NUCLEAR PHYSICS

Elements of Nuclear Physics. By F. RASETTI. New York: Prentice-Hall, Inc. $4.50.

WITH the publication of this and other books of the past year, the term "nuclear physics" may be regarded as having been officially admitted to the language. "Nuclear chemistry" seemed likely, for a time, to take the lead. Perhaps it would have been more appropriate on the whole, since a large part of the subject consists in reactions of transmutation for which the symbolism of chemistry is admirably fitted, and another part consists in measurement of the masses of atoms; but after all, almost the whole of the subject is a gift of the methods of physics to the sum of knowledge, and it would certainly ill beseem a physicist to complain.

Professor Rasetti, now of the University of Rome, was known as a notable experimental physicist even years before he belonged to the group at Rome which, with Fermi at their head, investigated transmutation by neutrons on a grand scale and discovered the enhanced transmuting power of slow neutrons, as well as much else. He is a familiar figure in this country, both in East and West. His English as exhibited in this book is flawless, though the style is dry and austere, largely because of the extreme condensation; for the book is packed with information, and scarcely a word is dispensable.

First (after a brief introduction) we find an account of the apparatus used for detection of fast-moving charged particles. Then come two chapters on what was formerly called "radioactivity" *tout court,* but must now be called "natural radioactivity"; taken together, they give a better share of the book to natural radioactivity than is frequently given nowadays, when so many writers are in haste to get to phenomena of newer interest. The latter of the chapters contains an account of alpha, beta and gamma ray spectra and of the Gurney-Condon-Gamow theory of the alpha-particle emission. Between them is inserted a long section concerning the interactions of alpha, beta and gamma rays with the atoms which they traverse or the electrons near which they pass, and including the creation and "annihilation" of electron-pairs (why must people speak of electrons being "annihilated" when their mass and energy go over into equal mass and energy of light?) Future classifiers of physics may take these topics out of nuclear physics altogether; for the present, it is relevant to insert them. Next come the tabulations of the masses and spins of the nuclei, with an exceedingly brief outline of the ways of measuring them. Next come two chapters on transmutation—an unexpectedly small share of the book! A considerable number of reactions are quoted, and there is a table of artificial radioactive substances. The book ends with a very concise account of cosmic rays.

The book is definitely an advanced text; students of the experimental side may find that all they require is the power of concentrated attention, but for the theoretical parts a grounding in quantum mechanics is needed. Readers already having some knowledge of the earlier stages of quantum theory will be glad to find the theories of scattering (after Born) and of penetration of potential barriers expounded without these usual preliminaries; and there is a good outline of the Heisenberg and Majorana theories of intra-nuclear interactions, and of the present state of the theory of the energy-loss suffered by fast electrons as they progress through matter. The author withstood too well the usual temptation of authors to lay undue stress on their own researches; one would like a fuller account of the work of the Roman school. The part about the Compton effect must have been written just too early to include the recent tests of the simultaneity of the recoils of electron and photon. The list of the naturally radioactive elements excludes all of atomic number less than 81, but for potassium, rubidium and samarium; it is not clear whether this represents a definitely adverse judgment of the author as to claims recently made for other elements.

KARL K. DARROW

SPECIAL ARTICLES

STUDIES ON THE PRODUCTION OF ANTIBODIES IN VITRO

IN 1912, Carrel and Ingebrigtsen[1] cultivated the bone marrow and lymph glands of guinea pigs in homologous blood plasma to which were added small amounts of red cells from the goat. On the fifth day, the culture fluid hemolyzed red cells from the goat without the addition of complement. After being heated at 56° C., the culture fluid lost its hemolytic power. Then, by addition of complement, this lost power was regained. On the basis of these and other tests, it was concluded that immune hemolysins had been formed. Since that time, numerous investigators have employed this direct method of adding the antigen to the tissue at the time of explantation. Some have reported positive results, others negative. A quite recent paper by Salle and McOmie[2] records negative findings in experiments in which chick embryonic tissue and rabbit or guinea pig spleen and lung were

1 A. Carrel and R. Ingebrigtsen, *Jour. Exp. Med.,* 15: 287, 1912.

2 A. J. Salle and W. A. McOmie, *Jour. Immunol.,* 32: 157, 1937. (Extensive bibliography.)

cultivated in media containing heterologous sera or foreign red cells.

Still other investigators have worked with tissues taken from animals that were injected with the antigen before explantation. Lüdke[3] injected killed cultures of typhoid bacilli into rabbits and guinea pigs, removed fragments of the spleen and whole femur after from 24 to 60 hours and incubated them in various culture media. After from 2 to 5 days, he was able to detect agglutinins in extracts prepared from the spleen and bone marrow. Przygode,[4] Reiter[5] and Meyer and Loewenthal[6] have also reported antibody production in tissues removed after injection of the animal. In contrast, however, similar attempts by Kuczynski, Tenenbaum and Werthemann[7] were unsuccessful. The experiments described in this paper were undertaken to reinvestigate the problem, utilizing recent improvements in the tissue culture techniques.

Fragments of adult rabbit spleen removed from animals injected 2 and 3 days previously with washed guinea pig red cells were found to produce easily demonstrable agglutinins against guinea pig red cells after 4 days' incubation in a fluid medium. The medium consisted of 3 parts "normal" rabbit serum, 1 part isotonic sodium bicarbonate (1.4 per cent.), 2 parts Tyrode's solution containing 4 times the usual amount of glucose, and 0.005 per cent. phenol red to serve as an indicator. For each culture, approximately 100 mg of tissue (75 fragments) were suspended in 2 cc of medium contained in H-8 Carrel flasks. These flasks have a total capacity of about 70 cc. In addition to the fluid medium, each culture was supplied daily with an atmosphere consisting of 80 per cent. O_2, 8 per cent. CO_2 and 12 per cent. N_2. The high concentration of O_2 is necessary in order to keep the fragments alive. The CO_2 acts together with the rest of the medium to keep the pH constant at 7.2. This method of cultivation[8] makes for functional survival of the tissue fragments without any marked proliferation of the constituent elements.

The serum in which the tissues were cultivated was usually taken from one or more untreated rabbits that had previously been found to contain at most mere traces of natural agglutinating antibodies against guinea pig red cells. But occasional use was made also of autologous serum taken from the injected animal at the time the spleen was removed. As controls, all culture media were incubated without tissue for the period of the experiment. Additional controls consisted of duplicate cultures kept at 4° C. Ordinarily, all these yielded negative tests, whereas hemagglutinins produced by the tissues were detected in the culture fluid in various dilutions sometimes as high as 1:320. Furthermore, no increase in antibody output was ever obtained by using serum from animals whose spleens had previously been found to produce antibodies in more than moderate amount.

Under the same conditions of cultivation, adult rabbit spleens taken from animals injected 1 to 24 hours previously with washed guinea pig red cells failed to produce demonstrable antibodies. This indicated the possibility that the production of antibodies outside the body may be dependent upon certain reactions occurring within the organism and that these reactions must reach a certain stage before the process can readily be completed *in vitro*.

Negative results were obtained also when spleens taken from animals injected 24 hours previously were cultivated in the sera of rabbits injected three days previously with a proportionate amount of the same antigen. This was true even when the serum in which they were cultivated had been taken from animals whose spleens had produced demonstrable antibodies in dilutions as high as 1:256 and 1:320 when cultivated in normal serum. It appears then that if the serum of an animal injected three days previously contained certain necessary substances not present after one day, these substances were incapable of acting together with tissues that had not undergone the same period of preparation.

Next, an attempt was made to shorten this period by first injecting a bacterial antigen (*V. metchnikovi*), followed several days later by the washed guinea pig red cells. But when the spleens were removed for cultivation 24 hours after the last injection, they still failed to produce agglutinins against the foreign red cells.

Other experiments were made in which the spleen was perfused with the antigen by injecting it directly with the foreign red cells by way of the splenic artery. After from five to ten minutes, the spleen was removed and cultivated in the usual manner. Again, the results were negative.

Interesting observations were made also in the matter of animal individuality. When sera from different animals were used in the cultivation of tissues taken from a single organ, some proved to be excellent culture media, whereas others were decidedly toxic. It was found also that tissues removed from different animals that had been injected previously with proportionate amounts of the same antigen may, upon cultivation in a given sample of serum, remain in an equally good state of preservation and yet differ in antibody response.

[3] H. Lüdke, *Berl. klin. Woch.*, 49: 1034, 1912.
[4] P. Przygode, *Wien. klin. Woch.*, 26: 841, 1913.
[5] H. Reiter, *Z. Immunitätsforsch.*, 18: 5, 1913.
[6] K. Meyer and H. Loewenthal, *Z. Immunitätsforsch.*, 54: 420, 1928.
[7] M. H. Kuczynski, E. Tenenbaum and A. Werthemann, *Virchows Arch. path. Anat.*, 258: 687, 1925.
[8] R. C. Parker, SCIENCE, 83: 579, 1936.

Some of the experiments reported above were also performed using bacterial antigens. The results were similar to those obtained when foreign red cells were used.

Finally, attempts were made to repeat the experiments of Meyer and Loewenthal,[6] who reported antibody production in hanging drop cultures of spleen taken from rabbits injected one hour previously with bacterial antigens. Although all the older procedures were carefully adhered to, the results were entirely negative.

In view of the positive results obtained when the antigen was allowed to remain for two to three days in the animal, the negative results obtained when this period was shortened have a very definite significance. They not only suggest that antibody production is a more complicated process than is usually assumed, but they imply that it is not easy to demonstrate a production of antibodies *in vitro* unless the tissues have first been acted upon by some unknown mechanism within the body.

All the serological tests in the course of these experiments were made under the supervision of Dr. Karl Landsteiner, upon whose experience the plan of investigation was entirely dependent.

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PREPARATION OF AN ACTIVE AGENT FROM INACTIVE TUMOR EXTRACTS

THE majority of fowl tumors of spontaneous origin which have been transplanted have proved to be transmissible by cell-free filtrates or desiccates of the tumors. On the other hand, chemically induced fowl tumors, with the exception of three reported by MacIntosh,[1] are transferable only by grafts of living tumor cells. In this respect the latter resemble the mammalian tumors. It has been shown in this laboratory that not infrequently the low activity of filtrates or desiccates, occasionally encountered in transmitting the filterable tumors, is due to the presence of an inhibiting factor rather than the absence of the agent. This was established by the fact that the removal of the inhibitor by adsorption on alumina gel rendered the extract highly active in tumor production.[2] However, this method failed to explain the non-filtration of a slow-growing fibro-sarcoma (Chicken Tumor 10) which has been under observation in this laboratory for the past ten years. A strong inhibitor has been shown to be present in this tumor by cross tests with Chicken Tumor I, but treatment of extracts with alumina gel failed to render the extracts active in the transmission of the tumor. Yet there was a suggestion that the tumor possessed a transmissible agent from the fact that once or twice tumors resulted from injection of desiccates, but this was a rare occurrence and there was no clear-cut transmission by filtrate in the many attempts which have been made.

In recent studies of Chicken Tumor I, it has been shown that the agent could be sedimented by high-speed centrifugation, and this method seemed clearly to separate the agent from its own inhibitor.[3] This observation suggested a further attempt to transmit the fibro-sarcoma.

Experiment: A water extract was prepared from an eight-week old Chicken Tumor 10 and the extract passed through a Berkefeld V candle. The filtrate was submitted to a centrifugal force of 14,000 times that of gravity for 2½ hours. The resultant sediment was taken up in Tyrode's solution and redeposited at high speed. This washed sediment was next suspended in a volume of Tyrode's equal to 1/10 that of the original filtrate. For activity tests, 0.4 cc of the suspension were injected into normal hens, the same birds also receiving the same amount of the original filtrate in another area for control. No tumors developed as the result of injection of the unspun filtrate. Tumors did arise in 50 per cent. of the areas injected with the washed sediment, reaching a size of 3.1 × 2.3 cm within 40 days. Later some of them retrogressed. The histology of the original tumor was duplicated in the induced tumors.

In a second experiment an extract was prepared from a desiccate of Chicken Tumor 10, and this extract was treated in the same manner as that described above. Again the unspun extract gave negative results, while the injection of the washed sediment resulted in 33 per cent. positive results.

That the production of tumors in these experiments was not simply an effect of concentration of the agent was shown by the following test. The supernatant fluid, depleted of the agent, was saved. Part of the sediment, after being washed and resuspended in Tyrode's solution, was mixed with an equal volume of the original supernatant fluid. The remaining sediment was diluted to the same degree with water as a control. The injection of the diluted sediment gave positive results in 50 per cent. of the areas injected, while the part diluted with the original supernatant fluid failed to induce tumors in any of the areas injected.

The complete neutralization of the active sediment by its own supernatant fluid indicates that the failure

[1] J. McIntosh, *Brit. Jour. Exp. Med.*, 14: 422, 1933.

[2] Jas. B. Murphy, O. M. Helmer, A. Claude and E. Sturm, SCIENCE, 73: 266, 1931.

[3] A. Claude, paper in press.