Alexander Thomas Glenny, 1882-1965

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ALEXANDER THOMAS GLENNY
1882-1965

Elected F.R.S. 1944

ALEXANDER THOMAS GLENNY was born at Dulwich on 18 September 1882, the youngest of six children. His father, Thomas Armstrong Glenny, was an Irishman of distant Scottish descent who was born in County Sligo and studied at Dublin with a view to becoming a Protestant minister, but before he completed the course turned nonconformist and joined the Plymouth Brethren. Though young Glenny never joined this strict sect, he was brought up with all the restraint imposed by it. Smoking, theatre- or concert-going and card-playing were all strictly forbidden; there were no pictures in the house and only framed texts on the walls. This life of restraint left a permanent mark on him, and he never lost the diffidence and shyness he attributed to it. Moreover, his next elder brother was six years older, so Glenny was brought up with his two sisters, and in addition he was always overshadowed by his eldest brother William Thomas Glenny, C.B.E., a man of exceptional ability, who held successive posts as Official Translator to the Board of Trade, Inspector General of Overseas Trade, and Trade Counsellor to Sweden.

So long as Glenny lived with his parents he attended the meetings of the Plymouth Brethren; when he was married he was confirmed in the Church of England, and some years later took an active part as sidesman and member of the Church Council.

He was educated at Alleyn's School, Dulwich (headmaster Dr H. Baker, F.R.S.), where mathematics was his strong point. He played football for the school and later for the Old Boys for several years; during one winter, in which the school second eleven did not lose a single match, the Captain was A. J. Ewins (later F.R.S.) and the goalkeeper Glenny. Glenny was hopeless at playing cricket, but acted as official scorer to the school for several years; after he left the school he kept up his interest by frequent visits to Kennington Oval.

In the spring of 1899 the Wellcome Physiological Research Laboratories moved to Herne Hill, and Dr W. Dowson the Director asked the authorities at Alleyn's School to recommend two boys who had passed the matriculation examination as possible laboratory assistants, on the understanding that they would have ample time for studying and would be given some coaching for a science degree. Glenny had already gained a scholarship to University
College, London, where he had intended to continue his mathematics, with a view to becoming an actuary after he had taken an Arts degree. The work in the Wellcome Laboratories at Brockwell Hall, Herne Hill, so near his home, seemed too attractive to miss. The two boys chosen were Ewins and Glenny.

Ewins became assistant to Pinkus, a chemist who was also something of an engineer, and Glenny assistant to Dowson in the Bacteriological Laboratory. The staff at Brockwell Hall, besides Pinkus and Dowson, consisted of H. J. Südmersen as bacteriologist, one laboratory assistant in charge of media making, with a small boy as assistant, an old soldier who lived on the premises and looked after the guinea-pigs, and a stable superintendent who lived on the estate, bought the horses, injected and bled them, and was in charge of two stablemen and ten horses. Of the five women members of staff, one was the Director’s secretary; the others were engaged in filling antitoxic sera into small bottles and affixing labels that not only described the contents but also included a warning that the serum should not be used if it had an ‘offensive odour’!

From the beginning of his long service with the Wellcome Physiological Research Laboratories Glenny showed a passion for order, method, organization and tidiness in work that made his Department far and away the most efficient I have ever had anything to do with. Not only did he arrange his own work and that of his assistants in an extraordinarily effective way, but he learnt constantly by experience, and as he had a phenomenal capacity for understanding a sheet of figures almost at sight, he was often able to rearrange practice to the general advantage. For example, when he started work at Brockwell Hall, horses were given weekly injections of diphtheria toxin and bled small amounts ‘occasionally’ to determine antitoxic titres. Glenny carried out an analysis of past records that showed that the full bleedings were often taken weeks or even months after the highest titres had been reached, so that the titres at full bleeding were far lower than they need have been, and time had been wasted in obtaining usable antitoxic serum. So as to simplify future analysis he devised the 7 × 10 in. ‘horse card’, on which all relevant information about the horse was entered, to replace the double foolscap size temperature charts on which hardly anything but the horse’s temperature was recorded. These horse cards were in the earlier period carried in a small rack round the stables, so that the responsible person could easily decide what injections should be made and what bleedings taken. Later, as the number of horses increased, each stable had its own duplicate set of horse cards. Glenny’s earliest record books show this search for easy, clear and useful recording, and so effective was it that he was able to get related departments to accept it, and himself to extend it as the work of his own and other departments increased, until during the 1939-1945 war he was with little difficulty controlling about 1500 horses. Even with the vast amount of work on antitoxin and prophylactic production then going on, it was easily possible, as I have good reason to know, to discover all the
essential details about a bleeding from a horse, however remote in time, and everything about the toxins or toxoids used to immunize it, within 90 seconds or so. With recording for its own sake, however, he had little patience, and he once told me that if we tried to devise a recording system that would reduce the 90 seconds further, we should be bothering more about recording than about the facts we were setting down.

For statistics he had no respect at all, as he held that results were obvious and useful, or doubtful and valueless; but this was mainly because he often calculated probabilities in his head, and saw little point in wasting time on indifferent data when better could be obtained. Certainly his experimental work was well designed, and he used what amounted to statistical methods whenever it suited him. When I knew him, he did no experimental work with his own hands, preferring to have it done for him, and to have it repeated until he got the level of accuracy he wanted.

When I joined Langley Court in 1934, eleven years after the removal from Brockwell Hall, Glenny's arrangements for the removal of all documents from one place to another were still almost legendary; everything—and there was a vast amount of material—was easily found, and nothing was lost.

In the autumn of 1900 Glenny started studying for a degree at Chelsea Polytechnic, where he went three evenings a week to study mathematics and physics. He obtained a Pass degree in science at London University, and then continued with evening classes in botany and zoology at Chelsea Polytechnic, where he helped to start a tennis club of which he was captain for several years.

In 1910 he married Emma Blanche Lilian Gibbs, who survives him. There were three children—John, the eldest, who never married; Peter, who was killed in 1940 in a road accident; and Barbara, the youngest, who is married and has two sons.

In 1906 Dowson resigned from the Directorship of the Wellcome Physiological Research Laboratories and Sir Henry Dale (as he now is) was appointed in his place. Sir Henry tells me that

'With Glenny, on the other hand, my contacts at this period had been few, until I found myself thus suddenly faced with a new kind of responsibility; but from such as we made, I had formed a general respect for his quiet competence... He was responsible for everything that was necessary, and possible, under the conditions till then provided, for the discipline and supervision of the young women engaged in the important job of distributing the supposedly sterile sera, etc. into ampoules, then to be sealed and labelled correctly, with the nature and unit-strength of the contents. This job, under Dowson as Director, occupied much of the room-space in the Brockwell Hall house, which might otherwise have been, and was, under me, eventually to become suitable for researches such as my own. I had, therefore, had plenty of opportunity of seeing, from outside, the way in which these rooms were being used by Glenny, and of admiring the ingenuity with which he was making the best that he could of what he knew to be not really suitable conditions... It was
very largely due to Glenny's wholly loyal support and assistance that I
was able to make the necessary changes; I had splendid cooperation
from him, and we enjoyed working together."

About this time Glenny was made Head of the Immunology Department,
and must, under O'Brien, who had in 1914 succeeded Dale as Director, have
been responsible during the First World War for arranging for the enor­
mously increased demands for antitoxic sera to be met. To judge from the
tales he himself told, he cannot then have been an easy man to get on with;
he did not suffer fools gladly, particularly those with no arithmetical
capacity, and his rather limited sense of humour seems to have been of a
malicious kind, though the tales may have altered with time. In 1923 the
lease of Brockwell Hall ran out, and the Laboratories were moved to Park
Langley, Beckenham, Kent, where they still are. When I joined the
Laboratories in 1934, Glenny and his staff, now much increased, were
working in a set of laboratories made from what looked like a converted
garage, with the packing and filling in another ancient building, which most
of us thought of as a fire-trap; it was not until about 1936 that he was
accommodated in up-to-date buildings. He was already something of a
legend: remarkable, remote, not very much liked. Moreover, he did his best
to encourage the legend. Though he was only 52, he was always referring to
his advanced age; he always occupied the same rather ornate armchair at
the head of the dining table—he even took the chair with him when he
retired (woe betide any newcomer who took it in error!) and there he made
himself the centre of conversation. I had little to do with him until I started
work on influenza in about 1935, when, knowing his reputation for difficulty,
I was very surprised to find how easy it was to make arrangements with him
for immunizing horses, and how smoothly everything went once the arrange­
ments had been made. But I did not learn much about him until Dr G. H.
Warrack and I started some research on Clostridium welchii toxins, a subject
on which he had done some remarkable work; then it became obvious to me
how willing he was to help much younger people, and to put the very
considerable resources of his department at their disposal, if they were only
prepared to accept the most pungent criticism of what they did. It would
never have been possible to do what my colleagues and I did at Langley
Court without his interest, his constant criticism and his interest in our
education, and we owe him an enormous debt of gratitude.

It is necessary to say this, because it was very much easier, for younger
people at any rate, to respect Glenny than to like him. His extreme shyness
made it very difficult for him to establish friendly relations with anyone he
did not know well, and often led him to make remarks of a rather extreme
character, which were much resented—as when he once said that to praise
anyone for doing a good job was really the worst of insults; it was the least
that could be expected of him. He certainly never praised anyone himself,
and therefore perhaps earned less devotion from his staff than his own
unquestioned passion for good work might have stimulated. He seldom unbent,
and his criticism was often harsh; besides this he had little understanding of the difficulties most people have in dealing with lists of figures, and he would often try out half-formed ideas on people who had considerable difficulty in filling them in. Moreover, he was not a very happy man, even perhaps a disappointed one, who felt that his work had not received the attention it should have had, partly because he was not a medical man, and partly because he was working in a commercial institution. Possibly there was something in these views, but it seems to me that his work was far more generally recognized than he had supposed, and that the difficulty people had with it was due to the density and sometimes the obscurity of his papers. He had little interest in writing them—his mind was usually full of new ideas—and indeed he seldom knew exactly what he had published, and I have known very uncomfortable discussions between him and outside workers on his work, which were resolved only by the discovery that the work in question had never been printed. His election to the Royal Society in 1944 when he was admitted by his former Director, Sir Henry Dale, came therefore as a great delight to him; afterwards he mellowed a little, and the award of the Addingham Gold Medal and the Jenner Medal in 1953 added further enjoyable laurels.

In 1939, with the outbreak of the Second World War, he found himself involved in the provision, for authorities who grossly underestimated their requirements, of vast amounts of tetanus and gas-gangrene antitoxins. It had always been the proud boast of the Department that, whatever the failures of our suppliers, every customer got his material on or before the promised date; this was kept up throughout the war, whatever the amount of work thrust on him. Moreover, research was always going on, though during the second half of the war the neighbouring area was heavily bombed, and difficulties of every kind were constantly cropping up. Glenny seemed to have provided for everything; he even kept a summary collection of horse cards at home, in case his Records Office should suffer a direct hit.

He retired from Langley Court in 1947 at the age of 65, after about 48 years' service, during which time he had done a great deal to establish it as an immunological research centre. For the next thirteen years he occupied a room in one of the buildings at Langley Court, where he was to write up his unpublished work; he certainly did a great deal of this, but he was still full of ideas, and he found it far more enjoyable to start up new work than to write up the old. His last paper was published in 1955, when he was 73. A vast amount of work probably remains unpublished.

Already in 1946 his memory, which had been extraordinary, even for the details of the responses of many individual horses over many years, had begun to show signs of slight deterioration, but he continued working actively till 1959, though he suffered a good deal from osteoarthritis of his hip. By 1960, however, he found that his memory for recent events had almost completely gone, and it was clear that he was suffering from severe arteriosclerosis. He died on 5 October 1965.
As a young man he was remarkably handsome, and even in his old age he was a striking figure. He was often said to have no interest but his work, and certainly he fostered this opinion of himself, saying that he had no ear for music and little time for the arts. But it is difficult to believe that so restlessly inquiring a man, who never missed anything in his own line or his own department, could have been as limited as he pretended, and every now and then he would let drop a remark that revealed the extent of his knowledge of subjects other than his own.

His reputation is likely to depend more than anything on his work on prophylactics against diphtheria and tetanus and the methods of testing them, on the development of carrier prophylactics, and the discovery of the best ways of using them. His work on the most efficient ways of immunizing horses is now much less important than it was, as the value of prophylactic and therapeutic antitoxins diminishes, but it led to much still important work on methods of discrimination of toxins in bacterial filtrates, which he undertook, and indeed almost invented, to make testing of sera for antitoxins more meaningful. Perhaps his most exciting work, apart from these, was his pioneer investigation of the avidity of antitoxins. Most of all, perhaps, he should have the credit for his constant application of quantitative methods to practical immunological problems, something very remarkable when one considers the vagueness of many of the ideas current when he began his work.

Lastly he showed, as many others have, but not many then realized, that, given good staff, first-rate research work could be done in a commercial institution; and not only that, but that it paid the institution to get it done.

**Scientific work**

Though Glenny’s work is all interconnected, it covers such a wide range that it is convenient to divide it up into (a) miscellaneous; (b) antigens and active immunity; (c) passive immunization; (d) measurements of antigenic potency, antitoxin unitage, and avidity; (e) discrimination of toxins in bacterial filtrates.

**(a) Miscellaneous papers**

I have dealt with these first, as they are some of the first Glenny wrote, and show something of his quality. Südemersen & Glenny (1)* show that the mallein reaction, then generally regarded as specific for glanders infection, may readily be produced in some immunized horses without any evidence of glanders, and that a similar reaction may be provoked by injection of filtrates from a wide variety of bacterial cultures, and suggest methods by which true and false mallein reactions may be distinguished. Glenny & Walpole (4) deal with absorption of mercury salts by rubber, and emphasize its importance for antisepsis.

In 1914 and 1925 Glenny (8, 31) considered the formulae suggested for the relation between dosage of toxin and death-time, and showed how

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* The numbers in parentheses refer to the serially numbered entries in the Bibliography.
formulae with very different parameters will fit the observations, suggested conditions essential for the necessary experimental work, and commented on the way in which the conditions affect the answers one obtains. (See also Svädersen & Glenny (2), for seasonal variation in the lethality of diphtheria toxin for guinea-pigs.) He then guardedly suggests a reasonable formula. (Glenny was a confirmed anti-interpolator and anti-extrapolator, and was constantly filled with gloom by the ease with which, as he felt, some investigators treated results obtained in this way as having the same value as observations.)

Glenny had always hoped and perhaps believed that with constantly improved purification and concentration of diphtheria and other toxins (and later toxoids) much higher concentrations of antitoxin might be produced in horses immunized with them. Glenny & Walpole (3) deals with toxin concentration and purification by ultrafiltration and pressure dialysis.

Glenny & Allen (12) describes an outbreak of infectious disease in guinea-pigs fed on a deficient diet; after this, though he did no experimental work on it, Glenny was always interested in dietetic problems in infection and fought a running battle with his suppliers to get sufficient green-food for his guinea-pigs.

(b) Antigens and active immunization

Primary and secondary responses in immunized animals

Most of Glenny's early work was done with diphtheria toxin-antitoxin mixtures injected into guinea-pigs, mostly waste guinea-pigs from potency tests. He used them for investigation of the time needed to establish immunity, and showed (Svädersen & Glenny (5, 6)) that diphtheria toxin-antitoxin mixtures were more effective antigens than sublethal doses of toxin, and that guinea-pigs immunized with them might remain immune for two years, even though they transferred large amounts of antitoxin to their offspring. The passive immunity so conferred on the offspring had usually disappeared by two months after birth, almost invariably by three months.

Glenny & Svädersen (9) repeated and confirmed much of this work under better controlled conditions, and extended it by showing the shape of the response curves in guinea-pigs given one dose of diphtheria toxin-antitoxin mixture (the slow primary response) and that in guinea-pigs given a second dose of the same antigen (the much more rapid and efficient secondary response). Moreover, they showed that these responses occurred in rabbits, goats, sheep, man and horses as well as in guinea-pigs, and that the shape of the secondary response is modified by altering the time-interval between the primary and secondary stimuli. These observations form the basis of all subsequent schemes of immunization, both of man and horse, and later work has shown that they apply to almost all responses to antigentic stimuli.
Toxoid as an immunizing agent

Glenny & Südmersen (9) also contains the first reference to toxoid as an immunizing agent; the references (pp. 184 and 196) are not easy to find, and the very limited account of the uses of toxoid no doubt accounts for the unfortunate controversy between Glenny and Ramon on priority of discovery of toxoid (or 'anatoxine' as Ramon called it). There is, however, plenty of unpublished evidence that Glenny had known and used toxoid some years before this publication. The discovery was accidental; diphtheria toxin production had become much more efficient, and large stocks were being built up. The large earthenware containers that were all that were available at that time could not be autoclaved, so they were washed out with formalin before the phenolized toxin was added to them. It is perhaps surprising that any antigenic material survived at all; but Glenny soon found that the material in the jars became non-toxic but still retained its antigenicity. He seems to have used it for horses very soon after his discovery; its use in man is first referred to in Glenny & Hopkins (23).

Toxoid-antitoxin floccules as an immunizing agent

Toxin was known to be a poor immunizing agent when it was injected intravenously. Glenny & Pope (34) showed that intravenous toxin would act as a secondary stimulus, and that both toxin-antitoxin and toxoid-antitoxin mixtures given intravenously were effective primary stimuli. Consequently, when Ramon first described the diphtheria toxin-antitoxin flocculation reaction in 1922, Glenny, Pope & Waddington (42) soon took up an investigation of toxoid-antitoxin floccules as immunizing agents, and showed that they were non-toxic, as good immunizing agents as toxin-antitoxin floccules, and could be heated to 80 °C without loss of antigenicity.

The antitoxin used for floccule production was horse antitoxin; Glenny, Hopkins & Waddington (36) showed that rabbits sensitized to horse serum produced little antitoxin as compared with controls when they were given injections of toxoid-antitoxin floccules, and suggested that this failure to produce antitoxin was due to crowding-out of the response by vigorous precipitin formation—something that he returned to later on in work on combined prophylactics, where it was shown (90) that the presence in a prophylactic of an antigen to which the subject already had some immunity would greatly depress his response to antigens of which he had no previous experience.

Alum-toxoids as immunizing agents

As part of his work on purifying and concentrating diphtheria toxoid, Glenny had enlisted Pope as a chemist, and during attempts at purification with metallic salts (39, 40) for which Pope was responsible, they discovered the greatly enhanced immunizing power of alum-precipitated toxoid. Later papers (54, 55, 64, 72) extend the use of alum-toxoids to tetanus...
prophylaxis, and give further details of its action and the means of preparing it. Glenny (49, 52) seems to have decided early in the work that it is the slow absorption of toxoid from the precipitate that makes it such an excellent antigen; this has never been proved.

**Immunizing methods**

Glenny’s early views are summed up in (37), and his later ideas in (76, 88). As early as 1925 Glenny (7) had suggested that natural immunity to diphtheria was due to repeated exposure to amounts of toxin too small to produce disease, and had suggested that effective immunization of man and animals might depend on methods resembling those accidents by which natural immunity is acquired. This led him to devise the ‘method of rest’ by which he was able to immunize horses to toxins against which they had no natural antitoxin so as to obtain sera of high antitoxin value and good avidity, and to realize the importance of the choice of horses with natural antitoxin for the rapid production of high value antitoxins (38). A by-product of this work is the paper (30) on natural diphtheria antitoxin in horses, based on some 1350 animals, where he shows that the percentage of horses with detectable antitoxin has fallen over the previous ten years, no doubt because of their more limited association with man; and that the antitoxin titre in many horses fluctuates for no very obvious reason.

**Combined active and passive immunization**

The two papers on this subject (73, 80) show that administration of antitoxin at the same time delays and to some degree inhibits the antitoxic response to diphtheria alum-precipitated toxoid, but that the final result does not seem very different from that of APT alone; the method can be used to abort outbreaks of diphtheria in schools or homes. Increase in the amount of prophylactic used makes little difference.

**Immunization of babies**

Glenny was always interested in early immunization of children, and in attempting to do this earlier and earlier came up against a natural form of combined active and passive immunization, since the new-born children of mothers that possessed diphtheria antitoxin had been passively immunized by transfer of antitoxin during foetal life, and this interfered with the active response to diphtheria alum-precipitated toxoid.

In a series of papers (81, 84, 85, 86) it was shown that satisfactory immunization of such babies to diphtheria was possible in the majority of cases at 6 weeks of age; and in 1952 Barr, Glenny, Hignett, Randall & Thomson (91) showed that very young lambs could readily be immunized against diphtheria, thus supporting the view that the difficulty in immunizing babies was due rather to passively acquired maternal antitoxin than to age-determined incapacity to respond. Barr, Glenny & Howie (92) reported that antitoxin
passively acquired from colostrum delayed antitoxin production in lambs, but that the apparently ineffective toxoid still acted as a primary stimulant. Barr, Glenny & Butler (97) reported good responses to combined diphtheria-tetanus-pertussis antigens in babies given their first injection when 3 to 4 months old. Again as a by-product it was shown (84) that new-born babies have a higher concentration of serum antitoxin than their mothers have; how babies concentrate antitoxin against a gradient is not yet known.

**Maintenance of immunity**

Barr & Glenny (78, 82) suggested, after long experience with horses and guinea-pigs, that it might be possible to provide life-long immunity in man by immunization in childhood, and pointed out that guinea-pigs might still possess circulating antibody ten months after a secondary stimulus, particularly if this secondary stimulus was toxoid rather than *APT*, and, more interestingly, that hyperimmunized horses might show steady levels of circulating antitoxin years after injections of antigen had been stopped. The longer the course of immunization the higher the steady level was, and the sooner after cessation of antigen injections it was reached.

**Non-specific effects on immunization**

Howie, Barr & Glenny (93) showed that supplementation of diet in Blackface ewes increased the antitoxin response to diphtheria alum-precipitated toxoid if the interval between toxoid injections was four weeks, but had no effect if the interval was nine weeks.

*Clostridium welchii* type-D toxoid

Batty & Glenny (79) making use of the fact that *Cl. welchii* type D produces a non-toxic protoxin that is readily converted into ε-toxin by *Cl. welchii* type-D proteases or by trypsin, toxoided trypsinized *Cl. welchii* type-D filtrates with formalin and showed that they were far better antigens than toxoids made from untrypsinized material.

**General**

In these papers Glenny laid the foundations of all modern immunizing practice, especially as regards those diseases in which soluble toxins are important. It is clear that most of the important matters had already been settled by 1926 or so, and it seems to me that only the unsatisfactory character of the papers has deprived Glenny of some little of the credit for the broad comprehension of immunizing principles they show.

(c) Passive immunization

In four papers (19, 24, 25, 26) Glenny & Hopkins first described the phases of loss of passively acquired homologous and heterologous antitoxin
—phase A, of equilibration of antitoxin between circulation and tissue fluid, and phase B of logarithmic antitoxin loss, both occurring with both homologous and heterologous antitoxin, and phase C, of rapid loss due to precipitin production, observed only with heterologous antitoxin. Besides these, there was, especially when precipitin was poorly developed, a continuation of phase B after phase C. As usual, the experiments are widely developed: older rabbits produce precipitin more readily than young ones; rabbits sensitized with horse serum (even with as little as 0.00001 ml.) destroy horse antitoxin faster than control rabbits do; sensitized rabbits destroy consecutive injections of horse antitoxin at an increasing rate; repetition of injections of horse antitoxin even in unsensitized animals leads to faster elimination of the material injected later; sheep and goats eliminate horse serum slowly, and show hardly any phase C.

Later, after Pope had produced pepsin-refined antitoxin, Glenny & Llewellyn-Jones (70) showed that this antitoxin was absorbed more readily into the circulation after subcutaneous injection and eliminated more slowly from it, than crude antitoxin.

\(d\) Measurements of antigenic efficiency, antitoxic unitage and avidity

Glenny was constantly interested in measurement, and in making it more reliable. Glenny, Allen & O’Brien (10) and O’Brien et al. (15) early reported the use of the Schick test for determining immunity to diphtheria; it is apparently the first record of its use on any scale in England, and there is at the end of paper (10) a note on the apathy of English physicians in this respect. The paper (10) also refers to the fact that a second Schick test might be negative in a person previously positive—an observation that later led to the work on the Schick test as a secondary stimulus (18).

Titration of Schick toxin

Glenny, Allen & O’Brien (10) were already titrating their Schick toxin against diphtheria antitoxin as well as by MRD determination, and later Glenny & Allen (21) always insisted that both combining power and MRD were important. Glenny & Allen’s (18) work on the Schick dose as a secondary stimulus led to work on its use as a test of the antigenicity of prophylactics (the immunity index (46) and to a redetermination of the antitoxin level corresponding to the change from Schick-positive to Schick-negative, which he found to be much lower (0.001 to 0.004 units per ml. serum) than had previously been supposed (47). The stability of Schick toxin was also investigated (43, 68); in work in the main based on Pope’s ideas: it was shown that phenol was highly destructive, no doubt because it was concentrated in the surface layer and destroyed toxin on shaking, and that peptone was a good stabilizer, but caused severe reactions; more unfortunately, perhaps, human serum was recommended as an alternative.
Antigenicity of toxins and toxoids

Reference has already been made to the immunity index method of determining antigenicity; Glenny soon turned to others. By 1925 Glenny, Pope & Waddington (34) were suggesting that the antigenicity of diphtheria toxins was dependent on their combining power rather than their MRD, which might depend on the amount of toxoiding, and that the antigenicity of toxoids could be determined from the results of flocculation tests (see below). For most of his work on prophylactics he preferred to give guinea-pigs two doses of prophylactic at a month's interval and test their serum antitoxin levels 10 days after the second dose. This was greatly helped by his development of Römer & Sames's intracutaneous test for diphtheria toxin and antitoxin, which he modified so that he could detect as little as 0.0005 units of diphtheria antitoxin per ml. of serum (13, 56, 57).

Flocculation tests

Very soon after Ramon published his flocculation test for diphtheria toxin and antitoxin, Glenny & Okell (27) had reduced it to a routine procedure, and defined the $L_f$ to add to the $L_o$, $L_+$ and $L_r$ as characteristics of a toxin or toxoid; and Glenny & Wallace (33) developed it further. Multiple zones of flocculation were observed by Glenny, Pope, Waddington & Wallace (38).

Avidity

It soon became evident that the unit values of sera in animal and flocculation tests, though they were usually the same, did not always agree. This, among other observations, led to the idea of avidity—i.e. the degree of firmness of binding of antitoxin to toxin. Antitoxins that combined strongly with their antigens and were not dissociated from them by dilution would give *in vivo* values equal to their flocculation values, whereas antitoxins that were of low avidity, and readily dissociated from their antigens would give *in vivo* values that fell with reduction in the level of test and would give values at all levels less than their *in vitro* values (34). Glenny, Pope, Waddington & Wallace (38) note the fact that the *in vivo*/*in vitro* value of a serum is not always 1; Barr & Glenny (59, 60) show that fractions may be obtained from sera, by ammonium sulphate precipitation, with very different *in vivo*/*in vitro* ratios. Later the 'dilution ratio' was employed by Glenny & Barr (62) as a measure of avidity, and shown to be fairly well correlated with the *in vivo*/*in vitro* ratio. Glenny & Barr (63) and Glenny, Barr, Ross & Stevens (65) showed with extraordinary ingenuity how non-avidity could be demonstrated. Rabbits could be killed with small volumes of toxin plus non-avid antitoxin, but not with larger volumes, because they were diluted less; mixtures non-toxic to mice might be toxic to guinea-pigs or rabbits, in which they were diluted more; mixtures of diphtheria toxin and non-avid antitoxin might produce a 'ring' toxin reaction when injected intradermally into guinea-pigs, and if the mixture was made from a serum only slightly
non-avid, the toxin reactions might appear faintly at the ‘edges’ of the guinea-pig. Obviously non-avid sera had no unit values determinable in the usual way against an antitoxin standard; the answer one obtained in such tests depended on the relative avidity of standard and test serum, and varied with the level of test. Only avid sera could be usefully compared for unit value.

(e) Discrimination of toxins in bacterial filtrates

If a serum is to be compared with a standard for antitoxin unitage, not only must both sera be sufficiently and equally avid, but the end-point used in the test must be for the same toxic component of the filtrate. When only one effective toxin is present, no difficulty arises, but where, as in Clostridium welchii filtrates, several different substances may be effective in a test, comparison between standard and test serum may be extremely misleading. Glenny had always been interested in tests of sera against numerous indicators; as early as 1922 Glenny & Allen (16) had shown that diphtheria antitoxic sera gave the same unitage values in lethal tests in mice and guinea-pigs, although the mouse was much less sensitive to diphtheria toxin than the guinea-pig. In 1931 Glenny, Llewellyn-Jones & Mason (58) applied the intracutaneous method of testing to the titration of sera against Cl. welchii type-A filtrates, Cl. welchii type-B filtrates, and Cl. oedematiens, Cl. septicum and Cl. histolyticum filtrates (Glenny & Allen (13) had already referred casually to this) and had compared the answers, where appropriate, with those obtained in lethal or haemolytic tests (44). Generally the values obtained in the different tests agreed, but Glenny soon realized that discrepancies in value were an indication that more than one toxin might be effective in the tests. The systematization of these ideas produced what is still the central paper on multiple toxin systems (66) in which evidence is provided that the various types of Clostridium welchii produce at least five different lethal substances (α, β, γ, δ, and ε; see also (77)) and lists many of their properties. The paper is a mine of information on the production of sera with different ratios between the units of various antitoxins, and on methods of analysis. The same methods were subsequently applied to filtrates of Staphylococcus aureus with the discrimination of α- and β-haemolysins (67).

As will readily be seen from the bibliography, Glenny seldom worked alone; indeed while I knew him he did little of the work himself, though he liked reading reactions in guinea-pig and rabbit skins, and was very good indeed at deciding whether they were specific or not; but the ideas were in the main his, though he unhesitatingly took up those of others, used them and improved on them. Many of his methods of testing were those subsequently recommended for use in the regulations under the Therapeutic Substances Act. The mass of material he published, much of it revolutionary in its day, is a remarkable production by a man constantly engaged in
commercial production and testing of antisera and prophylactics; and I have little doubt that as much, though perhaps less important, work remains unpublished.

A good deal of the information about Glenny’s early life is derived from an incomplete account he sent me in 1960; I am very grateful to Sir Henry Dale, F.R.S., and Dr C. G. Pope for other information, and to Miss Mollie Barr for a nearly complete set of Glenny’s papers.

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C. L. Oakley

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