with solutions of sodium chloride and glucose was instituted again, with only partial success. The extract of the suprarenal cortex sent by Drs. Swingle and Pfiffner arrived on the sixth day after the patient's admission to the hospital and treatment was begun with daily doses of 20 cc given subcutaneously. Within thirty-six hours a marked effect on appetite and strength was apparent. The patient, who had been so nauseated as to retain water with difficulty, now asked for wieners and sauerkraut and in lieu of the latter ate a double order of beefsteak with relish.

This extract produced considerable local irritation at the site of injection and because of the content of epinephrine could not be given intravenously in therapeutic doses. A further supply of the extract was not available at that time; therefore the patient was put back on the Muirhead regimen. He did well for a few weeks, but gradually failed and again went into collapse, from which the timely arrival of a fresh supply of extract sufficed to insure temporary recovery.

This cycle has been repeated three times in this case. The last time it was possible to use Swingle and Pfiffner's newest extract, which is free from epinephrine. This was given intravenously in divided doses in a quantity of 20 cc daily with a total dosage of 50 cc. Before its use the patient was excessively weak, bedridden, depressed, nauseated, losing weight and showed evidence of failing circulation. Within forty-eight hours he had taken a new lease on life, his appetite was excellent, his strength was greatly improved and he appeared to be in a state of perfect health. He gained 9 pounds in weight in the next eight days and has been in good condition since then.

Since that time it has been possible to observe the effect of the preparation on three other patients suffering from Addison's disease. The condition of one patient was not considered serious at the time of his examination and he was kept on the treatment for only four days. There were no spectacular changes during this period and the small supply of extract precluded its further trial. In the other two cases the clinical condition of the patients and the results obtained by treatment were similar in character to those observed in the first case. Metabolism studies were made in one case during the period of observation. The results will be reported later, but preliminary observations indicate disappearance of creatinuria and retention of nitrogen in consequence of the administration of the suprarenal extract.

The results in these cases convince us of the apparent efficacy of this cortical extract. There was no striking change in the blood pressure, but the disappearance of anorexia, increase of appetite to the point of hunger, the gain in weight and the definite feeling of increased strength and well-being were striking. As long as the preparation was administered, the results were all that could be desired. However, our supply of the preparation has been limited, so that we have not been able to observe the results following consistent dosage and continued administration. The first preparation was not free from epinephrine and caused local irritation when given subcutaneously. The later supply, however, is almost free from epinephrine; it is suitable for intravenous administration and is almost non-irritating locally. As has been shown, the immediate results in a crisis were excellent. Addison's disease, however, is chronic, and it will be necessary for several years to elapse before a final appraisal can be made of the value of this new therapeutic agent in its treatment.

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THE suprarenal cortical extract used intravenously by Dr. Rowntree on patients with Addison's disease represents the modification of our original aqueous preparation mentioned in an earlier communication to this journal.[1] This extract, 1 cc of which represents 30 gm of fresh beef cortex, contains only 0.3 per cent. of solids. The epinephrine content as measured by blood pressure assay on dogs is at most between 1:1,000,000 and 1:2,000,000. The method of fractionation used is based on our observation that, by the proper use of permutit, epinephrine can be practically quantitatively separated from the cortical hormone. The 70 per cent. alcohol-soluble fraction obtained by our previously described method[2] is simply filtered in alcoholic solution through an adequate amount of permutit which removes the epinephrine. Much inert material including most of the contaminating pigment is also removed by this fractionation step.

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ON THE CHEMICAL ALTERATION OF PURIFIED ANTIBODY-PROTEINS

DIAZONIUM salts of well-defined chemical compounds coupled to proteins have been used in the study of the relation of biological specificity to chemical constitution, in particular by Landsteiner[1] and his coworkers in the last two decades. It has usually been found that the coupled compound fully determines the

[1] SCIENCE, 72: 75–76, 1930.
[2] SCIENCE, 71: 321–322, 1930.
[1] Landsteiner and Lampl, *Biochem. Zeitschrift*, 86: 343, 1930.

specificity of these proteins as antigens, but some experiments have been published in which the original biological specificity of the proteins also remains.[2]

It would seem possible, therefore, to alter chemically with the same methods such substances as display a specific biological activity without destroying this latter quality. This process appeared to us of special interest in the case of animal proteins, which play an important rôle in pathology because they carry the immune properties of the animal body, namely, the antibodies. The antibodies have a specific affinity towards their antigens (pathologic bacteria) but they usually do not destroy them or do not even lower their resistance enough to permit them to be phagocytized. We thought that in some instances a chemical alteration of the type mentioned above might increase the destructive effect of antibodies on pathogenic antigens and convert these antibodies into a quasi specific disinfectant or chemotherapeutic agent. We are attempting to obtain such an effect by introducing groups to change the physical properties of the immunebody-carrier proteins, or groups which are known to possess disinfecting or chemotherapeutic activity, or known to be apt to increase the disinfecting power of organic disinfectants.

Experimental work along this line was started in these laboratories some months ago, and without knowledge of the somewhat similar experiments and results which were recently published by Bronfenbrenner.[3] In view of the accordance of our findings (with respect to the fact that chemical alteration, if carefully conducted, does not destroy immune properties) with his (presumably using different agents) a preliminary report upon some phases of our work would seem to be in order.[4]

In certain of our experiments para-aminophenylarsonic acid (atoxyl) was used for diazo-coupling because of its activity as a chemotherapeutic agent in certain protozoan diseases. The antibody protein was a Type I and II pneumococcus antibody, for this can be prepared in a comparatively highly purified state and its strength can be measured more easily than that of any immune serum produced against a protozoan parasite. The diazotization was carried out in the usual way. However, the pH was not allowed to change during the whole process of coupling more than from 5.0 to 7.5, approximately. A product resulted which was almost insoluble around its isoelectric point at pH 6, and soluble to a dark brown solution at neutral or alkaline reaction, soluble with a light yellow color on the acid side of the isoelectric point. This "antibody-dye" could easily be reprecipitated by dialysis and adjustment of pH. On carrying out the process in the same way a second time, identical products were apparently obtained, the As_2O_3/N ratio being in one case 0.028, in the other 0.027. If the products were taken up in the same volume of physiological saline as the original, agglutination was observed up to the same dilution as with the original antibody preparation (1/320). A very marked prezone was found, which was not present in the original preparation. Mice infected with 100,000 lethal doses of virulent pneumococci could be protected fully, *i.e.*, cured with 0.2 cc of the preparation containing respectively 6.6 mg N and 0.18 mg As_2O_3, and 7.5 mg N and 0.2 mg As_2O_3 per cc, when injected intravenously, simultaneously with the infection, or 4 hours after, or 20 hours after the infection. Normal horse serum-globulin coupled with atoxyl had almost no effect. It is also interesting to note that 0.5 cc of the original antibody solution killed mice almost instantly when injected intravenously, whereas the same amount of the coupled product had no effect.

Finally, we also note that the introduction of the easily detectable arsenic into the antibody-carrier protein is helpful for quantitative study of the degree of purification of antibodies, as well as quantitative study of the antibody reaction. Further experiments are in progress.

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[2] A. Klopstock and C. E. Selter, *Zeitschrift für Immunitäts.*, 55: 118, 1928; M. Heidelberger and F. E. Kendall, *Proc. Soc. Exp. Biol. Med.*, 26: 482, 1929.

[3] Bronfenbrenner, *Proc. Soc. Exp. Biol. Med.*, 28: 734, 1930.

[4] Bronfenbrenner's object in starting his experiments was different from the above. He wanted to deprive immune sera of their original biological specificity in order to avoid anaphylactic shock at repeated injections of sera derived from the same species.

BOOKS RECEIVED

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