A Supposed Ancestral Man in North America.[1]

By Dr. A. SMITH WOODWARD, F.R.S.

PROF. H. F. OSBORN has just described a water-worn small molar tooth from a Pliocene formation in Nebraska, U.S.A., as the first evidence of an anthropoid primate discovered in the New World. The specimen was found in the Snake Creek beds by Mr. Harold J. Cook, who has already made known numerous important remains of Pliocene mammals from Nebraska, some showing marked Asiatic affinities. With the aid of Drs. W. D. Matthew, W. K. Gregory, and M. Hellman, Prof. Osborn has determined the tooth to be a second upper molar, and he has named the unknown genus and species to which it belonged *Hesperopithecus haroldcookii*. It is nearly as large as the second upper molar of an American Indian, and its two diameters are almost equal. The kind of wear shown by its evenly concave coronal surface "has never been seen in an anthropoid tooth." In type the tooth is "very distant" from the corresponding tooth of the gorilla, gibbon, and orang; it is "still very remote" from that of a chimpanzee. It is also "excluded from close affinity to the fossil Asiatic anthropoid apes" represented by teeth found in India; and "it cannot be said to resemble any known type of human molar very closely." Indeed, "it is a new and independent type of Primate, and we must seek more material before we can determine its relationships."

The statements quoted make it difficult for one who has not seen the tooth to understand why Prof. Osborn even refers it to a Primate; and the published figures are not very helpful. The crown may be described as nearly triangular in shape, with bluntly rounded angles, a slightly raised and partially crimped rim surrounding a gently concave surface. The root is very massive, and at a considerable distance below the crown it becomes bifid, the smaller portion extended beneath one margin of the crown, the larger portion beneath and inclined towards the opposite apex. On one side of the root, between the bifurcation and the crown, there is an irregular indentation, from which Prof. Osborn supposes a third root-fang has been broken away. No stump of this third fang, however, is shown in the drawing.

In determining the tooth to be an upper molar, Prof. Osborn regards the edge with the smaller portion of root as external, and the tapering opposite end with the larger portion of root as internal. The hypothetically restored piece of root thus becomes posterior. It is, however, equally reasonable to interpret the so-called external border as anterior and the tapering end as posterior. If, then, the indented lateral portion of the root never bore another fang, the tooth becomes a lower molar. If this interpretation be admitted, comparison should be made not with any Primate tooth, but with the last lower molar in the primitive bears. In general appearance and shape the crown is very suggestive of that of the last molar in the lower jaw of some species ascribed to Hyænarctos and related genera; and as primitive bears of this group are already known by several fragments from the Pliocene of North America, material will eventually be available for comparison. The root of the last lower molar of Hyænarctos unfortunately appears to be unknown; but in the modern Ursus, in which the tooth in question is extremely variable, the root is often bifid, as in the new fossil from Nebraska, while between the bifurcation and the crown there is a hollowing of its outer face. There is, indeed, some reason to suspect that Hesperopithecus has received an inappropriate name.

[1] H. F. Osborn, "*Hesperopithecus*, the first Anthropoid Primate found in America," American Museum Novitates, No. 37 (reprinted, without figures, in *Science*, vol. 55, pp. 463-465, May 5, 1922).

Synthetic Dyes as Antiseptics and Chemotherapeutic Agents.

By Prof. C. H. BROWNING, University of Glasgow.

GENERAL interest in this subject has been recently stimulated by accounts in the daily press of a communication to the Society of Chemical Industry at Manchester by Messrs. Fairbrother and Renshaw.[1] The fact, however, ought not to be overlooked that much work has been in the past devoted to these problems by a number of investigators. That certain dyes of the triphenylmethane class possess marked antiseptic properties has long been known. Thus Stilling[2] in 1890 noted the powerful effect of ethyl violet on staphylococci (one of the commonest group of organisms which cause suppuration). He suggested the use of a mixture of allied dyes in the treatment of infective conditions, especially of the eye. But Stilling's suggestion found little favour with practical surgeons. As compared with phenol or mercuric chloride, the antiseptic dye-stuffs in general exert their lethal action on bacteria relatively slowly; thus, when tested by the usual method, in which only a brief period of contact between the organisms and the chemical agent is permitted, these dyes appear to act very weakly. It is probably for this reason that they were neglected.

The fact was overlooked that from the beginning of contact very high dilutions of antiseptic dyes may inhibit bacterial activity and that such "bacteriostatic" action can be utilised advantageously for therapeutic purposes. Churchman,[3] however, in America has investigated more recently the allied product, gentian violet, and has emphasised its value in the treatment of certain local pyogenic infections. The diaminotriphenylmethane dyes, malachite green and brilliant green, were shown to be actively antiseptic by Drigalski and Conradi[4] in 1902, and brilliant green has been applied with success in the treatment of infected wounds.

Investigations carried out with the view of comparing the antiseptic properties of various classes of dyes by Browning and Gilmour[5] confirmed the fact that a considerable number of basic compounds showed such action; the series of compounds which they investigated included the acridine group, triphenylmethane group, indamines, azine dyes (safranin), thiopyronin, and thiazines (methylene blue). A continuation of this work showed that of all the substances examined diaminoacridine derivatives ("acriflavine" and "proflavine") stand out on account of a combination of three characteristics, namely, high antiseptic potency, low toxicity for mammalian tissues, and insusceptibility to the interfering action of serum proteins, which diminish markedly the efficacy of all other powerful antiseptics hitherto tested. Therefore these substances, the antiseptic properties of which had not been recognised before, have been widely employed for the treatment of localised pyogenic infections, *e.g.* in wounds; when suitably applied, their use has proved highly beneficial. Recently also non-ionised compounds of mercury with dyes of the eosin group have been successfully used in America (mercurochrome of Young, White, and Swartz).[5A] In the case of generalised infections, however, the therapeutic problem is attended by much greater difficulties, and there is probably no synthetic compound so far available which will exert curative action in generalised bacterial infections in the human subject.

Selective Action.

When the antiseptic potency of a series of compounds is determined for organisms of various types, striking instances of selective action are met with, *i.e.* one compound will act very powerfully upon a particular organism and be relatively inert toward another; other compounds may exhibit the reverse order of activity on the same two organisms. Selective action of this kind was noted by Rozsahegyi[6] in 1887. Probably the most striking example of this is exhibited by the cyanine dye, "sensitol red," the ratio of the sterilising concentrations for *B. coli* and *Staphylococcus aureus* being probably greater than 2000 : 1 (Browning, Cohen, and Gulbransen).[7]

Relationships between Chemical Constitution and Antiseptic Action.

Within narrow limits, in groups of closely related compounds, certain laws have been established. In the triphenylmethane series, both with the diamino and the triamino derivatives, the substitution of methyl and ethyl groups in the amino radicals has been found to enhance the antiseptic action. Thus the penta- and hexamethyl triaminotriphenylmethane dyes, methyl violet and crystal violet, have been found by Dreyer, Kriegler and Walker,[8] and others to be more potent against staphylococci than the unsubstituted analogues, rosaniline or parafuchsine; similarly malachite green (the tetramethyl diamino derivative) and brilliant green (tetraethyl derivative) are much more powerful than the unsubstituted diaminotriphenylmethane dye, Doebner's violet.[5] In the acridine and azine series it has been established that potency of action in a serum medium is a characteristic of the diamino derivatives which have an alkyl group attached to the medial nitrogen atom (Browning, Cohen, Gaunt, and Gulbransen).[9] But general principles correlating chemical structure with antiseptic action cannot be formulated in the present state of knowledge. There is certainly no relationship between colour and effect on micro-organisms.

Action on Protozoa.

Ehrlich and Shiga[10] discovered that by means of injections of a benzidine dye, which they named trypan red, mice infected with the trypanosomes of the South American horse disease, *mal de caderas*, could be completely sterilised; thereby an otherwise acutely fatal infection could be cured. This work gave the impetus to the search for chemotherapeutic agents, and the greatest success achieved in this line has been the discovery of the "salvarsan" group of compounds by Ehrlich and his co-workers. In this department of research, again, it is impossible so far to enunciate general principles which should guide us in the search for effective substances. The therapeutic action is frequently not simply that of an antiseptic operating in the tissues and circulation of the infected animal; thus *in vitro* the parasites of *mal de caderas* are not killed by concentrated solutions of trypan red. Further, selective action is exhibited to a very marked degree by chemotherapeutic agents in protozoal infections; the efficacy of quinine in malaria and its relative inertness in trypanosomiasis is an instance of this. Certain compounds, however, are lethal for protozoa *in vitro* in concentrations which permit bacteria, of some species at least, to survive. Fairbrother and Renshaw suggest that such substances may be utilised with advantage in circumstances in which the process of bacterial purification of sewage fails, owing, it is believed, to an overgrowth of certain protozoa destroying the bacteria.

The search for chemical substances which shall exert curative effects in bacterial and protozoal infections appears to be well worth pursuing, since there are many diseases in which it would seem to be impossible to influence to a significant extent the natural defensive mechanisms of the body by procedures of specific immunisation; tuberculosis is an outstanding instance. But the successes hitherto achieved, especially in protozoal and spirochætal diseases (quinine in malaria, salvarsan in syphilis and other spirochætal infections, trypan blue in piroplasmosis, and emetine in amœbic dysentery), and the promising results in certain bacterial diseases (diaminoacridine derivatives, triphenylmethane compounds and mercurochrome in local pyogenic infections, and ethylhydrocuprein in experimental pneumococcus infections) are still more or less isolated phenomena. If it be possible to establish general principles in chemotherapy, this result will only be attained by much further investigation.

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