and manufacturing laboratories on both sides of the Atlantic are straining their resources in the attempt to make and to isolate penicillin, and to determine, perhaps, its constitution, or that of the penicillins if there should prove to be more than one active constituent. Then finally, perhaps, may come a synthesis of a penicillin, or of some simpler analogue with similar action. There seems to be a possibility, even a likelihood, that this remedy against infection from a new kind of source may approach, more nearly than any other yet available, to the ideal of toxicity for the infecting organism and complete absence of it for the patient. Here again, however, the effect on the organisms is merely to prevent their multiplication, and not to kill them outright. There can be little doubt that the first pages only are being turned, as yet, of a new and brilliant chapter in the specific treatment of infections.

Conclusion

If we are to form an idea of the prospect which I took as the subject of my lecture, I think that it is important to recognize how much of the change which I have been discussing has taken place in the latter part of the period covered by the survey—in the years, in fact, since the last war came to an end. This is not only true of the progress of chemotherapy, which I have considered in more detail, but equally so of exact knowledge of the natural remedies for deficiencies. At the end of the last war only one hormone, adrenaline, had yet been chemically identified, and no vitamins. It was still possible then to suggest of many of the hormones that their very existence was problematic, and that they, and the vitamins as well, might in any case be so labile and otherwise inaccessible that the methods of chemical isolation and structural study would never be applied to them. Yet before the present war broke out large and rapidly growing series of both hormones and vitamins had been isolated, identified, and made available for practical use by artificial synthesis; and a beginning had even been made of the discovery of simpler synthetic substitutes. In chemotherapy, though salvarsan had appeared before the last war began, there was still, when it ended, no clear prospect of further advance by routes which could be mapped on scientific principles. Wholesale and almost haphazard trial of derivatives or analogues of any substance which had shown a promise of activity seemed to be the only way open; the marvel was, and still is, that so much has been achieved by such methods.

I have tried to trace the progress since that time, from the picturesque but frankly empirical conceptions which Ehrlich had bequeathed, based apparently on his knowledge of selective staining with dyes and of the extreme specificity of immune reactions. From these ideas of magic bullets, bringing down only the parasites by virtue of a mysterious affinity for them alone, we passed to recognition of the effect as stopping their reproduction rather than slaying them outright, turning to their defeat the tide of battle with the host's natural resistance to infection. We came thus to the conception of the effect as usually a mild and persistent one, dependent for that persistence, in some cases, on affinity of the remedy for the host's tissues and not merely for the parasites. And, finally, we reached a conception, just emerging, of the nature of the effect on the reproduction of the parasites, stated in biochemical terms of an interference with known factors of their growth. Look back with me again to medicinal treatment at the opening of this century, and consider that the portentous change between then and now has been so largely an achievement of the years of uneasy armistice between two open wars, at a time when the full impact of research on practical medicine was only just beginning to be felt. Portentous, I said; but what does it portend? Does it not mean that, when we have won freedom from war and from fear of war, the prospect of further achievement in this field of experimental therapeutics, so newly opened to enterprise, is brilliant beyond anything that experience yet enables us to picture? What an opportunity, I am moved to exclaim, for those who still have the years before them in which to use it! I hope that it may fall to the lot of one of them, when the passage of years may justify another review, to tell again in one of these lectures how much of this present prospect has by then become a reality, and to survey yet further possibilities, beyond any that we can now imagine, which will then be coming into view.

CUTANEOUS AND CONJUNCTIVAL DIPHTHERIA

A SERIES OF CASES

BY

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Medical literature records that cutaneous diphtheria was not an uncommon condition in the nineteenth century, but nowadays it is so rarely recognized in this country that a series of cutaneous and conjunctival infections admitted to the Isolation Hospital, Southampton, seems worth recording. All the cases were admitted from a military hospital. Rolleston (1925), describing a large number of diphtheria admissions, found that approximately 1% showed cutaneous involvement, and Cameron and Muir (1942) reported a series of 66 cases occurring among troops in Palestine.

Details of Cases

During the eight months prior to April, 1943, there were admitted to the Isolation Hospital, Southampton, from a military hospital, 19 patients who had lesions of the skin or eyes from which *C. diphtheriae* had been isolated. Of these, 12 were infected with virulent and 4 with avirulent organisms; in the remaining 3 cases tests for virulence were not carried out.

The 12 infections with virulent organisms comprised: (i) 6 cases of cutaneous diphtheria; (ii) 2 cases of cutaneous and conjunctival diphtheria; (iii) 3 cases of conjunctival diphtheria with associated skin lesions from which *C. diphtheriae* was not isolated (one of these was also a faucial carrier); (iv) 1 case of cutaneous and faucial diphtheria. The avirulent infections were 3 cases of cutaneous infection and 1 of conjunctival infection. The 3 cases in which tests for virulence were not carried out were two of cutaneous and faucial infection, and one of conjunctival infection with an associated skin lesion from which diphtheria bacilli were not isolated. All 19 patients were males aged between 21 and 37 years.

Case 1.—Admitted to the military hospital for treatment of seborrhoea of the scalp and forehead and acute purulent conjunctivitis of four days' duration. An eye swab contained diphtheroid organisms. After two weeks the conjunctivitis became more purulent, and a few days later bilateral keratitis was present. The eye was again swabbed, and was found to be infected with *C. diphtheriae* (gravis type I). When admitted to the isolation hospital bilateral conjunctivitis and keratitis were present. There were a dense opacity of the right cornea and an ulcer of the left cornea with hypopyon. No membrane was seen. Treatment consisted of 20,000 units of diphtheria antitoxin i.m., and bland irrigations to the eyes. The inflammation settled down in two weeks, leaving corneae with a frosted-glass appearance. Two months later the vision of the right eye was 6/18 and the cornea was moderately scarred, especially in the lower segment. The pupil was active, but posterior synechiae were present. The left cornea was extensively scarred and staphylomatous in the lower quarter. Vision of left eye was C.F. at 6 in. only.

Case 2.—Admitted to military hospital with impetigo of face and ear. Skin swab reported positive five weeks after admission, but later reported avirulent.

Case 3.—Admitted to the military hospital with dermatitis affecting the "respirator" area. Two weeks later developed a sore throat, a swab from which proved to contain *C. diphtheriae*. A skin swab was also positive. On admission to the isolation hospital the dermatitis cleared up within a fortnight. 10,000 units of antitoxin were given, but later skin swabs showed the presence of diphtheroids only.

Case 4.—Admitted to the military hospital with purpura and pyoderma. A skin swab was reported positive for *C. diphtheriae* shortly before transfer to the isolation hospital, where on admission the patient was found to have an ulcer the size of a five-shilling piece on the outer aspect of the right thigh. The ulcer had a well-marked edge and a grey membranous slough covering its base. 10,000 units of antitoxin were injected, and sulphanilamide powder was applied after the ulcer had been soaked to remove slough. The ulcer healed in about two months.

Case 5.—Admitted to military hospital with impetigo of the face. Three weeks later a skin swab was found to contain virulent *C. diphtheriae* (gravis).

Case 6.—Admitted to military hospital with impetigo of the face and neck of four days' duration. Five days later he developed

conjunctivitis, and the discharge contained *C. diphtheriae*. The virulence of the organism was not determined.

Case 7.—Admitted to the military hospital suffering from impetigo of the chin of fourteen days' duration. Ten days later he developed bilateral purulent conjunctivitis. White membrane was seen on the edge and inside of the lower eyelids two days later. Swabs from eyes and skin showed the presence of *C. diphtheriae* (gravis). The patient was afebrile. At the isolation hospital 60,000 units of antitoxin were given and local treatment was applied to the eyes. Skin and eyes cleared up completely in about four weeks.

Case 8.—This man had impetigo of the face and neck, and two weeks after admission to the military hospital he developed rhinitis. A nasal swab was reported positive for *C. diphtheriae*, but the organisms were avirulent. After transfer to the isolation hospital skin swabs contained virulent *C. diphtheriae* (gravis type I), but throat and nose swabs were negative. The skin condition improved rapidly after the injection of 10,000 units of antitoxin.

Case 9.—Admitted to the military hospital with sycosis barbae. Three weeks later virulent *C. diphtheriae* (gravis type I) were isolated from the skin.

Case 10.—A case of impetigo of the face, neck, and left ear which developed a yellowish-white membrane on the skin behind the left ear one month after admission to the military hospital. A swab from this membrane was found to contain avirulent *C. diphtheriae*. At the isolation hospital only diphtheroids were found in swabs from the skin until one month later, when virulent mitis organisms were reported, presumably due to cross-infection. The skin healed in three weeks.

Case 11.—Admitted to the military hospital with seborrhoea capitis. Three weeks later conjunctivitis developed and virulent *C. diphtheriae* (gravis) were found in the purulent discharge. Swabs taken at the isolation hospital were negative, and the conjunctivitis soon cleared up. 20,000 units of antitoxin were given.

Case 12.—Eleven weeks after admission to the military hospital for treatment of impetigo this patient developed a mild purulent conjunctivitis. The discharge contained avirulent *C. diphtheriae*. At the isolation hospital eye swabs were negative, but throat and nose swabs were positive on two occasions within a week of admission.

Case 13.—Admitted to the military hospital as a case of impetigo, this patient was swabbed and found to have *C. diphtheriae* (gravis) on the skin, but the organism proved to be avirulent.

Case 14.—This man had impetigo of the chin and face three weeks before and a sore throat two days before admission to the military hospital. Throat and skin swabs contained virulent *C. diphtheriae*. The skin persisted positive after the patient had been transferred to the isolation hospital, but swabs from the throat and nose were negative.

Case 15.—This man had impetigo for one month before admission to the military hospital. Five days after admission he complained of sore eyes, and his left eyelid was found to be scabbed. A swab from the eye contained virulent *C. diphtheriae*. At the isolation hospital throat and nose swabs contained virulent organisms of the same type as those found in the eye.

Case 16.—Admitted to the military hospital with sycosis barbae of nine months' duration, this man two months later developed purulent conjunctivitis, and *C. diphtheriae* was found in a swab from the eye. The organism proved to be avirulent.

Case 17.—Five days after admission to the military hospital for treatment of impetigo of the face a blister appeared on one knuckle of this man's right hand. A slough developed, and was found to be infected with virulent *C. diphtheriae*. The infection persisted after transfer of the patient to the isolation hospital, and on two occasions virulent organisms were found in the throat and nose without clinical evidence of infection.

Case 18.—This man had impetigo for three weeks before admission to the military hospital. After two weeks' treatment only slight crusting remained. Following contact with cases which proved to be diphtheritic infections *C. diphtheriae* were found in throat and skin swabs.

Case 19.—After three months' treatment for impetigo in the military hospital a lesion thought to be keloid developed on the neck. A scraping from the skin contained virulent *C. diphtheriae* of gravis type. Swabs at the isolation hospital were all negative, and the skin healed quickly after diphtheria antitoxin had been given.

Commentary

General Features.—No toxæmias could be ascribed to the action of diphtheria bacilli in any of these cases. No paralysis ensued. Membrane was seen in three cases of cutaneous infection (in one of these the diphtheria bacillus isolated was avirulent) and in one conjunctival infection. In all the other cases the lesions had the usual characteristics of the skin condition originally diagnosed. The average length of stay in the military

hospital before transfer to the isolation hospital was four and a half weeks. The average in the latter hospital was six weeks.

Treatment.—In the isolation hospital diphtheria antitoxin was injected intramuscularly in every case. The other treatment was that usually given for the particular cutaneous or conjunctival infection.

Infectivity.—It is of interest to note that in addition to the 19 cases mentioned above there were admitted from the military hospital during the same period 18 other cases of diphtheria, including 7 of the staff. These 18 cases were faucial infections in all but one instance, the latter being a case of rhinitis.

Conclusion.—Recognition of cutaneous diphtheria among patients with a variety of skin infections suggests the need for more frequent bacteriological investigation of such cases.

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ACUTE ALEUKAEMIC MYELOID LEUKAEMIA

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The occurrence of acute myeloid leukaemia in the aleukaemic phase during adult life is rare enough to make the following cases worth reporting.

Case I

A man 63 years old, a window-cleaner by trade, was admitted to the Royal Hospital on Sept. 13, 1942, with a history of a severe sore throat and difficulty in speaking for the past two weeks. These symptoms became progressively worse, and one week before admission he complained of severe malaise and generalized pains over the body; the temperature was then found to be 103° F. Five days before admission a haemorrhagic rash appeared on the legs and arms; this became purple after 48 hours. On the day of admission he complained of headache, shortness of breath, and stiffness of the neck. During the illness he became increasingly drowsy, but could be roused and was quite rational. He had been on a course of sulphanilamide (1 g. four-hourly) and vitamin C (150 mg. daily). Past and family history revealed no significant facts. Bowels and micturition had been normal; there was no loss of weight.

On admission the patient was very drowsy, but roused easily; temperature 102° F., pulse rate 94, and respiration rate 28 per minute. The legs showed a number of papulo-macular haemorrhagic spots with small yellow vesicular centres and irregular edges, located mainly over the shins; the size varied considerably, the largest being 1 cm. in diameter; there was no fading on pressure. The arms were covered with red indurated nodules larger than those observed on the legs, up to 2.5 cm. in diameter, chiefly localized around the elbow, resembling erythema nodosum and not showing the vesicular centre present in the leg lesions. There were also a few macular spots on the back and abdomen. The limbs presented cogwheel rigidity and the joints were very tender on movement. In spite of the increased respiration rate there was no clinical evidence of abnormalities in the respiratory system. Heart and vessels normal; blood pressure 120/70; spleen and liver not palpable; no glandular enlargement. Pupils and fundi normal; all reflexes normal; tongue and pharynx coated with dried mucus; breath fetid.

On the day after admission the patient developed herpes labialis, which later became haemorrhagic. Though remaining rational he became progressively more drowsy and dyspnoeic; the pulse rate rose to 120 and the respirations to 40 a minute. Death took place on Sept. 17.

The laboratory investigations carried out in the short period of time during which the patient was under observation showed: No abnormalities in the urine except a large amount of urobilin; haemoglobin, 62%; red cells, 3,940,000 per c.mm.; mean diameter of the red cells, 7 μ ; white cells, 2,800 per c.mm.—polymorphs 18%, eosinophils 1%, mononuclear cells 81%. Some of the mononuclear cells were typical lymphocytes, but the great majority were of primitive type; one normoblast was seen while counting 100 white cells; platelets in the films appeared to be very scanty.

At first sight the primitive cells were taken to belong to the lymphatic series; but on account of the presence of azur granules in the more immature forms it was decided to investigate the case more fully by means of sternal puncture and the peroxidase reaction. Sternal puncture, performed on Sept. 15, showed: primitive cells