reticulum cells are found in periphery.

Table 5. Serum protein of Group A

Rabbit No.	Date of blood sample	Remarks	Area cm × 1/10						% of total area					Plasma protein in Grams per 100cc						A/G	PAT
			alb	α_1	α_2	β	γ	Total	alb	α_1	α_2	β	γ	Total	alb	α_1	α_2	β	γ		
10	8 June	Before extirpation of left kidney	11.4	1.3	1.6	2.0	3.0	19.3	59.1	5.7	8.3	10.1	15.5	5.2	3.1	0.3	0.4	0.5	0.8	1.5	N
	20 June	1 week after extirpation of left kidney 3 cc homogenate of kidney injected after bloodletting (Death due to shock)	12.6	1.2	1.4	3.0	3.7	21.9	57.5	5.5	6.4	13.7	16.9	6.0	3.5	0.3	0.4	0.8	1.0	1.4	β
11	8 June	Before extirpation of left kidney	10.7	0.9	2.3	2.2	2.5	18.6	57.5	4.8	12.4	11.8	13.4	5.6	3.2	0.3	0.7	0.7	0.8	1.3	N
	24 June	1 week after extirpation of left kidney 0.5 cc injection of homogenate of kidney after bloodletting	10.7	1.2	1.5	2.5	3.2	19.1	56.0	6.3	7.9	13.1	16.8	6.2	3.5	0.4	0.5	0.8	1.0	1.3	β
	9 July	1 week after 0.5 cc injections (7 times)	11.9	1.2	1.6	2.6	3.1	20.4	58.3	5.9	7.8	12.3	15.2	6.2	3.6	0.4	0.5	0.8	0.9	1.4	N
	16 July	2 weeks after 0.5 cc injections (7times) (sacrificed on same day)	11.5	1.2	1.9	3.2	3.3	21.1	54.5	5.7	9.0	15.2	15.6	6.0	3.3	0.3	0.5	0.9	0.9	1.3	β
12	8 June	Before extirpation of left kidney	12.0	1.5	1.8	2.1	3.6	21.0	57.1	7.1	8.6	10.0	17.1	6.5	3.7	0.5	0.6	0.7	1.1	1.3	N
	24 June	1 week after extirpation of left kidney 0.5 cc injection of homogenate of kidney after bloodletting	13.7	1.3	1.7	2.6	3.3	22.6	60.6	5.8	7.5	11.5	14.6	6.5	3.9	0.4	0.5	0.7	0.9	1.5	β
	9 July	1 week after 0.5 cc injections (7 times)	14.7	1.9	2.4	3.6	5.2	27.8	52.9	6.8	8.6	12.9	18.7	7.0	3.7	0.5	0.6	0.9	1.3	1.1	β
	16 July	2 weeks after 0.5 cc injections (7 times) (sacrificed on same day)	12.8	1.8	1.8	2.5	3.8	22.7	56.4	7.9	7.9	11.0	16.7	7.0	3.9	0.6	0.6	0.8	1.2	1.2	N
13	8 June	Before extirpation of left kidney	15.0	1.1	2.4	1.9	5.7	26.1	57.5	4.2	9.2	7.2	21.8	7.0	4.0	0.3	0.6	0.5	1.5	1.4	N
	24 June	1 week after extirpation of left kidney 0.5 cc injection of homogenate of kidney after bloodletting	13.0	1.5	2.1	2.4	5.9	25.2	52.8	6.0	8.3	9.5	23.4	7.0	3.7	0.4	0.6	0.7	1.6	1.2	γ
	9 July	1 weeks after 0.5 cc injections (7 times)	12.4	1.4	2.6	2.3	6.6	25.3	49.0	5.5	10.3	9.1	26.1	7.0	3.4	0.4	0.7	0.6	1.8	1.0	γ
	16 July	2 weeks after 0.5 cc injections (7 times) (sacrificed after 1 week)	8.4	1.0	1.6	1.5	4.4	16.9	50.0	5.9	9.5	8.9	26.0	7.0	3.5	0.4	0.7	0.6	1.8	1.0	γ

Table 6. Serum protein of Group B

Rabbit No.	Date of blood sample	Remarks	area cm × 1/10						% of total area					Plasma protein in Grams per 100 cc						A/G	PAT
			alb	α_1	α_2	β	γ	Total	alb	α_1	α_2	β	γ	Total	alb	α_1	α_2	β	γ		
15	10 June	Before X-ray irradiation	12.5	1.0	2.3	2.4	6.2	24.4	51.2	4.1	9.4	9.8	25.4	7.8	4.0	0.3	0.7	0.8	2.1	1.1	N
	25 June	1 week after X-ray irradiation	13.8	1.9	2.4	2.9	6.6	27.4	50.0	6.9	8.7	10.5	23.9	7.0	3.5	0.5	0.6	0.7	1.7	1.0	β
	1 July	2 weeks after X-ray irradiation (sacrificed on the same day)	14.7	1.3	1.9	2.4	5.0	25.3	58.1	5.1	7.6	9.5	19.8	6.2	3.6	0.3	0.5	0.6	1.2	1.4	N

16	11 June	Before X-ray irradiation	12.8	2.0	1.8	3.6	4.3	24.5	52.2	8.2	7.3	14.7	17.6	5.6	2.9	0.5	0.4	0.8	1.0	1.0	β
	15 June	1 week after X-ray irradiation	13.9	2.1	2.0	3.5	5.4	26.9	51.7	7.8	7.4	13.0	20.1	7.0	3.6	0.5	0.5	0.9	1.1	1.1	N
	1 July	2 weeks after X-ray irradiation (sacrificed on the same day)	12.9	1.4	1.8	2.2	4.1	22.4	57.6	6.3	8.0	9.8	18.3	7.0	4.0	0.4	0.6	0.7	1.3	1.3	N
17	11 June	Before X-ray irradiation	12.4	0.9	1.6	2.6	2.7	20.2	61.5	4.5	7.9	12.9	13.4	6.4	5.9	0.3	0.5	0.8	0.9	1.5	N
	25 June	1 week after X-ray irradiation	12.2	0.8	1.5	2.6	3.0	20.1	60.7	4.0	7.5	12.9	14.9	6.4	3.9	0.3	0.5	0.8	1.0	1.5	N
	1 July	2 weeks after X-ray irradiation	12.9	1.1	1.7	2.7	3.4	21.8	59.2	5.0	7.8	12.4	15.6	6.2	3.7	0.3	0.5	0.8	1.0	1.4	N
	9 July	3 weeks after X-ray irradiation (sacrificed after 1 week)	13.1	0.9	1.6	2.3	3.1	21.0	62.4	4.3	7.6	11.0	14.8	7.0	4.4	0.3	0.5	0.8	1.0	1.7	N
18	11 June	Before X-ray irradiation	13.6	1.3	1.9	2.0	3.6	22.4	60.7	5.8	8.5	8.9	16.1	6.5	3.9	0.5	0.6	0.6	1.0	1.4	N
	25 June	1 week after X-ray irradiation	11.6	1.1	1.4	2.3	3.0	19.4	59.8	5.7	7.2	11.9	15.5	6.0	3.6	0.3	0.4	0.7	0.9	1.6	β
	1 July	2 weeks after X-ray irradiation	8.8	0.6	1.2	1.5	2.3	14.4	61.1	4.2	8.3	10.4	16.0	5.1	3.1	0.2	0.4	0.5	0.8	1.6	N
	9 July	3 weeks after X-ray irradiation (sacrificed after 1 week)	14.8	1.5	1.9	2.4	4.2	24.8	59.7	6.0	7.7	7.7	16.9	6.5	3.9	0.4	0.5	0.6	1.1	1.5	N
19	11 June	Before X-ray irradiation	11.7	1.5	2.1	2.3	3.4	21.0	55.7	7.1	10.0	10.9	15.1	6.0	3.3	0.4	0.6	0.7	0.9	1.1	N
	25 June	1 week after X-ray irradiation	11.1	1.4	2.2	3.5	3.8	22.0	50.5	6.3	10.0	16.0	17.2	6.2	3.1	0.4	0.6	1.0	1.1	1.0	β
	1 July	2 weeks after X-ray irradiation	12.3	1.3	2.7	3.4	4.2	23.9	51.5	5.4	11.3	14.2	17.6	6.2	3.2	0.3	0.7	0.9	1.1	1.1	β
	9 July	3 weeks after X-ray irradiation	9.1	1.2	1.3	1.7	2.7	16.0	56.9	7.5	8.1	10.6	16.9	5.8	3.3	0.4	0.5	0.6	1.0	1.3	N
20	11 June	Before X-ray irradiation	11.5	0.7	1.2	1.8	3.3	18.5	62.2	3.8	6.5	9.7	17.8	6.5	4.0	0.2	0.4	0.6	1.2	1.5	N
	25 June	1 week after X-ray irradiation	11.6	1.2	1.4	2.3	3.0	19.5	59.4	6.2	7.2	11.8	15.4	6.2	3.7	0.4	0.4	0.7	1.0	1.5	β
	1 July	2 weeks after X-ray irradiation	12.4	1.1	1.4	2.2	2.8	19.9	62.3	5.5	7.0	11.1	14.1	6.2	3.9	0.3	0.4	0.7	0.9	1.7	β
	9 July	3 weeks after X-ray irradiation	12.4	1.2	1.2	1.7	2.8	18.9	63.3	6.4	6.4	9.0	14.8	6.4	4.1	0.4	0.4	0.6	0.9	1.8	N

Table 7. Serum protein in Group C

Rabbit No.	Date of blood sample	Remarks	area cm × 1/10						% of total area					Plasma protein in Grams per 100cc						A/G	PAT
			alb	α_1	α_2	β	γ	To-tal	alb	α_1	α_2	β	γ	To-tal	alb	α_1	α_2	β	γ		
21	11 June	Before burns	13.1	1.3	1.4	2.2	2.5	20.5	63.9	6.3	6.8	10.7	12.2	6.5	4.2	0.4	0.4	0.7	0.8	1.8	N
	25 June	1 week after burns	12.7	1.2	1.2	2.5	3.4	21.0	60.5	5.7	5.7	11.9	16.2	6.5	4.1	0.4	0.4	0.8	1.1	1.5	β
	2 July	2 weeks after burns (sacrificed on same day)	13.7	1.5	1.5	2.5	4.1	23.3	58.8	6.4	6.4	10.7	17.6	6.4	3.8	0.4	0.4	0.7	1.1	1.5	N
21	12 June	Before burns	14.4	1.6	1.5	2.4	6.1	26.0	55.4	6.2	5.8	9.2	23.5	6.5	3.6	0.4	0.4	0.6	1.5	1.2	γ
	26 June	1 week after burns (Died on 29/VI)	11.5	1.9	2.1	3.9	6.3	25.7	44.7	7.4	8.2	15.2	24.5	7.8	3.5	0.6	0.6	1.2	1.9	0.8	β
	12 June	Before burns	13.8	0.9	1.6	2.6	3.8	22.7	60.8	4.0	7.0	11.5	16.7	6.4	3.9	0.3	0.4	0.7	1.1	1.6	N
	26 June	1 week after burns	12.3	2.0	1.5	4.2	4.0	24.0	51.3	8.3	6.3	17.5	16.7	6.8	3.5	0.6	0.4	1.2	1.1	1.0	β

23	2 July	2 week after burns (sacrificed on same day)	12.0	1.4	1.8	3.1	4.5	22.8	52.6	6.1	7.9	13.6	19.7	6.4	3.4	0.4	0.5	0.9	1.3	1.1	N
24	13 June	Before burns	15.1	2.3	2.3	4.1	3.7	25.2	60.0	9.1	9.1	16.3	14.7	6.6	4.0	0.6	0.6	1.0	1.0	1.2	N
	26 June	1 week after burns	12.6	1.3	4.4	7.3	4.2	29.8	42.3	4.4	14.8	24.5	14.1	6.4	2.7	0.3	0.9	1.6	0.9	0.7	β
	2 July	2 week after burns	13.5	1.2	2.3	3.1	5.4	25.5	52.9	4.7	9.0	12.2	21.2	7.2	3.8	0.3	0.6	0.9	1.5	1.2	N
	16 July	3 week after burns (sacrificed after 1 week)	14.1	2.2	1.7	3.5	5.6	27.1	52.0	8.1	6.3	12.9	20.7	7.0	3.6	0.6	0.4	0.9	1.4	1.1	N
25	22 June	Before burns	10.4	0.8	2.4	3.0	4.6	21.2	49.1	3.8	11.3	14.2	21.7	5.8	2.8	0.2	0.7	0.8	1.3	0.9	N
	26 June	1 week after burns	15.0	3.2	2.9	5.1	5.5	31.7	47.3	10.1	9.1	16.1	17.4	7.4	3.5	0.7	0.7	1.4	1.3	0.8	β
	2 July	2 week after burns	11.3	1.2	1.5	2.7	4.7	21.4	52.8	5.6	7.0	12.6	21.6	6.0	3.2	0.3	0.4	0.8	1.3	1.1	N
	16 July	3 week after burns	12.8	1.8	2.0	3.0	5.8	25.4	50.4	7.1	7.9	11.8	22.8	6.0	3.0	0.4	0.5	0.7	1.4	1.0	N
	18 July	4 week after burns (sacrificed on same day)	12.4	1.5	2.0	2.6	5.2	23.7	52.3	6.3	8.4	11.0	22.0	6.2	3.2	0.4	0.5	0.7	1.4	1.1	N
26	12 June	Before burns	13.7	1.2	1.6	2.8	3.0	22.3	61.4	5.4	7.2	12.6	13.5	6.2	3.8	0.3	0.4	0.8	0.8	1.4	N
	26 June	1 week after burns	12.7	1.6	2.0	3.0	4.6	23.9	53.1	6.7	8.4	12.6	19.2	7.2	3.8	0.5	0.6	0.9	1.4	1.1	N
	2 June	2 week after burns	8.4	1.1	2.3	4.7	4.2	20.7	40.6	5.3	11.1	22.7	20.2	6.9	2.8	0.4	0.8	1.6	1.4	0.8	β
	10 July	3 week after burns	13.5	3.6	2.2	5.4	7.3	32.0	42.2	11.3	6.9	16.9	22.8	7.0	3.0	0.8	0.5	1.2	1.6	0.7	β
	18 July	4 week after burns	11.8	2.2	1.4	4.4	4.8	24.6	48.0	8.9	5.7	17.9	19.5	7.0	3.4	0.6	0.4	1.3	1.4	0.9	N

Table 8. Mean value of plasma protein in each group

	Experimental pre-treatment and time elapsed		area cm × 1/10						% of total area					Plasma protein in Grams per 100cc						A/G
	Outline of pre-treatment	Date	alb	α_1	α_2	β	γ	To-tal	alb	α_1	α_2	β	γ	To-tal	alb	α_1	α_2	β	γ	
Group A	Before extirpation of kidney	8 June	12.2	1.2	2.0	2.1	3.7	21.2	57.8	5.5	10.0	9.8	17.0	6.1	3.5	0.4	0.6	0.6	1.1	1.4
	1 week after extirpation of left kidney	24 June	12.6	1.3	1.7	2.6	4.0	22.2	56.7	5.9	8.0	12.0	17.0	6.4	3.7	0.4	0.5	0.8	1.1	1.4
	1 week after 0.5 cc injection of homo-genate of left kidney (7 times)	9 July	13.0	1.5	2.2	2.8	5.0	24.5	53.4	6.1	8.9	11.4	20.0	6.7	3.6	0.4	0.5	0.8	1.0	1.2
	2 week after injection	16 July	10.9	1.3	1.8	2.4	3.8	20.2	53.6	6.5	8.8	11.7	19.8	6.7	3.6	0.4	0.5	0.8	1.3	1.2
Group B	Before X-ray irradiation	10 June	12.4	1.2	1.8	2.5	3.9	21.8	53.9	5.6	8.3	11.2	17.6	6.5	3.7	0.4	0.6	0.7	1.2	1.3
	1 week after X-ray irradiation	25 June	12.4	1.4	1.8	2.9	4.1	23.7	55.4	6.2	8.0	12.7	17.8	6.5	3.6	0.4	0.5	0.8	1.2	1.3
	2 week after irradiation	1 July	12.3	1.1	1.8	2.4	3.6	21.3	58.3	5.3	8.3	11.2	16.9	6.2	3.6	0.3	0.5	0.7	1.1	1.4
	3 week after irradiation	9 July	12.4	1.2	1.5	2.0	3.2	20.2	60.6	6.1	7.5	10.2	15.9	6.4	3.9	0.4	0.5	0.7	1.0	1.6
Group C	Before burn	11 June	13.4	1.4	1.8	2.9	4.0	23.0	58.4	6.8	7.8	12.4	15.4	6.3	3.7	0.4	0.5	0.8	1.1	1.4
	1 week after burn	25 June	12.8	1.9	2.4	4.3	4.7	21.7	49.9	7.1	8.8	16.3	18.0	7.2	3.5	0.5	0.6	1.2	1.3	1.0
	2 weeks after burn	2 July	11.8	1.3	1.9	3.2	4.6	18.7	51.5	5.6	8.3	14.4	18.1	6.6	3.4	0.4	0.5	1.0	1.3	1.7
	3 weeks after burn	10 July	13.5	2.5	2.0	4.0	6.2	28.2	48.2	8.8	7.0	14.1	22.1	6.7	3.2	0.6	0.5	0.9	1.5	0.7
	4 weeks after burn	15 July	12.1	1.9	1.7	3.5	5.0	24.1	50.2	7.6	7.1	14.5	20.8	6.6	3.3	0.5	0.5	0.7	1.4	1.0

later the pattern was likewise inconsistent.

Quantitative study of the serum protein fraction showed an increase of beta and gamma globulins during and after homogenate injections which genera.ly coincided with the accentuation of the pattern. On daily quantitative examination of the serum protein, the pace of occurrence of changes was similar in all cases.

5) The results of daily examination of the migration of the serum protein fraction of group B are shown in table 6.

The migration pattern changed from the N-pattern to the beta pattern 1 week following completion of radiation exposure in 4 out of 6 cases. The remaining 2 cases showed little change in the N-pattern. Two weeks later, the beta pattern persisted in 2 cases while 4 cases were N-pattern. Three weeks later, all cases demonstrated a N-pattern.

On quantitative examination of the serum protein fraction, generally only temporary changes in beta and gamma globulins were seen, and as a whole, fluctuations were mild.

6) The results of daily examination of the serum protein fraction of group C are shown in table 7.

As shown in the table, the migration pattern showed the beta pattern 1 week after cauterization of the left kidney in 5 out of 6 cases. In the second week, 4 cases returned to the N-pattern, but 1 case showed the beta pattern for the first time. Subsequently, there was tendency to return to the N-pattern.

On quantitative examination of the serum protein fraction, an increase consistent with the accentuation of the pattern was seen, and as a whole, a marked increase was noted in beta and gamma globulins.

The results of these experiments are summarized in table 8. It is evident that all groups A, B and C show similar trends and the only difference is that the changes are the most mild in the irradiated group and the most marked in the cauterized group.

V. Summary and Discussion

In summary, the experiments described show that immunization by injections of the homogenate prepared from the kidney of one side or by damage to one kidney by either radiation or cauterization will produce effects in the other normal kidney. Such changes were histologically confirmed. These findings support the hypothesis presented in the section where the general concept of autoantibodies was discussed. Moreover, the histological pictures in each group were entirely identical in nature although there were some quantitative differences in the lesions. Even though the method of pre-treatment differed, it is evident that the purely secondary biological effect are due to a common mechanism.

These experimental animals did not show any appreciable gross change during the 2 or 3 days after the above pre-treatment except for loss of appetite. Subsequently, they recovered their strength,returned to normal and survived.

Examination of the serum protein by paper electrophoresis during this period showed that all 3 groups followed the same course. In the cases immunized by homogenate prepared from the left kidney, an increase in both beta and gamma globulins was noted with elapse of time and subsequently the migration recovered to the pattern which we have termed the N-pattern. Thus, a characteristic pattern showing accentuation corresponding to the quantitative changes was seen during the course. The picture was entirely the same in both the irradiated and cauterized groups except that the changes were mild in the group exposed to 1800 r of X-rays and marked in the cauterized group. The beta and gamma globulins showed a marked increase in all groups.

When the histological findings and the migration and quantitative changes of the serum protein in our experiments are considered, the methods we used not only produced common changes but also affirmed the possibility of autoantibody production.

In the X-ray irradiated group, the expected histological changes were induced but the change in serum proteins was not as great as anticipated. This presumably is due to the fact that the exposure dose had been determined after considering the usual clinical dose.

In the histological study, the liver and spleen had been included in addition to the kidney because we had been concerned with the problem of autoimmunity and interested in the effects upon these organs which are abundant in reticuloendothelial tissues. It is noteworthy that considerable effects were noted in these organs also. In a previous study on irradiation to experimental and clinical cancer, we had examined the energy metabolism of the liver and spleen and the catalase activity of the liver. It was confirmed that there is hyperfunction of the liver and spleen in cases that follow a satisfactory course of progress after radiation.

These experiments demonstrated that the destroyed products of the kidney not only affect the other normal kidney but also act upon the two organs which were selected as belonging to the reticuloendothelial system. The mechanism of this action has been described by Caspari as specific and non-specific actions of the destroyed cellular substance upon the whole body.

Although Caspari has presented a hypothesis which assumes actions involving the whole body, there are many workers who consider that the localized actions play the major role in the mechanism of radiobiological effects. In our experiments, however, considerable changes were produced in the liver and spleen so that if delivery of radiation were to be done by considering only the local changes, it would mean that the mechanisms of the beneficial or detrimental biological actions that presumably are produced within the body will be ignored. For example, in radiation therapy of cancer, there first occurs destruction of the cancer cells but the destroyed products act as an antigen which produces autoantibodies against the cancer cells so as to further enhance the therapeutic results. This has been confirmed in our study of treatment of gastric cancer in which the presence of autoantibodies was demonstrated. It is presumed that when such destroyed products are produced in excessive amounts, they act as antigenic toxins which cause the opposite effects to occur in the body,such as the changes observed above in the liver and spleen, so as to result in radiation intoxication.

We have found that the key to whether the effects are beneficial or detrimental lies in the antigen-antibody balance. The complex nature of the factors involved in radiation exposure is even more impressive when we consider that this delicate quantitative relation is affected by the conditions under which the radiation exposure is given. In other words, in determining the condition of exposure, the biological changes that follow the changes at the level of the atom, that is, the biological amplification must be considered.

In our studies, the serum protein fraction showed changes in the pattern as well as quantitative changes which, when considered together with the clinical laboratory findings, make possible further assumptions on the biological amplification. The appearance of the beta pattern and the gamma pattern in electrophoresis, as reported previously in a paper on the serum protein of A-bomb sruvivors, indicates an unstable state (or a fluctuating state) of the serum protein fraction and suggests the production of antibodies. In the present experiments, all groups showed beta and gamma patterns in the early period

which with elapse of time became stabilized to the N-patterns and gamma patterns. As previously reported, the gamma pattern suggests antibody production.

We feel that some insight into one aspect of the generalized reaction to radiation exposure may be possible from these changes in serum protein and the clinical observations. Actually, as reported in our paper on radiation therapy of cancer in which detailed study of the changes in protein fraction was done, cases which followed a satisfactory course had shown N-patterns or gamma patterns while cases with a poor prognosis demonstrated beta patterns.

With respect to the clinical significance of the present experimental study, radiation therapy in the past had been considered to be ineffective because the radiation energy was inadequate and because the focal dose was insufficient. Therefore, in order to increase the energy and concentrate it upon the target tissue, supervoltage equipment have been designed and studies have been done on methods to concentrate the radiation such as by pendulum motion, rotation, beam condensation, etc., and it appersa that techniques along these lines have been perfected. If this theory were correct, the results of treatment should be proportional to the dose delivered. Wonderful results, of course, have been obtained at sites where such improved results are naturally expected, but there are many cases in which unanticipated detrimental effects have been produced.

It has been known from the past that the results of large doses delivered to a large field are poor regardless of the type of apparatus used. This has been confirmed by our experiments also and much attention should be paid to this point. In vitro exposure of tumor will not result in destruction even when the dose is several hundred times greater than that given in vivo. This indicates the importance of the secondary biological actions. The results of the present study show that following the primary destruction of cells by radiation, the destructed products act as an autoantigen with production of autoantibodies causing an antigen-antibody reaction to occur which results in disruption of the cellular metabolism or a lethal chemical change within the cell itself so that grave effects upon the life of the cells continue even after the radiation energy has been delivered.

Thus, it seems that the method of irradiation must be modified according to this concept. In our follow-up study on autoantibodies by the sensitized cell agglutination reaction in radiation therapy for gastric cancer, the antibodies reached the peak level at about 20 days to 1 month after irradiation and the reaction disappeared in about 3 months. In view of this observation and the results of the present study in which antibody production was definitely demonstrated 2 weeks following radiation, it seems proper theoretically that in future radiation therapy, an initial focal dose of about 1000—2000 r should be applied and this should be repeated at intervals of 2 to 3 months using the improvement in clinical symptoms as a measure. Moreover, regardless of the method of radiation exposure, the technique should consist of divided doses by multiple ports to a small field. Further, with respect to preoperative irradiation, a method we have suggested, our experiments show that surgery about 2 weeks after irradiation is appropriate. Another possible treatment method would be the therapeutic transplantation of extirpated irradiated cancer tissue as a means of administering antigen following surgery so as to maintain the antibody level. At present, studies to confirm this are in progress on a small number of cases by following the agglutination reaction. We feel that if this therapeutic transplantation were to be incorporated into the plan of surgery, we can expect greater success in post-operative irradiation.

It shall be mentioned here that successful results have been obtained from the clinical application of

these considerations.

In conclusion, we wish to express our appreciation for the cooperation of Drs. Monzen and Matsutani of the Department of Laboratories, Hiroshima Prefefctural Hospital and Dr. Takeuchi, Director of the Takeuchi Surgical Hospital.

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