CONVALESCENT SERUM IN PROPHYLAXIS OF MEASLES, CHICKEN-POX, AND MUMPS

WITH OBSERVATIONS ON VARIATIONS IN THE WASSERMANN REACTION*

BY

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The aggregation of patients in hospitals or institutions presents many problems, medical and administrative, but few so pressing and disturbing as the outbreak of infectious disease in a susceptible population. Certain common infectious fevers, like diphtheria, and scarlet and typhoid fevers, usually occasion little alarm, as, being mildly contagious, they are unlikely to lead to a widespread epidemic. Prompt isolation usually suffices to avert a succession of cases, while adequate means of providing immunity are readily available if required. Moreover, the incubation period of these diseases is relatively short, so that prolonged detention in quarantine is unnecessary. On the other hand, in the three infections under consideration—namely, measles, mumps, and chicken-pox—the quarantine period is protracted (twenty-one to twenty-eight days), and the necessity of placing “cross-infected” wards in isolation seriously reduces the effective accommodation of the hospital, and entails economic loss both to the individual and to the hospital authorities. Furthermore, the concurrence of two and occasionally of three diseases renders the patient more prone to the complications peculiar to each disease. The association of measles and scarlet fever is particularly unfortunate in this respect, frequently threatening the life of the patient.

All three diseases mentioned are contagious to a marked degree, but not equally so; and the same disease may vary in infectiousness and virulence at different times, irrespective of the susceptibility or otherwise of the population exposed to the infection. The sequence of events was observed in a number of ward outbreaks, in which no action was taken other than immediate removal of the infecting case. It was found that secondary cases of chicken-pox followed on nine occasions after ten outbreaks, and further cases of measles ensued on eight occasions after ten outbreaks, while mumps was seen to be much less contagious—the chances of further cases developing the disease being almost even.

FACTORS IN SERUM THERAPY

At least three factors must be taken into consideration when classifying the individual units of an exposed population, before administration of serum—namely, (a) whether susceptible or immune, (b) distance from the infecting case, which should be removed forthwith, and (c) age and body weight. In the case of measles, in the absence of a reliable test to denote susceptibility or otherwise, the history is the sole guide. It is frequently found to be untrustworthy; many children have had an attack of measles which was unrecognized at the time or forgotten by the parents; others have been wrongly diagnosed as measles; while a certain proportion appear to possess a permanent immunity, either inherited, or acquired as the result of successive subinfecting doses. In chicken-pox, a careful search usually reveals the presence of characteristic scars indicative of a previous attack; but in the case of mumps the history alone must be accepted, in the absence of the sequelae peculiar to the disease.

* The full text, with tables and references, is given in the Medical Supplement, Annual Report of the London County Council for 1930.

The distance of susceptible contacts from the primary infecting case is of vital importance in measles; the patients in the immediate vicinity nearly always contract the disease on the first exposure, and they alone, while more distant contacts succumb in the second or third “generation.” In chicken-pox and mumps the effective striking distance is much greater, and secondary cases occur almost as frequently in beds at a considerable distance as in adjacent beds.

The dose of serum should be adjusted to the body weight of the individual, but in practice it is found more convenient, and sufficiently accurate, to take age as the dosage standard. To obtain strict control conditions, injections are given simultaneously to alternate contacts of approximately the same age, placed at equal distances from the infecting case, using a dose suitably adjusted to the body weight. Only by taking such precautions can the data obtained in different outbreaks be comparable; even then, unequal and unexpected results may follow, depending on such factors as chance, season of the year, bed spacing, efficiency of nursing, and general resistance of population.

HUMAN AND ANIMAL SERUMS

The employment of immune measles serum in the prevention of measles was first suggested by inoculation experiments on monkeys. In the course of these experiments it was found impossible to reinfect the animals after successful primary inoculation, presumably on account of the development of immune substances in their blood. Convalescent serum was used in the earliest investigations on passive immunization in measles and has remained the only reliable prophylactic agent, although numerous serums of animal origin have been tried or are still on trial. In 1928 the writer subjected the three best-known animal serums (Degkwitz, Tunnicliff, and Ferry and Fisher) to a critical examination by controlled experiments on the human subject, and compared the potency of each with that of pooled convalescent serum. It was concluded that animal serum contained no antibody, or, if it was present, it was insufficient in amount to prevent the onset of measles or to modify its course. Convalescent serum, on the other hand, gave consistently good results, and is, moreover, free from the unpleasant effects which frequently follow the injection of a foreign protein. The earlier experiments with convalescent serum, at a time when the appropriate dose for a given case was a matter of doubt, were naturally less successful than the later injections, which conferred complete immunity in 100 per cent. of cases. These satisfactory results are the outcome of care in the selection of donors, accurate adjustment of dosage to body weight, and administration of serum at the optimum time after exposure.

DOSAGE OF SERUM IN MEASLES

The failure of a particular serum to protect is usually attributable to an erroneous diagnosis of measles in the donor, with comparatively low antibody content in consequence. Much less frequently a given sample of serum is found to be weak and to lower the protective value of a pooled serum, on account of low antibody production in the donor. This may be due to a defective mechanism for immunity production, or, probably, more frequently to inadequate stimulation of the mechanism in mild forms of the disease. Inadequate dosage is occasionally the cause of failure to ward off attack. To ensure complete protection a minimum dose of 5 c.cm. is advisable, although smaller doses of a potent serum are effective; from the age of 3 years onwards the dose is reckoned in cubic centimetres by multiplying the age in years by two. All injections are given intramuscularly and as soon as possible after exposure to infection. After the sixth

day a modified attack is the rule, although protection has been afforded apparently as late as the eighth day of exposure. During the last two measles epidemics (1927-28 and 1929-30) a total of 206 susceptible contacts were injected, with an average protection rate of 94.2 per cent. For the last 52 cases in the series the protection rate was 100 per cent.

DURATION OF IMMUNITY IN MEASLES

Certain data bearing on the duration of the immunity conferred by the injections were made available. Modified or attenuated attacks of measles followed re-exposure to infection on the twenty-fifth, twenty-eighth, and thirty-second days, respectively, indicating the approximate rate of disappearance of complete as distinct from partial immunity. In two instances the incubation period was lengthened to eighteen and twenty-one days, respectively; but as such occurrences are not infrequent under normal conditions, undue stress should not be laid on the possible effect of the serum in delaying the onset of the disease.

IMMUNIZATION IN CHICKEN-POX

Inasmuch as chicken-pox is a comparatively innocuous disease, it might be questioned whether it is worth the trouble and expense incurred in seeking to provide protection. The long incubation period—necessitating a prolonged quarantine for infected wards—and the extreme contagiousness and high resistance of the virus—rendering mere isolation measures useless—furnish sufficient cause for active interference. Moreover, the simultaneous onset of eruption and state of infectivity provide what would appear to be ideal conditions for successful immunization.

The literature on chicken-pox prophylaxis is extremely meagre, and the published reports reveal conflicting evidence on the efficacy of the method. In the present series, forty-three presumably susceptible contacts were given pooled convalescent serum at intervals varying from the first to the sixth day after exposure to infection. The scheme of dosage was that followed in the measles series. Of the forty-three patients injected, 33 (76.7 per cent.) did not develop the disease subsequently; but, as exactly half the cases in the control group escaped attack, the actual protection rate was reduced to 26.7 per cent. Some of the failures had very mild attacks, but not more so than may be encountered in a series of chicken-pox cases under normal conditions. It is evident that, in the doses employed, convalescent chicken-pox serum is far inferior to convalescent measles serum as a prophylactic agent. A more generous dosage is advisable in future experiments.

IMMUNIZATION IN MUMPS

The arguments advanced against passive immunization for chicken-pox have also been urged against the method for mumps. In addition, the short period of infectivity, the low grade of contagiousness, and the increased risk of complications (should the disease be deferred until adolescence) lend support to those arguments. On the other hand, a long incubation period should theoretically favour ready immunization; and, moreover, the protected subject would probably not be exposed again during his lifetime, as mumps is a comparatively infrequent disease in the general population.

As in the case of chicken-pox, no records of experiments in passive immunization for mumps have been hitherto published in this country, although several American and Continental writers have reported results as uniformly successful as in measles prophylaxis. In the present series nineteen contacts were injected at intervals varying from the first to the fifth day after exposure, and a further two cases were injected on what was later discovered to be the thirteenth and fourteenth days respectively. The first-day injections proved very satisfactory, as none of

the presumably susceptible contacts developed the disease, while three controls (33.3 per cent.) were attacked. Those patients who escaped on the first exposure contracted mumps on the thirty-first, forty-third, and eighty-seventh days, respectively, after injection, subsequently being reinfecting by the control cases which had developed the disease. Of five patients who were injected on the fifth day none contracted the disease, but the results were valueless from the experimental point of view as the control group escaped also. In the whole series of forty-three cases (twenty-one injected and twenty-two controls), 14.3 per cent. developed the disease in the test group and 22.8 per cent. in the control group. The results are admittedly unsatisfactory, but justify a further trial of the method with larger doses of serum.

TECHNIQUE FOR COLLECTING SERUM

The donors selected should be vigorous and healthy, free from syphilitic or tuberculous taint, and well able to stand the loss of blood. They should be kept under observation for twenty-one days, if possible, to ensure that they are not incubating any infectious disease. Amounts of blood up to 20 c.cm. may be taken from a child of 5 years, 100 c.cm. from a child of 10 years, and 250 to 500 c.cm. from an adult. The blood should be withdrawn on the fourteenth to twenty-first day of the disease, or on the tenth to fourteenth day after defervescence. The attack should be of moderate to marked severity, and the recovery complete and uncomplicated. For taking amounts up to 50 c.cm. an all-glass 50 c.cm. syringe with peripheral nozzle, lubricated with liquid paraffin, is recommended; the blood is withdrawn quickly and expelled gently into specially prepared agar-lined test tubes of 20 c.cm. capacity. The maximum clot contraction and yield of serum are obtained in tubes of this size. When greater amounts are taken a piece of rubber tubing (about 6 inches long) attached to an intravenous needle—both paraffin-treated—is preferred, and larger tubes (50-60 c.cm. capacity) are more convenient. The test tubes are immediately placed in the incubator at 37° C. for one hour, and thereafter in the cold room (4° C.) for twenty-four hours, when the serum is pipetted off and the Wassermann reaction is performed on each batch. Three more samples are pooled, the mixed product is filtered, and 0.5 per cent. phenol is added. The serum is tested for sterility, aerobically and anaerobically, distributed in sterile ampoules of 5 c.cm., 10 c.cm., and 20 c.cm. capacity, and stored at 4° C. until required for use. At this temperature the potency is maintained for at least a year, and probably much longer.

WASSERMANN REACTION IN INFECTIONS

Numerous workers on the Wassermann reaction have recorded positive results in various infectious diseases, such as typhus, scarlet, and typhoid fevers, pneumonia, and tuberculosis, in the absence of syphilitic infection, but in many instances there is reason to suspect defective technique in the performance of the test. As a result of accumulated experience from all parts of the world the conclusion is generally accepted that scarlet fever and tuberculosis are both capable of returning a positive reaction, although some authorities still deny that it is ever present apart from syphilis.

Every sample of convalescent serum was tested by the Wassermann reaction. The technique employed was that commonly known as the Medical Research Council Method No. 1, in which the reactions are graded quantitatively (+++, ++, +, ±, -). The test was usually carried out one to three days after the blood was withdrawn, although occasionally an interval of five to six days elapsed before it was done.

In Measles.—Fifty-three samples of blood from convalescent measles donors were tested. In six instances a positive reaction was obtained; in one instance it was ++, in two instances it was +, and in three it was ±. The strongly positive serum was retested one week later; it was found to be still +, and was discarded as unfit for use. The two serums giving + reactions were retested a week later and found to be completely negative, and were accordingly pooled with other samples for injection. All three serums giving doubtful reactions were completely negative on retesting a week afterwards. In two instances in which the reaction was + another sample of blood was withdrawn a week later, and the fresh serum was found to be negative. The blood of three patients examined on the fourth day of the disease gave a ± reaction, but on the fifteenth, sixteenth, and seventeenth days, respectively, the reaction was negative.

In Chicken-pox.—In the chicken-pox series twenty-five donors were utilized. On three occasions a frankly positive reaction was returned, while on one occasion it was doubtful. Two of the three positive serums were re-examined a week afterwards and found to be negative, while the third sample was pronounced unfit for use, as the significance of these doubtful reactions was not appreciated at the time. The serum which gave the doubtful reaction was found to be negative on retesting a week later.

In Mumps.—Six samples of serum were taken from mumps convalescents; the Wassermann reaction was negative in every instance.

The Interpretation of these changes in the Wassermann reaction is not clear, but it would appear that in the acute fevers there is an increase in the normal lipoidophile antibody content of the human serum, or a physical or chemical alteration of its constitution which permits complement-deviation to occur even in the absence of luetic infection (Mackie and Watson, 1926). This change in the serum is present only for a short time (third to twenty-first day), and rarely persists into the fourth week. Moreover, it is only found in fresh serum (first to fourth day after withdrawal) and always disappears within a week after storage at 4° C. It is not improbable that the positive reactions reported in the acute fevers by various workers are attributable to the presence of this or like substance in fresh serum, and have no relation to luetic infection.

LEAD POISONING AS A CAUSE OF PEPTIC ULCER

BY

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In 1839 Tanquerel published his classic treatise, which proved to be the best work on industrial plumbism in the early part of the nineteenth century; he was presented with a galaxy of material at the hospital of La Charité, Paris. From 1831 to 1839 he saw no fewer than 1,217 cases of lead colic, and so accurate were his clinical observations that little of importance has been subsequently added to his conclusions. Tanquerel mentioned that peritonitis was often a sequel of lead poisoning; in his day gastric ulcer had not become a definite clinical entity. About the same time Cruveilhier (1829-35) was investigating the morbid appearances and sequelae of gastric ulcer, and, as Bolton describes, it was Cruveilhier who gave the disease its present status in medicine. Our knowledge of the cause of gastric ulcer is still imperfect, and it is recognized that many conditions may be con-

cerned in its production. An increased concentration of hydrochloric acid in the gastric juice and general malnutrition seem to be constant factors.

RESULTS OF PRESENT INVESTIGATION

For the purpose of this investigation, which has taken ten years to carry out, over a thousand spelter workers were kept under observation. The ore from which spelter is obtained includes lead, zinc, cadmium, and traces of arsenic. Lead, zinc oxide, and cadmium are constituents of the atmosphere of a distillation-house plant. Cadmium, being the most volatile, comes off first in the process of distillation. The soil within a mile or two of the spelter works is impregnated with zinc oxide, and it has been found on rhubarb plants at a distance of two miles from the works. When our present civilization is extinguished a chemist may come along and infer that Swansea was a centre of a huge metallurgical industry. Zinc, apparently, has no toxic action on the human body. The effects of cadmium on the spelter worker are not known, or at least not distinguishable from the effects of lead. Gadamer and Arbour Stephens maintain that cadmium produces a disturbed metabolism and sets up a gastritis, which prepares the way for lead absorption. Stephens has described a case of a spelter worker who received compensation for ten years on the grounds of plumbism. At necropsy, in this particular case, Stephens found in the liver cadmium (0.91 grain to the pound) but no lead. The absence of lead in the liver was no proof that the man did not suffer from plumbism, for Minot has proved that lead may be present in large quantities in bones when no trace may be found in other organs.

Recently cases of lead absorption and poisoning have been observed in other industrial workers where cadmium is not present in the ore, and we failed to find any particular symptoms other than those usually found in the plumbic spelter worker. One hundred spelter workers were selected for investigation, and these included twenty-five that had been, or were later, certified by the medical referee as definite cases of lead poisoning. Fifty had shown signs of lead absorption, and the remaining twenty-five were apparently in good health. All the men had worked for more than a year at the spelter works, and their ages varied from 20 to 60. The Workmen's Compensation Act covers lead poisoning only, and makes no provision for lead absorption. It was therefore important from the medico-legal point of view to distinguish between lead absorption and lead poisoning. This is not always an easy task, for some workmen may show signs of grave toxæmia without even the classical signs of colic or wrist-drop. Loss of appetite, discomfort on taking food, and loss of weight are very early signs of lead absorption. Nearly all such patients complain of vague pains in the stomach, and on palpation there is invariably a tenderness in the left iliac fossa.

The blood of the 100 men was examined for punctate basophilia: Giemsa's stain was used. Of the twenty-five proved plumbic cases 80 per cent., of the fifty suffering from lead absorption 20 per cent., and of the remaining twenty-five—who complained of no symptoms—5 per cent., showed stippling of 100 or more per million red cells. The presence of basophilia, therefore, is of help only when taken in conjunction with other symptoms of lead poisoning, and its absence is no proof that a man is not suffering from plumbism. Another line of investigation adopted was the systematic testing for lead in the urine of men exposed to lead fumes and dust. In carrying out this investigation Mr. Richards, the chemist to the Swansea Vale Spelter Works, gave valuable assistance.

The urine of the thirty men of the selected 100 was examined, and lead in varying quantities was found in