

## ILLUSTRATIONS FROM THE WELLCOME INSTITUTE LIBRARY

### SIR HENRY DALE'S LABORATORY NOTEBOOKS, 1914–1919

by

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The laboratory notebooks of scientists are among the sources available to historians trying to reconstruct and understand the past. The usefulness of such material varies immensely, providing at the very least a bare outline of experimental procedures and results. At a different level notebooks have been used to illuminate the cognitive processes of the scientists themselves, an approach that has had some success, for example, in studies of the oil-drop experiments of the physicist Robert Millikan.<sup>1</sup> The presence of laboratory notebooks amongst archival collections is patchy, for several reasons. Many scientists discard records when the main results have been published, as a routine matter of good housekeeping; others later deliberately destroy what are, after all, very intimate accounts of their working lives; or merely jettison such material in ignorance of its interest to later historians. In more recent times, as written records have been superseded by graphic and photographic data, which in turn have been replaced by machine-readable material, the sparse survival of the conventional notebook is simply an accurate reflection of its declining use. Among the laboratory records deposited in the Contemporary Medical Archives Centre (CMAC) of the Wellcome Institute is a small but unique collection of notebooks that belonged to Sir Henry Dale, dating from the First World War.<sup>2</sup>

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I am most grateful to Mrs Helen Brown for permission to publish details of these notebooks, and to the Archivist of the CMAC, Miss J. G. A. Sheppard and her assistant Dr Lesley Hall, for their help. The Medical Research Council generously provided research facilities at the NIMR and I thank the Director and in particular the Librarian, Mr R. J. Moore for his assistance. This work was supported by the Wellcome Trust.

<sup>1</sup> See, e.g., G. Holton, 'Subelectrons, presuppositions, and the Millikan—Ehrenhaft dispute', *Hist. stud. phys. sci.*, 1978, 9: 166–224; A. D. Franklin, 'Millikan's published and unpublished data on oil drops', *ibid.*, 1981, 11: 185–201. A most helpful discussion of the advantages and limitations of laboratory notebooks for the historian is F. L. Holmes, 'The fine structure of scientific creativity', *Hist. Sci.*, 1981, 19: 60–70.

<sup>2</sup> For details of other scientific collections see [Julia Sheppard and Lesley Hall] *Contemporary Medical Archives Centre: consolidated accessions list*, 2nd ed., 1985, Wellcome Institute for the History of Medicine, London.

Henry Hallett Dale, FRS (1875–1968) was one of the most noted practitioners of medical research in modern Britain, sharing the Nobel Prize in Physiology or Medicine in 1936 and achieving most honours and distinctions available to a scientific man, including knighthood (1932), the Order of Merit (1944) and Presidency of the Royal Society (1940–45).<sup>3</sup> His independent research career began in 1904 when, after scientific and medical training in Cambridge and London, he joined the Wellcome Physiological Research Laboratories (WPRL) in south London. He remained in these laboratories, of which he became Director in 1906, for ten years until he joined the scientific staff of the newly created Medical Research Committee (later Council, MRC).<sup>4</sup> The Committee's first Secretary, the Cambridge physiologist Walter Morley Fletcher, was appointed in early 1914, following which Dale accepted, from July of that year, the Headship of the Department of Biochemistry and Pharmacology, one of four envisaged for a projected National Institute of Medical Research (NIMR). The outbreak of the First World War completely disrupted these plans and the idea of a central institute was temporarily abandoned, the intended building, Mount Vernon Hospital, Hampstead, being handed over to the War Office for use as a military hospital. The early research departments were given makeshift accommodation in London: Dale's was housed in the Lister Institute of Preventive Medicine on the Chelsea Embankment, and equipped as best as possible under difficult supply conditions.<sup>5</sup> The outbreak of war clearly altered the research priorities of the MRC and Dale and his small staff of George Barger and Arthur Ewins (both recruited also from the WPRL) prepared to work on a wide variety of problems.<sup>6</sup>

Sir Henry Dale is best remembered for his work on the elucidation of the mechanism of chemical neurotransmission, for which he received the Nobel Prize. However, his writings, both published and unpublished, and these notebooks in particular, demonstrate that his research embraced a diversity of subjects although one can discern a common theme, an interest in the role of endogenous chemicals in the control of physiological and pathological function.<sup>7</sup> The books contain notes, observations, and calculations relating to several experimental protocols, the majority being either on anaphylaxis or on chemotherapeutic approaches to protozoan infections. Some of this work was a natural extension of that begun by Dale at the WPRL; some was new, dictated by wartime contingencies and concerns. Much was done in collaboration with colleagues, although Dale's is the predominant handwriting in all the books. The following descriptions of the notebooks will concentrate on the major series of experiments.

<sup>3</sup> W. S. Feldberg 'Henry Hallett Dale, 1875–1968', *Biog. mems. FRS Lond.*, 1970, 16: 77–174.

<sup>4</sup> The Medical Research Committee was reconstituted as the Medical Research Council in 1920; the abbreviation MRC will be used for both.

<sup>5</sup> The Lister Institute Archives are also in the CMAC, although there are no details there of Dale's department; Lesley Hall and Neil Morgan, 'The Archive of the Lister Institute of Preventive Medicine', *Med. Hist.*, 1986, 30: 212–15. The Dale papers at the Royal Society also contain Lister Institute files but these are from the period when Dale was a Governor of the Institute.

<sup>6</sup> 'The research schemes of the Medical Research Committee: the influence of War', *Lancet*, 1914, ii: 1315–16; see also A. L. Thomson, *Half-a-century of medical research*, 2 vols., London, HMSO, 1973–5, especially 'The First World War (1914–1918)', vol. 2, pp. 273–91.

<sup>7</sup> See Feldberg, *op. cit.*, note 3 above, pp. 163–74.

## Sir Henry Dale's notebooks

### THE NOTEBOOKS

Although the bulk of Sir Henry Dale's papers are deposited in the Library of the Royal Society, 24 items, including biographical material and copies of some lectures, are in the CMAC. The collection also includes six hardback laboratory notebooks, the only such material known to be extant. None of the books is paginated and entries have frequently been made, for different experiments, from both the front and the back of the book. On the inside of each is a handwritten note to the effect that it is an experimental notebook of Sir Henry Dale from Hampstead. On closer examination this is clearly incorrect as they date back to the earlier, Lister Institute, period. The provenance of the notebooks is unknown; they were transferred to the CMAC from the Western Manuscripts Collection of the Wellcome Institute in 1980, and they bear accession numbers for both. In this paper those of the CMAC (PP/HHD/2-PP/HHD/7) will be used.

*PP/HHD/2*: The principal experiments recorded in this book are on liver nitrogen in anaphylactic shock. The few remaining entries are of drug effects on the blood pressure of anaesthetised animals and, written in a different hand, some notes, dated to early 1915, on similar experiments with isoquinoline derivatives. The details are too sparse to permit an analysis, but throughout the war years the Department was involved in a systematic study of the absorption, distribution, and effects of potential therapeutic drugs. Much of this work was never published, and it seems likely that some of the "miscellaneous" experiments recorded in these notebooks are part of these more extensive investigations. The main records are of work on the liver nitrogen content of normal and anaphylactic guinea-pigs. These experiments, performed between 31 August and 13 October (1914), were undertaken in response to work by Hashimoto and Pick, which suggested that anaphylactic shock (the acute symptoms produced by the injection of an antigen into a previously sensitized animal) was associated with an increase in the uncoagulable component of the liver nitrogen, although total nitrogen content was unaffected.<sup>8</sup> Dale and his chemist colleague George Barger used two different rigorously tested techniques for measuring liver nitrogen, and showed quite clearly that the amounts of uncoagulable nitrogen were similar in the livers from control and anaphylactic guinea-pigs. In their subsequent publication they commented, "whatever its origin, the condition described by them [Hashimoto and Pick] had no relation to anaphylaxis", and bemoaned the fact that wartime restrictions on international communications prevented further discussion of the discrepancy.<sup>9</sup>

Work on shock, of which the anaphylaxis experiments were a part, was a major concern of the MRC, which instigated research in many departments and centres throughout the war.<sup>10</sup> Dale himself had started to investigate anaphylaxis whilst at the WPRL, showing in 1913 that the anaphylactic reaction of plain (smooth) muscle

<sup>8</sup> M. Hashimoto and E. P. Pick, 'Über intravitale und postmortale Leberautolyse bei sensibilisierten und anaphylaktischen Meerschweinchen', *Zentralbl. Physiol.*, 1913, 27: 847-8.

<sup>9</sup> George Barger and Henry Hallett Dale, 'Liver nitrogen in anaphylaxis', *Biochem. J.*, 1914, 7: 670-9. This was the first publication from the new Department.

<sup>10</sup> *Annual Report of the Medical Research Committee*, 1914-15, pp. 17-18. See also H. H. Dale, 'The biological significance of anaphylaxis', *Proc. Roy. Soc. Lond.*, 1920, 91B: 126-46.

was the result of the formation of cell-fixed antibodies.<sup>11</sup> Further pre-war work done with P. P. Laidlaw had suggested that an ergot derivative  $\beta$ -iminazoyl-ethylamine (histamine), found in many organs and released upon injury, might play a role in the production of part of the shock-syndrome because *in vivo* it caused peripheral vasodilation and consequent circulatory stagnation.<sup>12</sup> Dale continued work in both these areas during the war years. Further experiments on anaphylaxis were recorded in notebook PP/HHD/5; however, the extensive collaborative work undertaken in the later years of the War with the American A. N. Richards and with Laidlaw, on the role of histamine in wound-shock, is not recorded in these books.<sup>13</sup>

*PP/HHD/3*: This book, labelled 'Protozoan infections', contains records of experiments on rats and mice artificially infected with Trypanosomes and subsequently exposed to a variety of chemotherapeutics. Pathogenic protozoa such as Trypanosomes were responsible for a wide variety of human and animal tropical diseases, the most prevalent being sleeping sickness, and therefore were of considerable economic and military significance. The MRC initiated several studies, laboratory-, clinic-, and field-based, on such infections, and collaborated closely with other organizations in the prosecution of such research.<sup>14</sup> Dale worked in close collaboration with the protozoologist Clifford Dobell and used the resources of the Wellcome Bureau of Scientific Research, which the proprietor, Henry Wellcome, had put at the disposal of the War Office.<sup>15</sup>

Figure 1 is a reproduction of the first page of notebook PP/HHD/3. The experiments started on 15 December 1914, when two mice were infected with the blood of a horse that had died from Surra, a Trypanosome infection, obtained "from Herne Hill" (the south London premises of the Wellcome Physiological Research Laboratories). Blood samples were taken from these infected mice at regular intervals to assess the state of protozoan infection; the records for 18 December show that both mice were clear of Trypanosomes. The following day blood from one mouse showed numerous *Trypanosoma evansii* and the animal was dosed with cusparine, identified *in vitro* as a possible chemotherapeutic agent. These experiments were part of the Department's major commitment to drug research. The importance of finding specific

<sup>11</sup> *Idem*, 'The effect of varying tonicity on the anaphylactic and other reactions of plain muscle', *J. Pharmacol.*, 1913, 4: 517–37.

<sup>12</sup> H. H. Dale and P. P. Laidlaw, 'The physiological action of  $\beta$ -iminazolyethylamine', *J. Physiol.*, 1910, 41: 318–44; *ibidem*, 'Further observations on the action of  $\beta$ -iminazolyethylamine', *ibid.*, 1911, 43: 182–95.

<sup>13</sup> E.g., H. H. Dale and A. N. Richards, 'The vasodilator action of histamine and of some other substances', *ibid.*, 1918, 52: 110–65; H. H. Dale and P. P. Laidlaw, 'Histamine shock', *ibid.*, 1918, 52: 355–90; H. H. Dale, 'The activity of the capillary blood vessels, and its relation to certain forms of toxæmia', *Br. med. J.*, 1923, i: 959–62, 1006–10. See also, several authors, including H. H. Dale, 'General discussion on shock', *Proc. R. Soc. Med.*, 1919, 12: 11–34.

<sup>14</sup> H. B. Newham, 'Trypanosomiasis', in *History of the Great War based on official documents: Medical Services. Diseases of the War*, vol. 1, ed. W. G. MacPherson and others, London, HMSO, [1922], pp. 305–15.

<sup>15</sup> C. A. Hoare and D. L. MacKinnon, 'Clifford Dobell 1886–1949', *Obit. Not. FRS*, 1950, 7: 34–61, especially pp. 44–5. The *Annual Report of the Medical Research Committee*, 1915–16, p. 48, recorded the MRC's "great indebtedness" to Wellcome for the provision of these facilities, an acknowledgement repeated in later reports. The Royal Society was also associated with this work.

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Dec. 15<sup>th</sup> 1914.  
Two mice (brown & white strain) infected from  
blood of mouse just read of Serra, obtained  
from Bonehill.

Dec. 18<sup>th</sup> - Blood clear.

Dec. 19<sup>th</sup>. White strain mouse - blood shows very many  
Trypanosoma evansi. Bone clear.  
11.15 a.m. Dye at 10µg. Cuparine Hydro-  
chloride hypodermically (in 0.5 c.c. of salt)  
Mouse not examined later on the 19<sup>th</sup>, nor on  
the 20<sup>th</sup>.

Dec. 21<sup>st</sup>. <sup>White strain</sup> Mouse dead. Heart's blood shows no  
trypanosomes. No significance can be attached  
to the result.

Brown mouse - well & vigorous. Abundant trypanosomes  
in blood. 12.45 - 0.5 µgms. Cuparine hypodermically.  
6.45 p.m. - peripheral blood  
showing with large numbers  
trypanosomes.  
Dye at 2 µgms. Cuparine treated hypodermically.

Figure 1: The first page of PP/HHD/3, recording observations on mice infected with Trypanosomes. Photo: Wellcome Institute Library, London.

remedies was particularly acute as the most effective compounds then in use against them were manufactured by German companies and unavailable during the war years.<sup>16</sup>

Further observations in the book refer to experiments with other possible chemotherapies; there is a similar series of experiments on infections with *Bilharzia*;

<sup>16</sup> The arsenical compound Salvarsan (606) had been developed by Paul Ehrlich in Frankfurt-am-Main in 1909. It, and its derivatives, were produced by the Hoechst company, and the wartime interruption of

details of toxicity tests with a batch of Kharsivan, one of the British-made copies of Salvarsan; and a short series of experiments on local anaesthetics.<sup>17</sup>

*PP/HHD/4*: This notebook, labelled 'Deficiency diets' is a record of observations taken in February 1915 on several groups of rats. The notes are of the body weights of the rats, housed two to a cage and maintained on a variety of diets, and detail the amount of food consumed by each pair. There is no precise information about the composition of the various diets or of individual intakes, and the experiments do not appear to have been continued for very long or published. There is no mention of this work in the *Annual Reports* of the MRC and it therefore seems likely that it was rapidly abandoned. Nutrition had been a high priority for research in the original schemes of the MRC, and during the First World War it worked closely with the Royal Society's Food (War) Committee and supported several other experimental schemes on nutrition and deficiency diets.<sup>18</sup>

*PP/HHD/5*: The front part of this book contains accounts of experiments on anaphylaxis, undertaken from March to November 1915. At the back of the book are brief details of a miscellany of *in vivo* experiments and the beginnings of an extensive study of induced amoebiasis in cats.

The anaphylaxis examination was of three separate proteins isolated from horse serum: euglobulin, pseudoglobulin, and albumin: a continuation of work started by Dale and Percival Hartley at the WPRL. Sensitization of virgin female guinea-pigs to horse whole serum was followed at intervals ranging from 12 to 31 days, by the testing of the uterine smooth muscle for anaphylactic sensitivity to the test proteins.<sup>19</sup> This method, devised by Dale, consisted of exposing each uterine horn *in vitro* to a different pure protein, although some mistakes did occur: "two guinea-pigs were sensitised on Sept. 7th with 1 mgm. of Hartley's albumin. On Sept. 29th it was discovered that both were males" and these animals were therefore discarded.

The important new finding of Dale and Hartley was an enhanced sensitivity to albumin after previous treatment with whole serum. Initially, like previous workers, they had been unable to detect any sensitivity to albumin and so definite and reproducible had this negative result been that experiments with albumin were abandoned. As part of a separate project, a small series of albumin tests were undertaken, and maximal responses were obtained 31 days after the initial serum sensitization. This change in response was attributed by the authors to the increased

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supplies necessitated urgent production and testing by British manufacturers. The MRC and Dale in particular were closely associated with these efforts. See Feldberg, *op. cit.*, note 3 above, pp. 106–7. See also H. H. Dale, 'Chemotherapy', *Physiol. Revs.*, 1923, 3: 359–93, especially 'Chemotherapy of trypanosome infections', pp. 369–81.

<sup>17</sup> G. Barger, H. H. Dale and Florence M. Durham, "'Collosol' cocaine", *Lancet*, 1917, ii: 825.

<sup>18</sup> The papers of Sir Edward Mellanby deposited in the CMAC (PP/MEL) contain correspondence, experimental notebooks, and records of his nutritional research, including work done on behalf of the Medical Research Committee during the First World War. Some of this material is duplicated in the Dale papers in the Royal Society (93HD 'E Mellanby' 40.15).

<sup>19</sup> H. H. Dale, 'The anaphylactic reaction of plain muscle in the guinea-pig', *J. Physiol.*, 1912, 45: xxvii–xxix.

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length of time between the sensitizing injection and testing (from 2 to 3 weeks in the early, negative experiments, to 4 to 5 weeks in the positive experiments).<sup>20</sup>

Other, complementary experiments in this book were done in conjunction with G. S. Walpole (who had also started his career at the WPRL), and were based on the discovery that fresh guinea-pig serum, when shaken with chloroform, acquires a notable toxic action by causing pronounced blood clotting.<sup>21</sup> This was of interest because intravascular clotting is a component of the anaphylactic shock syndrome, although gradually the study developed into a closer examination of the biochemistry of thrombin formation.<sup>22</sup>

The records in the rest of the book are from an experimental study of amoebic dysentery in cats. These are continued in notebook PP/HHD/6 and will be described below.

*PP/HHD/6*: Amoebic dysentery, known to be caused by *Entamoebae histolytica*, was a major military medical problem and many wartime research resources were devoted to studying its transmission and examining chemotherapeutic approaches to its prevention, treatment, and cure.<sup>23</sup> The work undertaken by Dale and his colleague Clifford Dobell, and recorded in these notebooks, was an attempt to develop a reliable animal model of amoebic dysentery for the further study of the disease.<sup>24</sup>

This book continues until the end of November 1916 the sequence of records on the experimentally infected kittens started in April and recorded in the previous notebook. The experiments were broadly similar to those performed on Trypanosomes, as recorded in *PP/HHD/3*, although there were several difficulties in transmitting the disease. After many attempts to infect kittens with cysts of *Entamoeba histolytica*, a successful inoculation was achieved with infective faeces obtained from a patient in Guy's Hospital, which enabled a detailed study of anti-amoebic agents to be planned. The laboratory books contain daily reports on an eventual series of more than 150 animals—clinical observations on infected and inoculated animals; laboratory assessments of amoebae in faecal samples; the passage, by several routes, of infected samples from human patients and experimental animals to fresh kittens; the dose, course, and effect of drug regimens prescribed for infected animals; and post-mortem reports on casualties.

Figure 2 is reproduced from this book and shows observations made on seven cats (numbers 63, 65–70) on Sunday, 16 July. A more detailed history of these experimental animals illustrates the general pattern of the work:

<sup>20</sup> Henry Hallett Dale and Percival Hartley, 'Anaphylaxis to the separated proteins of horse-serum', *Biochem. J.*, 1916, **10**: 408–33.

<sup>21</sup> E.g., S. W. Jobling and W. Petersen, 'Soaps as ferment-inhibiting agents; studies on ferment action' *J. exp. Med.*, 1914, **19**: 239–50, and several other papers by these authors in the same volume.

<sup>22</sup> Henry Hallett Dale and George Stanley Walpole, 'Some experiments on factors concerned in the formation of thrombin', *Biochem. J.*, 1916, **10**: 331–62.

<sup>23</sup> The especial importance of the disease is emphasized in C. Dobell and D. Harvey, 'Amoebic dysentery' in *History of the Great War based on official documents: Medical Services Pathology*, ed. W. G. MacPherson, W. B. Leishman and S. L. Cummins, London HMSO, 1923, pp. 277–318.

<sup>24</sup> Clifford Dobell and F. W. O'Connor, *The intestinal protozoa of man*, London, For the Medical Research Council, 1921, provides a succinct account of attempts to provide animal models of amoebiasis, especially on pp. 55–7.

Sunday July 16<sup>th</sup>.

63 }  
65 } Nil. 65 has severe diarrhoea.  
69 - Diarrhoea. No amoebae.  
70 - has passed mucus with white flakes;  
no amoebae found.  
68 - Mucus with dead amoebae.  
66 - Blood-flecked mucus, with dead  
amoebae.  
67 - Very abundant blood & mucus. Not  
examined. Animal vomiting, but  
not seemingly ill yet.

Monday July 17<sup>th</sup>

63 }  
65 } Nil.  
69 - Nil.  
68 - Passed blood & mucus. Some dead  
amoebae found.  
70 - Nil.  
66 - Blood, mucus, dead amoebae (B. belli diagnosis  
says they are not amoebae).

Figure 2: Page taken from PP/HHD/5. Details of observations made on 16 and 17 July 1916 on cats infected with amoebic cysts. Photo: Wellcome Institute Library, London.

Cats 63 and 65 were inoculated on 6 July; cat 63 died on 19 July, cat 65 was ill and killed on the same day. Post-mortem examinations revealed no obvious cause of death.

Cats 66 and 67 received, on 10 July, emulsions of infective material prepared from an experimental animal that had shown, *post-mortem*, an active amoebic infection. By Sunday 16 July both were passing bloody mucus. Cat 67 was killed on 17 July and extensive ulceration was found in the rectum and caecum, so an emulsion was prepared from bowel scrapings for inoculation into kittens 71 and 72. Cat 66 was killed four days later after developing conjunctivitis, and post-mortem examination uncovered no evidence of amoebic infection.



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Cat 68 was inoculated on 12 July with material from an earlier experimental animal, and received a second dose three days later when cat 70 was inoculated. Both cats developed signs of amoebic dysentery and their faeces were used to prepare further emulsions for the infection of other animals. Cat 68 was killed, whilst still vigorous, on 24 July. The post-mortem examination revealed numerous active amoebae in the mucus of the large intestine but no indication of associated ulceration. By Monday 24 July, cat 70 was sufficiently infected to be entered into a trial with the anti-amoebic drug emetine.

Kitten 69 was infected orally on 14 July with an emulsion of fresh material taken from a patient passing abundant amoebic cysts. Two days later the kitten exhibited diarrhoea but examination of its faeces and blood showed no active protozoa, and further doses of emulsions made from human faeces were given on 19, 20, and 21 July. Shortly after the second dose the animal passed a large fluid stool that was full of cysts, but microscopic examination suggested that they were from the previous day's inoculum and the animal had not become infected. On Monday 24 July the kitten died without exhibiting any symptoms of amoebiasis. Post-mortem findings could find no reason for its death.

Despite the promising advances indicated by the progress of cat 70, that a reproducible and sustained infection could be induced in experimental animals, the therapeutic trials were not successful. Tests of several alkaloids, particularly naturally occurring derivatives of ipecacuanha,<sup>25</sup> established that the experimental dysentery resisted all kinds of treatment, although some of the data were useful in assessing drug toxicity levels. Simultaneous clinical trials revealed that some of the alkaloids, emetine and emetine-bismuth in particular, *were* effective in combating the human disease, leading Dale and Dobell to suggest that the action of such drugs in amoebic dysentery clearly needed re-evaluating as their results suggested an action on the host rather than on the parasite.<sup>26</sup> The associated clinical work resulted in emetine-bismuth iodide's adoption as the standard treatment by the War Office Dysentery Committee.

*PP/HHD/7*: The front part of this book records experiments on the toxin of gas gangrene, whilst the back part continues work associated with the experimental study of amoebiasis. Although dated only from "September" to "December 5th" the subsequent publication in December 1915 suggests that the gangrene experiments were performed in that year. This was a study of the toxic principle of one of the anaerobic bacteria isolated from soil-infected gangrenous wounds. When injected into guinea-pigs this caused acute convulsive symptoms and death within five to six days. Chemical analysis and pharmacological experiments revealed however that the

<sup>25</sup> A helpful summary is Ian M. Rollo, 'Drugs used in the chemotherapy of amebiasis' in *The pharmacological basis of therapeutics*, ed. L. S. Goodman and A. Gilman, 5th ed., New York, Macmillan, 1975, pp. 1069–80.

<sup>26</sup> H. H. Dale, 'A preliminary note on chronic poisoning by emetine,' *Br. med. J.*, 1915, ii: 895; *idem*, 'Treatment of carriers of amoebic dysentery. Note on the use of the double iodide of emetine and bismuth', *Lancet*, 1916, ii: 183–4; *idem*, 'The treatment of amoebic dysentery', *Lancet*, 1917, i: 780; H. H. Dale and Clifford Dobell, 'Experiments on the therapeutics of amoebic dysentery', *J. Pharmac. exp. Ther.*, 1917, 10: 399–459. See also Dale, *op. cit.*, note 16 above, pp. 386–88.

acute symptoms were entirely dependent upon ammonium salts produced by the bacteria and not to a true bacterial toxin. This was of immediate practical relevance to those who had been attempting to produce a conventional anti-toxin.<sup>27</sup>

The experiments in the other half of the notebook are a series of toxicity tests on drugs specifically associated with the amoebiasis work, like emetine and other alkaloids derived from ipecacuanha, and also on drugs included in the routine series of examinations undertaken by the department. These are also dated from October to December and were probably performed in 1915.

These notebooks are important for two reasons: as examples of the type of medical research necessary during the First World War and also as close indicators of Dale's approach to scientific problems. The range of work undertaken shows the urgency of the need for research on such basic physiological problems as shock mechanisms and the mode and effect of protozoan infections, and the equally desperate need for the integration of that research with clinical knowledge and practice. With regard to Dale's own scientific attitudes, the notebooks exemplify his detailed and conscientious style, as shown by the work on thrombin referred to in PP/HHD/5, which started as a small problem associated with the development of the anaphylactic shock syndrome, but developed into a major study of the chemical factors that promote blood clotting. He also worked very economically—the experiments on rat deficiency diets that seem to have been inconclusive were abandoned quickly, the work on gas gangrene was performed rapidly and, once a clear-cut answer emerged, it was immediately written up and published.

Henry Dale's activities during the years covered by these notebooks were not confined to the research documented within them. As indicated earlier, he carried out other work, such as that on histamine and shock; he continued to deliver and publish lectures and reviews on many topics; in 1916 and again in 1917 when Fletcher was seriously ill, Dale spent several mornings a week assisting in the administration of the MRC; and he served on several government, Royal Society, and MRC advisory boards and committees.<sup>28</sup> A major duty throughout the war years, and one that is hinted at by some of the entries in these books, was the routine standardization and testing of British and French pharmaceutical preparations, especially those produced to replace Salvarsan. The first post-war *Annual Report* of the MRC acknowledged the tremendous amount of work done by Dale and his staff:

Altogether, Dr. Dale and his colleagues have borne a heavy burden of responsibility, and have met unflinchingly a constant drain upon their activities, which were deeply pledged in other important directions . . . he and his colleagues have rendered conspicuous service to the medical profession, to the public and to the manufacturers.<sup>29</sup>

<sup>27</sup> G. Barger and H. H. Dale, 'Note on a supposed soluble toxin, produced in artificial culture by the bacillus of malignant oedema', *Br. med. J.*, 1915, ii: 808–9.

<sup>28</sup> A brief review of Dale's other activities during this period is given in Feldberg, op. cit., note 3 above, pp. 102–15.

<sup>29</sup> *Annual report of the Medical Research Committee*, 1918–19, p. 23.

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The end of the War brought an increase in Dale's public and professional duties: he supervised the transfer of his department to the NIMR at Hampstead and headed the Management Committee that ran the Institute until 1928 when he was appointed the NIMR's first Director, which he remained until 1942; he continued to serve on numerous official committees; became Secretary of the Royal Society in 1925 for ten years and was President from 1940 to 1945, a period that brought many additional responsibilities. Throughout, Dale continued his personal and collaborative researches on a broad front, concentrating in the late 1920s and 1930s especially on providing experimental evidence of the chemical mediation of neural transmission. Some manuscript drafts of papers and laboratory tracings from this inter-war period do survive, but experimental notebooks of the type described here have not been found.<sup>30</sup>

<sup>30</sup> Feldberg, *op. cit.*, note 3 above, pp. 115–26.