DEVELOPMENT STAGES OF IMMUNOLOGY

Dadaxonova R.A
assistant
phthisiology and pulmonology, microbiology department of virology and immunology Andijan State Medical Institute

Abstrakt: *This article provides some information on the history of immunology.*

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Theories of Acquired Immunity From the earliest of humankind's social organizations, epidemic disease must have been a frequent visitor; both the annals of the oldest dynasties of Egypt as well as the Babylonian Epic of Gilgamesh record visitations of disease and pestilence. However, most early societies and even many modern primitive peoples have held that both humans and nature are ruled by the magical influences of spirits and demons, or the mystical influences of the gods. It was thus natural to assume that disease represents a punishment for some infraction of a tribal taboo, or some sin against the gods. The pantheons of many cultures contain a god of disease, and throughout the Old Testament, God frequently smites those who trespass against Him, often employing pestilential disease. Even in Greek legend, the sun god, Phoebus Apollo, was held to have caused the plague of Thebes as punishment for the misdeeds of Oedipus Rex, and Apollo is supposed to have rained plague arrows on the Greek army before Troy, because Agamemnon had abducted the daughter of Apollo's priest. While the cause of these various epidemics might be unknown, it could not fail to be noticed that those who had survived a disease might be spared further involvement on its return. Thucydides described this phenomenon in his history of the plague of Athens of 430 bc, when he wrote: 'Yet it was with those who had recovered from the disease that the sick and the dying found most compassion. These knew what it was from experience, and had now no fear for themselves; for the same man was never attacked twice – never at least fatally'. This 'plague' was most probably not

due to Pasteurella pestis, but the plague of Justinian some thousand years later was more likely to have been bubonic plague, and of this Procopius said, ‘At a later time it [the plague] came back; then those who dwelt round about this land, whom formerly it had afflicted most sorely, it did not touch at all’. In time, this resistance to reinfection came to be known by the term immunity, from the Latin immunitas, which in ancient Rome originally described the exemption of an individual from service or duty to the state. The idea that disease might originate from a vengeful deity carries with it an implicit theory of immunity. If disease be considered as punishment for sin, then being spared during a raging epidemic (i.e. natural immunity) would automatically be viewed as the inevitable result of having led a pious life. But a significant change occurred in early Christian times. Now, not only does God punish the sins of man with disease, but He might also employ disease to cleanse man of his sins. If disease can be viewed as an expiation and purgative, then the recovery from a deadly plague would not only imply that one’s sins had been minor but also that, once cleansed of these sins, one would not merit further punishment when the plague returned (i.e., acquired immunity). It has only been during the last millennium that explicit theories of acquired immunity were advanced; these were invariably imaginative, and were all eminently consistent with the then-prevailing notion of disease pathogenesis. Since smallpox was one of the earliest diseases to be identified clinically, and because the lifelong immunity that it conferred could hardly escape notice, it is not surprising that most early theories of immunity would be formulated in terms of this disease.

Expulsion theories of acquired immunity The tenth-century Islamic physician Rhazes differentiated smallpox from measles and other exanthematous diseases for the first time. He recognized that recovery from smallpox infection provides lasting immunity, and advanced the first explicit theory of acquired immunity. Rhazes followed the Hippocratic tradition which held that disease is due to quantitative imbalances among the four humours, or to their fermentation. He claimed that smallpox is due to a fermentation of the blood, which helps to dispel the ‘excess moisture’ that he thought was present in the blood of the young. Thus,

the pustules that form on the skin during this disease and break to release fluid provided the presumed exit through which the body expels the excess moisture contained in the blood. He compared the maturation of an individual to the fermentation of wine from grape juice, wherein the blood, like grape Article Contents Introductory article . Early Theories of Acquired Immunity . The Origins and Research Programme of Early Immunology . Immunology in Transition, 1912–1950s . The Immunobiological Revolution . Nobel Prize Highlights in Immunology ENCYCLOPEDIA OF LIFE SCIENCES © 2001, John Wiley & Sons, Ltd. www.els.net 1 juice, matures by progressively losing excess moisture; he even suggested that smallpox disease itself might assist in this normal process! This theory seemed to explain well all that was known about smallpox: almost everyone is affected, especially during youth (since then the blood is most moist). Further, the disease is seldom seen in adults and almost never in old age (because by then the normal ageing process would have sufficiently dried the blood, so that it no longer could support the infection). Finally, a single infection induces lasting immunity, since recurrence of the disease is impossible because the initial attack would have expelled all of the 'excess moisture' which the theory required as a prerequisite for the disease process. It is interesting that Rhazes presented the smallpox of the tenth century as an almost benign childhood disease, and even as a salutary phenomenon. In his 1546 book On Contagion, Girolamo Fracastoro claimed that all disease is caused by small seeds or germs (seminaria) which may spread from person to person, each of which possesses a specific affinity for a given plant or animal, and for a given organ or humour. Fracastoro claimed that the germ of smallpox has an affinity for and causes the fermentation only of that trace of menstrual blood contaminant which he supposed taints all mammalian young in utero. When a (young) person was infected, then the menstrual contaminant would ferment, rise to the surface beneath the skin in the form of pustules, and be expelled when the pustules break. 'This ebulition is a kind of purification of the blood _ That is why almost all of us suffer from this malady, _ and this fever is of itself seldom fatal (sic!), but is rather a purgation _ the malady usually does not

recur because the infection has already been secreted in the previous attack'. Depletion theories of acquired immunity The introduction of variolation (the use of material from a diseased smallpox victim to immunize normal recipients) early in the eighteenth century led to renewed interest in the nature of acquired immunity. The inoculation of pustular fluid as a preventive appears to have been employed extensively in the folk medicine of many cultures. While it was condemned on both religious and medical grounds, it did attain a degree of acceptance, especially in England, thanks to the example set in 1722 by the Prince and Princess of Wales in permitting their children to be inoculated. Inoculation proved especially popular during periods of smallpox epidemic, when the case mortality rate often reached 15–20%; the rate of disfigurement was even higher. In contrast, inoculation protected well against reinfection, caused little or no facial scarring, and was accompanied by at most a 2–3% death rate. When the practice of inoculation was given currency in the pages of the Philosophical Transactions of the Royal Society, some were led to speculate on its meaning. In 1721, the New England divine Cotton Mather advanced a theory of acquired immunity which held that some unidentified substrate in the blood is depleted either forcefully during natural infection or more benignly following inoculation; the absence of this material thenceforth prevents development of the disease a second time. It was in the context of three-quarters of a century of smallpox inoculation that Edward Jenner published in 1798 his report on a safer and even more efficacious vaccine against smallpox, derived from cowpox pustules. Jenner seems never to have speculated on why his vaccine caused immunity, perhaps influenced by the earlier advice of his teacher John Hunter: 'Why think? Why not try the experiment?' There developed, during the seventeenth and eighteenth centuries, a most interesting concept of disease pathogenesis and thus of disease immunity, that of the innate seed. Humans (and animals) were thought to be born with the seeds or ovula for every different disease to which they were subject, each of which could be 'fertilized' specifically by the appropriate contagious agent to produce the given disease. Here was not only a concept of specific aetiology, but in the depletion of

the seeds of a given disease it offered a plausible explanation of acquired immunity that is at once specific and lasting. The idea of an immunity based upon the depletion of some type of substance required by the disease process itself was repeated often during the eighteenth century. Thus, one finds statements in the contemporary literature such as one in 1755, 'I lately tried this experiment [inoculation] upon myself, _ and it had no effect upon my blood, as it had been sufficiently defecated 15 years before'. Again, susceptibility to smallpox was likened to a body which a single spark might set afire, but which thenceforth has become 'incombustible' although surrounded by flames, and thus immune to further infection.

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