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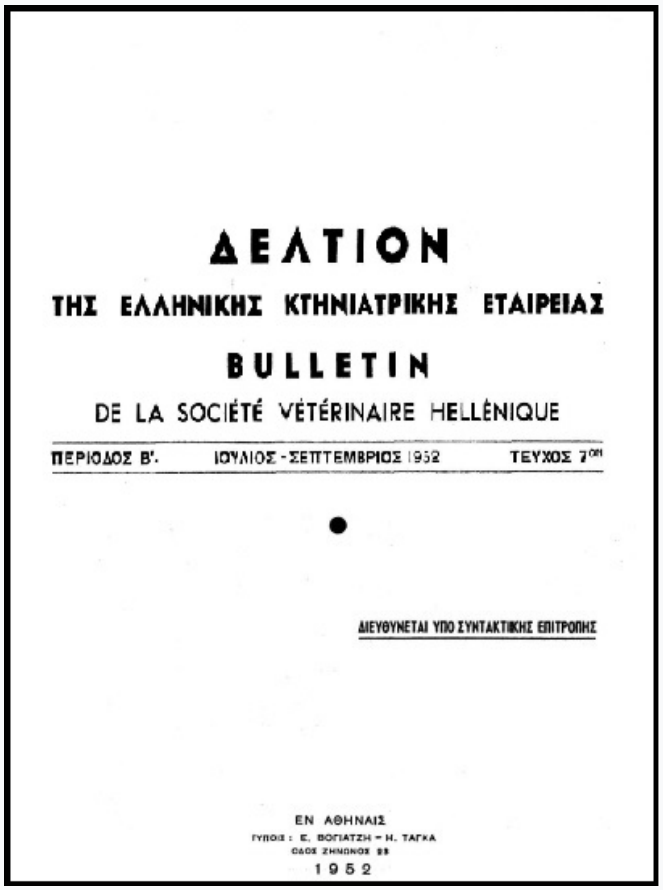

ΔΕΛΤΙΟΝ

ΤΗΣ ΕΛΛΗΝΙΚΗΣ ΚΤΗΝΙΑΤΡΙΚΗΣ ΕΤΑΙΡΕΙΑΣ

BULLETIN

DE LA SOCIÉTÉ VÉTÉRINAIRE HELLÉNIQUE

ΠΕΡΙΟΔΟΣ Β'. ΙΟΥΛΙΟΣ - ΣΕΠΤΕΜΒΡΙΟΣ 1952 ΤΕΥΧΟΣ 7ον

ΔΙΕΥΘΥΝΕΤΑΙ ΥΠΟ ΣΥΝΤΑΚΤΙΚΗΣ ΕΠΙΤΡΟΠΗΣ

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# ΤΟ ΦΑΙΝΟΜΕΝΟΝ ΤΗΣ ΚΥΤΤΑΡΟΕΜΠΛΟΚΗΣ (INTERFERENCE PHENOMENON)

*THOMAS DALLING*

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# ΔΕΛΤΙΟΝ

## ΤΗΣ ΕΛΛΗΝΙΚΗΣ ΚΤΗΝΙΑΤΡΙΚΗΣ ΕΤΑΙΡΕΙΑΣ

# BULLETIN

## DE LA SOCIÉTÉ VÉTÉRINAIRE HELLÉNIQUE

ΠΕΡΙΟΔΟΣ Β'. ΙΟΥΛΙΟΣ - ΣΕΠΤΕΜΒΡΙΟΣ 1952 ΤΕΥΧΟΣ 7ΟΝ

*Κατὰ τὸ Β' Συνέδριον τῶν Κτηνιάτρων ὑπαλλήλων Ὑπουργείου Γεωργίας, τὸ λαβὸν χώραν τὸν παρελθόντα Μάϊον, παρέστη καὶ ἐτίμησε τὰς ἐργασίας του, κατόπιν προσκλήσεως τῆς Ὀργανωτικῆς Ἐπιτροπῆς, ὁ* Sir Thomas Dalling, *τέως Διευθυντὴς τῶν Κτηνιατρικῶν Ὑπηρεσιῶν τῆς Μεγ. Βρετανίας καὶ νῦν Τεχνικὸς Σύμβουλος τοῦ Κτηνιατρικοῦ τμήματος τῆς Διεθνοῦς Ὀργανώσεως Τροφῶν καὶ Γεωργίας.*

*Ὁ διακεκριμμένος καὶ διεθνοῦς φήμης ἐπιστήμων εὑρεστήθη νὰ προβῇ εἰς ἐξαιρετικῶς ἐνδιαφέρουσαν ἀνακοίνωσιν ἐπὶ τοῦ φαινομένου τῆς Κυτταροεμπλοκῆς, ἣν τὸ Δελτίον μας θεωρεῖ ἐξαιρετικὴν τιμὴν νὰ δημοσιεύσῃ αὐτουσίαν, καθότι ἀποτελεῖ μίαν ὅλως νέαν καὶ πρωτότυπον συμβολὴν εἰς τὸ καθόλου θέμα τῆς ἀνοσοποιήσεως τῶν ζωϊκῶν ὀργανισμῶν.*

# ΤΟ ΦΑΙΝΟΜΕΝΟΝ ΤΗΣ ΚΥΤΤΑΡΟΕΜΠΛΟΚΗΣ (INTERFERENCE PHENOMENON)

Ὑπὸ τοῦ καθηγητοῦ

Sir THOMAS DALLING, M.A., M.R.C.V.S., F.R.S.E.

Πρόκειται περὶ νέας σχετικῶς θεωρίας. Ἐκεῖνοι ἐξ ἡμῶν, οἱ ὁποῖοι ἐνδιαφέρονται διὰ τὰ προβλήματα τῆς ἀνοσίας καὶ ἀνοσολογίας, τὰ ἀφορῶντα εἰς τὰς μικροβιακὰς λοιμώξεις, εἶναι ἐξοικειωμένοι μὲ τὴν ἀρχὴν τοῦ θέματος.

Γνωρίζομεν καὶ κατανοοῦμεν, ὅτι ἡ ἔγχυσις ἐναιωρημάτων ζώντων, ἐξησθενημένων ἢ ἀπονεκρωθέντων μικροβίων, προκαλεῖ τὴν παραγωγὴν διαφόρων εἰδῶν ἀντισωμάτων. Θεωροῦμεν ὡς ἀντισώματα, τὰς συγκολλητίνας, τὰς ἰζηματίνας, καὶ εἰδικῶς τὰ ἀντισώματα ἐκεῖνα, τὰ ὁποῖα ἐξουδετεροῦσι τὴν δρᾶσιν τῶν μικροοργανισμῶν.

Τὰ ἀντισώματα ταῦτα καλοῦμεν θεραπευτικοὺς ὀρρούς. Γνωρίζομεν

ἐπίσης καὶ εἴμεθα ἐξοικειωμένοι μὲ τὴν δρᾶσιν τῶν τοξινῶν καὶ τὴν παραγωγὴν τῶτ ἀντιτοξινῶν καὶ μὲ τὴν ἐξουδετερωτικὴν ἱκανότητα αὐτῶν ἔναντι τῶν τοξινῶν. Ἐξεπαιδεύθημεν εἰς τὴν σχολὴν τῶν βακτηρίων καὶ θεραπευτικῶν ὀρρῶν, τοξινῶν καὶ ἀντιτοξινῶν. Ἐδιδάχθημεν καὶ ἐπείσθημεν ὅτι αἱ ἀντιμικροβιακαὶ οὐσίαι εἶται ἀπαραίτητοι διὰ τὴν ἐξουδετέρωσιν τῶν ἀποτελεσμάτων τῶν μικροβίων καὶ αἱ ἀντιτοξῖναι τῶν τοξινῶν.

Πράγματι ἡ συνολικὴ ἀντίληψίς μας περὶ ἀνοσίας εἶναι σχετικῶς ἁπλῆ καὶ ἐφηρμόσαμεν τὰς ἰδέας καὶ ἀντιλήψεις ταύτας προσπαθοῦντες νὰ δημιουργήσωμεν ἐνεργητικὴν μὲν ἀνοσίαν διὰ τῆς ἐγχύσεως ἀντιγόνων, τὰ ὁποῖα συνήθως ὀνομάζομεν ἐμβόλια, παθητικὴν δὲ τοιαύτην διὰ τῆς χρησιμοποιήσεως ἀντιμικροβιακῶν οὐσιῶν ἢ ἀντιτοξινῶν ἤδη παραχθεισῶν ὑπὸ ἑτέρου ζῴου, συνήθως τοῦ ἵππου καὶ τὰς ὁποίας ἀποκαλοῦμεν θεραπευτικοὺς ὀρρούς.

Ἀναφέρω ἁπλῶς τὴν ἐνεργητικὴν ἀνοσίαν τὴν παραγομένην εἰς τὰ ζῷα, διὰ τῆς ἐγχύσεως τοῦ κλωστηριδίου τοῦ Σωβείου ἐπὶ σκοπῷ προστασίας κατὰ τοῦ πνευματάνθρακος ὡς παράδειγμα μικροβίων χρησιμοποιουμένων πρὸς τὸν σκοπὸν τοῦτον. Ἕτερον παράδειγμα συνίσταται εἰς τὴν χρησιμοποίησιν *τετανικῆς τοξίνης ἢ καλύτερον τετανικῆς ἀτοξίνης* (toxoid) διὰ τὴν προφύλαξιν κατὰ τοῦ τετάνου ὡς καὶ τὴν παρασκευὴν ὀρροῦ κατὰ τῆς ἐρυθρᾶς τῶν χοίρων ἐπὶ ἵππων, ὡς μέσον διὰ παθητικὴν ἀνοσοποίησιν τῶν χοίρων ἐναντίον τῆς μικροβιακῆς ταύτης νόσου. Ἐπίσης ὑπομιμνήσκω τὴν χρησιμοποίησιν τῶν ἀντιτοξινῶν τῶν παραγομένων ὑπὸ τοῦ κλωστηριδίου Welchii (διαθλαστικοῦ), ὡς καὶ ὑπὸ ἄλλων ἀναεροβίων μικροοργανισμῶν, ὡς παραδείγματα παγκοσμίου χρησιμοποιήσεως τῶν ἀντιτοξινῶν ἐναντίον τῶν ὑπὸ τοξινογόνων μικροβίων προκαλουμένων λοιμώξεων.

Ἡ ἀνακάλυψις τῶν ἀτοξινῶν ἐναντίον τῶν τοξινῶν, ἐν τῇ ἀνοσολογίᾳ, ἐπέφερε σημαντικὴν πρόοδον εἰς τὰς γνώσεις μας τὰς σχετικὰς μὲ τὴν παραγωγὴν τῶν ἀντισωμάτων καὶ ὑπῆρξε λίαν ἐπωφελὴς εἰς τοὺς ἀσχολουμένους μὲ τὴν ἀνοσολογίαν, ὧν ὁ ἀντικειμενικὸς σκοπὸς ἦτο ἡ δημιουργία ἐνεργητικῆς ἢ παθητικῆς ἀνοσίας ἐναντίον τινῶν ἐκ τῶν σπουδαιοτέρων νόσων τοῦ ἀνθρώπου καὶ τῶν ζώων, διὰ τῆς ἀσφαλεστέρας καὶ λυσιτελεστέρας μεθόδου.

Πλεῖστοι ἐξ ἡμῶν ἔσχομεν τὴν εὐκαιρίαν νὰ χρησιμοποιήσωμεν τὰς οὐσίας καὶ μεθόδους ταύτας καὶ ἤχθημεν εἰς τὸ συμπέρασμα ὅτι, ἐπὶ τέλους ἐλύσαμεν τὸ λίαν ἐνδιαφέρον πρόβλημα τῆς ἀνοσοποιήσεως. Συνεχάρημεν ἑαυτοὺς ὅτι αἱ μέθοδοι ἡμῶν ἦσαν καλαὶ καὶ ὅτι ἐπετύχομεν τὸν σκοπὸν τῆς ἐργασίας μας. Εἴμεθα τελείως δικαιολογημένοι τὴν ἐποχὴν ἐκείνην, διότι ἀσχολούμεθα τότε καὶ ἐμελετῶμεν μικρόβια.

Ἀσχέτως πρὸς τὰς τότε θεωρίας περὶ ἀνοσίας καὶ ἀνεξαρτήτως τοῦ εἰς ποίαν Σχολὴν ἀνήκομεν, εἴμεθα εἰς θέσιν νὰ καταλήξωμεν εἰς ἐπιτυχῆ

ἀποτελέσματα, ἅτινα ἦσαν πολύτιμα εἰς τὴν καταπολέμησιν τῶν ἀσθενειῶν τῶν ζώων. Αἱ μέθοδοι αὗται εἶναι ἀκόμη ἐν χρήσει καὶ δίδουν ἀκόμη ἱκανοποιητικὰ ἀποτελέσματα. Ἡ κτηνοτροφία εἰς ὅλας τὰς χώρας πρέπει νὰ εὐγνωμονῇ τοὺς ἀσχολουμένους μὲ τὴν ἀνοσολογίαν κτηνιάτρους καὶ ὅλους τοὺς ἄλλους, οἵτινες ἠδυνήθησαν νὰ εἰσαγάγουν τοιαύτας μεθόδους καταπολεμήσεως τῶν νόσων.

Μετὰ τὴν ἀνακάλυψιν τῶν ἰῶν ὡς αἰτίων τῶν νόσων τῶν ζώων, μετεχειρίσθημεν παρομοίας μεθόδους ἀνοσοποιήσεως καὶ πάλιν λίαν ἐπιτυχῶς. Δὲν θὰ σᾶς ἀναφέρω παρὰ μόνον τὴν χρῆσιν ἐμβολίων παραγομένων ἐκ ζωϊκῶν ἱστῶν, ἐναντίον τῆς πανώλους τῶν βοοειδῶν, τὴν χρῆσιν τῶν ἐμβρυοφόρων ὠῶν ὄρνιθος ὡς ὑποστρώματος διὰ τὴν καλλιέργειαν τῶν ἰῶν, τὴν χημικὴν ἐξεργασίαν τῶν καλλιεργειῶν καὶ τῶν πολλαπλασιαζομένων ἰῶν καὶ τὰς μεθόδους καλλιεργείας ἐπὶ ἱστῶν, ὡς αὗται λαμβάνουν χώραν κατὰ τὰς πλέον προσφάτους μεθόδους παραγωγῆς ἀντιαφθώδους ἐμβολίου. Θεραπευτικοὶ ὀρροὶ παρήχθησαν ἐπίσης λίαν ἐπιτυχῶς καὶ ἐναντίον ἰῶν, καὶ ἓν ἐνδιαφέρον παράδειγμα ἔστω ὁ ὀρρὸς ἐναντίον τῆς νόσου τῶν νεαρῶν κυνῶν (Carré).

Τὸ πᾶν, ὅθεν, τόσον εἰς τὸν τομέα τῶν βακτηρίων ὅσον καὶ εἰς τὸν τῶν ἰῶν, ἐφαίνετο λίαν ἁπλοῦν. Τὸ 1935 ὅμως ὁ Hoskinson καὶ ἐκ νέου τὸ 1937 οἱ Tindlay καὶ Mac Callum, ἐργαζόμενοι ἐπὶ τοῦ κιτρίνου πυρετοῦ, ἐπέσυραν τὴν προσοχὴν ἐπὶ ἑνὸς ἐνδιαφέροντος καὶ περιέργου φαινομένου. Διεπίστωσαν δηλαδὴ ὅτι, πίθηκοι ἐνοφθαλμισθέντες διὰ παντρόπου στελέχους ἰοῦ κιτρίνου πυρετοῦ ἔθνησκον, ἐνῷ ἐὰν ἰός, ὅστις εἶχεν ἀποκτήσει νευροτρόπους ἰδιότητας καὶ ὅστις κανονικῶς δὲν ἦτο θανατηφόρος διὰ τὸν πίθηκον, ἐνίετο ταὐτοχρόνως μὲ λίαν παθογόνον παντρόπον στέλεχος, τότε οἱ πίθηκοι ἐπέζων.

Αὐτὴ ἡ παρατήρησις ἦτο ἡ ἀπαρχὴ ἀριθμοῦ ἄλλων παρατηρήσεων, αἵτινες νῦν συγκεφαλαιοῦνται ὑπὸ τὸν ὅρον «φαινόμενον κυτταρο - ἐμπλοκῆς» (Interference phenomenon).

Τυγχάνει σήμερον κοινῶς γνωστόν, ὅτι μόλυνσις ἑνὸς μικροβίου, φυτοῦ ἢ ζῴου ὑπὸ ἑνὸς ἰοῦ συχνάκις προλαμβάνει ἢ μερικῶς παρεμποδίζει ταὐτόχρονον μετάδοσιν ἄλλου ἰοῦ εἰς τὸν ἴδιον ξενιστήν. Αὐτὴ ἡ ἐμπλοκὴ (interference) παρατηρεῖται μὲ τὸν ὁμοειδῆ ἰὸν ὡς π.χ. τῆς πανώλους τῶν ἵππων (African horse sickness) ἔνθα ὁ νευροτρόπος διὰ τὸν μῦν τῦπος τοῦ ἰοῦ παρεμποδίζει τὴν δρᾶσιν τοῦ ἀρχικοῦ τύπου τοῦ ἰοῦ καὶ προλαμβάνει τὴν μόλυνσιν ἐνῷ ταὐτοχρόνως ἀναπτύσσεται ἐνεργητικὴ ἀνοσία. Εἰς τὴν καταπολέμησιν τῆς πανώλους τῶν βοοειδῶν συναντῶμεν παρόμοιον παράδειγμα: ὁ ἰὸς τῆς πανώλους τῶν βοοειδῶν ὑποστὰς ἐπανειλημμένας διόδους ἐπὶ ἐμβρυοφόρων ᾠῶν ὄρνιθος, αἰγῶν κ. λ. π. προκαλεῖ τὸ φαινόμενον τῆς κυτταροεμπλοκῆς μὲ τὸν ἰὸν τὸν

προερχόμενον ἐκ βοοειδῶν. Παρόμοιον ἀποτέλεσμα δυνατὸν νὰ παρατηρηθῇ καὶ μὲ ἑτεροειδεῖς ἰούς, π.χ. τὸν ἰὸν τῆς λεμφο - κυτταρο - χοριο - μηνιγγίτιδος καὶ τὸν ἰὸν τῆς ἐγκεφαλίτιδος τοῦ St. Louis. Ἡ κυτταροεμπλοκὴ αὕτη δὲν ὀφείλεται εἰς τὴν δρᾶσιν ἀντισωμάτων, ὡς γνωρίζομεν ταῦτα ἐκ τῆς ἐνεργητικῆς καὶ παθητικῆς ἀνοσίας. Δὲν γνωρίζομεν τὶ ἀκριβῶς προκαλεῖ τὴν κυτταροεμπλοκὴν ταύτην, ἀλλὰ πιστεύεται καὶ πρέπει νὰ εἶναι ἀληθές, ὅτι αὐτὰ ταῦτα τὰ κύτταρα τῶν ἱστῶν ὑπεισέρχονται. Γενικῶς πιστεύεται, ἂν καὶ ἀκόμη τοῦτο εὑρίσκεται εἰς τὸ θεωρητικὸν στάδιον μέχρις οὗ ἀνακαλυφθῇ μέθοδός τις ἀποδείξεως, ὅτι, ἐὰν ὁ ἰός, εἴτε παθογόνος εἶναι εἴτε οὔ, εἰσέλθῃ ἐντὸς τοῦ κυττάρου, ἡ νόσος θὰ εἶναι τὸ ἀποτέλεσμα : ἡ τύχη τοῦ ζώου θὰ ἐξαρτηθῇ ἐκ τῆς ποσότητος τοῦ παρόντος ἰοῦ δηλ. ἐκ τοῦ ἀριθμοῦ τῶν προσβεβλημένων κυττάρων καὶ τῆς λοιμογόνου δυνάμεως τοῦ ἰοῦ. Ἐὰν ὁ ἀριθμὸς τῶν προσβληθέντων κυττάρων εἶναι ἐπαρκῶς μέγας ὥστε νὰ προκληθῇ ζωτικὴ βλάβη εἰς τὸν μεταβολισμὸν μεγάλου ἀριθμοῦ οὐσιωδῶν κυττάρων, τότε ὁ θάνατος τοῦ ἀσθενοῦς θὰ ἐπέλθῃ. Ἐὰν ὅμως ὁ ἀριθμὸς τῶν προσβληθέντων κυττάρων εἶναι μικρὸς καὶ ἡ γενικὴ ἢ ἡ τελικὴ βλάβη δὲν εἶναι μεγάλη, τότε θὰ ἀναπτυχθῇ ἀνοσία. Ἐάν, ἐξ ἄλλου, τὸ κύτταρον κατέχεται ὑπὸ μὴ παθογόνου τύπου ἰοῦ, τύπου ὅστις δὲν προξενεῖ τὸν θάνατον τοῦ κυττάρου, ἀλλὰ προκαλεῖ ἐπαρκῆ ἀντίδρασιν ὥστε νὰ ἐπιφέρῃ γένεσιν ἀνοσίας, οὐδεὶς ἄλλος ἰὸς δύναται νὰ διεισδύσῃ ἐντὸς τοῦ κυττάρου καὶ ὡς ἐκ τούτου, ἀκόμη καὶ ὅταν μεγάλαι ποσότητες παθογόνου ἰοῦ ἐνιεθῶσιν εἰς ἕν ζῶον εὑρισκόμενον εἰς τοιαύτην κατάστασιν, οὐδεμία βλάβη ἐπέρχεται : ὅλα τὰ εὐπαθῆ κύτταρα ἔχουν ἤδη καταληφθῇ καὶ ὁ ἰὸς δὲν δύναται πλέον νὰ εἰσέλθῃ. Ὅθεν δὲν δύναται νὰ ἐπέλθῃ θάνατος τῶν κυττάρων. Εἰς ἓν δράσει νόσον, κατὰ τὴν ὁποίαν τὸ ζῶον ἐξετέθη εἰς παθογόνον ἰόν, εἶναι δυνατὸν ὅλα τὰ κύτταρα νὰ μὴ ἔχουν προσβληθῇ, τινὰ νὰ εἶναι ἀκόμη ἀνέπαφα. Ἐὰν μεγάλη δόσις μὴ παθογόνου ἰοῦ χορηγηθῇ ἐκείνην τὴν στιγμήν, θὰ εἰσδύσῃ εἰς τὰ κύτταρα τὰ οὐδόλως ἢ ἐν μέρει μόνον προσβληθέντα μέχρι τότε καὶ θὰ ἀρχίσῃ οὕτω νὰ τονώνῃ ταῦτα ταχέως ὥστε προκύπτει ἀνοσία ἄνευ παραγωγῆς συμπτωμάτων προκληθέντων ὑπὸ τοῦ ἀρχικῶς μολύναντος παθογόνου ἰοῦ, ἐν ἄλλοις λέξεσιν, ὁ μὴ λοιμογόνος ἰὸς παρεμποδίζει τὴν δρᾶσιν τοῦ λοιμογόνου τοιούτου.

Χρῆσις τῆς παρατηρήσεως αὐτῆς λαμβάνει χώραν κατὰ τὸν ἐμβολιασμὸν ζῴων ἐναντίον νόσου ἐξ ἰοῦ, καὶ ὅταν ἀκόμη τὸ ζῷον ἔχει ἤδη ἐκτεθῇ εἰς τὸν παθογόνον ἰόν. Ἔστω ὡς παράδειγμα ἡ καταπολέμησις τῆς ψευδοπανώλους τῶν ὀρνιθοειδῶν : πτηνόν τι ἤδη μολυνθέν, δύναται, ὅταν δεχθῇ μεγάλην δόσιν μὴ παθογόνου ἰοῦ, νὰ μὴ δείξῃ συμπτώματα τῆς λοιμώξεως, ἀλλὰ νὰ ἀναπτύξῃ ἐνεργητικὴν ἀνοσίαν. Τὸ ἀντίθετον ἰσχύει ἐπίσης, δηλ. ἔγχυσιν μεγάλης δόσεως μὴ παθογόνου ἰοῦ δύναται νὰ ἀκολουθήσῃ μετὰ βραχὺ χρονικὸν διάστημα, 3 - 4 ἡμερῶν, δευτέρα ἔγχυσις μεγάλης δό-

σεως παθογόνου ἰοῦ, ἄνευ ἐμφανίσεως συμπτωμάτων. Φυσικά, εἰς ὅλην αὐτὴν τὴν ἐργασίαν, ἡ ποσότης τοῦ παθογόνου ἰοῦ, εἰς τὸν ὁποῖον τὸ ζῷον ἐξετέθη πρὶν ἢ τὰ κύτταρα καταληφθῶσι τελείως ὑπὸ τοῦ μὴ παθογόνου ἰοῦ, ρυθμίζει τὰ ἀποτελέσματα, δηλαδὴ ἐὰν τὸ ζῶον θὰ παρουσιάσῃ συμπτώματα ἢ ἐὰν πάραυτα θὰ ἀρχίσῃ δημιουργοῦν ἀνοσίαν.

Ἐν περιπτώσει ἑτεροειδῶν ἰῶν, τὸ πρόβλημα περιστρέφεται γύρωθεν τῆς τροπῆς (συγγενείας) τῶν διαφόρων ἰῶν πρὸς τὸν αὐτὸν τύπον κυττάρων. Ἐνῷ ὅταν χρησιμοποιῶνται ὁμοειδεῖς ἰοὶ διαφόρου βαθμοῦ λοιμογόνου δυνάμεως, ἡ ἐπερχομένη ἀνοσία, εἶναι πάντοτε μακρὰ καὶ ἴσως ἰσόβιος, ἐνῷ μὲ ἑτεροειδεῖς ἰούς, ἡ ἀνοσία εἶναι συνήθως βραχείας διαρκείας, διαρκοῦσα τὸ πολὺ ὀλίγους μῆνας.

Τὸ ὅλον ζήτημα τῆς κυτταροεμπλοκῆς (interference phenomenon) ἢ ὡς ἐνίοτε ὀνομάζεται «pre-emptive immunity» ἀνακινεῖ τὸ ζήτημα τὸ ἀφορὸν εἰς τὴν κυτταρικὴν ἀνοσίαν ἐν ἀντιθέσει πρὸς τὴν *χυμολογικὴν* τοιαύτην. Μέγας ἀριθμὸς ἐργασιῶν ἐπὶ τῆς ἀνοσίας ἀφεώρα εἰς τὴν χυμολογικὴν ἀντίληψιν ταύτης: στερούμεθα ἀκόμη ὁριστικῆς ἀποδείξεως ἢ μαρτυρίας ὅτι ὑπεισέρχεται κυτταρικὴ ἀνοσία, ἐὰν ὅμως διὰ περαιτέρω μελέτης τοῦ φαινομένου τῆς κυτταροεμπλοκῆς ριφθῇ περισσότερον φῶς ἐπὶ τῆς δράσεως τῶν κυττάρων, τότε θὰ ἔχωμεν διατρέξει μακρὰν ὁδὸν πρὸς τὴν καλυτέραν κατανόησιν τῆς κυτταρικῆς ἀνοσίας. Εἶναι ἀξιοσημείωτον ὅτι εἰς τὰ φυτά, εἰς τὰ ὁποῖα ἐν τοσούτῳ δὲν ὑπάρχει παραγωγὴ χυμολογικῶν ἀντισωμάτων ἕνας τύπος ἀνοσίας παράγεται, ἐπὶ τῶν ἰδίων ἀρχῶν ὡς ἡ παραγομένη κατὰ τὸ φαινόμενον τῆς κυτταροεπλοκῆς. Εἰς τὰ ζῷα ὁ τύπος οὗτος τῆς ἀνοσίας ἀσφαλῶς δὲν ἔχει σχέσιν μὲ τὸ δίκτυο-ἐνδοθηλιακὸν σύστημα: φαίνεται ὅτι αὐτὰ ταῦτα τὰ κύτταρα ὑπεισέρχονται καὶ νομίζεται ὅτι τὰ ἐνδιαφερόμενα κύτταρα δὲν εἶναι πάντοτε ἐκεῖνα ἅτινα ὑπέστησαν τὴν εἰσβολὴν τοῦ ἰοῦ· ἄλλοι τύποι κυττάρων εἶναι δυνατὸν νὰ προσβληθῶσι.

Ἐνῷ ὅλαι αἱ ἐνδείξεις μαρτυροῦν ὅτι αὐτὴ ἡ ἀνοσία καὶ τὸ φαινόμενον τῆς κυτταροεμπλοκῆς ἔχουν σχέσιν μὲ τὰ κύτταρα τῶν ἱστῶν ἡ ἐξήγησις τοῦ τί πράγματι συμβαίνει εἶναι ἀκόμη ἀμφισβητήσιμος. Πρὸς τὸν σκοπὸν τοῦτον διάφοροι θεωρίαι ἔχουν διατυπωθῇ, ἐξ ὧν τινες ἀπεδείχθησαν ἤδη ἐσφαλμέναι. Εἶναι ἐνδιαφέρον νὰ ὑπομνήσωμεν τινας ἐκ τῶν θεωριῶν αὐτῶν:

α) Πρόληψις ἐπεκτάσεως τοῦ ἰοῦ τοῦ ἀποκλεισθέντος διὰ τῆς φλεγμονώδους ἀντιδράσεως τῶν ἱστῶν, τῆς παραχθείσης ὑπὸ τοῦ ἐμπλέκοντος παράγοντος.

β) Ἐξάντλησις ὑπὸ τοῦ ἰοῦ τῶν μεταβολιτῶν οἵτινες ἀναγκαιοῦσι διὰ τὴν ἀνάπτυξιν τοῦ δευτέρου ἰοῦ.

γ) Ἀντι - ἰωτικαὶ ἐνέργειαι τοῦ ἑνὸς ἰοῦ ἢ προϊόντος τινὸς ἐκ τῆς πρωτοπαθοῦς λοιμώξεως.

δ) Ἀποκλεισμὸς ἢ καταστροφὴ τῶν εὐπαθῶν κυττάρων εἰς τὰ ὁποῖα ἕκαστος τῶν ἰῶν ὀφείλει νὰ προσκολληθῇ, ἵνα εἰσδύσῃ εἰς τὰ κύτταρα τοῦ ξενιστοῦ.

ε) Ἀποκλεισμὸς ἢ ἀνταγωνισμὸς δ' ἕνα ἔνζυμον - κλεῖδα εὑρισκόμενον ἐντὸς τῶν κυττάρων τοῦ ξενιστοῦ καὶ ἀπαραίτητον διὰ τὸν πολλαπλασιασμὸν ἀμφοτέρων τῶν ἰῶν.

στ) Πρόληψις διεισδύσεως τοῦ ἐκβληθέντος διὰ τοῦ κυτταρικοῦ τοιχώματος ἰοῦ, λόγῳ μεταβολῶν ἐπενεχθεισῶν εἰς τὴν ἐπιφάνειαν τοῦ κυττάρου ὑπὸ τοῦ ἀρχικοῦ ἰοῦ.

Ὀλίγα τινα παραδείγματα δύνανται νὰ ἀναφερθοῦν, τὰ ὁποῖα θὰ βοηθήσουν εἰς τὴν περαιτέρω ἐκτίμησιν τοῦ προβλήματος.

**1) Ἐμπλοκὴ ἀνοσολογικῶς συγγενῶν ἰῶν**

| Ξενιστής | Ἰός | Ἐμπλέκον στέλεχος ἰοῦ | Ἀποκλειόμενον στέλεχος ἰοῦ |
|---|---|---|---|
| Πίθηκος | Κίτρινος πυρετὸς | Νευροτρόπος | σπλαγχνοτρόπος |
| Ἀλώπηξ ἀργυρόχρους | Νόσος τῶν νεαρῶν ἀλωπέκων (distemper) | Ἐθισμένος ἐπὶ ᾠῶν | Ἐθισμένος ἐπὶ ἀργυροχρόων ἀλωπέκων |
| Βοοειδῆ | Πανώλης | Ἐθισμένος ἐπὶ ᾠῶν | Παθογόνον στέλεχος διὰ βοοειδῆ |
| Πτηνὰ | Newcastle | Μὴ παθογόνος | Λίαν παθογόνος |
| Ἔμβρυα πτηνῶν | Ὁμὰς γρίππης | χοίρειος γρίππη | Γρίππη τύπου Α |

**2) Ἐμπλοκὴ μεταξὺ ἀνοσολογικῶς μὴ συγγενῶν ἰῶν**

| | | | |
|---|---|---|---|
| Βοειδῆ | Ἀφθώδης πυρετὸς | Ἀφθώδης πυρετὸς | Λύσσα |
| Πρόβατα | Louping ill | Louping ill | Λύσσα |
| Ἄνθρωπος | Λεμφοκυττο-χοριομηνιγγῖτις | Λεμφοκυττο-χοριομηνιγγῖτις | Ἰὸς πολιομυελίτιδος |

**3) Ἐμπλοκὴ μεταξὺ ἀδρανῶν καὶ δραστικῶν ἰῶν**

| | | | |
|---|---|---|---|
| Μῦς | Ἐκτρομελία | Ἀδρανοποιηθεὶς | Δραστικὸς |
| Μῦς, Σκίουρος | Γρίππη τύπου Α | Ἀδρανοποιηθεὶς | Δραστικὸς |
| | | Ἐπίσης γρίππη Α Παρωτῖτις, χοίρειος γρίππη | Δραστικὸς |

Ὑπάρχουν ἐπίσης παραδείγματα ἀποτυχίας εἰς τὸ φαινόμενον τῆς κυτταροεμπλοκῆς, ὡς ἀκολούθως:

**4) Παραδείγματα διπλῆς λοιμώξεως ἢ ἀποτυχίας τῆς κυτταροεμπλοκῆς**

| Πρῶτος παράγων | Δεύτερος παράγων |
|---|---|
| Λεμφοκυτταρικὴ χοριομηνιγγῖτις | Νόσος Carré |
| Louping ill | Ἀφροδίσειον λεμφοκοκκίωμα |
| Newcastle | Παρωτῖτις |
| Πολιομυελῖτις | Λύσσα |
| Ἐπιδημικὸς τῦφος | Γρίππη Α |
| Εὐλογία | Ἕρπης ἁπλοῦς ἢ διφθερῖτις πτηνῶν |
| Κίτρινος πυρετὸς | Εὐλογία |

Τοιαῦτα παραδείγματα ὑπαινίσσονται ἰσχυρῶς ὅτι ἡ κυτταροεμπλοκὴ λαμβάνει χώραν μόνον ὅταν οἱ δύο παράγοντες ἕλκονται ὑπὸ τοῦ ἰδίου κυττάρου καὶ οὐχὶ ὅταν οἱ παράγοντες ἕλκονται ὑπὸ διαφόρων ὀργάνων ἢ ἱστῶν, ὑπὸ διαφόρων κυττάρων ἐντὸς τοῦ αὐτοῦ ὀργάνου ἢ ἱστοῦ, ἢ ἀκόμη ὑπὸ δύο στοιχείων ἐντὸς τοῦ αὐτοῦ κυττάρου. Περαιτέρω μελέτη τοῦ τρόπου τῆς ἕλξεως τῶν ἰῶν ὑπὸ τῶν κυττάρων δύναται νὰ αὐξήσῃ τὰς γνώσεις μας ἐπὶ τοῦ φαινομένου τούτου.

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# INTERFERENCE PHENOMENON

By

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This is a comparatively new idea. Those of us who have been interested in problems of immunity and immunology concerning bacterial infections are familiar with the principle of the subject. We know and realise that the injection of bacterial suspensions, live, attenuated or killed, stimulate the production of antibodies of various kinds. We recognise as antibodies, agglutinins, precipitins, and especially antibodies which neutralise the action of bacteria. We name such antibodies—anti-sera. We also recognise and are familiar with the action of toxins and the production of antitoxins and their neutralising value against the toxins. We have been educated and reared in the school of bacteria and antisera, toxins and

antitoxins. We have been trained and our experience is that anti - bacterial substances are required to neutralize the effects of bacteria and antitoxins for toxins. In fact, the whole conception of immunity in our minds has been one of comparative simplicity and we have put into practice these ideas and views in the stimulating of active immunity by the injection of antigens, normally termed vaccines and of passive immunity in the form of anti bacterial substances or antitoxins, already produced in another animal, usually the horse : substances we usually refer to as antisera. I need only mention the active immunity produced in animals following upon the injection of Cl. c h a u v o e i, in the protection against blackleg as an example of bacteria being used for that purpose : of the use of tetanus toxin or better tetanus toxoid in the protection against tetanus and the preparation of swine erysipelas antisera in horses, as an agent for the passive immunisation of pigs against a bacterial disease, of the antitoxins of the C l. W e l c h i i and other anaerobic organisms as examples of the antitoxins in common use throughout the world against infections caused by the toxin - producing organisms. The discovery of toxoids as opposed to toxins in immunological processes marked a considerable advance in our knowledge of antibody production and was of much value to immunologists, whose objective was to create a state of active or passive immunity against some of the important diseases of human beings and livestock by the safest and most efficient method. Many of us have had occasion to use these substances and methods and we had come to the view that we had, at last, conquered the important problem of the production of immunity We congratulated ourselves that our methods were good and that we were highly successful in our work. At that time, we were quite right. We were dealing with and studying bacteria. No matter what the theories of immunity might have been, no matter to what school of thought we belonged, we were able to produce successful results which were valuable in the control of animal diseases. These methods are still in use and are still giving satisfactory results. The livestock industry in all countries must be grateful to immunologists, veterinary and otherwise, who were able to introduce such methods of control, with resulting saving of disease and life.

With the discovery of viruses as causes of animal disease, we practiced similar methods of immunisation and again they were successful. I need only mention the use of vaccines produced from ani-

mal tissues against rinderpest, the developing chick embryo as a medium for the cultivation of viruses and the chemical treatment of the growths or cultures ; and tissue culture methods as carried out in the most recent method of producing foot - and - mouth disease immunising vaccines. Anti-sera against viruses were also successfully produced-an important example being anti-serum for canine distemper.

Everything, than, both in the bacterial and virus world seemed quite straightforward and comparatively simple. In the year 1935, however, Hoskinson and again in 1937, Findlay and MacCallum working with yellow fever, drew attention to an important and peculiar phenomenon. They found that monkeys inoculated with a pantropic strain of yellow fever virus died: while, if the virus which had acquired neurotopic qualities and which is not normally fatal to monkeys lived. This observation was the beginning of a number of observations which are now grouped under the term «interference phenomenon». It has now become common knowledge that infection of a bacterium, a plant or an animal with one virus frequently prevents or partially inhibits simultaneous propagation of another virus agent in the same host. This interference occurs with the homologous virus e.g. in African Horse Sickness where the neurotropic mouse form of the causal virus «interferes with» the action of the original type of virus and prevents infection, while active immunity still develops. In Rinderpest control work, we find a similar example: rinderpest virus propagated in eggs, goats etc. «interferes» with the virulent virus taken from cattle. A similar result can be observed with heterologous viruses e.g. the virus of lympho-chorionic meningitis and the St. Louis encephalitis virus. This «interference» cannot be due to the action of antibodies as we know them in active and passive immnity. We do not know exactly what happens to cause this «interference» but it is believed and it must be true that the tissue cells themselves are concerned. It is generally believed, although it must still be a theory, until some method of proof has been devised, that if the virus, be it virulent or avirulent enters the cell, disease will be the result: the fate of the animal will depend upon the amount of virus present i.e. the number of cells occupied and the virulence of the virus. If the number of cells entered is sufficiently large to cause vital damage to the metabolism of a large number of essential cells, then death of the host will occur - if the number ot cells involved is small and the general damage is not

great, then immunity, will be developed. If, on the other hand, the cell is occupied by a non-virulent form of the virus-a form which does not cause the death of the cell, but causes sufficient reaction to engender the production of immunity, no other virus can enter the cells and therefore, even though large amounts of virulent virus are injected into an animal in such a state, no damage occurs: all the receptive cells are already occupied and no more virus can gain entrance. Hence no death of the cells can occur. In actual disease in which the animal has been exposed to virulent virus all the cells may not be involved-some are still free. If a large dose of avirulent virus is now given, it will enter the cells which are not already occupied or are only partly occupied and will begin so to stimulate the cells rapidly that immunity results without the production of symptoms caused by the original infecting virulent virus: in other words, the nonvirulent virus «interfered» with the action of the virulent virus. Use of this observation is made in the vaccination of animals against virus infection, even although the animal has already been exposed to virulent virus. An example is in the control of Newcastle disease in poultry. A bird already infected may, when it receives a large dose of non-virulent virus, show no symptoms of the infection but will develop an active immunity. The opposite also holds good viz. a large dose of a virulent virus, can be followed in a short time say, 3-4 days with a dose of virulent virus without the production of symptoms. Naturally, in all this work, the amount of virulent virus to which the animal is exposed before the cells are completely filled with avirulent virus, regulates the effects i.e. whether the animal will develop symptoms or will at once begin to develop an immunity.

In the case of heterologous viruses the problem revolves around the affinity of different viruses for the same type of cells. While with homologous viruses in different states of virulence, the resulting immunity will always be long and probably life-long, with heterologous viruses, the immunity is usually of short duration, lasting at the most for a few months.

The whole question of «interference phenomenon» or as it is sometimes called «pre-emptive immunity» raises the point covering «cellular» as opposed to «humoral» immunity. Most of the work on immunity has been concerned with the humoral conception of immunity: we have yet no definite proof or evidence that cellular immunity does occur — if through further study of the «interference phenomenon» further light can be shed on the action of the cells, then

we will have gone a long way to a better understanding of cellular immunity. It is significant that in plants, in which there is no production of humoral antibodies, a type of immunity does occur, much on the same lines as that concerned with the «interference phenomenon». In animals, this type of immunity is certainly not related to the reticulo endothelial system : it must be concerned with the cells themselves and it is thought that the cells concerned need not always be those which are regularly invaded by the virus: other types of cells may be involved.

While all the evidence goes to show that this immunity and the «interference phenomenon» is concerned with tissue cells, the explanation of what actually takes place is still very debatable. Different theories have been put forward, some of which have already been proved to be wrong. It may be of interest to recall some of these theories. They are :

a) Prevention of spread of the excluded virus by the inflammatory tissue response induced by the interfering agent.

b) Exhaustion of metabolites by the virus, which are needed for the propagation of the second.

c) Antiviral activities of one virus or some product resulting from the primary infection.

d) Blocade or destruction of the cell receptors to which either of the viruses has to become attached in other to gain entrance to the host cell.

e) Blocade of or competition for a «Key enzyme» whithin the host cell required for the multiplication of both viruses.

f) Prevention of penetration of the excluded virus through the cell wall, by changes induced in the surface of fhe cell by the primary virus.

A few examples may be given which may assist in a further appreciation of the problem,

**1) Interference with immunologically - related viruses.**

| Host | Virus | Interfering strain of Virus | Excluded Strain |
|---|---|---|---|
| Monkey | Yellow fever | Neurotropic | Viscerotropic |
| Silver Fox | Distemper | Egg - adapted | Silver - fox adapted |
| Cattle | Rinderpest | Egg - adapted | Virulent cattle strain |
| Poultry | Newcastle disease | Avirulent | Highly virulent |
| Chick embryo | Influenza group | Swine influenza | Influenza type A |

**2) Interference between immunologically-unrelated active agents.**

| | | | |
|---|---|---|---|
| Cattle | Foot-and-mouth disease | Foot-and-mouth disease | Rabies |
| Sheep | Louping ill | Louping ill | Rabies |
| Human | Lymphocytic choriomeningitis | L. C. M. | Poliomyelitis virus |

**3) Interference between inactivated and active agents.**

| | | | |
|---|---|---|---|
| Mice | Ectromelic | Inactivated | Active |
| Mice<br>Ferrets | Influenza A | Inactivated | Active |
| | | also :<br>Influenza A<br>Mumps<br>Swine influenza | Active |

There are also examples of failures of one agent to «interfere» with another, as follows :

**4) Instances of dual infection or failure of interference.**

| First agent | Second agent |
|---|---|
| L. M. C. | Canine distemper |
| Louping ill | Lymphogranuloma venereum |
| Newcastle disease | Mumps |
| Poliomyelitis | Rabies |
| Epidemic typhus | Influenza A |
| Vaccinia | Herpes simplex or fowl pox |
| Yellow fever | Vaccinia |

Examples like those are strongly suggestive that «interference» only takes place when the two agents are attracted by the same cell: inrerference does not take place when the agents are attracted to different organs or tissues, different cells whithin the same organ or tissue or even two structures whithin the same cell. A study of some of the features of cellular attraction to virus, active or inactive, might go some distance in increasing our knowledge of the phenomenon.