No noteworthy contributors among the ancients and semi-moderns have been omitted. Herrick, very appropriately, deals only briefly with the ancient physicians, for the real dawn of scientific cardiology coincides with Harvey's monumental dissertation, "De Motu Cordis" in 1628. Prior to this publication knowledge regarding the anatomy and the physiology of the heart and circulation was erroneous and fantastic and constructive advances in knowledge and understanding were only possible after correct, although unfinished concepts were clearly formulated.

The evolution of the science of cardiology up to the present time, although yet incomplete, is accurately portrayed. The correct basic premise of the anatomy of the heart and circulation inevitably led to physiologic understanding, the development of cardiovascular pathology, clinical cardiology and finally the more modern adjuncts such as roentgenography and electrocardiography.

Herrick, an outstanding clinician, has been remarkably able to present this brief but comprehensive work in a manner having particular appeal and interest to the internist. This is a book which merits the attention not only of the cardiologist, but all physicians and medical students.

F. A. WILLIUS

SPECIAL ARTICLES

A VIRUS RECOVERED FROM PATIENTS WITH PRIMARY ATYPICAL PNEUMONIA[1,2,3]

PRIMARY atypical pneumonia appears to be a clinical syndrome, but is probably not a single disease entity. The psittacosis group of viruses[4,5,6] *Rickettsia diaporica*,[7] and a virus infectious for the mongoose[8] each have been found to be etiologically related to certain groups of cases. That still other agents[9,10,11] may be associated with the syndrome has been suggested.

In this study specimens from patients were inoculated in different animal species by numerous routes and serial passages were carried out. In no instance were obvious signs of infection produced which could be reproduced in series. However, it was discovered that animals inoculated with certain specimens or with passage material from them developed antibodies capable of neutralizing a heterologous virus; the "pneumonia virus of mice"[12] hereinafter referred to as PVM. This observation suggested that there were in the agent recovered from current cases and in PVM minor common antigens.

Twelve strains of a virus have been recovered from 20 patients. Two were obtained from throat-washings, eight from sputa and two from plasma. All 12 possessed antigenic components also present in PVM. Although none produced obvious signs of infection on passage in available animals, nevertheless, immunological evidence indicated that the agent could be passed in series in both chick embryos and cotton rats. The virus was filterable through Berkefeld V candles, did not lose activity on storage at −70° C for 6 months, withstood freezing and thawing 10 times, and was inactivated by heating at 56° C for 30 minutes.

Three filtered throat washings were inoculated in chick embryos and serial passages carried out. Rabbits injected with embryo material from one throat washing developed neutralizing antibodies against PVM, whereas rabbits injected with embryo material from the other throat washings did not.

Two specimens of plasma were tested, one intravenously in a rabbit, and one was inoculated in chick embryos with which rabbits were immunized. These rabbits produced neutralizing antibodies against PVM. As might be expected, PVM itself stimulated the production of neutralizing antibodies in rabbits more rapidly and in far higher titer than did the agent obtained from patients with primary atypical pneumonia.

Eighteen specimens of sputum and one throat washing were tested intranasally in cotton rats. Eight of the sputa and the throat washing stimulated the production in rats of neutralizing antibodies against PVM whereas the other 10 sputa did not. Of 32 normal cotton rat sera tested none contained antibodies against PVM. As was anticipated PVM itself

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[2] The Bureau of Medicine and Surgery does not necessarily undertake to endorse views or opinions which are expressed in this paper.

[3] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and The Rockefeller Institute for Medical Research.

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[11] F. G. Blake, M. E. Howard and H. Tatlock, *Yale Jour. Biol. and Med.*, 15: 139, 1942.

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stimulated the production of neutralizing antibodies in rats more quickly and in higher titer than did the human virus.

The human agent was passed in series either in cotton rat lungs or in chick embryos as well as on the chorio-allantoic membrane. Evidence for the presence of the agent in passage material was obtained by the demonstration of neutralizing antibodies against PVM in the sera of inoculated cotton rats. Histological sections of infected rat lungs and infected egg membranes stained by the Giemsa method, and impression films stained by the Macchiavello or Gram method failed to reveal the presence of elementary bodies, inclusion bodies, rickettsiae or bacteria.

The mongoose infectious virus[8] was restudied in the light of these findings. A suspension of infected mongoose lungs, stored at −70° C for over 2½ years, was available. Cotton rats were inoculated intranasally with this material and lung passages were carried out. None of the rats showed visible signs of infection and pulmonary consolidation was not produced. The suspension of infected mongoose lungs was also inoculated on the chorio-allantoic membrane and passages carried out. Cotton rats inoculated either with the lung or membrane passage material produced neutralizing antibodies against PVM indicating that the mongoose infectious virus possessed antigenic components also present in PVM and moreover that it could be passed in cotton rats as well as chick embryos.

Neutralization tests with patients' sera and the human agent were difficult to devise since the virus failed to produce signs of infection on passage in available animals. However, advantage was taken of the fact that a large supply of one sputum known to contain the agent was available and that this particular sputum on primary inoculation in cotton rats, though not on serial passage, produced definite pulmonary consolidation. Eaton and his coworkers[10] have reported that sputa from certain cases contained an infectious agent which produced pulmonary consolidation in cotton rats.

Of 32 cotton rats inoculated with this sputum pulmonary consolidation developed in 78 per cent. Furthermore, without exception, rats inoculated with this sputum produced neutralizing antibodies against PVM. When diluted to 1 per cent. with broth the sputum still caused consolidation in rats. Equal parts of a 20 per cent. suspension of the sputum and either undiluted acute phase or convalescent serum, previously inactivated from 11 patients, were mixed. Each mixture was tested in a group of 3 or 4 cotton rats. With the sputum-acute phase serum mixtures from 6 patients, 68 per cent. of 25 inoculated rats developed pulmonary consolidation, whereas with the sputum-convalescent serum mixtures from the same 6 patients, none of 25 inoculated rats developed pulmonary consolidation. With the sera obtained from 5 other patients mixtures of the sputum and either acute phase or convalescent sera failed in all of 32 rats to produce pulmonary consolidation. It seems noteworthy that all 11 convalescent sera completely neutralized the agent responsible for consolidation in cotton rats.

Convalescent human sera not only neutralized the agent responsible for pulmonary consolidation but also neutralized the agent responsible for the stimulation of antibodies against PVM in cotton rats. Moreover, rats inoculated with the human virus or with chick-embryo material infected with it produced antibodies which neutralized not only PVM but also the agent in the sputum responsible for consolidation in cotton rats. On the other hand, cotton rats inoculated with inactive material failed to develop neutralizing antibodies against either PVM or the human virus. This evidence suggests that pulmonary consolidation in the cotton rat and the development of antibodies against PVM were the result of infection by one and the same agent.

Acute phase and convalescent sera from these 11 patients were also tested against PVM itself. In no case was an increase in neutralizing antibodies against PVM demonstrable during convalescence. This observation may be explained on the basis that the antibody response of human beings to the antigenic components common to both the human virus and PVM may be too small to be measured by the technique employed. All the human sera were also tested against psittacosis virus, and with but one exception against lymphocytic choriomeningitis virus antigen as well, using the appropriate complement fixation procedures.[6,13] All the human sera as well as all the immune rabbit sera and many of the immune cotton rat sera were also tested against influenza A and B viruses, using the RBC agglutination inhibition technique.[14] In no instance was a significant increase in antibodies against any of these four viruses demonstrable.

The available evidence suggests that the mongoose infectious virus, which appeared to be etiologically related to certain cases of primary atypical pneumonia studied in 1939, is related antigenically to the heterologous virus of mouse origin, the "pneumonia virus of mice." Since all twelve strains of the agent recovered from current cases of atypical pneumonia appear also to be antigenically related to PVM, it seems reasonable to think that they are either identical with the mongoose infectious virus or are very closely

[13] J. E. Smadel and M. J. Wall, *Jour. Exper. Med.*, 72: 389, 1940.

[14] G. K. Hirst, *Jour. Exper. Med.*, 75: 49, 1942.

related to it both in antigenic composition and biological characteristics.

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GONADECTOMY AND ADRENAL NEOPLASMS

CARCINOMA of the adrenal cortex is a relatively rare type of tumor in both man and in experimental animals. In man these neoplasms have been of unusual interest because of sexual disorders which have been associated with them. In experimental animals, carcinomas of the adrenal cortex have appeared too infrequently for critical study. Observations in this laboratory, however, indicate that primary carcinomas of the adrenal cortex can be produced in a high percentage of the individuals of at least one strain of mice by means of gonad removal.

It has been found that when mice of the extreme dilution strain (ce) were gonadectomized at two days of age, carcinoma of the adrenal cortex occurred in a high percentage of cases. Table 1 shows the frequency of these in various age groups up to one year. No such tumors have so far been observed in normal male and female mice of the ce strain. Adrenals of these mice are being studied in more detail, however.

Present knowledge indicates that sex hormones have an influence in the formation of certain types of neoplasms in mice. Increasing or decreasing these hormones is effective. It has been shown that injections of estrogenic hormones have been instrumental in producing interstitial cell tumors of the testes,[1] carcinomas of the cervices,[2] adenomas of the hypophyses[3] and mammary gland carcinomas[4] in mice. In the dba strain of mice gonad removal resulted in nodular hyperplasia of the adrenal cortex and carcinomatous changes of the mammary gland in both sexes.[5, 6] It seems likely that all these results may be explained by the theory that hormonal imbalance is at least one of the factors leading to these forms of cancer. A more detailed study is to be reported elsewhere.

TABLE 1

Sex	Mice of ce strain, Age at autopsy: 4 months		6–7 months		8–10 months		11–12 months	
	No. of mice	Per cent with adrenal cancer	No. of mice	Per cent with adrenal cancer	No. of mice	Per cent with adrenal cancer	No. of mice	Per cent with adrenal cancer
Ovariectomized ♀♀ ...	4	0	9	88.9	3	100	6	100
Castrated ♂♂.	4	0	7	28.6	7	85.7	5	100

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SCIENTIFIC APPARATUS AND LABORATORY METHODS

IMPROVED APPARATUS FOR LIVER PERFUSION

LIVER perfusion studies in which the R.Q. of the liver was found from the arterio-venous blood gas differences have resulted in extremely low R.Q.'s which have been interpreted as support for the theory that oxygen is being utilized by the liver in the formation of carbohydrate intermediates from fatty acid or fatty acid intermediates. The methods used in former studies did not control or measure the escape of CO_2 from the surface of the liver. It is conceivable that the amount of CO_2 passing from the liver into the surrounding air is considerable and would be related to the tension of the CO_2 in the perfusate and the production of CO_2 by the liver. If this loss of CO_2 from the liver could be measured exactly in terms of volumes per cent. of CO_2, the A.V. R.Q. could be corrected for the amount lost.

The escape of appreciable amounts of CO_2 is demonstrable by perfusing the liver in an air-tight tin box of known volume as shown in the accompanying diagram (Fig. 1). The box is washed out with warmed outside air at the start of the experiment. At the end of a given period of time the air in the box is sampled and analyzed for CO_2 and O_2. The CO_2 which enters the box from the surface of the liver is expressed in volumes per cent. from the total volume of perfusate passing through the liver during the period. The oxygen level in the box remains constant providing there are no leaks in the circulating system.

In Table 1 the average loss of CO_2 in volumes per

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[4] A. Lacassagne, *C. R. Acad. Sci.*, 195: 630, 1932.
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[6] George Woolley, Elizabeth Fekete and C. C. Little, *Endocrinology*, 28: 341–343, 1941.