A historical overview of the therapeutic use of bacteriophages

Andrzej Górski [1 2], Beata Weber-Dąbrowska [1], Ryszard Międzybrodzki [1 2], Jan Borysowski [2]

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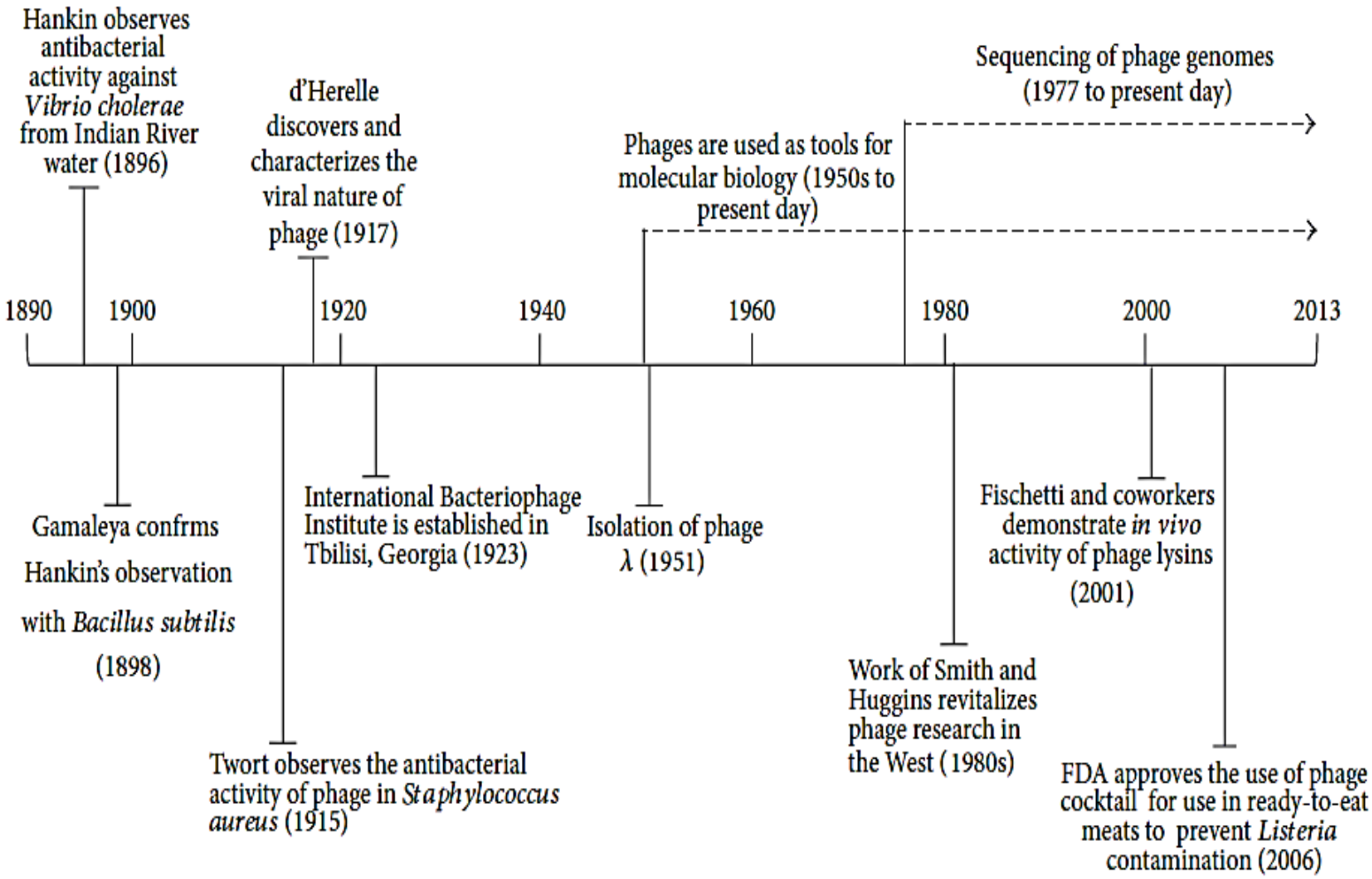
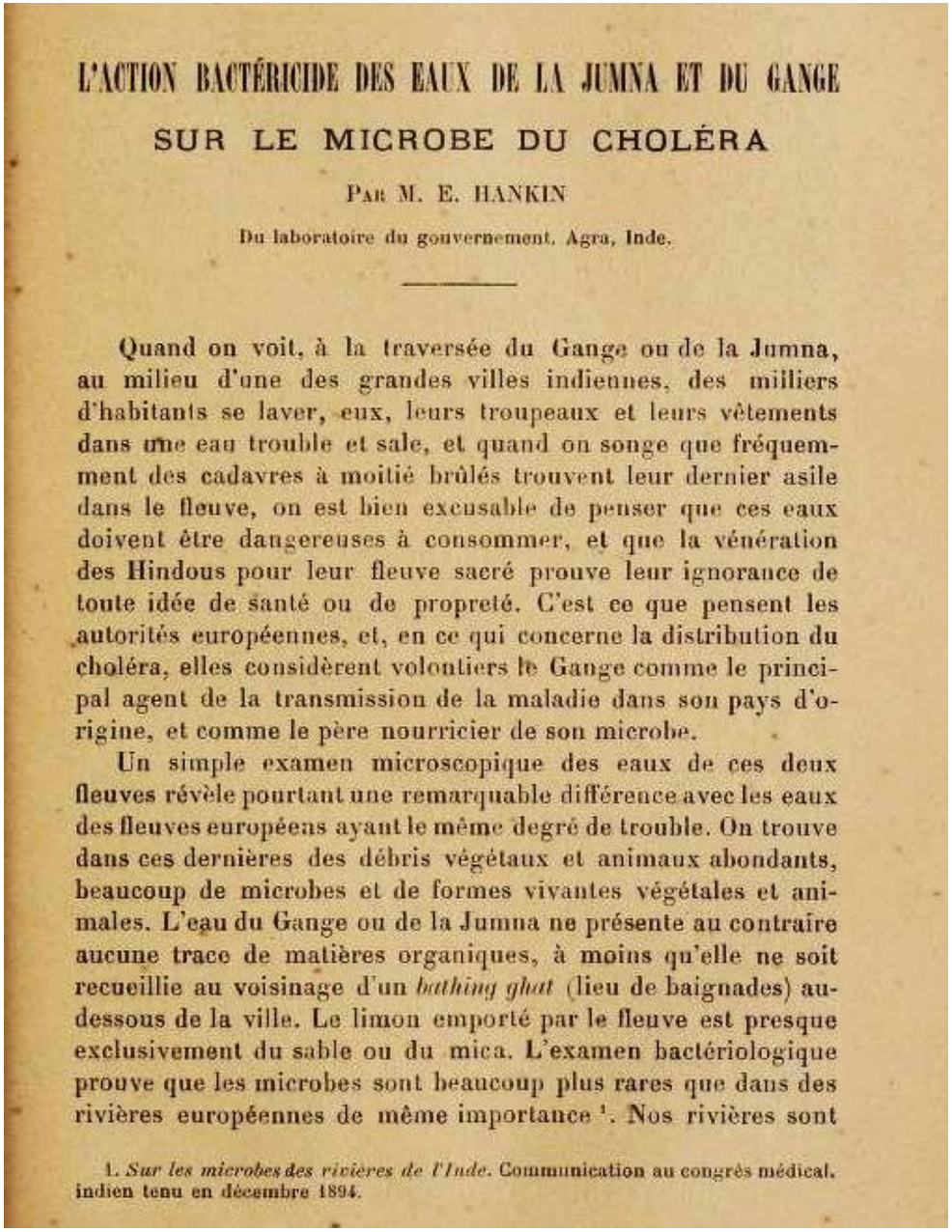
The milestones in phage history



Elbreki *et al*., 2014, Journal of Viruses ,vol.2014, Article ID 382539



L'ACTION BACTÉRICIDE DES EAUX DE LA JUMNA ET DU GANGE SUR LE MICROBE DU CHOLÉRA

PAR M. E. HANKIN

Du laboratoire du gouvernement, Agra, Inde.

Quand on voit, à la traversée du Gange ou de la Jumna, au milieu d'une des grandes villes indiennes, des milliers d'habitants se laver, eux, leurs troupeaux et leurs vêtements dans une eau trouble et sale, et quand on songe que fréquemment des cadavres à moitié brûlés trouvent leur dernier asile dans le fleuve, on est bien excusable de penser que ces eaux doivent être dangereuses à consommer, et que la vénération des Hindous pour leur fleuve sacré prouve leur ignorance de toute idée de santé ou de propreté. C'est ce que pensent les autorités européennes, et, en ce qui concerne la distribution du choléra, elles considèrent volontiers le Gange comme le principal agent de la transmission de la maladie dans son pays d'origine, et comme le père nourricier de son microbe.

Un simple examen microscopique des eaux de ces deux fleuves révèle pourtant une remarquable différence avec les eaux des fleuves européens ayant le même degré de trouble. On trouve dans ces dernières des débris végétaux et animaux abondants, beaucoup de microbes et de formes vivantes végétales et animales. L'eau du Gange ou de la Jumna ne présente au contraire aucune trace de matières organiques, à moins qu'elle ne soit recueillie au voisinage d'un *bathing ghat* (lieu de baignades) au-dessous de la ville. Le limon emporté par le fleuve est presque exclusivement du sable ou du mica. L'examen bactériologique prouve que les microbes sont beaucoup plus rares que dans des rivières européennes de même importance [1]. Nos rivières sont

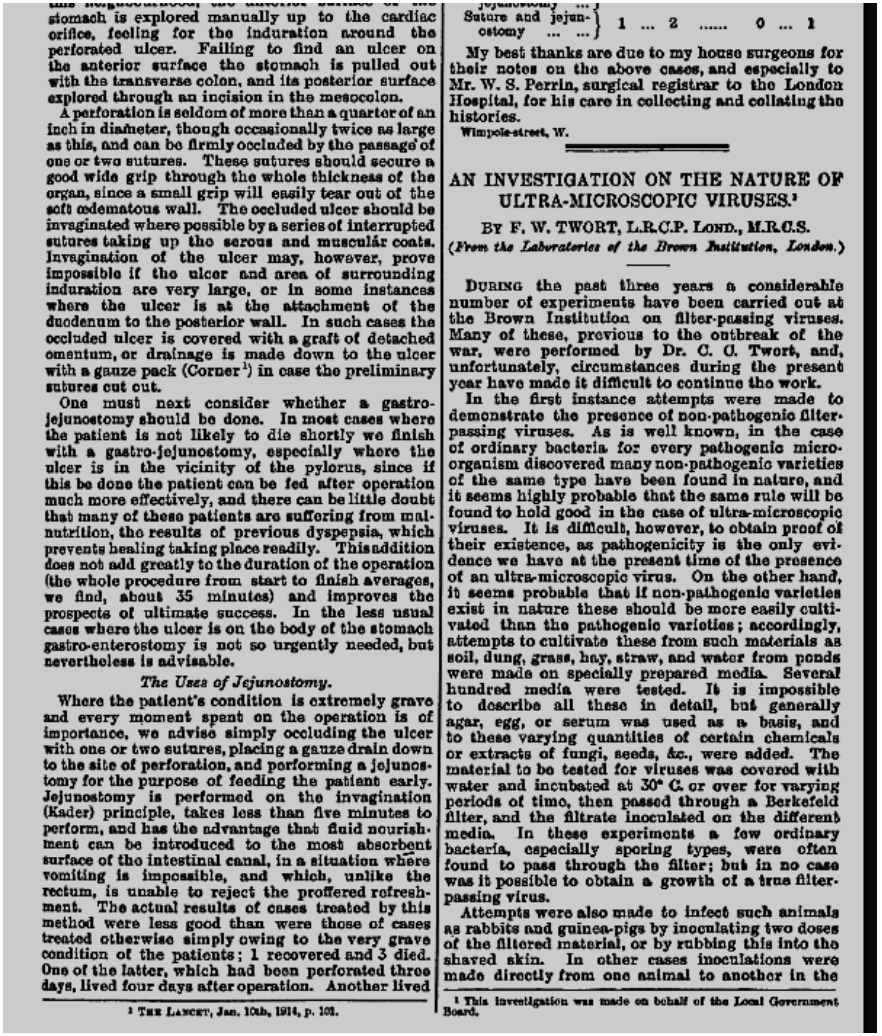
1. *Sur les microbes des rivières de l'Inde.* Communication au congrès médical indien tenu en décembre 1894.

Hankin published his observations in 1896 in the annals of the Institut Pasteur – that was the first evidence of the presence of bacteriophages in water and their antibacterial activities.

It was a viral-like agent with antibacterial properties. It was temperature sensitive and capable of passing through a porcelain filter, and it could reduce titres of the bacterium *Vibrio cholerae* in laboratory cultures.

"L'action bactericide des eaux de la Jumna et du Gange sur le vibrion du cholera„ *Annales de l'Institut Pasteur* (in French) 1896; 10: 511–523.

In 1915 The Lancet published an article written by Frederick Twort about ‘‘the transmissible bacterial lyses’’. It was the first publication on bacteriophages.



stomach is explored manually up to the cardiac orifice, feeling for the induration around the perforated ulcer. Failing to find an ulcer on the anterior surface the stomach is pulled out with the transverse colon, and its posterior surface explored through an incision in the mesocolon.

A perforation is seldom of more than a quarter of an inch in diameter, though occasionally twice as large as this, and can be firmly occluded by the passage of one or two sutures. These sutures should secure a good wide grip through the whole thickness of the organ, since a small grip will easily tear out of the soft œdematous wall. The occluded ulcer should be invaginated where possible by a series of interrupted sutures taking up the serous and muscular coats. Invagination of the ulcer may, however, prove impossible if the ulcer and area of surrounding induration are very large, or in some instances where the ulcer is at the attachment of the duodenum to the posterior wall. In such cases the occluded ulcer is covered with a graft of detached omentum, or drainage is made down to the ulcer with a gauze pack (Corner[1]) in case the preliminary sutures cut out.

One must next consider whether a gastro-jejunostomy should be done. In most cases where the patient is not likely to die shortly we finish with a gastro-jejunostomy, especially where the ulcer is in the vicinity of the pylorus, since if this be done the patient can be fed after operation much more effectively, and there can be little doubt that many of these patients are suffering from malnutrition, the results of previous dyspepsia, which prevents healing taking place readily. This addition does not add greatly to the duration of the operation (the whole procedure from start to finish averages, we find, about 35 minutes) and improves the prospects of ultimate success. In the less usual cases where the ulcer is on the body of the stomach gastro-enterostomy is not so urgently needed, but nevertheless is advisable.

The Uses of Jejunostomy.

Where the patient's condition is extremely grave and every moment spent on the operation is of importance, we advise simply occluding the ulcer with one or two sutures, placing a gauze drain down to the site of perforation, and performing a jejunostomy for the purpose of feeding the patient early. Jejunostomy is performed on the invagination (Kader) principle, takes less than five minutes to perform, and has the advantage that fluid nourishment can be introduced to the most absorbent surface of the intestinal canal, in a situation where vomiting is impossible, and which, unlike the rectum, is unable to reject the proffered refreshment. The actual results of cases treated by this method were less good than were those of cases treated otherwise simply owing to the very grave condition of the patients; 1 recovered and 3 died. One of the latter, which had been perforated three days, lived four days after operation. Another lived

[1] THE LANCET, Jan. 10th, 1914, p. 103.

Suture and jejunostomy	1 ...	2	0 ... 1

My best thanks are due to my house surgeons for their notes on the above cases, and especially to Mr. W. S. Perrin, surgical registrar to the London Hospital, for his care in collecting and collating the histories.

Wimpole-street, W.

AN INVESTIGATION ON THE NATURE OF ULTRA-MICROSCOPIC VIRUSES.[1]

BY F. W. TWORT, L.R.C.P. LOND., M.R.C.S.

(*From the Laboratories of the Brown Institution, London.*)

DURING the past three years a considerable number of experiments have been carried out at the Brown Institution on filter-passing viruses. Many of these, previous to the outbreak of the war, were performed by Dr. C. C. Twort, and, unfortunately, circumstances during the present year have made it difficult to continue the work.

In the first instance attempts were made to demonstrate the presence of non-pathogenic filter-passing viruses. As is well known, in the case of ordinary bacteria for every pathogenic micro-organism discovered many non-pathogenic varieties of the same type have been found in nature, and it seems highly probable that the same rule will be found to hold good in the case of ultra-microscopic viruses. It is difficult, however, to obtain proof of their existence, as pathogenicity is the only evidence we have at the present time of the presence of an ultra-microscopic virus. On the other hand, it seems probable that if non-pathogenic varieties exist in nature these should be more easily cultivated than the pathogenic varieties; accordingly, attempts to cultivate these from such materials as soil, dung, grass, hay, straw, and water from ponds were made on specially prepared media. Several hundred media were tested. It is impossible to describe all these in detail, but generally agar, egg, or serum was used as a basis, and to these varying quantities of certain chemicals or extracts of fungi, seeds, &c., were added. The material to be tested for viruses was covered with water and incubated at 30° C. or over for varying periods of time, then passed through a Berkefeld filter, and the filtrate inoculated on the different media. In these experiments a few ordinary bacteria, especially sporing types, were often found to pass through the filter; but in no case was it possible to obtain a growth of a true filter-passing virus.

Attempts were also made to infect such animals as rabbits and guinea-pigs by inoculating two doses of the filtered material, or by rubbing this into the shaved skin. In other cases inoculations were made directly from one animal to another in the

[1] This investigation was made on behalf of the Local Government Board.

The Lancet, Jan. 10th, 1914, p. 101

Courtesy of Ms Grace Philby

Courtesy of Ms Grace Philby

Felix d'Herelle

- ✓ In 1917 Félix d'Herelle isolated first bacteriophages from the stools of patients recovering from dysentery*.
- ✓ He supposed that bacteriophages were agents that cause natural recoveries*.
- ✓ He showed that bacteriophages could be used to treat bacterial infections in humans*.
- ✓ Bacteriophages have been used in medicine since 1919, ten years before the discovery of the penicillin – the first antibiotic*.

Felix d'Herelle at a bacteriophage research center.

.Thacker PD. (2003) *Set a microbe to kill a microbe: drug resistance renews interest in phage therapy*. JAMA;290(24):3183-5.

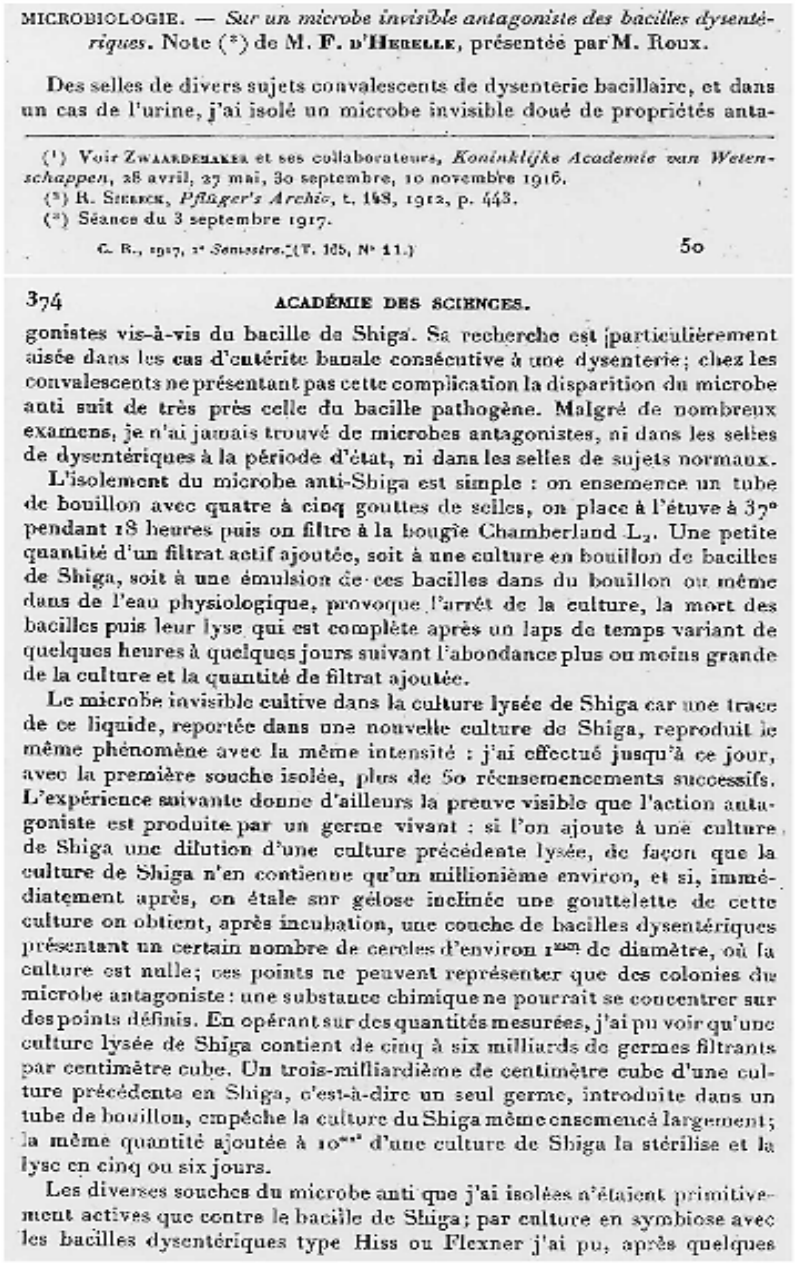
*http://www.pasteur.fr/en/brief-history-bacteriophages

- ✓ In 1917 d'Herelle and co-workers isolated phages with lytic activity against pathogenic bacteria:

  Escherichia coli, Neisseria meningitis, Pasteurella multocida, Pseudomonas aeruginosa, Salmonella typhi, Shigella dysenteriae, *Streptococcus* species, *Vibrio cholerae*, *Yersinia pestis*.

- ✓ He developed the idea of "phage therapy" as prophylactic and/or therapeutic use of selected bacteriophages in the destruction of pathogenic bacterial cells while remaining completely innocuous to host cells (d`Herelle, 1923).

- ✓ For this idea he deserved the Noble Prize, to which he was nominated eight times (every year since 1925), although he was never awarded one.



MICROBIOLOGIE. — *Sur un microbe invisible antagoniste des bacilles dysentériques*. Note (*) de M. F. D'HERELLE, présentée par M. Roux.

Des selles de divers sujets convalescents de dysenterie bacillaire, et dans un cas de l'urine, j'ai isolé un microbe invisible doué de propriétés anta-

(1) Voir ZWAARDEMAKER et ses collaborateurs, *Koninklijke Academie van Wetenschappen*, 28 avril, 27 mai, 30 septembre, 10 novembre 1916.
(2) R. SIEBECK, *Pflüger's Archiv*, t. 148, 1912, p. 443.
(3) Séance du 3 septembre 1917.

C. R., 1917, 2e Semestre. (T. 165, N° 11.) 50

374 ACADÉMIE DES SCIENCES.

gonistes vis-à-vis du bacille de Shiga. Sa recherche est particulièrement aisée dans les cas d'entérite banale consécutive à une dysenterie; chez les convalescents ne présentant pas cette complication la disparition du microbe anti suit de très près celle du bacille pathogène. Malgré de nombreux examens, je n'ai jamais trouvé de microbes antagonistes, ni dans les selles de dysentériques à la période d'état, ni dans les selles de sujets normaux.

L'isolement du microbe anti-Shiga est simple : on ensemence un tube de bouillon avec quatre à cinq gouttes de selles, on place à l'étuve à 37° pendant 18 heures puis on filtre à la bougie Chamberland L_2. Une petite quantité d'un filtrat actif ajoutée, soit à une culture en bouillon de bacilles de Shiga, soit à une émulsion de ces bacilles dans du bouillon ou même dans de l'eau physiologique, provoque l'arrêt de la culture, la mort des bacilles puis leur lyse qui est complète après un laps de temps variant de quelques heures à quelques jours suivant l'abondance plus ou moins grande de la culture et la quantité de filtrat ajoutée.

Le microbe invisible cultive dans la culture lysée de Shiga car une trace de ce liquide, reportée dans une nouvelle culture de Shiga, reproduit le même phénomène avec la même intensité : j'ai effectué jusqu'à ce jour, avec la première souche isolée, plus de 50 récensemencements successifs. L'expérience suivante donne d'ailleurs la preuve visible que l'action antagoniste est produite par un germe vivant : si l'on ajoute à une culture de Shiga une dilution d'une culture précédente lysée, de façon que la culture de Shiga n'en contienne qu'un millionième environ, et si, immédiatement après, on étale sur gélose inclinée une gouttelette de cette culture on obtient, après incubation, une couche de bacilles dysentériques présentant un certain nombre de cercles d'environ 1^{mm} de diamètre, où la culture est nulle; ces points ne peuvent représenter que des colonies du microbe antagoniste : une substance chimique ne pourrait se concentrer sur des points définis. En opérant sur des quantités mesurées, j'ai pu voir qu'une culture lysée de Shiga contient de cinq à six milliards de germes filtrants par centimètre cube. Un trois-milliardième de centimètre cube d'une culture précédente en Shiga, c'est-à-dire un seul germe, introduite dans un tube de bouillon, empêche la culture du Shiga même ensemencé largement; la même quantité ajoutée à 10^{cm^3} d'une culture de Shiga la stérilise et la lyse en cinq ou six jours.

Les diverses souches du microbe anti que j'ai isolées n'étaient primitivement actives que contre le bacille de Shiga; par culture en symbiose avec les bacilles dysentériques type Hiss ou Flexner j'ai pu, après quelques

Fruciano D.E., Bourne S.(2007) *Can J Infect Dis Med Microbiol*. 18(1): 19–26.

http://www.pasteur.fr/ip/portal/action/WebdriveActionEvent/oid/01s-00002q-016

Hankin EH. L'action bactericide des eaux de la Jumna at du Gange sur le vibrion du cholere. *Ann Int Pasteur (Paris) 1896,10,511-23.*

Twort TW. An investigation on the nature of ultramicroscopic viruses. *Lancet 1915,186,1241-3.*

d'Herelle F. Sur un microbe invisible antagoniste des baccilles dysenteriques. *CR Acad Sci Paris 1917,163,173-5.*

I

Co-discovery of phages: 1915 F.Twort, 1917 F. d'Herelle

II

1920 – 1934 high expectations

1921 – first article on phage therapy: Bruynoghe, R. and Maisin, J., Essais de thérapeutique au moyen du bactériophage du Staphylocoque, J Compt Rend Soc Biol 85, 1120-1121, 1921.4 (Staph skin infections)

III

1934 - critical review of the available literature on phage therapy, conclusions not in favor of the therapy (phage effect = enzyme) Eaton MD, Bayne-Jones S. *JAMA 1934,103,1769-76.*

IV

Displacement of phage therapy after WWII by antibiotics

V

Phage therapy "rediscovered" by the English literature

Smith, H. W. Huggins, M. B. Successful treatment of experimental *Escherichia coli* infections in mice using phage: its general superiority over antibiotics. *J Gen Microbiol* 1982, 128, 307–318.

France

1919 – early 1990 (Pasteur Institute in Lyon)

D'Herelle tested safety of phage preparations on himself, family and colleagues (orally and injections), no ill effects.

A boy with a severe dysentery – the symptoms ceased after a single administration of phage
Hopital des Enfants Malades, Paris, 1919 (unpublished)

1916 – 30 d'Herelle in China, Laos, India, Vietnam, Africa combating epidemics of cholera and plague

1931 – first intravenous use (d'Herelle, treatment of cholera in India)
Staph bacteriemia, 1 hr iv infusion

USA

1920 – 30s

Eli Lilly, Abbott Laboratories sterile phage lysates

Discouraging JAMA report (based on > 100 studies of phage therapy), except staph infections and cystitis

Eaton M.D., Bayne-Jones S. Bacteriophage therapy. JAMA 1934,103;1769-76

MacNeal W., Frisbee F. One hundred patients with *Staphylococcus* septicaemia receiving bacteriophage service. Am. J. Med. Sci. 1936;191:179–195. doi: 10.1097/00000441-193602000-00004

1936 – 40 typhoid patients, Los Angeles area

1950 – 1994 Staph Phage Lysate (SPA) (Delmont Labs) intranasally, topically, orally, sc iv only minor side effects

1987 A veterinary license for SPL, clinical effe4icacy confirmed in dogs by clinical trial

Clinical trial in the Czech Republic (Stafal, 1992-94) registered in the Czech Republic and Slovakia for the topical treatment of Staph. skin infections

Georgia

Eliava Institute In Tbilisi, established in 1930 by Eliava and d'Herelle

1980: 1200 employees, production capacity: 2 tons /week
(Kutter et al., *Curr Pharm Biotechnol 2010,11,69)*

Tablets, liquid (in the past 80% for the Soviet Army)

Complex cocktails: Pyophage (S,aureus, E.coli, P.aeruginosa, Proteus, Streptococcus)

Intestiphage (23 different enteric bacteria)

Russia 1920s – currently

Vestn Otorinolaringol. 2015;80(1):80-3.

[Prospects for the application of bacteriophages in otorhinolaryngology].

[Article in Russian] Nosulya EV.

Abstract

The objective of the present work was to summarize the available literature data concerning the importance of and prospects for for the application ofbacteriophages for the treatment of the most common diseases of the upper respiratory tract and the ear.

PMID: 26003968 [PubMed - in process]

Brazil : Institute Oswaldo Cruz 1924 - ? (anti-dysentery phage)

Romania 1960s (synergism with antibiotics)

Military use

The Finnish Campaign (1939-40)

Afrika Korps 1941-43

Soviet – German war 1941-45

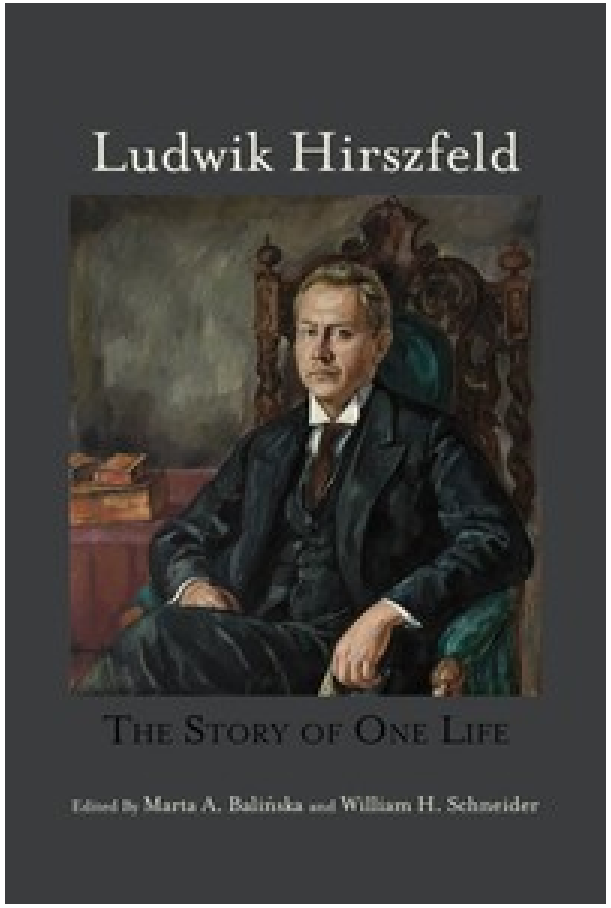
Poland

1920s – 2015

1945 – 54 L.Hirszfeld establishment of phage bank, Institute of Immunology and Experimental Therapy, PAS

1954 – 1987 Slopek, > 1000 pts 84-97% success rate reported

2005 – establishment of phage therapy unit (compassionate use based on Declaration of Helsinki and relevant Polish legislation (Constitution of Poland, act on the profession on doctors, ethical code of the Polish Medical Association)



Eds: MA Balińska, WH Schneider
University of Rochester Press, 2010

Ludwik Hirszfeld (1884-1954), one of the most prominent serologists of the twentieth century, established the nomenclature and the inheritance of blood groups, and opened the field of human population genetics. He also carried out groundbreaking researchin the genetics of disease and immunology. Following World War II, he founded Poland's first Institute of Immunology in Wroclaw, which now bears his name. His autobiographical memoir, *The Story of One Life*, first published in Poland in 1946, immediately became a bestseller and has been reedited several times since. It is an outstanding account of a Holocaust survivor and a writer capable of depicting the uniqueness and the tragedy of countless individuals caught up in the nightmare of 1939-45. Herecollects his time as a physician in the Serbian army in 1915 and his satisfaction as one of the scientific elite who rebuilt Poland …

Rok IV. Warszawa, 15 kwietnia 1923 r. № 4.

Lekarz Wojskowy

Miesięcznik

REDAKTOR: W. OSMOLSKI KOMITET REDAKCYJNY: O. BUJWID, W. HORODYŃSKI, L. KARWACKI, J. KOELICHEN, T. KORZON, S. RUDZKI, B. SABAT, S. SKŁADKOWSKI, Z. SOWIŃSKI, B. SZARECKI, Z. SZYMANOWSKI, L. ZEMBRZUSKI, E. ŻEBROWSKI.

REDAKCJA: ul. Szucha № 23; w poniedziałki i czwartki od g. 12 do 13.
ADMINISTRACJA: Wojskowy Instytut Sanitarny Szpital Ujazdowski, tel. 30370.

TREŚĆ:

SOMMAIRE:

Attempts to use bacteriophagy in surgery

Polish Medical Journal 1927,6,67

na. Zaraz po przyjściu chorego na oddział podano 0,6 gr. neosalwarsanu dożylnie. W ciągu nocy wystąpiły objawy ze strony jelit, gwałtowne bóle brzucha, biegunka krwawa. Tak w wydzielinie przyrannej jak i w kale stwierdzono mikroskopowo i w hodowli laseczki wąglikowe.

Chory zmarł po 48 godzinach wśród silnego zapadu.

Sekcja zwłok wykazała: (asystent dr. Janusz):

Pustulae malignae et infiltratio oedematosa cutis antibrachii dextr. Hyperaemia pulmonum maioris gradus. Lymphadenitis haemorrhagica acuta glandularum mesaraicarum. Tumor lienis acutus. Ecchymoses multiplices pleurae ac pericardii. Focus metastitici haemorrhag. partim exulcerantes mucosae tractus digestorii.

Leczenie wąglika dożylnemi wlewaniami neosalwarsanu zapoczątkował w ostatnich latach Becker, który po jednorazowem podaniu 0,6 gr. neosalwarsanu uzyskał w przypadku posocznicy wąglikowej niezwykle korzystny wynik leczniczy. Chory, który uchodził za zupełnie straconego, został uratowany, a krew, badana bakterjologicznie na drugi dzień po podaniu neosalwarsanu, okazała się zupełnie jałową. Bettmann podaje korzystne wyniki leczenia neosalwarsanem w dwóch przypadkach wąglika, a Gsell w jednym, u 28-letniego mężczyzny. Materjał znaczniejszy, bo obejmujący 54 przypadków wąglika miał w leczeniu Grasser. Niekorzystne wyniki otrzymał w 4 przypadkach, mimo podania neosalwarsanu, co stanowi 7.4% śmiertelności. Podług Grassera jednorazowe podanie 0,45 gr. neosalwarsanu wystarcza przy wąglíku skórnym o lekkim przebiegu. W przypadkach cięższych należy podawać neosalwarsan dwu do trzechkrotnie, w odstępach dwudniowych. Przypadki wąglika jelitowego dają prognozę bardzo niekorzystną. Einecker opisuje 5 przypadków wąglika jelitowego, które bez wyjątku zakończyły się zejściem śmiertelnem. Początek był nagły, wśród objawów nieżytu jelit, przy stanie podgorączkowym. Po 1—3 dniach schorzenia o średniem nasileniu wystąpił nagle obraz śmiertelnego zapadu. Myślano o stadjum asfik-

Dr. Jerzy JASIEŃSKI asystent kliniki. Kraków.

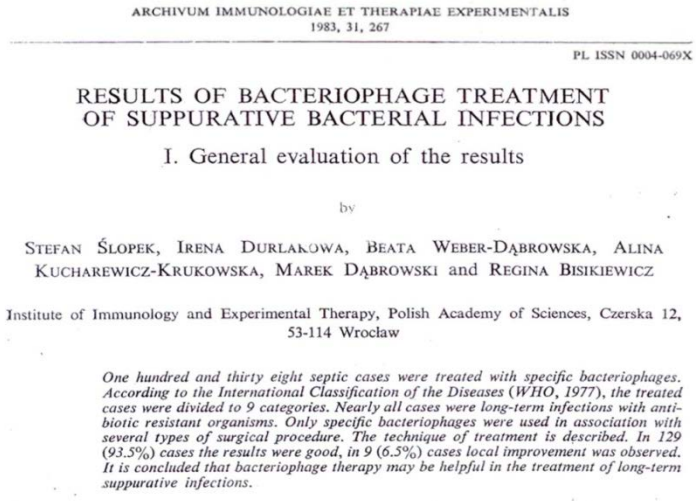
Próby zastosowania bakterjofagji w chirurgji [1]).

Z Kliniki chirurgicznej U. J. Dyrektor: Prof. Dr. M. Rutkowski.

Kiedy d'Herelle przed niespełna 10 laty odkrył w przesączu stolca ozdrowieńca po czerwonce to, czego natury do dziś jeszcze nie znamy, a co nazwał bakterjofagiem, gdyż przesącz ten rozpuszczał w probówce prątki czerwonki, kiedy wykrył dalej podobne bakterjofagi i podobne ich działanie w całym szeregu innych chorób, przypuszczał, że odkryciem tem spowodował przewrót w całej nauce o zakażeniu, odporności i lecznictwie. Na podstawie doświadczeń pracownianych i pierwszych prób zastosowania bakterjofaga w celach zapobiegawczych i leczniczych w klinice zwierząt i ludzi — powstała wówczas jego śmiała hipoteza o odporności. Przebieg uodpornienia miał być walką między bakterjami, a czynnikiem uodporniającym t. j. bakterjofagiem, wyzdrowienie — skutkiem bakterjofagji, a odporność w równym stopniu zakaźną, co i choroba, bo sztuczne czy naturalne zakażenie człowieka bakterjofagiem miało ją wywoływać. Hipoteza ta i próby zastosowania bakterjofaga w klinice spotkały się z bardzo ostrą krytyką w literaturze niemieckiej, samego odkrycia jednak nie można było nie docenić. Kilkaset prac, poświęconych temu zjawisku, wykazało szereg właściwości bakterjofagów, pod każdym względem ciekawych, zmieniło poniekąd nasze poglądy o morfologji bakterji, nie rozstrzygnęło jednak natury bakterjofaga, nad którą najzawziętszy spór się toczy co do tego, czy jest zaczynem czy też ustrojem żywym. Nie silono się jednak dalej nad wyjaśnieniem biologicznego znaczenia zjawiska, nie podając nawet żadnych innych hipotez, jak tylko tyczących się jego natury. Próby leczniczego działania bakterjofaga, w sztucznych zakażeniach zwierząt wypadły naogół niepomyślnie. Próby zaś stosowania go w klinice ludzkiej nie były zbyt liczne, a naogół są dość sprzeczne w otrzymanych wynikach. Trudności w ich ocenie stanowi rów-

1. Ślopek S., Weber-Dąbrowska B., Dąbrowski M., Kucharewicz-Krukowska A.: Results of bacteriophage treatment of suppurative bacterial infections in the years 1981-1986. Arch Immunol Ther Exp 1987; 35: 569-583. (550 cases were analyzed)

2. Ślopek S., Kucharewicz-Krukowska A. Weber-Dąbrowska B., Dąbrowski M.: Results of bacteriophage treatment of suppurative bacterial infections. V. Evaluation of the results obtained in children. Arch Immunol Ther Exp 1985; 33: 241-259. (114 cases were analyzed)



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1983, 31, 267

PL ISSN 0004-069X

RESULTS OF BACTERIOPHAGE TREATMENT OF SUPPURATIVE BACTERIAL INFECTIONS

I. General evaluation of the results

by

STEFAN ŚLOPEK, IRENA DURLAKOWA, BEATA WEBER-DĄBROWSKA, ALINA KUCHAREWICZ-KRUKOWSKA, MAREK DĄBROWSKI and REGINA BISIKIEWICZ

Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, Czerska 12, 53-114 Wrocław

One hundred and thirty eight septic cases were treated with specific bacteriophages. According to the International Classification of the Diseases (WHO, 1977), the treated cases were divided to 9 categories. Nearly all cases were long-term infections with antibiotic resistant organisms. Only specific bacteriophages were used in association with several types of surgical procedure. The technique of treatment is described. In 129 (93.5%) cases the results were good, in 9 (6.5%) cases local improvement was observed. It is concluded that bacteriophage therapy may be helpful in the treatment of long-term suppurative infections.

3. Weber-Dąbrowska B., Mulczyk M., Górski A.: Bacteriophage therapy of bacterial infections: an update of our Institute`s experience. Arch Immunol Ther Exp 2000; 48: 547-551. (the results of the phage treatment of 1307 patients were summarized)

4. Weber-Dąbrowska B., Mulczyk M., Górski A. Bacteriophages as an efficient therapy for antibiotic-resistant septicemia in man. Transplant Proc. 2003; 35: 1385-1386. (94 cases were analyzed)

Phage Therapy Unit

Ludwik Hirszfeld Institute of Immunology and Experimental Therapy

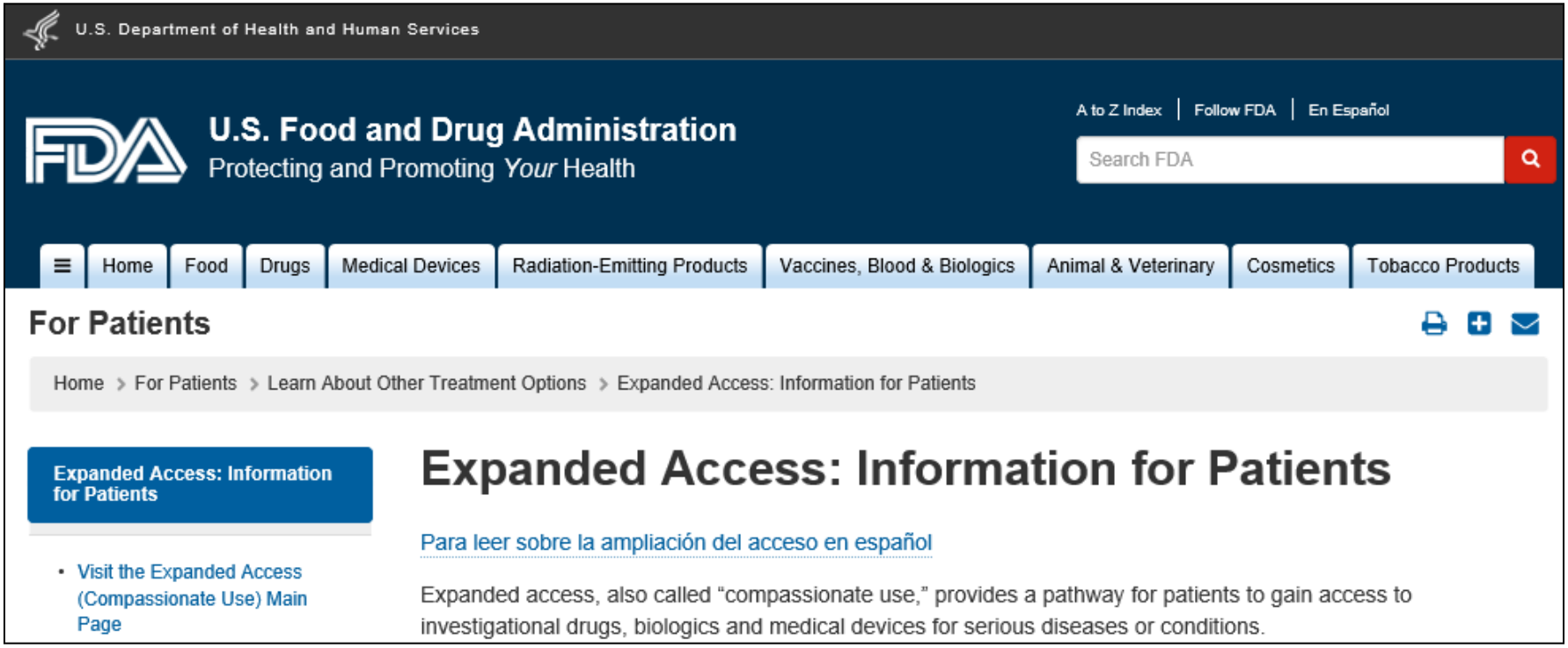
Polish Academy of Sciences, Weigla 12, 53-114 Wroclaw, Poland

Head: prof. Andrzej Górski

The Phage Therapy Unit at the Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, was opened at the end of 2005.

According to Polish law, phage therapy is considered an experimental treatment which is carried out on the basis of the respective legislation (pharmacological law, regulations of the Minister of Health) and Declaration of Helsinki. Experimental treatment (or, translated literally, *a therapeutic experiment*) occurs when a physician introduces new or only partially tested diagnostic, therapeutic, or prophylactic methods for the direct benefit of the person being treated. In contrast, an investigational experiment has the primary purpose of broadening medical science (and is tantamount to clinical research). To satisfy the existing requirements, two basic items are prerequisites for experimental therapy: the written informed consent of the patient and approval by bioethics commission. Furthermore, it may be implemented only by a qualified doctor and when available treatment has failed (arts. 29/1, 21/2, and 21/3 of the law on the physician's profession). Therefore, our current therapy involves cases in which prior antibiotic treatment did not lead to the eradication of infection.

EMA: compassionate use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Expanded access, also called “compassionate use,” provides a pathway for patients to gain access to investigational drugs, biologics and medical devices for serious diseases or conditions.

Bioethics Committee
of the Medical Academy in Wrocław,
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DECISION OF THE BIOETHICS COMMITTEE
No. KB-349/2005

The Bioethics Committee of the Medical Academy in Wrocław, appointed by the President of the Medical Academy in Wrocław, directive No. 4XIII R/99 of September 27, 1999, and functioning in the manner foreseen by the directive of the Minister of Public Health and Welfare of May 1, 1999, (Law Gazette No. 47, item 480) on the basis of the act concerning the physician's practice of December 5, 1996 (Law Gazette No. 28 of 1997, item 152 and later amendments), composed of:

Prof. Karol Bal (philosophy)
Prof. Mieczysław Bernat (surgery)
Fr. Dr. Janusz Czarny (clergy)
Prof. Marian St. Gabryś (midwifery, gynecology, anesthesiology)
Prof. Bogumił Halawa (internal diseases, cardiology)
Dr. Henryk Kaczkowski (maxillofacial surgery, dental surgery)
Irena Knabel-Krzyszowska, M. S. (pharmacy), representative of the Lower Silesian Chamber of Pharmacists
Prof. Jan Kolasa (law)
Dr. Sławomir Sidorowicz (psychiatry)
Prof. Zenon Szewczyk (internal diseases, nephrology)
Danuta Tarkowska (midwifery)
Prof. Marian Wilimowski (pharmacology)
Andrzej Wojnar, MD (pathomorphology, dermatology), representative of the Lower Silesian Chamber of Physicians

under the chairmanship of:
Prof. Franciszek Iwańczak (pediatrics, gastroenterology)

in adherence to the principles of Good Clinical Practice and those of the Declaration of Helsinki, after becoming acquainted with the project:

"Experimental phage therapy in antibiotics-resistant bacterial infection, including MRSA infection"
(Short title: :Experimental phage therapy of bacterial infection")

proposed by

Prof. Andrzej Górski

employed at

The Institute of Immunology and Experimental Therapy PAN in Wrocław

Clinical Aspects of Phage Therapy

Ryszard Międzybrodzki,[*,†,1] **Jan Borysowski,**[‡] **Beata Weber-Dąbrowska,**[*,†] **Wojciech Fortuna,**[*,†] **Sławomir Letkiewicz,**[†,§] **Krzysztof Szufnarowski,**[†,‖] **Zdzisław Pawełczyk,**[†] **Paweł Rogóż,**[†,¶] **Marlena Kłak,**[*] **Elżbieta Wojtasik,**[#] and **Andrzej Górski**[*,†,‡]

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Advances in Virus Research, Volume 83
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Phage as a Modulator of Immune Responses: Practical Implications for Phage Therapy

Andrzej Górski,[*,†,#,1] Ryszard Międzybrodzki,[*,#] Jan Borysowski,[†] Krystyna Dąbrowska,[*] Piotr Wierzbicki,[†] Monika Ohams,[†] Grażyna Korczak-Kowalska,[†,‡] Natasza Olszowska-Zaremba,[†] Marzena Łusiak-Szelachowska,[*] Marlena Kłak,[*] Ewa Jończyk,[*] Ewelina Kaniuga,[†] Aneta Gołaś,[†] Sylwia Purchla,[†] Beata Weber-Dąbrowska,[*,#] Sławomir Letkiewicz,[#,§] Wojciech Fortuna,[*,#] Krzysztof Szufnarowski,[#,‖] Zdzisław Pawełczyk,[#] Paweł Rogóż,[#,¶] and Danuta Kłosowska[†]

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ISSN 0065-3527, DOI: 10.1016/B978-0-12-394438-2.00002-5

International Journal of Infectious Diseases (2008) 12, 466–471

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PERSPECTIVE

Is phage therapy acceptable in the immunocompromised host?

Jan Borysowski [a,*], Andrzej Górski [a,b]

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Received 16 October 2007; received in revised form 10 December 2007; accepted 20 January 2008

Corresponding Editor: William Cameron, Ottawa, Canada

Abstract

Viral Immunol. 2014 Aug;27(6):295-304. doi: 10.1089/vim.2013.0128. Epub 2014 Jun 3.

Phage neutralization by sera of patients receiving phage therapy.

Łusiak-Szelachowska M, Zaczek M, Weber-Dąbrowska B, Międzybrodzki R, Kłak M, Fortuna W, Letkiewicz S, Rogóż P, Szufnarowski K, Jończyk-Matysiak E, Owczarek B, Górski A.

Abstract

The aim of our investigation was to verify whether phage therapy (PT) can induce antiphage antibodies. The antiphage activity was determined in sera from 122 patients from the Phage Therapy Unit in Wrocław with bacterial infections before and during PT, and in sera from 30 healthy volunteers using a neutralization test. Furthermore, levels of antiphage antibodies were investigated in sera of 19 patients receiving staphylococcal phages and sera of 20 healthy volunteers using enzyme-linked immunosorbent assay. The phages were administered orally, locally, orally/locally, intrarectally, or orally/intrarectally. The rate of phage inactivation (K) estimated the level of phages' neutralization by human sera. Low K rates were found in sera of healthy volunteers ($K \leq 1.73$). Low K rates were detected before PT ($K \leq 1.64$). High antiphage activity of sera $K > 18$ was observed in 12.3% of examined patients ($n = 15$) treated with phages locally ($n = 13$) or locally/orally ($n = 2$) from 15 to 60 days of PT. High K rates were found in patients treated with some Staphylococcus aureus, Pseudomonas aeruginosa, and Enterococcus faecalis phages. Low K rates were observed during PT in sera of patients using phages orally ($K \leq 1.04$). Increased inactivation of phages by sera of patients receiving PT decreased after therapy. These results suggest that the antiphage activity in patients' sera depends on the route of phage administration and phage type. The induction of antiphage activity of sera during or after PT does not exclude a favorable result of PT.

PMID: 24893003 [PubMed - indexed for MEDLINE] PMCID: PMC4076984 [Available on 2015-08-01]

Cellular and Molecular Life Sciences
All Volumes & Issues

Volume 62, Issue 5, March 2005

ISSN: 1420-682X (Print) 1420-9071 (Online)

Review

The potential role of endogenous bacteriophages in controlling invading pathogens

Andrzej Górski, Beata Weber-Dabrowska Pages 511-519

Perspective

Free **Phages targeting infected tissues: novel approach to phage therapy**

Andrzej Górski , Krystyna Dąbrowska , Katarzyna Hodyra-Stefaniak , Jan Borysowski , Ryszard Międzybrodzki , Beata Weber-Dąbrowska

Future Microbiology, Vol. 10, No. 2, Pages 199-204.

Summary | Full Text | PDF (1682 KB) | PDF Plus | Reprints & Permissions

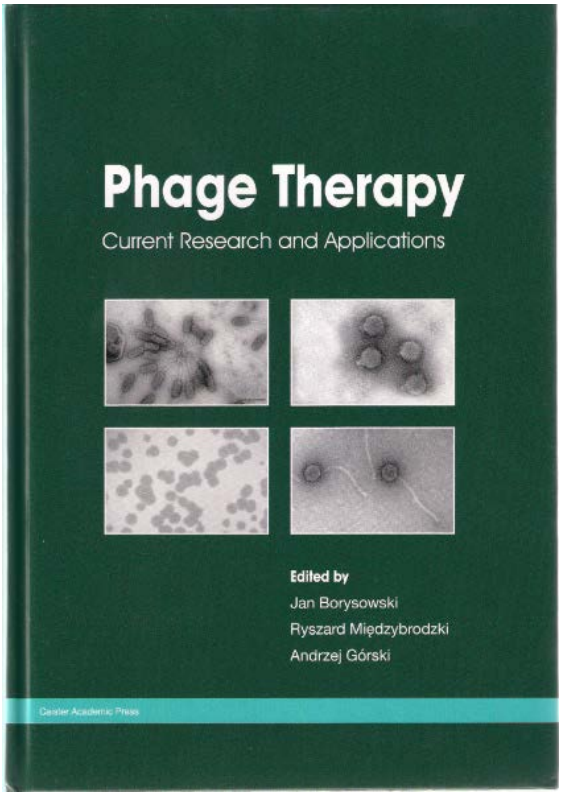
Preliminary Communication

T4 bacteriophage-mediated inhibition of adsorption and replication of human adenovirus *in vitro*

Maciej Przybylski , Jan Borysowski , Renata Jakubowska-Zahorska , Beata Weber-Dąbrowska ,Andrzej Górski

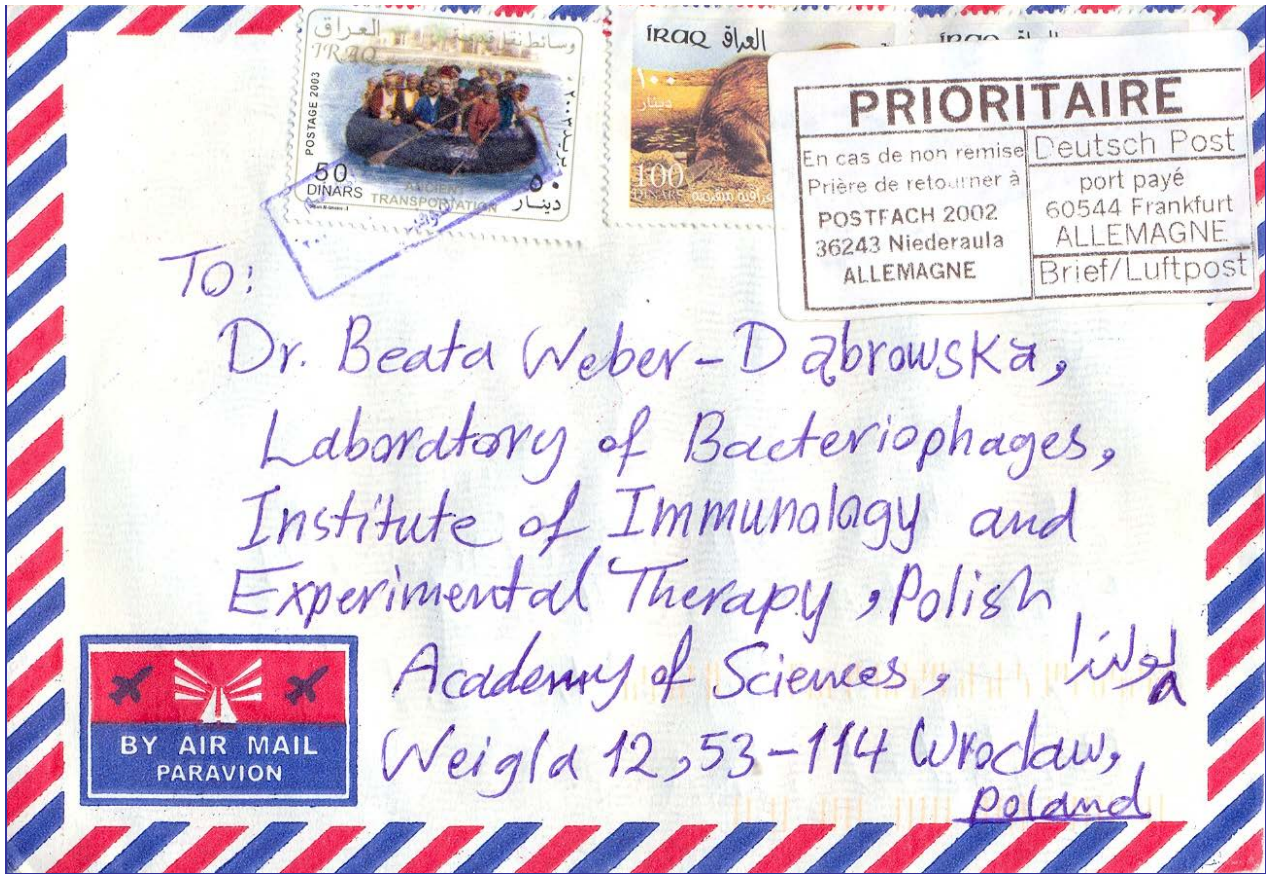
Future Microbiology, Vol. 10, No. 4, Pages 453-460.

Summary | Full Text | PDF (1764 KB) | PDF Plus (1797 KB) | Reprints & Permissions



“All in all, Phage Therapy: Current Research and Applications is a valuable resource for anyone interested in phages’ biology and/or biomedical significance. Although phage therapy has not yet made the leap from niche treatment to mainstream medicine in most of the world, this book presents a compelling case that phage-based medicine is an idea whose time has come.”

(Keen EC, Adhya SL. Review of Phage Therapy: Current Research and Applications. Clin Infect Dis. 2015 Mar 31. pii: civ257. doi: 10.1093/cid/civ257).



To:

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Randomized controlled clinical trials on bacteriophage application

Aim of the trial	Organizer/Sponsor time of realization	Comments and references
A single-center randomized and placebo-controlled trial on the safety and the bioavailability measure of oral phage	Nestlé Research Center, Nestec Ltd., Lausanne, Switzerland VI 2003	Fifteen healthy adult volunteers received two doses (10^3 and 10^5 PFU/ml) of purified ***Escherichia coli* T4 phage**, and placebo in 150 ml of drinking water. Neither adverse events nor significant change in population of commensal *E. coli* related to phage application were observed. Phages were detected in stools 1 day after exposure in all volunteers receiving the higher phage dose but a week after a 2-day course of phage application no phage was detected. Bruttin A and Brüssow H. Antimicrob Agents Chemother 2005;49: 2874-2878.
A double-blind placebo-controlled initial phase I/II clinical trial targeting chronic ear infections caused by *P. aeruginosa*	Biocontrol Ltd., London, UK VII 2006 – X 2007	Twelve patients suffering from otitis media caused by antibiotic refractory ***P. aeruginosa*** were treated with a single dose of **bacteriophage mixture** prepared by Biocontrol Ltd. and another twelve with placebo. It was presented that phage administration was safe, and there was significant reduction of clinical symptoms at day 42 in bacteriophage treated group (55% of total clinical score at the day zero) compared to the control group (104%). There was also 76% decrease in mean count of bacteria in samples taken from the patient's ears 6 weeks after phage application when in controls even small increase (9%) was observed. Wright A et al. Clin Otolaryngol. 2009;34:349-57.
A prospective, randomized, double-blind controlled study of WPP-201 for the safety and efficacy of treatment of venous leg ulcers	Southwest Regional Wound Care Centre in Lubbock, Texas, USA IX 2006 – V 2008	This was a phase I study of WPP-201 - a **cocktail of 8 lytic bacteriophages** against ***P. aeruginosa*, *S. aureus*, and *E. coli***. developed by Intralytix Inc., USA. It contained a concentration of approximately 1×10^9 PFU/ml of each of the component monophages isolated from environment and not genetically modified. The primary objective of this study was to evaluate the safety of the topical use of WPP-201 on the healing of the full thickness venous leg ulcers of greater than 30 days duration. Rhoads DD et al. J Wound Care. 2009;18:237-8, 240-3.

Clinical trials – cont.

Aim of the trial	Organizer/Sponsor time of realization	Comments and references
A limited clinical trial using bacteriophages against methycyllin-resistant *S. aureus* and multi drug-resistant *P. aeruginosa* on burn wounds	Burn Wound Centre of the Queen Astrid Military Hospital, Brussels, Belgium completed	A well-defined **cocktail of lytic bacteriophages** against **methycyllin-resistant *S. aureus* and multi drug-resistant *P. aeruginosa*** (BFC-1) was applied on **burn wounds** in 9 patients (10 applications). Phages were characterized by the fingerprint and electron microscopy and targeted against bacteria occurring in the Hospital. No adverse events, clinical abnormalities or changes in laboratory test results that could be related to the application of phages were observed (the follow-up period was 3 weeks). Unfortunately, this very prudent 'clinical trial' did not allow for an adequate evaluation of the efficacy of the phage cocktail. Ref.: Verbeken G et al. Future Microbiol 2007;2(5):485-91. Merabishvili M et al. PLoS ONE 2009;4(3): e4944. Rose T et al. Experimental phage therapy of burn wound infection: difficult first steps. Int J Burns Trauma. 2014;24(2):66-73.
Nasal decolonization of methicillin-resistant Staphylococcus aureus with mupirocin or phage ISP: a prospective randomized double blind comparison of both treatments	Burn Wound Centre of the Queen Astrid Military Hospital, Brussels, Belgium ongoing	This is a placebo controlled multicentre clinical trial focused on nasal/throat decontamination of **S. aureus** as well as **P. aeruginosa** in intensive care patients. Forty patients are intended to be enrolled into this study. Ref.: Merabishvili, M. (2012). The phage therapy experience of the Brussels burn wound centre [abstract]. In EuroPhages 2012: Bacteriophage in Medicine, Food and Biotechnology; Conference Handbook, p 21.
Randomized, Double Blind Placebo-controlled Studies to Evaluate the Effect of an Orally-fed Escherichia Coli (E. Coli) Phage in the Management of ETEC and EPEC Induced Diarrhea in Children	Nestlé Nutrition Corporate, Lausanne, Switzerland VIII 2009 - I 2013	This trial aims to evaluate the effect of oral administered ***E. coli*** phage in children aged 4-60 months of age with proven **ETEC and EPEC diarrhea**. Enrolled children will be randomly assigned, in equal numbers, to receive either: **(i) a new T4 phage cocktail** or **(ii) Russian anti-E. coli phage cocktail (Microgen)** at the dose recommended by the manufacturer or (iii) only oral rehydration solution (placebo) for 5 days in addition to management of dehydration and continued feeding in accordance with WHO guidelines. Ref.: ClinicalTrials.gov Identifier: NCT00937274

April 02, 2015

Endolysins: redefining antibacterial therapy

Clinical Microbiologist Bjorn Herpers speaks to Natasha Leeson, Commissioning Editor of Future Medicine, April 2015

This research was expanded to include a case series of eight patients with recurring dermatitis who were being treated by physicians that incorporated Staphefekt SA.100 in their treatment. In these eight patients, we looked at relief of symptoms and corticosteroid use. Overall, six had S. aureus and of these six S. aureus carriers, five of them showed a decrease in S. aureus burden and they reported relief of symptoms and less corticosteroid use. However, the other patient did not report relief of symptoms and the S. aureus did not disappear. So, unfortunately, one of them failed but in the other five patients we saw a positive effect. This was the first time that endolysin therapy has been observed in humans.

Phages given by the FDA in 2006 the designation

Generally Regarded As Safe (GRAS)

NATURE | OUTLOOK

Perspective: The age of the phage

Shigenobu Matsuzaki, Jumpei Uchiyama, Iyo Takemura-Uchiyama & Masanori Daibata

It's time to use viruses that kill bacteria again, say Shigenobu Matsuzaki, Jumpei Uchiyama, Iyo Takemura-Uchiyama and Masanori Daibata.

Nature 509, S9 (01 May 2014) doi:10.1038/509S9a
Published online 30 April

Nature | News

Phage therapy gets revitalized

The rise of antibiotic resistance rekindles interest in a century-old virus treatment.

Sara Reardon
03 June 2014

Future Microbiology
Vol. 10, No. 5, Pages 685-688 , DOI 10.2217/fmb.15.28 (May)
(doi:10.2217/fmb.15.28)

Re-establishing a place for phage therapy in western medicine

Elizabeth Martin Kutter[*,1], Sarah J Kuhl*[2] & *Stephen T Abedon*[**,3] Use of bacterial viruses as antibacterial agents has a history nearly as long as the now 100-year study of bacteriophages. Therapeutic phages are especially useful in the absence of alternative treatments, as was the case in the preantibiotic era and is again true in the face of declining antibiotic effectiveness and increasing awareness of their often-problematic consequences. As the dilemma of antibiotic resistance grows, new antimicrobial strategies must be found or our healthcare system will revert to a preantibiotic era for many pathogens. This has become a major priority of WHO, as well as politicians and public health systems around the world [1]. Antibacterial agents against which resistance has not yet evolved, ones that are inexpensive and also display low toxicities are needed. Bacteriophages, in particular, exhibit these characteristics and this, the 100th anniversary of their discovery [2], is a good time to consider how phages may be integrated into our antibacterial arsenal. The key issue is how to leverage an extensive history of clinical and experimental safety and efficacy toward re-establishing a place for phage therapy in western medicine. Here we suggest increased emphasis on collaborative compassionate use to lay the groundwork for physician and public acceptance as well as full-blown clinical trials.

We suggest compassionate use of *S. aureus* phages in combination with standard *Staphylococcus* treatment protocols, in collaboration with academic phage researchers and suppliers of existing phage products, moving as appropriate toward clinical trials of topical phage applications. Much pertinent clinical data [6–8] underlies this proposal, from the first phage therapy paper [20] to MacNeal *et al*.'s 1930s–1940s work with hundreds of patients in NY, USA [21], to extensive French, Polish and Georgian published clinical work extending up until current times [6–8,10]. The influential 1930s Eaton and Bayne-Jones *JAMA* report [17], exploring over 100 English-language articles, concluded that phage therapy of *Staphylococcus* infections was the one area where there was sufficient evidence to say that these phages clearly work: “A great many of the reported favorable results of bacteriophage therapy have come from the use of this agent in staphylococcal infections.” One also sees far less bacterial resistance to *Staphylococcus* phages than to other phages, or antibiotics, that are used clinically [7,8,11].

In many applications, introducing anti-*Staphylococcus* phage therapy into western clinical practice in a collaborative, compassionate-use fashion would not require further deviation from the current standard of care beyond careful record keeping as well as blinding for clinical trials. We predict that successes would facilitate progress toward large-scale clinical trials of a range of external phage applications. Such accomplishment would increase confidence and interest in the potential of phage therapy, encouraging commitment of both private and public funds to its further western

Professor Michael Kidd AM **(Flinders University, Australia)**

"In the era of evidence-based practice, we need practice-based evidence. The basis of this evidence is the detailed information from the case reports of individual people which informs both our clinical research and our daily clinical care".